Bronchodilator Therapy in Mechanically Ventilated Patients

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Introduction

The scientific principles underlying the use of therapeutic aerosols in ambulatory patients have been established by several decades of research.[1] The advantages of aerosol therapy include efficacy with a smaller dose (compared with that for systemic administration of the drug) and a rapid onset of action.[1] Inhaled drugs are delivered directly to the respiratory tract, their systemic absorption is limited, and systemic side effects are minimized.[2] Inhaled bronchodilators are routinely used with mechanically ventilated patients in the intensive care unit, yet information regarding their efficacy and the optimal technique for their administration has been limited.[3] The delivery of inhaled drugs in mechanically ventilated patients differs from that in ambulatory patients in several respects.[4] Nebulizers and MDIs are commonly used aerosol generators since they produce respirable particles with a mass median aerodynamic diameter (MMAD) between 1 and 5 μm.[5] Whereas MDIs are chiefly used to deliver bronchodilators and occasionally corticosteroids, nebulizers have greater versatility and can be used to administer bronchodilators, antibiotics, surfactant, mucokinetic agents, and other drugs.[6] Traditionally, nebulizers have been used for bronchodilator therapy in patients receiving mechanical ventilation; however, metered dose inhalers (MDIs) are equally effective. When MDIs and nebulizers are used optimally, bronchodilatation occurs with as few as 4 puffs of albuterol aerosol given by MDI or 2.5 mg by nebulizer. With proper techniques inhaled drugs can be administered safely, conveniently, and effectively in mechanically ventilated patients.

Basic Concepts of Aerosol Therapy

To better understand how aerosol delivery differs in mechanically ventilated versus spontaneously breathing patients, we begin with a review of the basic definitions of aerosol characteristics and their implications for deposition in the ambulatory patient.[7]

The particle size of an aerosol is the primary factor in determining deposition efficiency and distribution in the lung. Since medical aerosols are generally heterodisperse, the distribution of particle diameters in the aerosol is commonly represented by the log normal distribution, in which the aerodynamic diameter is plotted against frequency of particle mass, forming a bell-shaped curve. MMAD is the particle size (expressed in microns) at the apex of that bell curve or at 50% of the cumulative distribution curve of the same aerosol. Thus, half of the mass of particles in the aerosol are less than and half are greater than the MMAD.

Geometric standard deviation (GSD) is the ratio of median diameter to the diameter of particles at one standard deviation from the median. An aerosol with a GSD of < 1.2 is considered to be monodisperse. The greater the MMAD, the larger the median particle size; the greater the GSD, the wider the range of particle sizes in the aerosol.

Inertial Impaction

Inertial impaction is the primary mechanism for deposition of particles 5 μm or larger and an important mechanism for particles as small as 2 μm. Inertia is the tendency for an object with mass that is in motion to remain in motion in a straight line. The greater the mass and velocity of a particle, the greater the inertia keeping that particle in motion. When a particle is traveling in a stream of gas that is diverted by a turn in the airway, the inertia of the particle tends to keep it on the initial trajectory (or path). The greater the mass of the particle, the greater the tendency for the particle to impact with the surface, depositing on the airway, rather than continuing to travel with the flow of gas. The higher the inspiratory flow of gas, the greater the velocity and inertia of the particles, which increases the tendency for even smaller particles to impact and deposit in large airways. Turbulent air flow, convoluted passage, airway bifurcations, and inspiratory flows > 30 L/min increase the impaction of particles that are larger than 2 μm in the larger airways. These conditions affecting air flow abound during mechanical ventilation.

Gravitational Sedimentation

Gravitational sedimentation occurs when the aerosol particles lose inertia, their movement on a trajectory slows, and they settle due to gravity. The greater the mass of the particle, the faster it will settle. Gravitational sedimentation increases with time and affects particles as small as 1 μm. If ambulatory patients hold their breath for 4–10 s after inhaling an aerosol, residence time for the particles is increased in the lung, and thus extra time is allowed for deposition through gravitational sedimentation, especially in the last 6 generations of the airway. The influence of a breath hold on aerosol delivery during mechanical ventilation has not been reported.

Diffusion

Diffusion, or Brownian movement, is the primary mechanism for deposition of particles < 3 μm in diameter onto the lung parenchyma. As gas reaches this region of the lung, gas flow and inertia for particles is reduced to zero. Aerosol particles collide with other particles and deposit upon contact with the airway surfaces. Particles 1–3 μm in

size deposit in both central and peripheral airways.[8] In ambulatory adult patients, optimal deposition of particles < 3 μm in diameter is believed to occur when inspiratory flow is < 40 L/min.

Aerosol droplets in the respirable range (MMAD, 1–5 μm) have a better chance than larger or smaller particles to deposit in the lower respiratory tract of ambulatory patients.[9] A particle's depth of penetration into the bronchial tree is inversely proportional to the particle's size down to 1 μm. Particles < 1 μm are so small, light, and stable that a large proportion entering the lung do not deposit and are exhaled.

The Nebulizer

For ambulatory patients, a nebulizer is expected to deliver > 50% of its total dose of aerosol in the respirable range.[10] Nebulizer performance varies with diluent volume, gas flow, density, operating pressure, and nebulizer model.[10,11] During mechanical ventilation, nebulizers producing aerosols with MMADs of 1–3 μm are more likely to achieve deposition in the lower respiratory tract since larger particles impact on the ventilator circuit and endotracheal tube.[9] Within the limits of the design of the nebulizer, the higher the gas pressure or flow (or both) to the nebulizer, the smaller the particle size generated.[11] However, nebulizers that produce a smaller particle size may require considerably more time to deliver a standard dose of medication. Ambient humidity and temperature also affect the particle size and the concentration of drug remaining in the nebulizer. Evaporation of water and adiabatic expansion of gas can reduce the temperature of the aerosol to as much as 5° C below ambient temperature. Aerosol particles entrained into a warm, fully saturated gas stream increase in size.

The Metered Dose Inhaler

The MDI canister contains a pressurized mixture of propellants, surfactants, preservatives, and flavoring agents, with ~1% of the total contents being active drug. This mixture is released from the canister through a metering valve and stem, which fit into an actuator boot designed and extensively tested by the manufacturer to function with their specific formulation. Small changes in actuator design can change the characteristics and output of the aerosol from an MDI. Aerosol production from an MDI takes ~20 msec. Aerosolization of the liquid released from the metered dose canister begins as the propellants vaporize or "flash," leaving the actuator in a "plume," and continues as the propellant evaporates. The velocity of the liquid spray leaving the MDI is ~15 m/s, falling by 50% within 0.1 s as a cloud develops and moves away from the actuator orifice.[12] The particles produced from the flash of

propellants are initially 35 μm in size and rapidly decrease in size due to evaporation as the plume of particles moves away from the nozzle.[13] Due to the velocity and dispersion of the jet fired from the MDI, under ambulatory conditions, ~80% of the dose leaving the actuator impacts and deposits in the oropharynx, especially when the canister is fired from inside the mouth.[14,15]

Dolovich et al[13] and others have shown increased deposition in the lung when the MDI is placed 4 cm from an open mouth. This technique improves lung deposition while decreasing oral deposition. Similarly, MDI actuation into a chamber-style spacer decreases impaction losses by reducing the velocity of the aerosol jet,[12] allowing time for evaporation of the propellants and for the particles to age prior to impacting on a surface. The dose of medication with the MDI is much smaller than with the nebulizer.

Differences during Mechanical Ventilation

Deposition of aerosol in the endotracheal tube and ventilator circuit was thought to significantly reduce the fraction of aerosol delivered to the lower respiratory tract. Until recently, the consensus was that the efficiency of aerosol delivery to the lower respiratory tract in mechanically ventilated patients was much lower that that in ambulatory patients.[16] To better understand the complex array of factors that influence aerosol deposition in mechanically ventilated patients (Fig. 1),[4] a comparison of differences between aerosol therapy in mechanically ventilated and ambulatory patients is discussed below.

The Ventilator-Patient Interface

The ventilator circuit is typically a closed system that is pressurized during operation, requiring the nebulizer or MDI to be attached with connectors that maintain the integrity of the circuit. The MDI cannot be used with the actuator designed by the manufacturer: Use of a generic third-party actuator is required. Size, shape, and design of these actuators greatly effects the amount of respirable drug available to the patient and may vary with different MDI formulations.[4]

Breath Configurations

During controlled mechanical ventilation (CMV), the pattern and rate of inspiratory gas flow, as well as the rate and pattern of breathing, may differ from that during spontaneous respiration. Ambulatory patients under normal, stable conditions tend to have sinusoidal inspiratory flow patterns with peak flows of 30 L/min, whereas ventilators may use square or decelerating wave forms with considerably higher flow rates. As in the ambulatory patient, all

Ventilator Related

- Mode of ventilation
- Tidal volume
- Respiratory rate
- Duty cycle
- Inspiratory waveform
- Breath triggering mechanism

Device Related-MDI

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

Drug Related

- Dose
- Aerosol particle size
- Duration of action

Device Related-Nebulizer

- Type of nebulizer used
- Continuous/intermittent operation
- Duration of nebulization
- Position in the circuit

Patient Related

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

Circuit Related

- Endotracheal tube
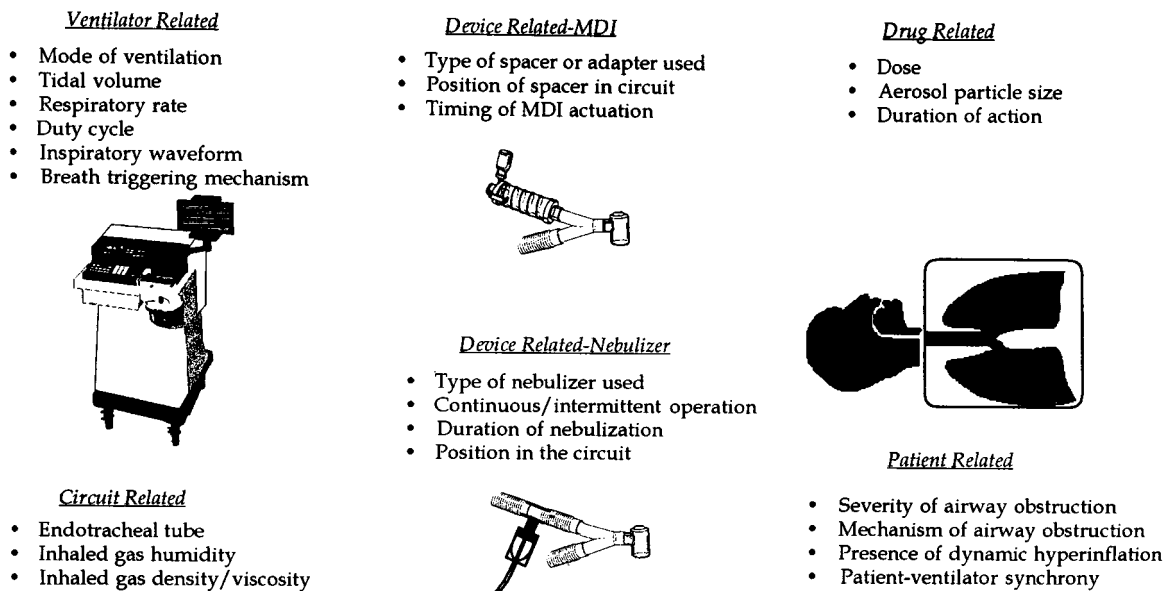- Inhaled gas humidity
- Inhaled gas density/viscosity

Fig. 1. Factors influencing lower respiratory tract deposition of aerosol in mechanically ventilated patients. MDI = metered dose inhaler. (Modified from Reference 4, with permission.)

of these factors influence aerosol delivery to the lower respiratory tract.

The Airway

Although the endotracheal tube (ETT) is commonly considered the major point of impaction of aerosol during mechanical ventilation, other factors merit consideration. The conduit between the aerosol device and the lower respiratory tract in mechanically ventilated patients is narrower than the oropharynx and has abrupt angles (eg, the 90-degree connector often used to connect the ventilator circuit wye to the ETT), which result in points of impaction and turbulence that are not found in the normal airway. While the ETT is narrower than the trachea, its smooth interior surface may create a more laminar-flow path than the structures of the glottis and be less of a barrier to aerosol delivery than the ventilator circuit. In support of this view, we recently found that twice as much aerosol from the MDI deposited in the ventilator circuit than in the ETT during CMV.[17]

The Environment

Ventilator circuits are typically designed to provide heat and humidity to inspired gas to compensate for bypassing the normal airway. Humidity has been shown to relate to an increase in particle size and reduced deposition during CMV, but no data exist to suggest that this reduction is unique to the ventilated patient. The ambulatory patient using an aerosol in a hot, high-humidity climate may well experience a similar reduction in delivered dose.

The Assessment

The common method to assess patient response to bronchodilator administration is through changes in expiratory flow rates. During mechanical ventilation, forced expiratory maneuvers are often impractical and rarely performed. Most investigators have relied on changes in the inspiratory airway resistance to quantitate a bronchodilator effect in mechanically ventilated patients.

Evaluation of Lower Respiratory Tract Aerosol Delivery with Bench Models of Mechanical Ventilation

In vitro studies using bench models of mechanical ventilation have been very helpful in determining the effect of each of a large number of variables on aerosol deposition.[18-25] These models provide an inexpensive mechanism to study specific factors under controlled conditions without the tedium associated with in vivo studies. Depending upon the type of model used, the efficiency of the aerosol delivery to the lower respiratory tract has been reported to vary from 0 to 42% with nebulizers[18-21,24] and from 0.3% to 97.5% with MDIs[18,22-25] (Fig. 2). These studies used different methods, and the models simulated the clinical scenario to a variable degree. The use of a standardized model for in vitro studies of aerosol deposition during mechanical ventilation could greatly facilitate
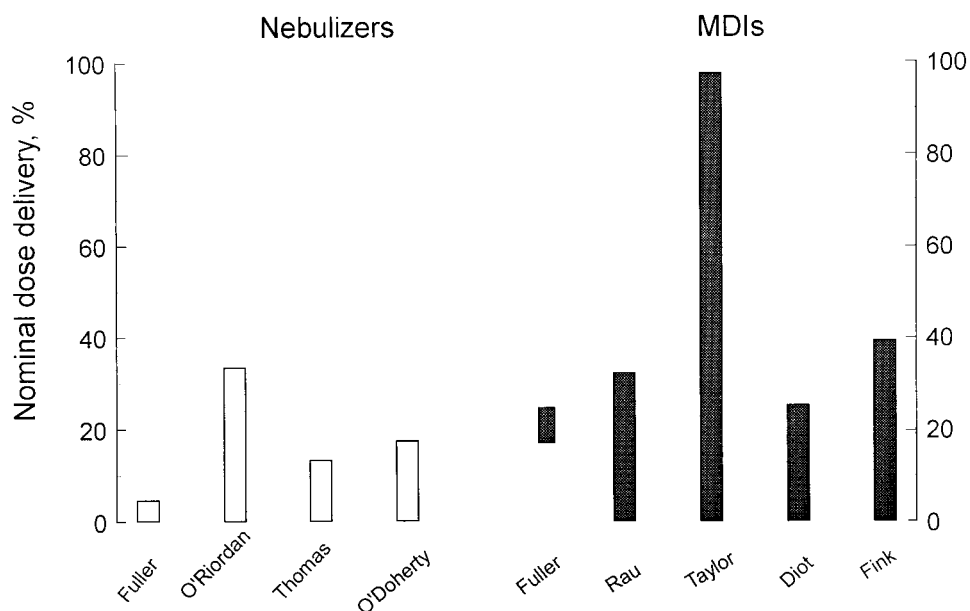
Fig. 2. Range of values reported in bench models of mechanical ventilation for the lower-respiratory-tract delivery of aerosol generated by nebulizers (open bars) and metered dose inhalers (MDIs; solid bars); the range is signaled by the upper and lower limits of bars. Depending on the technique of administration, between 0 and 97.5% of the nominal dose was delivered to the lower respiratory tract. Delivery was greatest when an MDI was actuated into a catheter[23] because the drug was released directly at the distal end of the endotracheal tube. Studies: Fuller,[18] O'Riordan,[19] Thomas,[21] O'Doherty,[20] Rau,[22] Taylor,[23] Diot,[24] Fink.[25] (Modified from Reference 4, with permission.)

comparison between the results of various investigators (Fig. 3). When standardized methods are used, the proportion of the nominal dose delivered to the lower respiratory tract with nebulizers and MDIs is similar (~15% with each device).[19,24,25]

Aerosol-Generating Devices

Nebulizers. The efficiency of aerosol generation varies highly among different brands of nebulizers.[9] For continuous aerosol generation, a nebulizer unit powered by pressurized gas from a piped (wall) system, cylinder, or compressor is connected in the ventilator circuit. Alternatively, the air flow generated by a ventilator can be used to power the nebulizer during inspiration (intermittent operation). A separate line provides driving pressure and gas flow from the ventilator to a nebulizer connected in the ventilator circuit. Operating the nebulizer during inspiration only is more efficient than continuous aerosol generation.[26] However, 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).[27] This reduction in driving pressure from the ventilator reduces the efficiency of pneumatic nebulizers, thus increases the MMAD and can markedly reduce the amount of aerosol delivered to the lower respiratory tract.

Position and Method of Connecting the Aerosol Generator in the Ventilator Circuit. Placement of a nebulizer at a distance of 30 cm from the endotracheal tube is more efficient than placement between the patient Y and the endotracheal tube because the ventilator tubing acts as a spacer for the aerosol to accumulate between inspirations.[19,20,26,28] Addition of a spacer between the nebulizer and the endotracheal tube further modestly increases aerosol delivery.[28]

Metered Dose Inhalers. Several types of commercially available adapters are available to connect the MDI canister to the ventilator circuit. MDIs can be used with adapters that attach directly to the endotracheal tube or with in-line devices that are placed in the inspiratory limb of the ventilator circuit. The latter include chamber adapters, such as cylindrical spacers and reservoir devices, or nonchamber devices (Fig. 4). Both in vitro and in vivo studies have found that the combination of an MDI and a chamber device results in a four- to- six-fold greater delivery of aerosol than MDI actuation into a connector attached directly to the endotracheal tube,[22,24,29,30] or into an in-line device that lacks a chamber.[31] Actuation of an MDI into an elbow adapter out of synchrony with inspiratory air flow achieved negligible aerosol delivery to the lower respiratory tract.[24] This observation may explain the lack of ther-
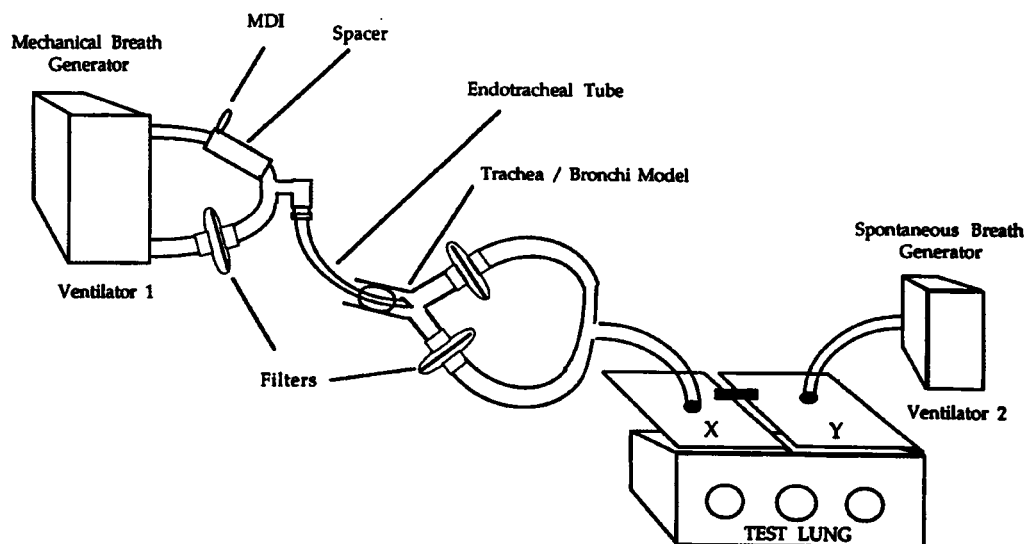
Fig. 3. Diagram of a bench model used to test aerosol deposition in mechanically ventilated patients. Ventilator 1 generated machine-delivered breaths. The metered dose inhaler (MDI) was actuated into a cylindrical spacer placed in the inspiratory limb of the ventilator circuit. The ventilator circuit was connected to an endotracheal tube with an elbow connector. The endotracheal tube with balloon inflated was positioned inside a model of the trachea and mainstem bronchi. The aerosol deposited on filters placed at the ends of each bronchus. Ventilator 2 was used to simulate patient respiratory effort (spontaneous breathing) by inflating section Y of the test lung, which produced corresponding displacement in section X because of a metal bar connecting the 2 sections. The negative pressure produced in section X triggered ventilator 1. A filter placed in the expiratory limb of the ventilator circuit trapped any aerosol that bypassed the endotracheal tube. (Modified from Reference 25, with permission.)

apeutic effect with this type of adapter after administration of very high doses of albuterol (100 puffs, 1.0 mg of albuterol) with an MDI.[32]

Aerosol Particle Size

In ambulatory patients, aerosols with a higher proportion of respirable particles (MMAD of 1–5 μm) are more efficient for aerosol delivery to the lower respiratory tract. In mechanically ventilated patients, the ventilator circuit and endotracheal tube act as baffles that trap larger-diameter particles en route to the lower respiratory tract. The MMAD of aerosols produced by different brands of nebulizers varies widely.[11] Nebulizers producing aerosols with particles of < 2 μm are likely to produce greater deposition in the lower respiratory tract of ventilator-supported patients.[19,33] When actuation of the MDI into a spacer was synchronized with inspiration, a significant proportion of aerosol emerging from the distal end of the endotracheal tube was in the respirable range, with a MMAD of $\leq$ 2 μm.[24] Therefore, deposition in the lower respiratory tract of mechanically ventilated patients is likely to be more efficient with devices that generate aerosols with a MMAD of 1–3 μm.

Characteristics of the Ventilator Circuit

Endotracheal Tube Size. Aerosol impaction in the endotracheal tube is thought to significantly reduce the efficiency of aerosol delivery in mechanically ventilated patients. The efficacy of aerosol delivery decreases when narrow endotracheal tubes (internal diameter of 3 or 6 mm) are used in pediatric ventilator circuits.[33,34] However, the efficiency with which various nebulizers delivered aerosol beyond the endotracheal tube did not vary between tube sizes ranging in internal diameter from 7 to 9 mm.[30]

Heating and Humidification Heating and humidification of inhaled gas decreases aerosol deposition with MDIs and nebulizers by ~40%,[19,24,25,34] probably due to increased particle loss in the ventilator circuit (Fig. 5). Therefore, some investigators have proposed bypassing the humidifier during aerosol administration.[6] Absence of humidification may not pose problems during the brief period required to administer a bronchodilator with an MDI; however, some nebulizers require up to 35 min to complete aerosolization,[24] and inhalation of dry gas for this length of time can be detrimental to the airway mucosa. In addition, disconnection of the ventilator circuit, which is required to bypass the humidifier, interrupts ventilation and may increase the risk of ventilator-associated pneu-
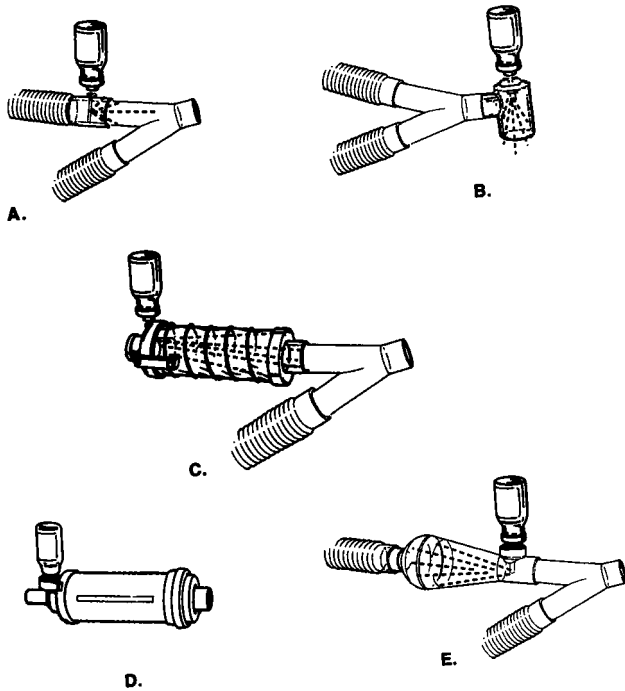
Fig. 4. Different types of commercially available spacers/adapters used to connect the metered dose inhaler (MDI) canister to the ventilator circuit. A, In-line adapter; B, elbow adapters; C, collapsible cylindrical spacer chamber that can be fitted in the inspiratory limb of the ventilator circuit; D, noncollapsible cylindrical holding chamber; E, aerosol cloud enhancer spacer, with which the MDI flume is directed away from the patient. (Modified from Reference 4, with permission.)

monia. With nebulizers, administration of aerosols in a dry circuit may be of some hypothetical advantage when administering expensive agents (eg, DNase) to reduce the amount of medication required. For routine bronchodilator treatment, we recommend nebulizer use with a humidified ventilator circuit.

Density of the Inhaled Gas. Inhalation of a less dense gas (ie, helium-oxygen [heliox]), decreases the turbulence associated with high inspiratory flow rates during mechanical ventilation. Therefore, breathing heliox may improve aerosol deposition during mechanical ventilation.[35] Studies in ambulatory patients with airway obstruction revealed higher aerosol retention when they are breathing heliox instead of air.[35,36] Preliminary reports indicate up to 50% increase in deposition of albuterol from an MDI during CMV of a simulated adult patient when breathing heliox compared to that while breathing air or oxygen.[37]

Ventilator Mode and Settings. The ventilator mode and settings influence aerosol delivery in mechanically ventilated patients. For optimal aerosol delivery, actuation of an MDI into a spacer needs to be synchronized with the precise onset of inspiratory air flow. Actuation of an MDI

into a cylindrical spacer synchronized with inspiration resulted in $\sim$30% greater efficiency of aerosol delivery compared with actuation during expiration (Fig. 6).[24] Aerosol can be delivered during assisted modes of ventilation if the patient is breathing in synchrony with the ventilator. We[25] found that albuterol deposition was up to 23% higher in vitro during simulated spontaneous breaths (continuous positive airway pressure) than with controlled breaths of equivalent V_T (Table 1).

For efficient aerosol delivery to the lower respiratory tract, the V_T of the ventilator-delivered breath must be larger than the volume of the ventilator tubing and endotracheal tube. V_T of $\geq$ 500 mL in adults are associated with adequate aerosol delivery (see Table 1),[19,25] but the higher pressures required to deliver a larger V_T can be detrimental to the lungs. Aerosol delivery is directly correlated with higher duty cycle (ratio of inspiratory time to total breathing cycle time [T_I/T_{TOT}]).[19,25] This relationship is easily understood with nebulizers because a longer T_I allows a higher proportion of the aerosol generated by the nebulizer to be inhaled with each breath. Because nebulizers generate aerosol over several minutes, a longer T_I has a cumulative effect in improving aerosol delivery. In addition, the diluent volume and the duration of treatment influence nebulizer efficiency.[19,20] MDIs produce aerosol over a finite portion of a single inspiration and the mechanism by which a longer T_I increases aerosol delivery is unclear. Perhaps aerosol particles that deposit in the spacer and ventilator tubing are swept off the walls and entrained by longer periods of inspiratory flow.

Approximately 5% of the nominal dose of albuterol administered by an MDI is exhaled in mechanically ventilated patients,[38] whereas < 1% is exhaled when MDIs are used in ambulatory patients.[14] The mean exhaled fraction (7%) with use of nebulizers in mechanically ventilated patients is similar to that with MDIs, but there is considerable variability between patients (coefficient of variation, 74%).[39]

The validity of the results of laboratory studies depends on the extent to which the models truly replicate the in vivo situation. We have performed in vitro tests with a model that provides accurate and reproducible results. The use of such a standardized model could be very helpful in comparing the results of various investigators, and in correlating in vitro findings with the results of in vivo deposition studies.[17]

Methods to Assess Lower Respiratory Tract Aerosol Deposition In Vivo

Radionuclide Studies

Imaging of radiolabeled aerosols has traditionally been employed to assess total and regional aerosol deposition in
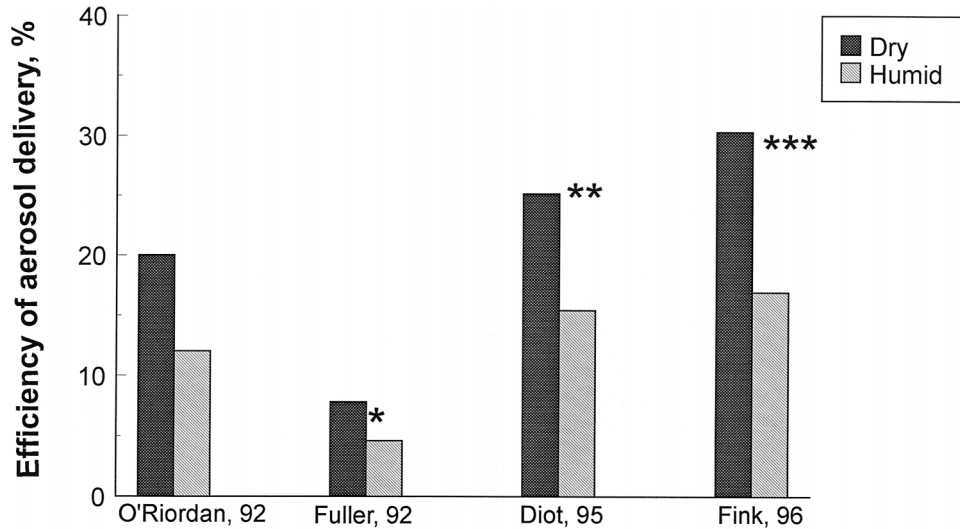
Fig. 5. Effect of humidity on aerosol delivery. The efficiency of aerosol delivery to the lower respiratory tract is shown for bench models of mechanical ventilation with dry and humidified ventilator circuits. The delivery of aerosol to the major airways is reduced by ~40% when the circuit is humidified. *, p < 0.05; **, p < 0.01; ***, p < 0.001. Studies: O'Riordan,[19] Fuller,[18] Diot,[24] Fink[25] (From Reference 4, with permission.)
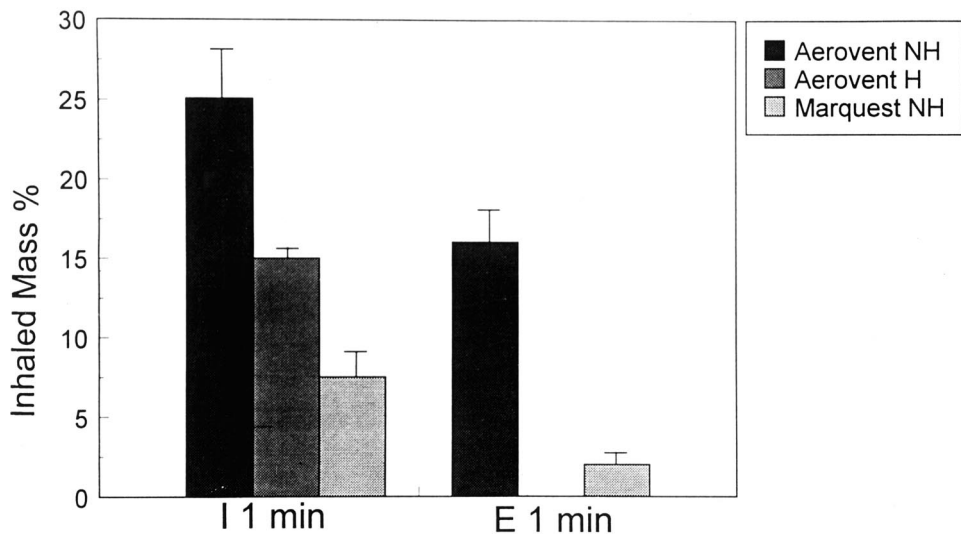

Fig. 6. Delivery of albuterol after administration with a metered dose inhaler (MDI). The inhaled mass of albuterol is expressed as a percentage of the nominal dose (90 μg/actuation). The inhaled mass when the puffs were synchronized with inspiration and actuated 1 min apart (I 1 min) is compared with actuation during expiration, with 1 min between each actuation (E 1 min). When actuation was synchronized with inspiration, aerosol delivery was greatest with MDI actuation into a chamber spacer (dark black bars) in a dry circuit compared with actuation into a chamber spacer in a humidified circuit (light black bars) or into an elbow adapter (gray bar). Aerosol delivery was significantly reduced by actuation of the MDI during expiration. The supplier of AeroVent is Monaghan Medical Inc. (Plattsburgh, NY), and the supplier of Marquest is Marquest Medical Products Inc. (Englewood, CO). (Modified from Reference 24, with permission.)

the lower respiratory tract. Although radionuclide studies are cumbersome in ventilator-dependent patients, they have been used to quantitate aerosol deposition in vivo. Initial reports of results with nebulized aerosol showed very low

deposition in the lungs of mechanically ventilated patients ranging from 1 to 3%.[15,40,41] (Figs. 7 & 8). When attention was given to the proper technique of administration and a "mass balance" technique was used to calculate deposi-

Table 1.   Effect of Tidal Volume (V_T) and Ventilatory Mode on Aerosol Delivery

Nebulizers				MDIs		
V_T (mL)	RR (Breaths/min)	Fill Volume (mL)	Delivery (%)	V_T (mL)	Mode	Delivery (%)
700	12	3	8.0	800	CMV	30.3
	20	3	16.0	800	AC	31.9
	20	2	22.5	800	CPAP	39.2
1000	12	3	8.0	500	CPAP	31.2
	20	3	20.5	300	CPAP	21.6
	20	2	31.5	100	CPAP	4.9

Data from O'Riordan et al[9] for nebulizers and Fink et al[17] for metered dose inhalers (MDIs). Means of values obtained with each ventilator setting are shown. RR = respiratory rate; CMV = controlled mechanical ventilation; AC = assist control; CPAP = continuous positive airway pressure.

tion, O'Riordan and co-workers[39] estimated that 15.3% ± 9.5% of the nebulizer charge deposited in the lungs. Similarly, Fuller and co-workers[15,31] reported that aerosol deposition in the lower respiratory tract with an MDI actuated into a cylindrical chamber placed in the inspiratory limb of a ventilator circuit (see Figs. 7 & 8) would be ~11% after correction for tissue absorption of radioactivity.[31] Thus, the values for pulmonary deposition obtained by in vivo radionuclide studies are comparable to the in vitro data obtained with humidified ventilator circuits (~15%). The difference between the two values (~4%) can be accounted for by the quantity of exhaled aerosol, which is not included in the in vivo measurement.[38] Therefore, the pulmonary deposition of a radioactive aerosol in mechanically ventilated patients is not as low as the values reported by earlier investigators.

Estimation of Plasma Levels

Estimation of plasma levels of drugs administered by inhalation can be used as an alternate method to assess aerosol deposition in mechanically ventilated patients. During mechanical ventilation, aerosol cannot deposit in the oropharynx and gastrointestinal absorption is negligible. Therefore, estimation of plasma levels of drugs administered by inhalation reflects lower respiratory tract deposition of aerosol.[42–44] Peak blood levels after administration of albuterol with an MDI and spacer in mechanically ventilated patients are similar to those in healthy control subjects (Fig. 9).[44] These findings, together with the corrected figures from radionuclide studies, demonstrate that the efficiency of aerosol deposition in the lower respiratory tract is marginally lower in ventilator-supported patients compared to ambulatory patients. The difference may be due in part to the humidity conditions for the controls (40% relative humidity at room temperature) and the ventilated patients (95% relative humidity at body temperature); nevertheless, satisfactory deposition can be obtained when the

administration technique is carefully regulated. These findings have important implications in deciding the technique of aerosol administration and the dosing sequence of drugs in mechanically ventilated patients.

Technique of Aerosol Administration

The results of in vitro studies have helped in developing recommendations for the technique of aerosol administration that should be used to achieve the greatest amount of aerosol deposition in the lower respiratory tract. In mechanically ventilated patients, the technique of aerosol administration often requires a compromise between the optimal operating characteristics of the aerosol generator and the patient's pulmonary mechanics. For example, a longer duty cycle increases aerosol deposition in the lung, but it may worsen dynamic hyperinflation in patients with airflow limitation.

For optimal delivery of aerosols during mechanical ventilation, the devil is in the details. Review of some of the data just presented and their implications on administration technique show that the best delivery with a nebulizer during CMV (15%) was accomplished using a specialty nebulizer (AeroTech II, CIS-US Inc, Bedford, MA) that produces an MMAD of < 2 μm (requiring 35 min to administer), in a dry ventilator circuit, with a duty cycle of 0.5.[39] This technique achieves optimal aerosol deposition but may be difficult for the patient to tolerate. Use of a commonly available nebulizer that produces aerosols with a 3.5-μm MMAD takes half the time but may reduce the dose delivered to the lung by half and the deposition to 7.5%. Providing active humidity during aerosol administration reduces delivery by another 40% (to 4%), as would reducing duty cycle to a more common 0.25 (reducing deposition to 2%).[19] The impact of each of these variables on aerosol delivery could explain the difference between
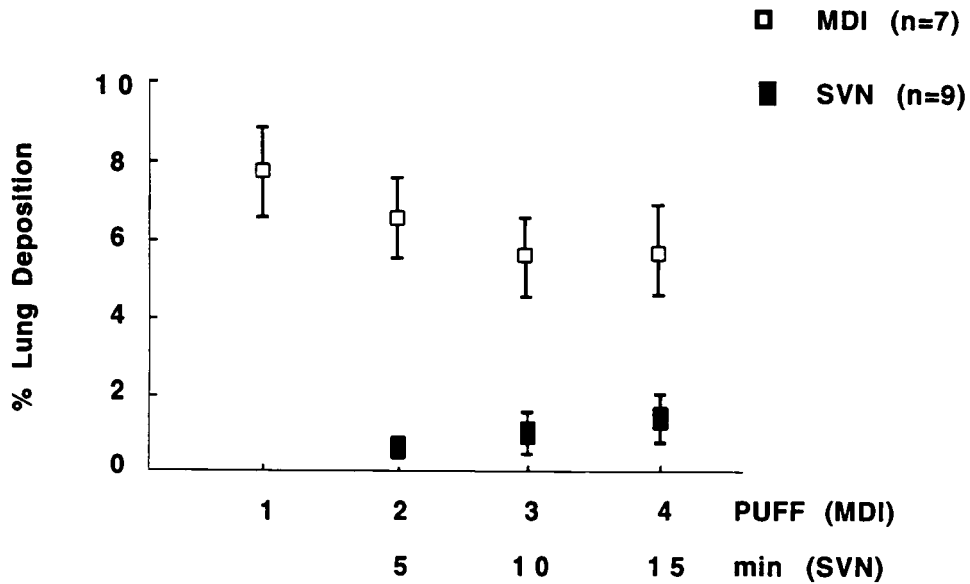
Fig. 7. Aerosol deposition to the lungs (expressed as a percentage of the dose delivered to patients receiving radiolabeled fenoterol) with a metered dose inhaler (MDI) or small-volume nebulizer (SVN). The cumulative dose delivered to the patient is expressed as the number of puffs for the MDI and as the time for the SVN. With the MDI ($n = 7$), 5.65% $\pm$ 1.09% of the dose deposited in the lungs compared with 1.22% $\pm$ 0.35% with the SVN ($n = 9$). (Modified from Reference 15, with permission.)
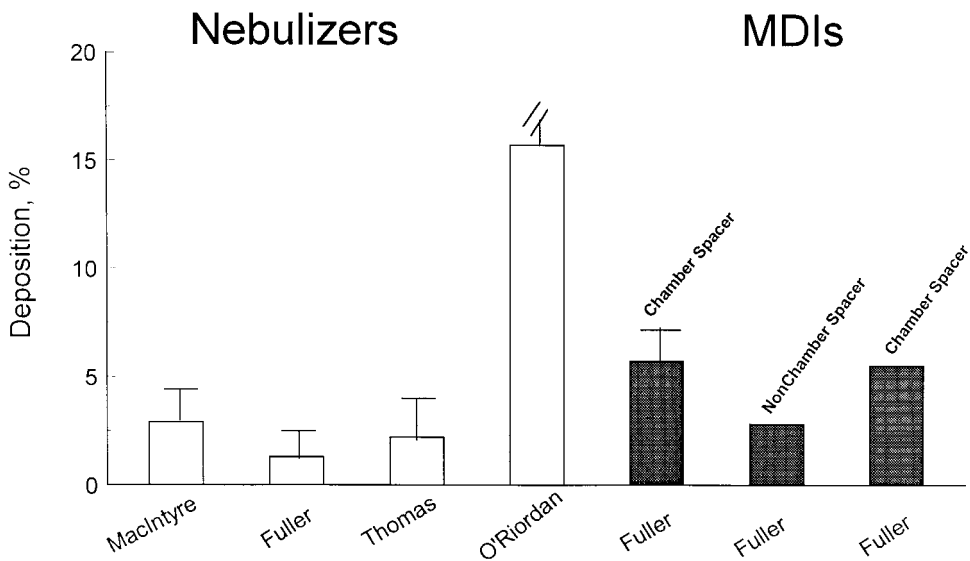

Fig. 8. Pulmonary deposition of aerosol generated by nebulizers (open bars) and MDIs (solid bars) with radiolabeled aerosols in vivo. Deposition of aerosol varied from 2.2% to 15.3% with nebulizers and from 3.2% to 6.8% with MDIs. The humidifier was bypassed in the study reported by O'Riordan et al,[39] whereas the other studies were conducted in a humidified circuit. Only the data reported by O'Riordan had been corrected for tissue adsorption of radioactivity (reported value ×1.9).[39] Studies (from left to right): MacIntyre,[41] Fuller, [15] Thomas,[40] O'Riordan,[39] Fuller,[15] Fuller, [31] Fuller.[31] (From Reference 4, with permission.)

15% of the nominal dose being delivered under optimal conditions and the more commonly reported 2% delivery. Thus, 50 μg of albuterol would be delivered to the lung with a nominal dose of 2500 μm with a nebulizer. This dose would be similar to the 60 μg of albuterol delivered from 4 puffs of an MDI with a chamber adapter in a humidified circuit (15% deposition).

The recommended technique of aerosol administration during mechanical ventilation with a nebulizer (Table 2) differs from that with an MDI (Table 3).
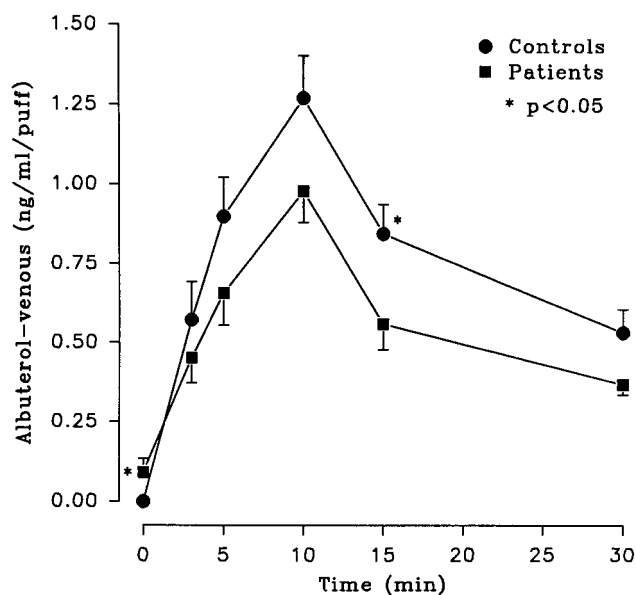
Fig. 9. Comparison of serum albuterol levels, per puff, with controls (normal volunteers using metered dose inhaler with holding chamber with optimal technique and breath hold under ambient conditions) and stable mechanically ventilated patients with chronic obstructive pulmonary disease using a chamber-style adapter in a humidified ventilator circuit. The serum albuterol levels in mechanically ventilated patients were comparable to those achieved in the normal volunteers. (From Reference 44, with permission.)

Care of Spacers and Nebulizers

Several investigators have shown that nebulizers placed in-line in the ventilator circuit can become contaminated with bacteria, which are then carried as microaerosols directly to the lower respiratory tract. This is often a product of condensate within the ventilator circuit, which is subject to retrograde contamination from the patient. Such contamination has been demonstrated after single use of a nebulizer.[45] The Centers for Disease Control and Prevention (Atlanta) recommend that nebulizers should be sterile at the start of nebulization, and after each use, they should be removed from the ventilator circuit, disassembled, cleaned with sterile water, rinsed, and air dried. Care should be taken to store the nebulizer aseptically between uses. Failure by respiratory care practitioners to observe these guidelines has resulted in epidemics of nosocomial pneumonia.[46] In addition, single-dose ampules of drug are preferred over the use of multi-dose vials, which more readily become contaminated. Similarly, the collapsible chamber spacer used with MDIs remains in the ventilator circuit between treatments and condensate collects inside it. The formation of condensate within the spacer can be reduced by using the heated-wire type of circuits or heat and moisture exchangers. Furthermore, care must be taken to prevent the condensate in the spacer from being washed down

Table 2. Technique for Using Nebulizers in Mechanically Ventilated Patients

1. Place drug solution in nebulizer to optimal fill volume (2–6 mL).*
2. Place nebulizer in inspiratory line at least 30 cm from the patient wye.†
3. Ensure airflow of 6–8 L/min through the nebulizer.‡
4. Ensure adequate tidal volume ($\geq$ 500 mL in adults). Attempt to use duty cycle $>$ 0.3, if possible.
5. Adjust minute volume, sensitivity trigger, and alarms to compensate for additional air flow through the nebulizer, if required.
5. Turn off flow-by or continuous flow mode on ventilator, remove heat and moisture exchanger from between nebulizer and patient.
6. Observe nebulizer for adequate aerosol generation throughout use.
7. Disconnect nebulizer when all medication is nebulized or when no more aerosol is being produced. Store nebulizer under aseptic conditions.
8. Reconnect ventilator circuit and return to original ventilator and alarm settings.

*The volume of solution associated with maximal efficiency of a nebulizer varies between nebulizers and should be known before using any of these devices.
†Placement of the nebulizer, placed between the ventilator and the inspiratory limb is more efficient for aerosol delivery than placement between the inspiratory limb and the patient.
‡The nebulizer may be operated continuously or only during inspiration; the latter method has been shown to be more efficient for aerosol delivery. Some ventilators provide inspiratory gas flow to the nebulizer. Continuous gas flow from an external source can also be used to power the nebulizer.

into the patient's respiratory tract when the spacer is pulled open during use. When a noncollapsible spacer chamber is used to actuate an MDI, it should be removed from the ventilator circuit between treatments. There is no evidence suggesting contamination problems with administration of aerosol from the MDI during CMV.

Efficacy of Bronchodilator Administration during Mechanical Ventilation

Bronchodilators are among the most commonly used drugs in patients admitted to the intensive care unit;[3] they are chiefly used in mechanically ventilated patients with severe asthma or chronic obstructive pulmonary disease (COPD).[32,47–54] Since the presence of air-flow limitation in mechanically ventilated patients is difficult to predict on clinical grounds,[55] the efficacy of bronchodilators in a heterogenous population of mechanically ventilated patients needs further study. A response to bronchodilator administration has been observed after administration of either aerosolized β-adrenergic[32,48,49,51–54,56–60] or anticholinergic bronchodilators.[47,49,50] Inhaled isoproterenol,[56,57] isoetharine,[58] metaproterenol,[59] fenoterol,[48] and albuterol[49,51–54] all produce significant bronchodilatation when administered to mechanically ventilated patients. In patients with COPD receiving mechanical ventilation, a combination of fenoterol and ipratropium bromide was shown to be more effective than ipratropium alone.[51]

Table 3.   Technique for Using Metered Dose Inhalers (MDIs) in Mechanically Ventilated Patients.

1. Assure tidal volume > 500 mL (in adults) during assisted ventilation.
2. Aim for an inspiratory time (excluding the inspiratory pause) > 0.3 of total breath duration.
3. Ensure that the ventilator breath is synchronized with the patient's inspiration.
4. Shake the MDI vigorously.
5. Place canister in actuator of a cylindrical spacer situated in inspiratory limb of ventilator circuit.*
6. Actuate MDI to synchronize with precise onset of inspiration by the ventilator.†
7. Allow passive exhalation.
8. Repeat actuations after 20–30 s until total dose is delivered.‡

*With MDIs it is preferable to use a spacer that remains in the ventilator circuit so that disconnection of the ventilator circuit can be avoided during bronchodilator treatment. Although bypassing the humidifier can increase aerosol delivery, it prolongs the time for each treatment and requires disconnection of the ventilator circuit.
†In ambulatory patients with an MDI placed inside the mouth, actuation is recommended briefly after initiation of inspiratory air flow. In mechanically ventilated patients, when an MDI and spacer combination is used, actuation should be synchronized with onset of inspiration.
‡The manufacturer recommends repeating the dose after 1 min; however, MDI actuation within 20–30 s after the prior dose does not compromise drug delivery.[17]

Bronchodilator Efficacy

The primary goal of aerosol therapy is to achieve the greatest amount of drug deposition in the lower respiratory tract. However, increased drug deposition in the lower respiratory tract does not necessarily correlate with greater therapeutic efficacy. The response to bronchodilator administration depends on the patient's airway geometry, severity of disease, presence of mucus, the effects of inflammation and other drugs, and the degree of airway responsiveness. Once a threshold response has been achieved, higher doses of the same drug produce minimal further increase in bronchodilatation.

Most investigators have assessed the effect of bronchodilators on inspiratory airway resistance to determine their clinical efficacy. Airway resistance in mechanically ventilated patients is commonly measured by performing rapid airway occlusions at constant flow inflation.[61] In this technique, a breath hold is performed at end-inspiration by occluding the expiratory port (Fig.10). The airway occlusion produces an immediate drop in airway pressure (P_{peak}) to a lower initial pressure (P_{init}). The pressure then declines gradually to reach a plateau after 3–5 s (P_{plat}). The value of P_{init} can be determined by back extrapolation of the slope of the latter part of the airway pressure, tracing to the time of airway occlusion.[62] This permits total or maximal inspiratory resistance (R_{rs}max) to be partitioned into a minimal inspiratory resistance (R_{rs}min), which reflects the "ohmic" resistance of the airways and an additional effective resistance(ΔR_{rs}); ΔR_{rs} represents two phe-

nomena—time constant inhomogeneities within the lung ("pendelluft") and the visco-elastic behavior or stress relaxation of the pulmonary tissues.[63] Similarly, airway occlusion at end-exhalation produces an increase in airway pressure, and its plateau value signifies the level of auto- or intrinsic positive end-expiratory pressure (PEEPi).[64] From these measurements (in a passively ventilated patient) by use of a square wave inspiratory flow pattern, respiratory mechanics can be calculated as

$$Rrs \ max = \frac{[P_{peak} - P_{plat}]}{air \ flow}$$

$$Rrs \ min = \frac{[P_{peak} - P_{init}]}{air \ flow}$$

$$\Delta Rrs = R_{rs} \ max - R_{rs} \ min$$

$$Respiratory \ system \ compliance \ (C_{rs}) = \frac{Tidal \ Volume}{[P_{plat} - PEEP_i]}$$

Most mechanically ventilated patients with COPD demonstrate a decrease in values of R_{rs}max and R_{rs}min following bronchodilator administration[48,49,51,53,54]. Since ΔR_{rs} did not decrease significantly after albuterol administration in our studies,[53,54] it appears that the effect of albuterol was manifested mainly in the central airways without much apparent effect on visco-elastic behavior or time constant inhomogeneities in the lung. The time constant (R_{rs}min × compliance of the respiratory system) in our patients improved after albuterol administration but was not significantly different than the value at baseline.[53] For the clinician at the bedside, it is important to realize that any respiratory effort by the patient reduces or eliminates the ability to reliably measure changes in ohmic resistance. Consequently, extrapolation of these measurements of changes in resistance may only be clinically useful with patients who are totally passive, or paralyzed, during mechanical ventilation.

The occurrence of a bronchodilator response is difficult to predict in mechanically ventilated patients. Neither an elevated airway resistance nor the presence of expiratory air flow limitation is predictive of a response to bronchodilators in ventilator-dependent patients.[55] Moreover, the technique of administration has a marked influence on the effects of bronchodilator administration with an MDI. Early studies in the anesthesia literature showed promising results following bronchodilator administration by an MDI.[47,56–58] Later, Manthous and colleagues[32] reported no benefit from administration of up to 100 puffs of a bronchodilator aerosol with an MDI and elbow adapter in ventilator-supported patients (Fig. 11). More recently, it has
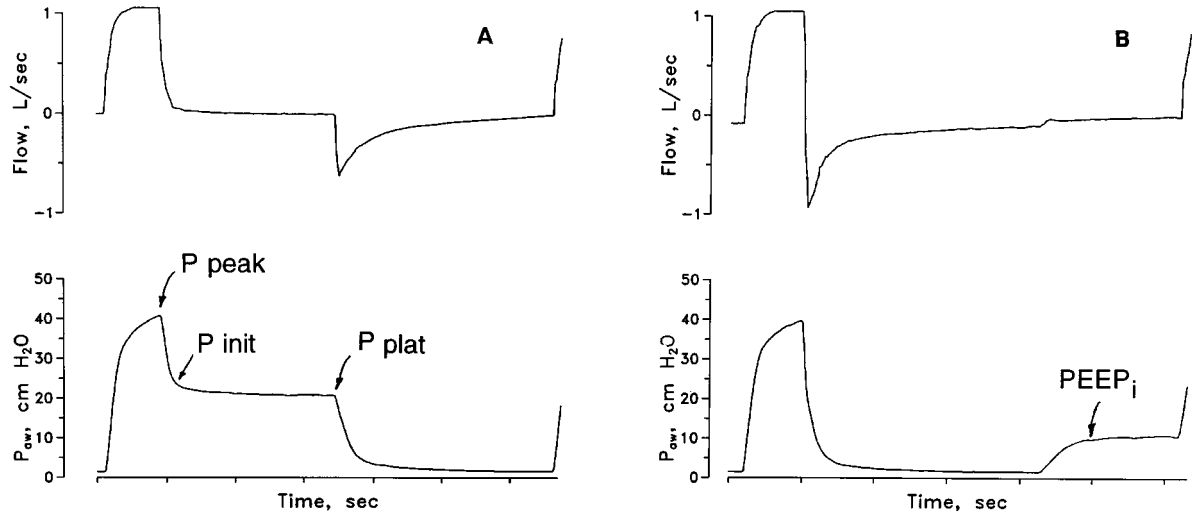
Fig. 10. Waveforms depicting the key parameters for monitoring patient response to inhaled bronchodilators. Resistance is determined by difference in peak airway pressure (P peak) and plateau pressure (P plat). A, Following a rapid airway occlusion, the airway pressure falls to an initial plateau (P init) and over 3 s stabilizes to the final P plat. B, Following a rapid occlusion during expiration, the intrinsic positive end-expiratory pressure (PEEPi) is determined. (From Reference 53, with permission.)

been established that effective use of an MDI for bronchodilator administration in ventilator-supported patients requires actuation into a spacer placed in the inspiratory limb of the ventilator circuit. The best results are obtained when the MDI actuation is synchronized with the onset of inspiration.[52–54]

Bronchodilator Dose

On the basis of earlier data that aerosol deposition was markedly lower in mechanically ventilated than in ambulatory patients, it was recommended that higher doses of bronchodilators be required for ventilator-supported patients.[7] However, the precise dosing regimen was not specified. This led some investigators to propose that the dose of bronchodilators should be titrated to their physiologic effect in ventilator-supported patients.[52] Significant bronchodilation has been reported with administration of 2.5 mg of albuterol with a standard nebulizer under less than optimal conditions (see Fig. 11)[32] or 4 puffs (400 μg) with an MDI (Fig. 12).[54] The MDI was administered to stable COPD patients through a humidified ventilator circuit with a chamber-style adapter placed in the inspiratory limb at the wye; actuations were synchronized to inspiration, with 20–30 s between actuations. Minimal therapeutic advantage was gained by administering higher doses (Fig. 13), whereas the potential for side effects was increased (Fig. 14).[32,54] In the routine clinical setting, higher doses of bronchodilators may be needed in patients with severe airway obstruction or if the technique of administration is not optimal. However, further studies are needed to assess the duration of the bronchodilator effect in order to estab-
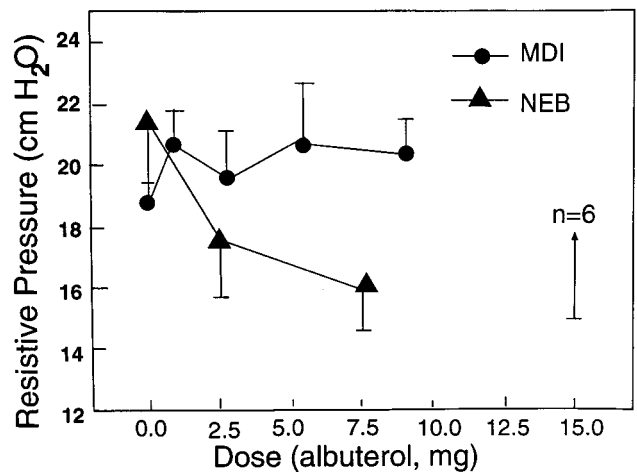

Fig. 11. Effect of albuterol on flow-resistive pressure in 10 mechanically ventilated patients. Administration of 2.5 mg of albuterol with a nebulizer NEB) produced a rapid fall in flow-resistive pressure (21.5 ± 5.7 cm H_2O at baseline vs 17.6 ± 5.4 after albuterol; p < 0.01). A cumulative dose of 7.5 mg of albuterol produced incremental benefit in 8 of the 10 patients, with a decrease in flow-resistive pressure to 15.8 ± 3.6 cm H_2O (p > 0.05 compared with values with 2.5 mg albuterol). In contrast, no change in flow-resistive pressure occurred after administration of up to 100 puffs of albuterol with a metered dose inhaler and elbow adapter (MDI). (Modified from Reference 32, with permission.)

lish a rational dosing schedule in ventilator-supported patients. In summary, when the technique of administration is carefully executed, most stable mechanically ventilated patients with COPD achieve near maximal bronchodilation after the administration of 4 puffs of albuterol with an MDI or 2.5 mg of albuterol with a nebulizer.
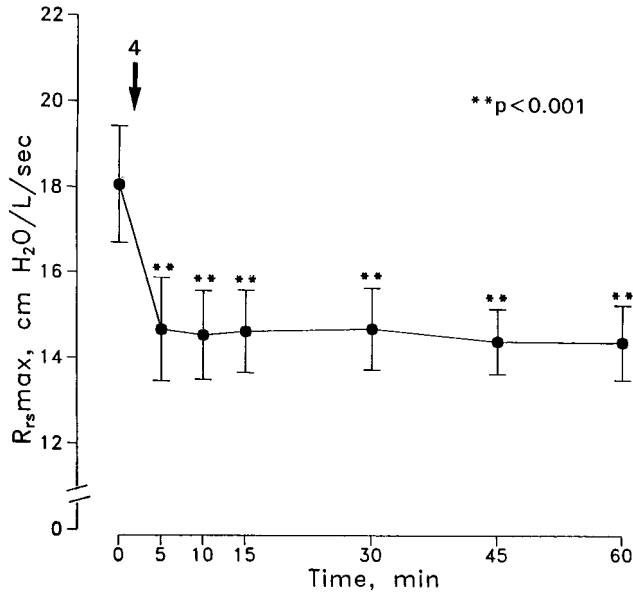
Fig. 12. Effect of albuterol on maximal inspiratory airway resistance (R_{rs}max) in mechanically ventilated patients with chronic obstructive pulmonary disease. Significant decreases in maximum inspiratory resistance (R_{rs}max) occurred within 5 min of administration of 4 puffs (indicated by arrow) of albuterol with a metered dose inhaler and chamber spacer, and the decreases were sustained for 60 min. Bars represent SE. (From Reference 54, with permission.)
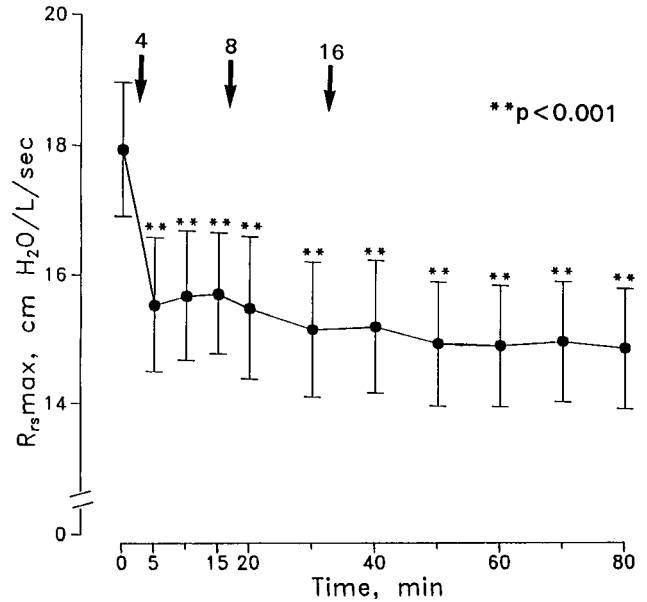

Fig. 13. Effect of albuterol on maximal inspiratory airway resistance (R_{rs}max) in 12 mechanically ventilated patients with chronic obstructive pulmonary disease. Significant decreases in R_{rs}max occurred within 5 min of administration of 4 puffs of albuterol with an MDI and chamber spacer, and they were sustained following administration of 8 and 16 puffs (cumulative doses of 12 and 28 puffs, respectively). However, the effect of 12 and 28 puffs was not significantly greater than that with 4 puffs ($p > 0.05$). Number of puffs is indicated above arrows. Bars represent SE. (From Reference 54, with permission.)

Drug Toxicity

In general, no serious adverse effects have been reported after bronchodilator administration in ventilator-supported patients. The risk of serious arrhythmias and hypokalemia is increased with the use of higher doses of β-agonists. Increase in heart rate (see Fig. 14),[32,54] and some instances of supraventricular and ventricular ectopy have occurred following administration of 3 to 6 times the recommended doses of albuterol.[32] The toxicity of chlorofluorocarbon propellants in the MDI formulation is minimal in normal clinical practice, requiring very rapid actuation of the MDI in over 20 successive breaths to be cardiotoxic. Oleic acid, which is used as a surfactant in some MDI formulations, may produce localized ulceration in the respiratory tract when administered with a catheter-type delivery system.[66,67]

Choice of Aerosol-Generating Device—Metered Dose Inhalers versus Nebulizers

MDIs traditionally 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, many investigators have demonstrated that nebulizers and MDIs are equally effective in the treatment of airway obstruction in ambulatory patients.[16,68] Similarly, nebulizers and MDIs delivered an equivalent mass of aerosol beyond the endotracheal tube in a model of mechanical ventilation. Diot and colleagues[24] demonstrated that 45 puffs from an MDI delivered a mass of albuterol similar to that delivered by a nebulizer (MMAD $< 2 \mu$m) in vitro. However, we have observed (unpublished data) 4 puffs (400 μg) via MDI and 2.5 mg of albuterol via a commonly used small-volume nebulizer (MMAD $\sim 2.9 \mu$m) delivered 30–90 μg of albuterol beyond the endotracheal tube during CMV. These observations help to explain the similarity in bronchodilator response achieved with the use of MDIs and nebulizers, despite a 6-fold higher nominal dose with the nebulizer.

The use of MDIs for routine bronchodilator therapy in ventilator-supported patients is preferred because of several problems associated with the use of nebulizers. The rate of aerosol production by nebulizers is highly variable.[69] Furthermore, the nature of the aerosol produced, especially the particle size, varies greatly among different nebulizers.[19,69] In addition, operational efficiency of a nebulizer changes with the pressure of the driving gas and with different fill volumes. Since the pressure of the gas
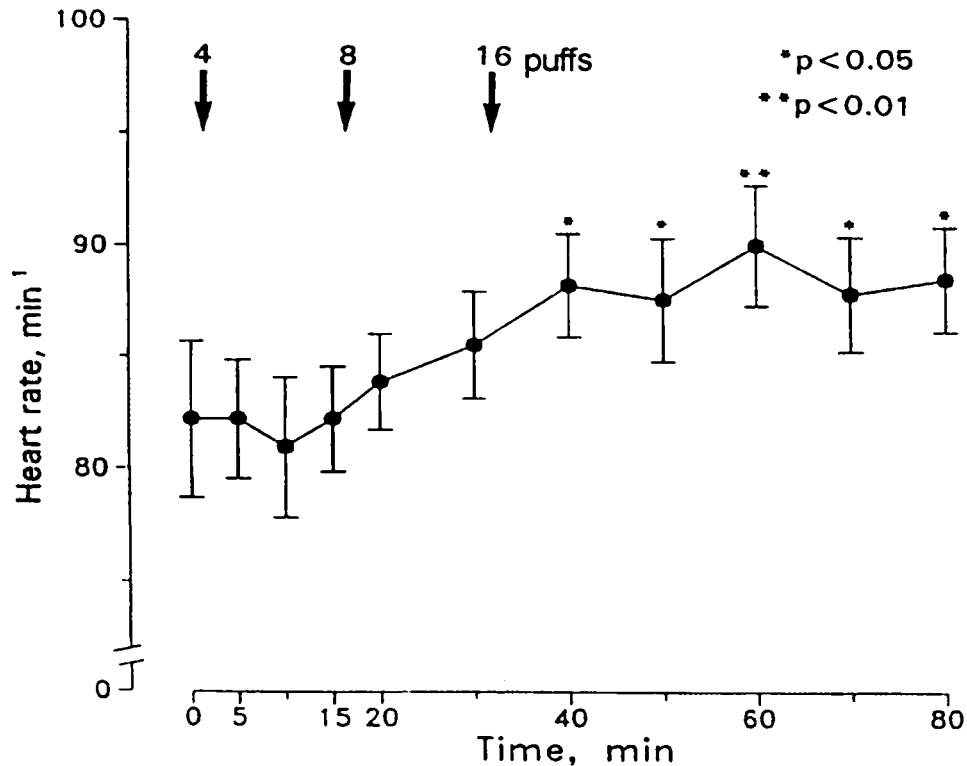
Fig. 14. Effect of doubling doses of albuterol (4, 8, and 16 puffs) on heart rate in 12 mechanically ventilated patients with chronic obstructive pulmonary disease. Heart rate did not change after administration of 4 puffs or a cumulative dose of 12 puffs ($p > 0.05$); a sustained increase in heart rate occurred after a cumulative dose of 28 puffs ($p < 0.01$). Number of puffs is indicated by arrows. Bars represent SE. (From Reference 54, with permission.)

supplied by a ventilator to drive the nebulizer during inspiration is lower than that supplied by a piped system or cylinder, the efficiency of some nebulizers can be drastically decreased in a ventilator circuit. Therefore, it is imperative to characterize the efficiency of a nebulizer in a ventilator circuit before employing it for therapy in ventilator-supported patients.

Another problem associated with the use of nebulizers is contamination with bacteria. Unless the nebulizers and solutions are scrupulously cleaned and disinfected, they could be a source for aerosolization of bacteria[45] and, thus, predispose patients to nosocomial pneumonia.[46] Moreover, the gas flow driving the nebulizer produces additional air flow in the ventilator circuit, necessitating adjustment of V_T and inspiratory flow when the nebulizer is in use. Some instances of hypoventilation have resulted in patients who cannot trigger the ventilator during assisted modes of mechanical ventilation because of the additional gas flow resulting from nebulizer operation.[70] In contrast, MDIs are easy to administer, involve less personnel time, provide a reliable dose of the drug, and are free from the risk of bacterial contamination. Moreover, when MDIs are used with a collapsible cylindrical spacer, the ventilator circuit need not be disconnected at the time of each treatment,

which might reduce the risk of ventilator-associated pneumonia.

Although direct costs of therapy in patients are difficult to reliably estimate, the use of MDIs for bronchodilator therapy instead of nebulizers has been thought to be a cost-saving and time-saving measure.[71] Bowton and co-workers[72] found that substitution of nebulizers by MDIs in a 700-bed hospital could decrease potential patient costs of aerosol therapy by $300,000 a year. In summary, MDIs offer several advantages over nebulizers for routine bronchodilator therapy in mechanically ventilated patients. In patients requiring medications not available in MDI formulations or for administration of higher-than-normal or more frequent doses, nebulizers may be more convenient.

Conclusions

Aerosol deposition in mechanically ventilated patients is governed by different factors compared to those in ambulatory patients. The administration of inhaled drugs to mechanically ventilated patients is complicated by deposition of the aerosol particles in the ventilator circuit and endotracheal tube. In addition, other variables (eg, the type of aerosol generator used, the method of connecting the

aerosol generator to the circuit and its position in the circuit, the timing of aerosol generation, the ventilator settings, circuit humidification, endotracheal tube size, aerosol particle size, and the severity and nature of the obstruction in the patient's airways) influence the efficiency of aerosol deposition and therapeutic response. We have shown that 4 puffs (0.4 mg) of albuterol with an MDI and spacer in a humidified ventilator circuit produce significant bronchodilatation in most patients with stable COPD, and further bronchodilatation with higher doses is minimal. The magnitude of the bronchodilator effect obtained with 4 puffs of albuterol is comparable to that obtained with 6 to 12 times the dose given by a nebulizer. Greater doses of bronchodilator with an MDI or nebulizer may be required in patients with acute severe airway obstruction.

ACKNOWLEDGMENT

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