

Aerosol Delivery During Mechanical Ventilation: From Basic Techniques to New Devices

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ABSTRACT

Pressurized metered-dose inhalers (pMDIs) and nebulizers are routinely employed for aerosol delivery in mechanically ventilated patients. A significant proportion of the aerosol deposits in the ventilator circuit and artificial airway, thereby reducing the inhaled drug mass. Factors influencing aerosol delivery during mechanical ventilation differ from those in spontaneously breathing patients. The English language literature on aerosol delivery during mechanical ventilation was reviewed. Marked variations in the efficiency of drug delivery with pMDIs and nebulizers occur due to differences in the technique of administration. Careful attention to five factors, viz., the aerosol generator, aerosol particle size, conditions in the ventilator circuit, artificial airway, and ventilator parameters, is necessary to optimize aerosol delivery during mechanical ventilation. Factors influencing drug delivery during NPPV are not well understood, and the efficiency of aerosol delivery in this setting is lower than that during invasive mechanical ventilation. With an optimal technique of administration the efficiency of aerosol delivery during mechanical ventilation is similar to that achieved during spontaneous breathing. Further research is needed to optimize aerosol delivery during NPPV.

Key words: aerosols, nebulizers, metered-dose inhalers, mechanical ventilation

INTRODUCTION

SUCCESSFUL DELIVERY of aerosols to the lung depends on the ability to optimize several factors, including the drug formulation, the aerosol generator, and the technique of administration. The factors mentioned above influence the mass of the drug inhaled by the patient, and these variables, along with the properties of the aerosol generated and the geometry of the airways, determine the quantity and site of drug deposition in the lung.⁽¹⁾ In addition to the total inhaled mass

of drug available to a patient, the precision, reliability, and consistency of dosing are other important factors that influence the response to treatment.⁽²⁾ For precision of lung dosing, drug deposition is targeted to its site of action in the respiratory tract, for example, larger airways versus more peripheral airways and lung parenchyma. Reliable drug dosing requires uniform drug deposition in the lung under a variety of conditions, for example, in different age groups, smokers, and patients with airways obstruction. Consistency of dosing requires uniformity in

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drug deposition across the life of a device [multidose pressurized metered-dose inhaler (pMDI), multidose dry powder inhaler, or repeated nebulizer dosing].

A variety of sophisticated aerosol generators have been developed for use in ambulatory patients. However, clinical therapy during mechan-

ical ventilation is still largely based on pMDIs and nebulizers. Drug losses in the ventilator circuit and endotracheal tube are well known to reduce the efficiency of drug delivery during mechanical ventilation (Fig. 1).⁽³⁻⁶⁾ In the past, the efficiency of drug delivered during mechanical ventilation was reported to vary widely; for pMDIs,

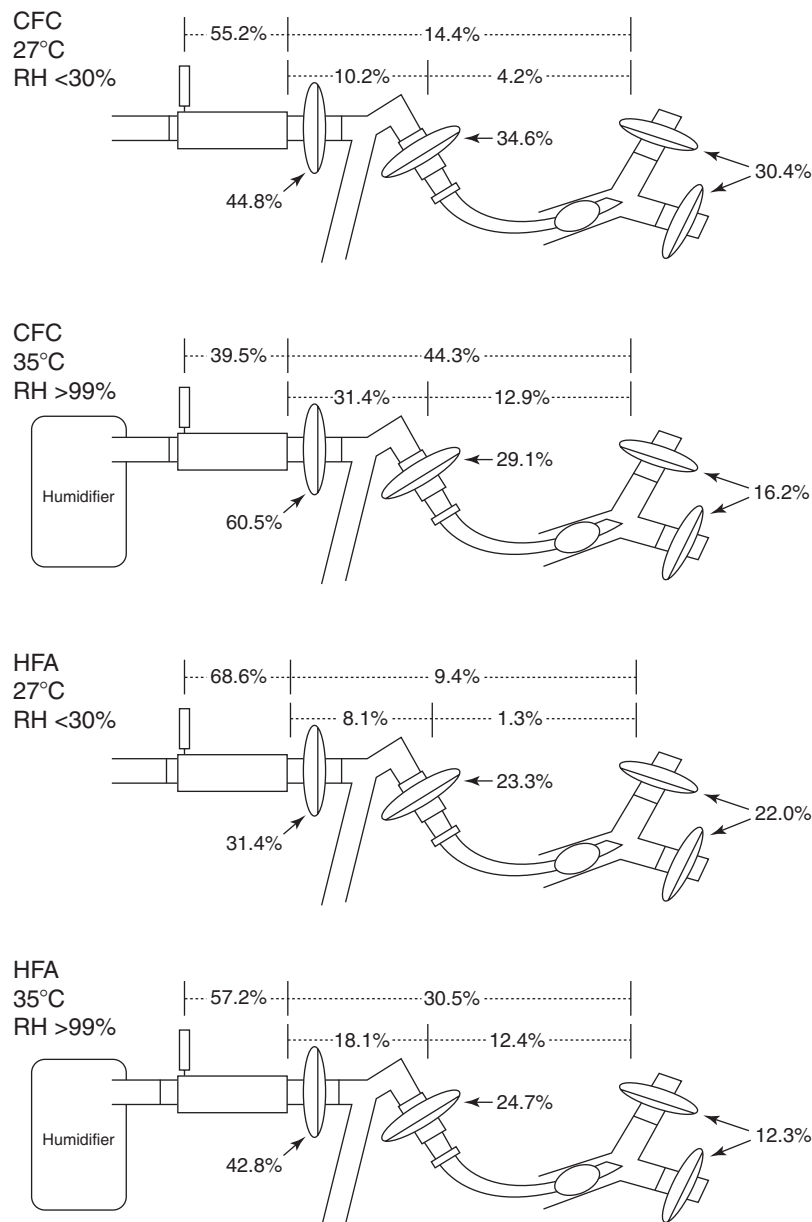


FIG. 1. Drug deposition, expressed as percent of nominal dose of albuterol from a CFC-propelled pMDI, in the spacer chamber, the ventilator circuit, the endotracheal tube, and on filters at the bronchi under dry and humidified conditions during controlled mechanical ventilation. Under dry conditions, 30.4% of the dose from a CFC-pMDI was deposited at the bronchi. The presence of humidity in the circuit reduced the delivery at the same site to 16.2%. With an albuterol HFA-propelled pMDI under dry conditions, 22.0% of the drug was delivered at the bronchi. The presence of humidity in the circuit reduced the delivery at the same site to 12.3%. Under both dry and humidified conditions drug delivery to the bronchi with the albuterol HFA-propelled pMDI was lower than that with the CFC-propelled pMDI. RH = relative humidity. (From Fink et al.,⁽³⁾ reproduced with permission.)

it varied from 0.3 to 97.5%, and for nebulizers from 0 to 42%.^(4,5) Both *in vitro* and *in vivo* studies have contributed towards improving our understanding of the complex factors governing aerosol delivery during mechanical ventilation (Fig. 2).⁽³⁻⁶⁾

The factors governing pulmonary deposition of aerosol in ventilated patients differ from those in spontaneously breathing patients. Five major variables need to be considered to optimize aerosol delivery during mechanical ventilation. These factors include: (1) the aerosol generator, (2) aerosol particle size, (3) conditions in the ventilator circuit, (4) the artificial airway, and (5) ventilator parameters.

THE AEROSOL GENERATOR

pMDIs

In mechanically ventilated patients, pMDIs are chiefly used to deliver beta-adrenergic and anticholinergic bronchodilators for treatment of airway obstruction.⁽⁴⁻⁶⁾ Within the past decade

pMDIs have become more popular than nebulizers for routine bronchodilator therapy in the intensive care unit (ICU).

CFC versus HFA-pMDIs. Previously, most pMDIs used chlorofluorocarbon (CFC) propellants, but these are being phased out, and these will be largely replaced by a newer generation of pMDIs containing hydrofluoroalkane (HFA) propellants. In the United States, full transition from CFC to HFA-pMDIs will probably occur by the end of 2008.⁽⁷⁾ Because HFA propellants are not compatible with surfactants, some of the HFA-pMDIs have been reformulated as solutions, resulting in a finer aerosol spray with greater peripheral lung deposition and improved efficacy compared to the CFC-pMDIs.^(8,9) In bench models of mechanical ventilation, albuterol HFA-pMDIs employed with an Aerovent spacer (Monaghan Medical, Plattsburgh, NY) provide drug delivery that is lower than that with CFC-pMDIs.⁽²⁾ Contrarily, beclomethasone HFA-pMDIs employed with an Aerochamber HC MV spacer (Monaghan Medical, Plattsburgh, NY) had a higher efficiency of drug delivery than the be-

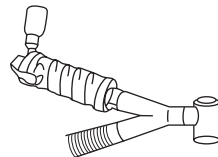
Ventilator-Related

- Ventilation mode
- Tidal volume
- Respiratory rate
- Duty cycle
- Inspiratory waveform
- Breath-triggering mechanism



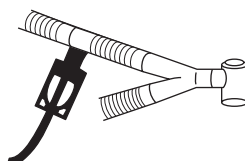
Device-Related - MDI

- Type of spacer or adapter
- Position of spacer in circuit
- Timing of MDI actuation
- Type of MDI



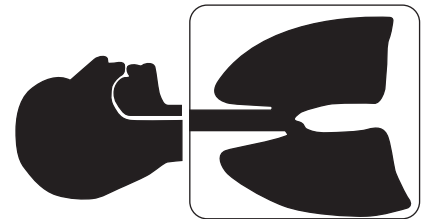
Device-Related - Nebulizer

- Type of nebulizer
- Fill volume
- Gas flow
- Cycling: inspiration vs continuous
- Duration of nebulization
- Position in the circuit



Drug-Related

- Dose
- Formulation
- Aerosol particle size
- Targeted site for delivery
- Duration of action



Patient-Related

- Severity of airway obstruction
- Mechanism of airway obstruction
- Presence of dynamic hyperinflation
- Patient-ventilator synchrony

Circuit-Related

- Endotracheal tube size
- Humidity of inhaled gas
- Density of inhaled gas

FIG. 2. Factors influencing aerosol delivery in mechanically ventilated patients. MDI-metered dose inhaler. (From Dhand and Tobin,⁽⁵⁾ reproduced with permission.)

clomethasone CFC-pMDI.⁽¹⁰⁾ The differences in the results of the studies could be explained by differences in the pMDI formulation and types of spacers employed by the two groups of investigators. The beclomethasone HFA-pMDI is formulated as a solution, and produces an extra fine aerosol with mass median aerodynamic diameter (MMAD) of $1.2 \mu\text{m}$, whereas the albuterol HFA-pMDI is a suspension with aerosol particle size comparable to that of the albuterol CFC-pMDI. Moreover, the size of the canister stem is different for each pMDI, and the efficiency of drug delivery depends on how well the canister stem fits into the actuator. To improve drug delivery with HFA-pMDIs in the setting of mechanical ventilation, the actuators required to connect them in ventilator circuits need to be matched to the size of the pMDI canister stem. No commercially available actuator is equally efficient with all pMDIs, and HFA-pMDIs will need to be matched

with suitable actuators to optimize their efficiency during mechanical ventilation.

Spacer or adapter devices. Several commercially available adapters or actuators are used to connect the pMDI canister to the ventilator circuit. The type of adapter employed could have a profound influence on the efficiency of drug delivery.^(2,4,11,12) The types of adapters available for clinical use include, elbow adapters, inline devices that may be unidirectional or bidirectional, and chamber or reservoir adapters^(2,4,5,12) (Fig. 3). A chamber spacer with a pMDI in a ventilator circuit results in four- to sixfold greater aerosol drug delivery compared with either an elbow adapter or a unidirectional inline spacer.⁽¹³⁻¹⁶⁾ A pMDI and chamber spacer placed at a distance of approximately 15 cm from the endotracheal tube provides efficient aerosol delivery and elicits a significant bronchodilator response.^(17,18) Rau

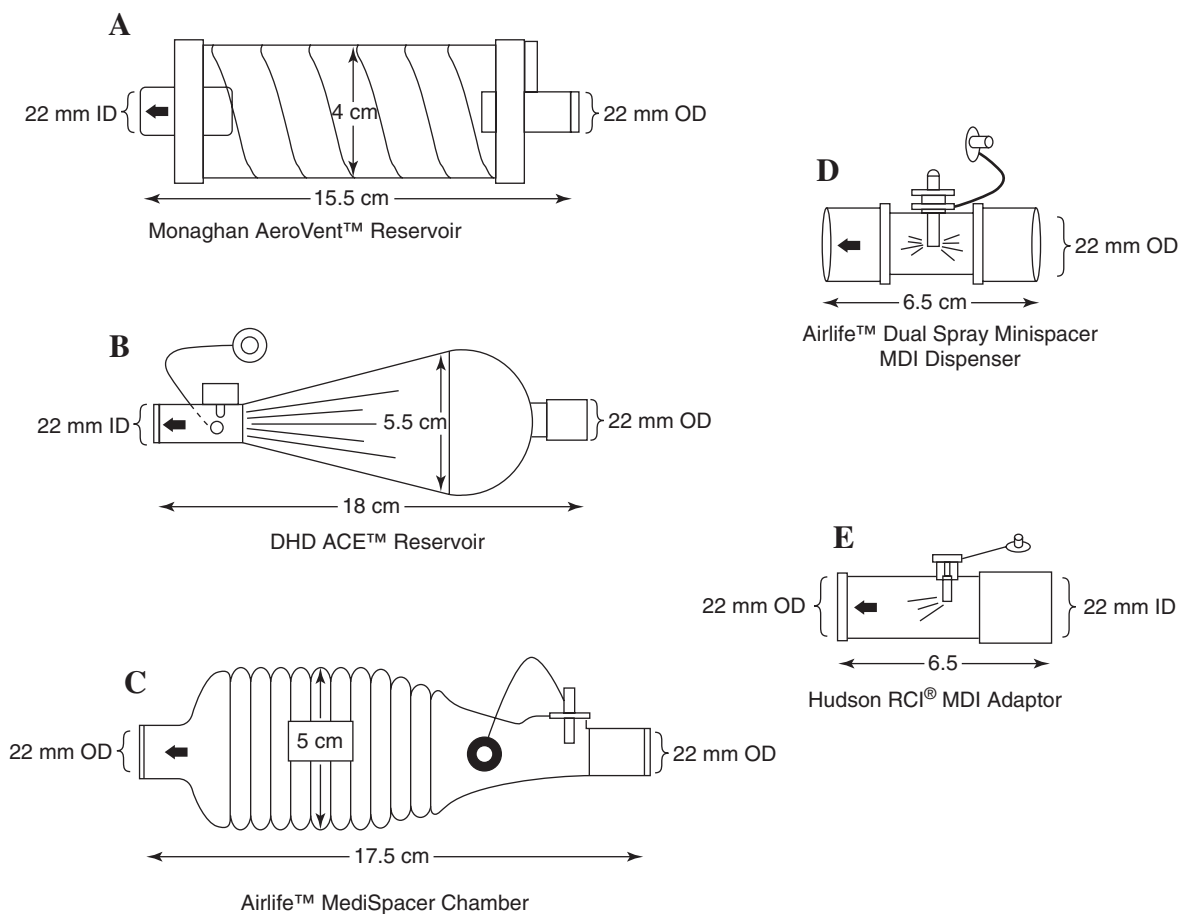


FIG. 3. Commercially available spacers/adapters that are used to connect a metered dose inhaler canister in the ventilator circuit. Top Left, collapsible spacer chamber; middle left, aerosol cloud enhancer, wherein the aerosol plume is directed away from the patient; bottom left, noncollapsible spacer chamber; top right, bidirectional actuator (Minispacer); bottom right, in-line adapter. (From Rau et al.,⁽¹⁹⁾ reproduced with permission.)

and colleagues⁽¹⁹⁾ found that the efficiency of a bidirectional inline spacer was higher than a unidirectional inline spacer, and was comparable to that achieved with chamber spacers;⁽¹⁹⁾ however, the performance of the bidirectional spacer has not been established in clinical studies.

The Aerochamber HC MV (Fig. 4) is another commercially available adapter for aerosol delivery with pMDIs in mechanically ventilated patients. As mentioned above, it is more efficient for aerosol delivery with beclomethasone HFA-pMDIs compared to beclomethasone CFC-pMDIs.⁽¹⁰⁾

Nebulizers

Both jet and ultrasonic nebulizers have been employed for aerosol delivery during mechanical ventilation. Nebulizers are employed to deliver a variety of agents such as bronchodilators, prostanoids, antibiotics, surfactant, mucolytic agents, and corticosteroids to mechanically ventilated patients.

Jet nebulizers. A jet of compressed air or oxygen under high pressure is employed to generate an aerosol. Jet nebulizers are connected in the inspi-

ratory limb of the ventilator circuit. They may be operated continuously by pressurized gas from a wall system or gas cylinder. Alternatively, the air flow generated by the ventilator could be employed to run the nebulizer during inspiration (intermittent operation) by using a separate line to provide driving pressure and gas flow from the ventilator to a nebulizer connected in the ventilator circuit. Intermittent operation is more efficient for aerosol delivery than continuous aerosol generation.^(20,21) The driving pressure provided to the nebulizer by some mechanical ventilators may be much lower than that provided by compressed air or oxygen sources. The lower pressure of the driving gas could significantly alter the efficiency of a nebulizer when it is connected in a ventilator circuit. Newer generations of ventilators are being marketed with nebulizers that have been tested to generate aerosols efficiently during intermittent operation. Availability of ventilators with in-built nebulizers will facilitate reproducible and consistent dosing with a variety of agents in ventilated patients.

The rate of aerosol production is highly variable, not only among brands of nebulizers but even in different batches of the same brand.⁽²²⁻²⁴⁾ The nature of the aerosol produced, especially

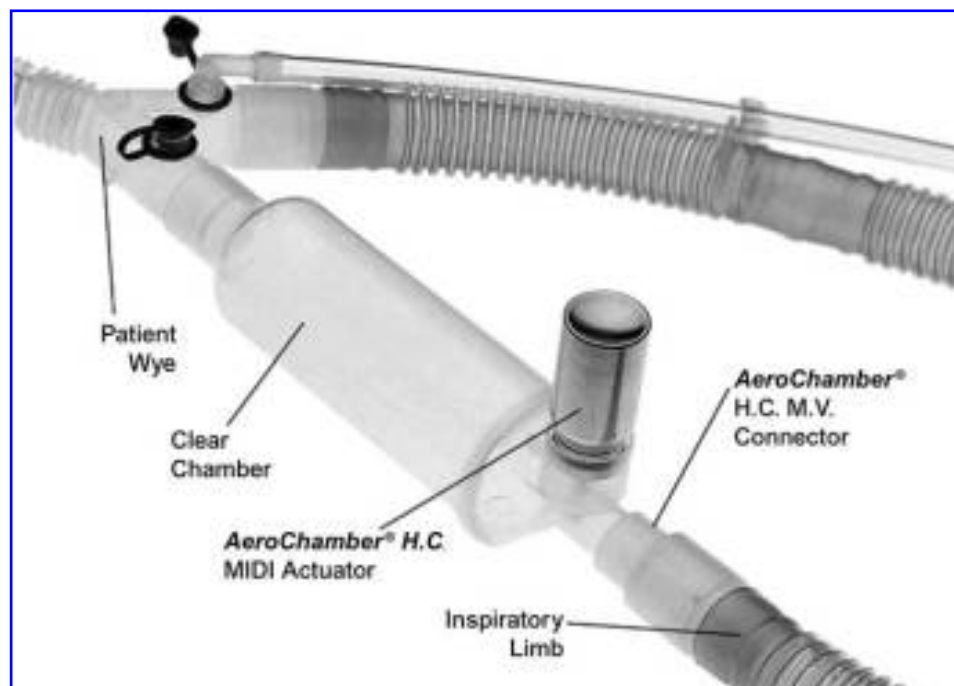


FIG. 4. The Aerochamber HC MV is designed for use during mechanical ventilation. The see-through chamber allows observation of the aerosol spray. It could be employed with HFA-pMDIs. It can be placed in the inspiratory limb of the ventilator circuit (as shown) or it could be connected directly to an endotracheal or tracheostomy tube.

particle size, differs among various nebulizer brands.^(24,25) Furthermore, the operational efficiency of a nebulizer changes with the pressure of the driving gas and with different fill volumes. Moreover, ventilator mode (pressure vs. volume controlled ventilation) and lung mechanics could also influence drug delivery from a nebulizer.⁽²⁶⁾ Therefore, before using a nebulizer in a ventilated patient it is imperative to characterize its efficiency in a ventilator circuit, under the typical clinical conditions in which it will be employed.⁽²⁰⁾

Placing a jet nebulizer at a distance from the endotracheal tube improves its efficiency compared with placing it between the patient Y and endotracheal tube.^(21,27,28) Addition of a reservoir between the nebulizer and endotracheal tube also modestly increases efficiency of drug delivery.⁽²⁹⁾

Ultrasonic nebulizers. In ultrasonic nebulizers, the vibration frequency and amplitude of vibration of the piezo-electric crystal influence aerosol particle size and drug output, respectively.^(30,31) The drug solution becomes more concentrated during operation of an ultrasonic nebulizer, and the solution temperature increases by 10° C to 15° C after a few minutes of ultrasonic nebulization.^(32,33) Several brands of ultrasonic nebulizers are available for use during mechanical ventilation. The SUN 345 (Siemens-Elcoma AB, Solna, Sweden) was adapted for use with the Siemens 300 series of ventilators. Likewise, the Easy Neb was marketed for use with the Puritan Bennett 700 and 800 series of ventilators (Puritan Bennett, Pleasanton, CA). The SUN 145 is another ultrasonic nebulizer introduced by Siemens for continuous use with a variety of ventilators. Most ultrasonic nebulizers have a higher rate of nebulization and require a shorter time of operation than jet nebulizers.⁽²⁸⁾ Generally, the aerosol particle size is larger with ultrasonic nebulizers compared to jet nebulizers. Ultrasonic nebulizers have a higher efficiency for aerosol delivery during mechanical ventilation than jet nebulizers.⁽³⁴⁾ The cost and bulk of ultrasonic nebulizers and their relative inefficiency in nebulizing drug suspensions are major limitations to their use. Small volume ultrasonic nebulizers with smaller residual volumes than jet nebulizers have been employed during mechanical ventilation.^(34,35) The contained portable power source also makes such ultra-

sonic nebulizers more easily portable and convenient to use. However, these devices are much more expensive than jet nebulizers.

Placement of ultrasonic nebulizers proximal or distal to the Y-piece in the ventilator circuit does not influence the efficiency of aerosol delivery.^(28,36) Likewise, placing the ultrasonic nebulizer in the inspiratory limb of the ventilator circuit 50 cm from the Y-piece did not improve its efficiency.⁽³⁶⁾ In contrast, the addition of a cylindrical storage chamber (volume 500 mL to 600 mL) in the inspiratory limb of the ventilator circuit doubles the efficiency of aerosol delivery with ultrasonic nebulizers.^(28,36) The efficiency of aerosol delivery with ultrasonic nebulizers could be modestly improved by employing a longer inspiratory time, by reducing the minute ventilation, and by employing a lower respiratory rate.^(28,36)

AEROSOL PARTICLE SIZE

During mechanical ventilation, larger particles produced by pMDIs and nebulizers are trapped in the ventilator circuit and endotracheal tube (Fig. 1); therefore, devices that produce aerosols with MMAD <2 μm are more efficient during mechanical ventilation than devices that produce aerosols with larger particles.⁽³⁷⁻³⁹⁾ Nebulizers and pMDIs delivered an equivalent mass of aerosol beyond the endotracheal tube in a ventilator model.⁽¹⁴⁾ While nebulizers that produce aerosols with smaller particle sizes have been employed during mechanical ventilation, they require a considerably greater time to deliver a standard dose.^(20,37)

CONDITIONS IN THE VENTILATOR CIRCUIT

Humidity

The gas in the ventilator circuit is heated and humidified to prevent drying of the airway mucosa. Humidification leads to an increased loss of aerosol in the ventilator circuit,^(2,4,20,40) and several investigators have found that drug delivery to the lower respiratory tract from both MDIs and nebulizers is reduced by 40% or more in a humidified compared to a dry circuit.^(2,4,20) Al-

though circuit humidity reduces drug delivery, bypassing the humidifier is not recommended for routine inhalation therapy in ventilator-supported patients. With careful attention to the technique of administration, the impact of humidity on drug delivery can be overcome by delivering a somewhat higher drug dose.^(17,18,41,42) A dry circuit could be employed for delivery of those agents that are very expensive or those agents for which the amount of drug deposition is critical (e.g., antibiotics). When a dry circuit is employed, drug administration should be achieved within a short period (less than 10 min) to minimize the effects of dry gas on the airway mucosa.

Heat and Moisture Exchangers (HMEs) are often employed to provide humidification of inspired air during mechanical ventilation.⁽⁴³⁾ The HME is a passive humidification system that captures the heat and moisture from the exhaled breath and transfers part of the heat and humidity to the next inspired breath. The filter in the HME is a barrier to aerosol delivery, and it has to be removed from the circuit during aerosol delivery. The Circuvent (DHD Health Care Corp., Wampsville, NY) allows aerosol delivery without removing the HME from the circuit (Fig. 5). A piece of tubing bypasses the HME, and this circuit is employed during aerosol generation by turning a dial on the device. After aerosol gener-

ation is completed, the dial is turned back to allow inspiratory airflow to pass through the HME. The efficiency of aerosol delivery appears to be reduced by this device,⁽⁴⁴⁾ and clinical studies are needed to establish its efficacy.

Gas density

Inhalation of a less dense gas than air or oxygen, such as helium–oxygen 70/30 mixture, improves drug delivery in both pediatric and adult models of mechanical ventilation.^(45,46) Likewise, studies in ambulatory patients have shown higher aerosol retention in the lungs when patients breathed heliox instead of air.^(47,48) Therefore, helium–oxygen could be employed to increase aerosol delivery to the lung. With pMDIs there may be as much as 50% increase in the amount of aerosol delivered to the lower respiratory tract when helium–oxygen is employed.⁽⁴⁶⁾ In contrast, nebulizer operation with helium–oxygen reduced drug output and respirable mass.^(46,49) A practical method to achieve maximum pulmonary deposition of aerosol from a nebulizer during mechanical ventilation is to operate the nebulizer with oxygen at a flow rate of 6 to 8 L/min and to entrain the aerosol generated into a ventilator circuit containing helium–oxygen.⁽⁴⁶⁾



FIG. 5. When an HME is employed to provide humidification during mechanical ventilation, the filter in the device traps aerosol particles. The Circuvent is designed to allow aerosol delivery without disconnecting the circuit to remove the HME. By turning a dial, aerosol can be delivered via an alternate circuit that bypasses the HME (shown by arrows). After aerosol delivery has been completed, turning the dial back returns the circuit to its original configuration.

ARTIFICIAL AIRWAY

Aerosol impaction on the endotracheal tube poses a significant barrier to effective drug delivery in infant and pediatric mechanical ventilation (endotracheal tube internal diameter (i.d.) 3 to 6 mm).^(38,50) In adult mechanical ventilation, there was no difference in nebulizer efficiency with endotracheal tubes of i.d. 7 mm versus i.d. 9 mm.⁽²⁷⁾ Drug losses within the endotracheal tube could be minimized by placing the aerosol generator at a distance from the endotracheal tube instead of being directly connected to it.⁽⁵¹⁾ When a pMDI and spacer are employed, the presence of humidity in the circuit increased aerosol deposition in the endotracheal tube by approximately threefold.^(3,4,52) *In vitro* studies show minimal drug deposition within endotracheal tubes with jet nebulizers; however, significant endotracheal tube deposition of aerosol occurs with ultrasonic nebulizers.⁽³⁴⁾

Aerosol deposition in tracheostomy tubes has not been studied in as much detail as endotracheal tubes. By using a mass balance technique O'Riordan and colleagues⁽³⁷⁾ found that approximately 10% of the nominal dose from a nebulizer deposited in the tracheostomy tube of mechanically ventilated patients. The majority of aerosol deposition (~7%) occurred during exhalation.⁽³⁷⁾ Because *in vitro* studies are unable to directly determine aerosol deposition during exhalation, such studies could significantly underestimate the actual deposition of aerosol in the artificial airway.

VENTILATOR PARAMETERS

Synchronizing aerosol generation with inspiratory airflow

The actuation of a metered-dose inhaler (MDI) must be synchronized with the precise onset of inspiratory airflow from the ventilator.^(53,54) As short as 1 to 1.5-sec delay between MDI actuation and a ventilator breath can profoundly reduce the efficiency of drug delivery.⁽¹⁴⁾ Likewise, intermittent operation of the nebulizer that is synchronized with inspiratory airflow from the ventilator is more efficient for aerosol delivery compared with continuous aerosol generation because it minimizes aerosol wastage during the exhalation phase of the breathing cycle.^(20,21) The

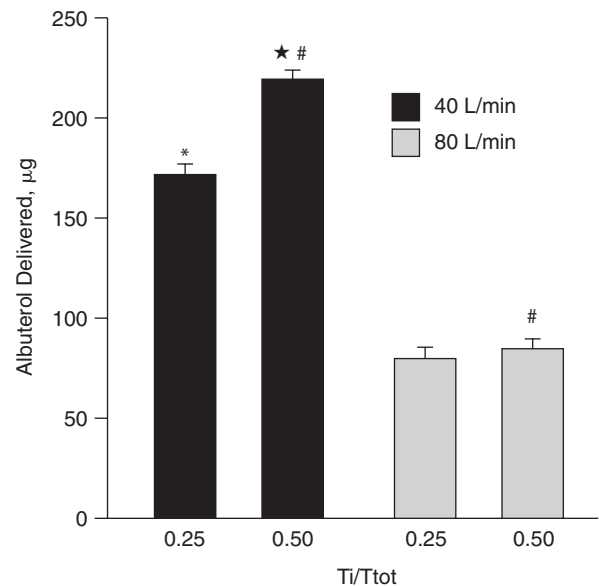


FIG. 6. Comparison of aerosol delivery at different inspiratory airflows and duty cycles (Ti/Ttot) in a bench model of mechanical ventilation. The ventilator delivered a tidal volume of 1000 mL with a constant inspiratory flow of 40 or 80 L/min, and the frequency of breathing was varied to achieve Ti/Ttot values of 0.25 or 0.50 at each inspiratory flow setting. Albuterol delivery to the bronchi was greater with a Ti/Ttot of 0.50 than at Ti/Ttot of 0.25 at inspiratory flows of 40 L/min and 80 L/min. For each value of Ti/Ttot, drug delivery with a slower inspiratory airflow (40 L/min) was almost twice that at the faster inspiratory airflow (80 L/min) (* $p < 0.01$, 40 L/min versus 80 L/min at Ti/Ttot of 0.25 and Ti/Ttot of 0.5; # $p < 0.01$, Ti/Ttot of 0.5 versus Ti/Ttot of 0.25 at 40 L/min and 80 L/min). (Reproduced from Fink et al.,⁽³⁾ with permission.)

lower driving pressure provided by the ventilator (<15 psi) than that provided by pressurized gas (≥ 50 psi) could decrease the efficiency of some nebulizers.⁽⁵⁵⁾ Aerosol generated by a nebulizer operating at the lower pressure may generate particles whose diameter is larger than the 1 to 5 μm that is optimal for aerosol deposition. When intermittent nebulizer operation is employed, the specific ventilator and nebulizer brand should be tested to determine the characteristics of the aerosol generated and the efficiency of drug delivery.⁽²⁰⁾

Characteristics of the ventilator breath

The characteristics of the ventilator breath have an important influence on aerosol drug delivery. A tidal volume of 500 mL or more (in an adult),⁽⁵²⁾ longer inspiratory time, and slower inspiratory flows improve aerosol delivery^(52,56) (Fig. 6). Drug delivery is linearly correlated with a longer

duty cycle (T_I/T_{TOT}) for both pMDIs and nebulizers.^(3,27,52) Moreover, drug delivery is improved when a pMDI is synchronized with a simulated spontaneous breath compared with a controlled ventilator breath of similar tidal volume.⁽⁵²⁾

The inspiratory waveform influences drug delivery from nebulizers but has much less influence on drug delivery from an MDI.⁽²⁶⁾ Unlike MDIs, nebulizer efficiency is notably lower during pressure-controlled ventilation than during volume-controlled ventilation⁽²⁶⁾ (Fig. 7). The breath-triggering mechanism does not significantly influence drug delivery from a 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.⁽⁵²⁾

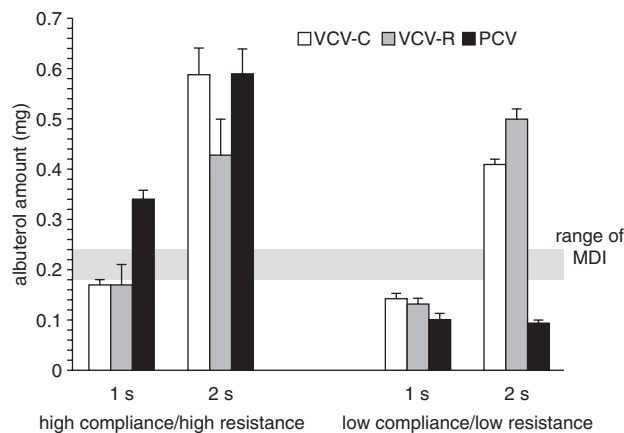


FIG. 7. Comparison of aerosol delivery from metered dose inhaler and jet nebulizer in bench models of pressure-controlled and volume-controlled ventilation. The lung mechanics were varied by selecting two settings of resistance and compliance to achieve high or low time constants. For each condition, the amounts of aerosol delivered during inspiratory times of 1 sec or 2 sec were measured. Increasing the duration of inspiration from 1 sec to 2 sec improved the nebulizer efficiency. In the high-compliance/high-resistance setting with 1-sec inspiration, nebulizer efficiency was higher during pressure controlled than during volume controlled ventilation, whereas the converse occurred in the low compliance/low resistance setting with 2-sec inspiratory time. In contrast, the efficiency of a MDI (horizontal stipled area) remained fairly constant under the various conditions simulated in the bench model. Thus, several factors, such as inspiratory time, pattern of inspiratory flow, and lung mechanics, that could influence drug delivery from a nebulizer have minimal influence on drug delivery from a MDI. (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). (Reproduced from Hess et al.,⁽²⁶⁾ with permission.)

EFFICIENCY OF DRUG DELIVERY DURING MECHANICAL VENTILATION

Bench studies with simulated models of mechanical ventilation, scintigraphy with radiolabeled aerosols, and pharmacokinetic studies⁽⁵⁷⁾ in patients have been employed to optimize techniques of administration with various aerosol generators. With a standardized technique of administration, approximately 11% of the nominal dose from a pMDI and spacer chamber deposits in the lower respiratory tract of ventilated patients.⁽³⁾ This value is remarkably close to values observed (10–14%) with the optimal use of a pMDI without a spacer in ambulatory patients.^(58,59)

Drug delivery from nebulizers also shows discrepancy between values obtained with bench models versus those obtained by gamma scintigraphy. Miller and colleagues⁽²⁰⁾ found that accounting for circuit humidity and breath-actuated nebulization could reconcile most observed differences. With an optimal technique of administration, an estimated 6 to 10% of the nominal dose placed in the nebulizer would be inhaled by a patient breathing through a humidified ventilator circuit.⁽²⁰⁾ A significant proportion of the inhaled mass deposits in the endotracheal tube and a smaller proportion is exhaled. Thus, the efficiency of drug deposition in the lower respiratory tract of ventilated patients is lower with nebulizers than with pMDIs. Higher drug doses are employed with nebulizers to offset their reduced efficiency. The total amount of drug depositing in the lower respiratory tract with jet nebulizers is probably comparable to that achieved with smaller drug doses employed with a pMDI.

TECHNIQUE OF ADMINISTRATION

The variations in the efficiency of pMDIs and nebulizers to deliver aerosol to the lung in mechanically ventilated patients underscore the need for carefully controlling the technique of administration. The recommended techniques of administration with pMDIs and nebulizers are shown in Tables 1 and 2,⁽⁶⁰⁾ respectively. With pMDIs the key steps are to employ an in-line chamber spacer and to synchronize the actuation of the pMDI with onset of inspiratory airflow from the ventilator. With nebulizers, a device that produces an aerosol with the majority of drug contained in particles smaller than 3 μm is ideal. Intermittent operation of the nebulizer and place-

TABLE 1. OPTIMAL TECHNIQUE FOR DRUG DELIVERY BY pMDI IN VENTILATED PATIENTS

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

pMDI, metered-dose inhaler; HME, heat and moisture exchanger.

ment at a distance from the patient also enhance drug deposition in the lung.^(2,4,5)

Selection of aerosol delivery device

Traditionally, pMDIs have been prescribed for out-patient treatment of airway obstruction, whereas nebulizers have been widely used during in-hospital visits. This has led to the erroneous belief that nebulizers are preferred for bronchodilator delivery in critically ill patients. In fact, when employed in an optimal manner, bronchodilator therapy with either pMDIs or nebulizers produces similar therapeutic effects in ventilator-supported patients.^(2,4,41,61)

NEWER AEROSOL-GENERATING DEVICES

Vibrating mesh nebulizers

Newer generation of nebulizers employ a vibrating mesh or plate with multiple apertures to

produce an aerosol.⁽⁶²⁾ These devices can be operated either with a battery pack or electrical source, and they are portable and less noisy than conventional jet nebulizers. Moreover, these devices have higher drug output because their residual volume is negligible. The Aeroneb Pro (Aerogen Inc., Mountain View, CA) is specifically designed as an in-line nebulizer; a breath-synchronized version of the Aeroneb Pro (Pulmonary Drug Delivery System, PDDS, Aerogen, Inc.) is undergoing clinical trials (Fig. 8). The control module of the PDDS is microprocessor driven and utilizes a pressure transducer to monitor changes in airway pressure and identify inspiratory time. The microprocessor delivers aerosol only during a specified portion of the inspiration (Fig. 9). The PDDS generates a fine particle aerosol that delivers inhaled amikacin with a high efficiency (~60% of the nominal dose) in ventilated patients.⁽⁶³⁾

The vibrating mesh nebulizers have a high rate of nebulization and drug output is two to three

TABLE 2. OPTIMAL TECHNIQUE FOR DRUG DELIVERY BY JET NEBULIZER IN VENTILATED PATIENTS

1. Review order, identify patient, and assess need for bronchodilator.
2. Suction endotracheal and airway secretions.
3. Place drug in nebulizer to fill volume of 4–6 mL.
4. Place nebulizer in the inspiratory line 18 in (46 cm) from the patient wye connector.
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 external source.
8. Adjust ventilator volume or pressure limit to compensate for added flow.
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. Modified from Fink.⁽⁶⁰⁾

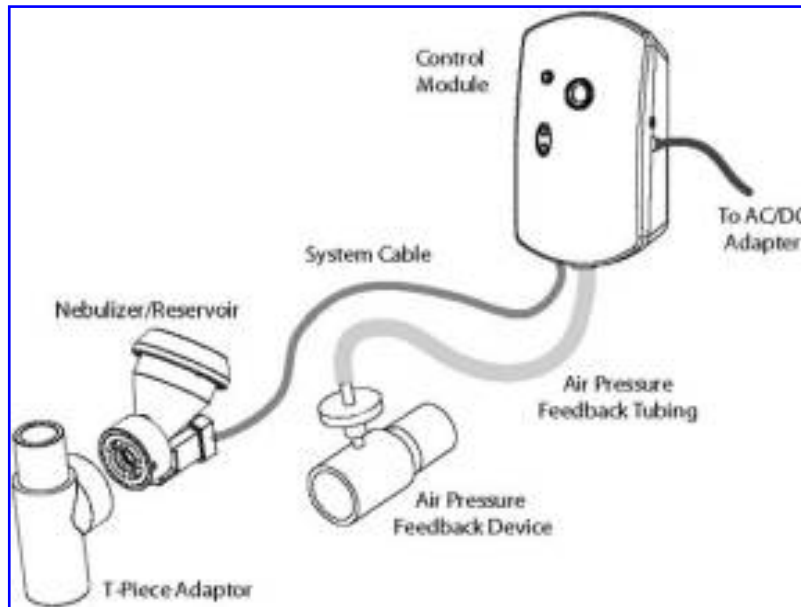


FIG. 8. Components of the Pulmonary Drug Delivery System (PDDS). The PDDS incorporates Aerogen’s onQ™ Aerosol Generator. A pressure transducer monitors airway pressure and identifies inspiratory time. The control module of the PDDS is microprocessor driven. (Nektar Therapeutics, Courtesy J. Fink)

times higher than with jet nebulizers.⁽⁶²⁾ Unlike ultrasonic nebulizers, the temperature of the solution does not change during operation of the vibrating mesh nebulizers, and proteins and peptides can be nebulized with minimal risk of de-

naturalization. The vibrating mesh nebulizers have many advantages over jet nebulizers, and they are likely to find increasing use for delivery of specific (nonbronchodilator) aerosols in ventilator-dependent patients.

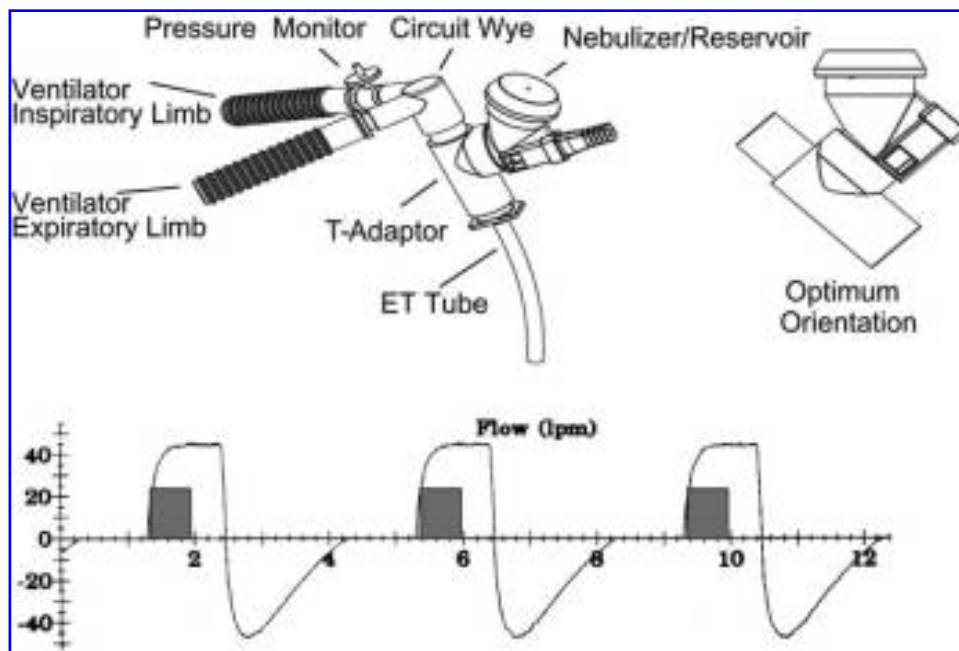


FIG. 9. The PDDS device connected in a ventilator circuit is shown in the top panel. The aerosol generator connects to a low-volume adapter that is, in turn, connected to the patient’s airway between the circuit wye and endotracheal tube. The optimum orientation of the device is shown. The bottom panel shows that aerosol of a specific size is generated only during a specific portion, as indicated by the dark bar, of the inspiratory cycle. By these techniques, aerosol delivery to the lower respiratory tract can be optimized in mechanically ventilated patients. (Nektar Therapeutics, Courtesy J. Fink)

Intratracheal catheter

The intracorporeal nebulizing catheter (Aero-probe; Trudell Medical International, London, ON, Canada) is a novel device that produces an aerosol in the trachea.⁽⁶⁴⁾ A central lumen transmits the solution to be nebulized and compressed gas is forced under high pressure (100 psi) at a variable flow rate (0.1–3.0 L/min) through several additional lumens that surround the central lumen (Fig. 10). Droplets of drug solution form at the tip of the catheter and aerosol is formed by the pressurized gas breaking up the liquid droplets. The catheter produces an aerosol continuously or intermittently when a pulsed gas flow is employed. The pressure and flow rate of the gas determine the aerosol particle size. Preliminary data suggest that lung deposition is improved with the use of the catheter compared to more conventional forms of aerosol administration.⁽⁶⁵⁾ The use of the intratracheal catheter is presently under investigation; however, it holds

considerable promise as a means of targeting inhalational delivery of a variety of therapeutic agents and genes in ventilated patients to the site of disease in the lung.

AEROSOL DELIVERY DURING NONINVASIVE POSITIVE PRESSURE VENTILATION

Noninvasive positive-pressure ventilation (NPPV) is being increasingly employed for treatment of patients with acute and chronic respiratory failure.⁽⁶⁶⁾ Successful application of NPPV with a nasal or face mask can often obviate the need for endotracheal intubation and improve mortality.^(67–71) NPPV may be employed as a first line mode of mechanical ventilation in as many as 50% of patients with hypercapnic respiratory failure.⁽⁶⁶⁾ Such patients with acute or acute-on-chronic hypercapnic respiratory failure who are

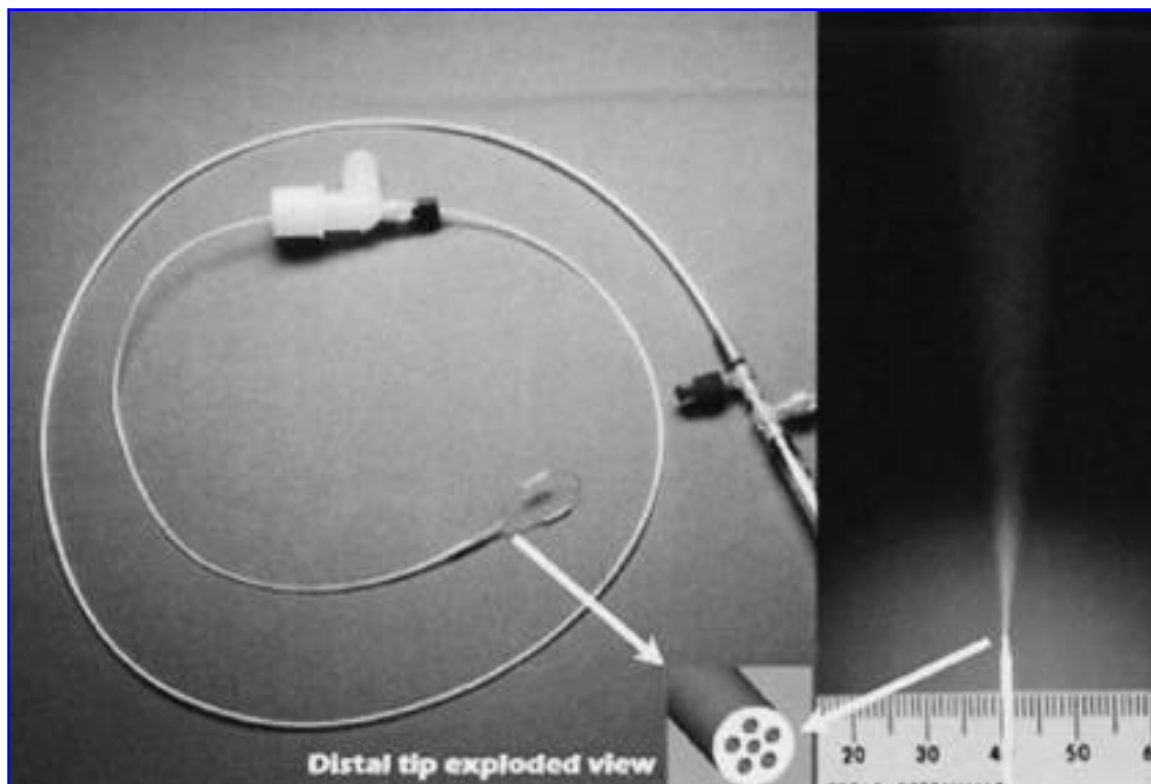


FIG. 10. The intracorporeal nebulizing catheter is a novel device that produces an aerosol in the airways. It can be used to bypass the upper airway or endotracheal tube. The liquid to be nebulized is placed in a syringe connected to the proximal end of the catheter. The liquid passes through a central lumen in the catheter to the distal end. The distal end of the catheter tapers to a fine tip (diameter ~ 0.5 mm). At the tip, the central lumen is surrounded by jets of compressed gas coming from apertures surrounding the central lumen (see inset). Drops of liquid that form at the tip of the catheter are aerosolized into a fine mist by the jets of compressed gas as shown in the right panel. (Reproduced from Dhand,⁽⁴⁾ with permission.)

receiving NPPV often require inhaled bronchodilators for relief of airway obstruction. In the past, acutely ill patients routinely received bronchodilators with intermittent positive-pressure breathing devices^(72,73) until it was determined that drug delivery was reduced by this technique of administration.⁽⁷⁴⁾ However, there may be a role for employing positive pressure ventilation in acutely ill patients requiring ventilatory support, as conventional methods of administering pMDIs or nebulizers may not provide optimal aerosol delivery in this setting. This topic has been previously reviewed.⁽⁷⁵⁾

The optimal techniques for aerosol delivery in patients receiving NPPV have been investigated with *in vitro* models. Similar to invasive positive-pressure ventilation, aerosol delivery can vary as much as fivefold (5% vs. 25% of the nominal dose) during NPPV, depending on the inspiratory and expiratory pressures employed (Fig. 11), position of the nebulizer, and synchronization of pMDI actuation with inhalation.^(76–78)

Although the optimum settings required for maximum drug delivery with a pMDI during NPPV have not been established, significant bronchodilator responses occur after albuterol administration with a jet nebulizer or a pMDI in stable patients,^(74,79) and in patients with acute asthma exacerbations receiving NPPV with a mask.⁽⁸⁰⁾ Similar to invasive mechanical ventilation, the use of helium–oxygen mixtures have

beneficial effects in patients with chronic obstructive pulmonary disease receiving NPPV.⁽⁸¹⁾ Both pMDIs and nebulizers could be employed during NPPV, but further studies are needed to optimize drug delivery from these devices during NPPV.

CONCLUSION

Delivery of aerosols to patients receiving mechanical ventilation is complex; many factors influence the amount of drug deposition in the lower respiratory tract, and the technique of administration needs to be carefully controlled. Optimal techniques for employing pMDIs and nebulizers have been developed as a result of better understanding of the factors influencing aerosol delivery to the lower respiratory tract of ventilator-dependent patients. With a proper technique of administration, drug deposition in the lower respiratory tract of ventilator-supported patients is comparable to that achieved in ambulatory patients. For routine therapy, a somewhat higher dose than that employed in ambulatory patients is recommended in mechanically ventilated patients to compensate for the effects of humidity in the ventilator circuit. Currently, there is increasing emphasis on the use of NPPV as first-line therapy for patients requiring ventilator support, but only a few investigators have studied

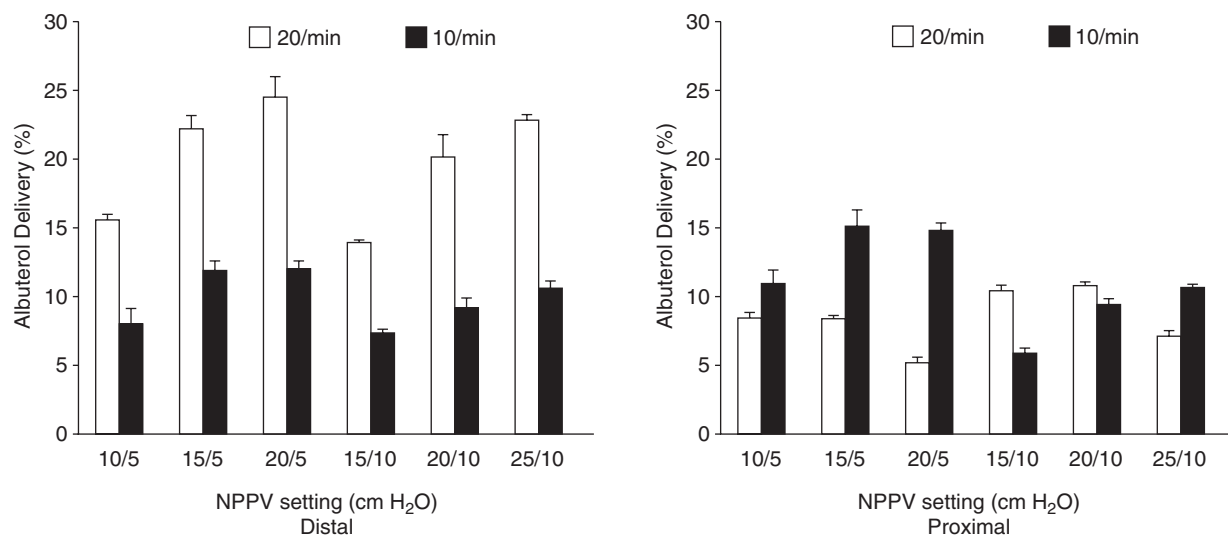


FIG. 11. Albuterol delivery as percent of the nominal dose at respiratory rates of 10/min (solid bars) and 20/min (open bars). Left panel: the nebulizer was placed between the whisper swivel and filter. Right panel: the nebulizer was placed at the outlet of the BiPAP ventilator. NPPV, noninvasive positive pressure ventilation. Albuterol delivery varied with breathing frequency, placement of the nebulizer, and the level of inspiratory and expiratory pressures employed during NPPV (Data from Chatmongolchart et al.). (From Hess⁽⁷⁵⁾ reproduced with permission).

aerosol delivery in this setting. Growing understanding of the factors influencing delivery of aerosols during mechanical ventilation coupled with the availability of highly efficient delivery devices is leading to increasing application of inhaled therapies in ventilated patients.

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