Administration of Therapeutic Aerosols to Mechanically Ventilated Patients*

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(A)RS=adult respiratory distress syndrome; DPI=dry powder inhaler; ETT=endotracheal tube; MDI=metered-dose inhaler; MMAD=mean mass aerodynamic diameter; PEEP=positive end-expiratory pressure; SVN=small-volume nebulizer

Aerosols are particles suspended in a gaseous medium that may be inhaled and, depending on their physical properties, the specific parameters of ventilation, and airway geometry, will deposit to varying degrees throughout the respiratory tract.1 Aerosols account for the spread of certain infectious lung diseases, as well as exposure to noxious agents resulting in interstitial lung disease and even malignancy.

Aerosols have been employed as a means of drug delivery in the treatment of respiratory disorders. The theoretical advantages of drug administration by inhaled aerosol include delivery of drugs that might not be active via other routes and local delivery of drug in large doses so as to maximize effect and minimize systemic toxic reactions. The details of drug delivery and kinetics must be determined if an agent is to be administered in a rational and predictable fashion. Most of the clinical data supporting the use of aerosol therapies have been derived from study of nonintubated patients, during treatment of airflow obstruction with bronchodilators or anti-inflammatory drugs. Nevertheless, bronchodilators are used frequently in intubated patients undergoing mechanical ventilation, and innovative therapies, including aerosolized surfactant and antibiotics, have also been administered to critically ill patients. There are a number of reasons why simple adaptation of techniques effective in administering drugs in the nonintubated patient may not be equally effective during mechanical ventilation. These include the following: (1) airway mucosal function and hence drug absorption may be altered during critical illness; (2) the endotracheal tube and ventilator circuit may trap aerosolized drug before it reaches the patient’s airway or may alter aerosol distribution within the respiratory tract; (3) ventilator settings may unpredictably and adversely affect aerosol delivery; and (4) patient airway anatomy or artificial airway geometry may limit distribution of aerosol. Accordingly, we review herein the clinical experience with aerosol therapy during mechanical ventilation and formulate recommendations for therapeutic agents commonly used in this setting.

**Aerosol Production**

Therapeutic aerosols are usually produced by one of two types of devices: nebulizers or metered-dose inhalers (MDIs). The gas used to create the aerosol is termed the vehicle. Nebulizers usually utilize oxygen-enriched air as the vehicle, with aerosolization of drug from a saline or other solution. The MDIs use artificial surfactant to suspend microparticulate crystals of drug in a mixture of propellant gases (currently chlorofluorocarbons). The mixture is contained in a cannister under pressures of approximately 300 to 500 kPa (at 20°C). Ideally, a fixed volume (and thus dose) of this mixture is released from the cannister on activation. Standard “dose per actuations” varies among agents: albuterol, 90 μg per dose; pirbuterol, 200 μg per dose; metaproterenol, 650 μg per dose; and ipratropium, 18 μg per dose. Dry powder inhalers (DPI) consist of tablets of powder that are broken open and inhaled by the patient; they have thus far been used only in ambulatory patients.2 Nebulizers, MDIs, and DPIs rely on patient effort or the mechanical ventilator to create the gas flow required for delivery of the aerosol. For patients undergoing mechanical ventilation, a variety of techniques are employed to provide delivery of aerosolized drug to the inspiratory limb of the ventilator at the appropriate point in the respiratory cycle; the details of such techniques are likely important to effective drug delivery and will be reviewed below.

Several nebulizer systems are commonly used. The

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Administration of Aerosols to Ventilated Patients (Manthous, Hall)
FIGURE 1. Design of the earliest therapeutic aerosol device—the nebulizer squeeze bottle. By squeezing the rubber bulb, flow is channeled above the fluid phase reservoir creating a pressure differential that causes aerosolization and entrainment in the gas flow toward the patient.

First, the hand-held squeeze-bulb nebulizer, used a rubber bulb attached to a thin hollow cylinder above a reservoir of liquid. By squeezing the bulb, a flow of air is created that creates a Bernoulli effect in the cylinder. Since the cylinder is open to the liquid phase reservoir, a pressure gradient develops between reservoir and cylinder, and dissolved drug is entrained in aerosolized form in the air stream, and exits from the open end of the cylinder (Fig 1). This device has been relegated to a place in history, due to its labor-intensive operation. Nevertheless, the physical principles by which it creates the aerosol are used in the jet nebulizer that uses an extrinsic gas flow through a narrow aperture (Venturi) which results in a pressure gradient entraining drug mixture from a liquid reservoir (Fig 2). Baffles are commonly placed above the Venturi constriction to filter larger particles, preventing their entrainment in the cylinder and returning them to the liquid phase reservoir. Most jet nebulizers for ventilator circuits have small reservoirs allowing for mixing of drug in 3 to 6 ml of saline solution—these are termed small-volume nebulizers (SVN). Ultrasonic nebulizers create an aerosol above a liquid reservoir by use of a high-frequency signal, typically 1 MHz (Fig 3).

Such devices are usually placed in various positions in the inspiratory limb of the ventilator circuit so that aerosol, once created, is entrained by a tidal breath to the patient. When jet nebulizers are used, they add an additional gas flow of 3 to 10 L/min and tidal volumes during nebulization increase by the amount required to create the aerosol. Some newer ventilators have the capacity to defer part of the tidal volume to a jet nebulizer. Thus, the precise desired tidal volume can be delivered even during nebulization therapy, and aerosol is created only during inspiration; this theoretically reduces loss of aerosol into the exhalation limb of the ventilator circuit.
Aerosol Delivery

General Principles

The aerosol droplet size (mean mass aerodynamic diameter [MMAD]) created by these devices is of central importance in determining delivery, since particles with MMAD greater than 10 μm are filtered in the proximal airways of humans. The particle sizes for SVN systems are heterogeneous, in the range of less than 1 μm to more than 15 μm. The particle characteristics vary between and within systems and are affected by the volume in the reservoir, the position of the nebulizer in the circuit, the gas flow (in nebulizer systems), and the frequency of the ultrasonic signal (for ultrasonic systems). Some data suggest that a significant amount of drug is retained on the side walls of the nebulizer. Furthermore, the particular design of the reservoir chamber and baffles impacts on particle sizes and retained drug so that there is considerable variability among products. The MDIs generally deliver particles in the 1 to 7 μm range but immediately upon actuation, MDIs create droplets that are much larger until the diluent evaporates and droplets decrease in size to the effective MMAD size range (1 to 10 μm).

There are several mechanisms by which aerosols are delivered and deposited within the respiratory tract. We include a brief overview herein and refer the interested reader to several excellent reviews. Diffusional transport refers to the random motion of particles in a uniform gas of homogenous temperature in response to bombardment by gas molecules; brownian motion is a manifestation of this mechanism of particle transport. Diffusional transport is most important in the distribution of small (<0.1 μm) particles in distal airways.

Inertial transport refers to the motion of particles that do not follow the stream of the inspired gas but rather impact upon conducting airway walls because of their inertial (velocity and mass) characteristics. The larger the particle size, the greater the contribution of this form of transport, which primarily operates on particles greater than 1 μm in diameter. Electrical transport refers to the propensity of electrically charged particles to deposit in airways and probably is not a major contributor to deposition in human lungs.

The most important external force that affects particle transport in the lungs is gravity. Gravity causes the sedimentation of particles based on size, with major influence on decelerated particles greater than 0.5 μm in MMAD. Gravitational forces affect transport and delivery from the fifth generation airways to the alveoli, areas of the lung where bronchoconstriction is thought to occur.

In summary, the following are key determinants of where and to what extent aerosolized particles will deposit in human airways:

1. Particle Size: Particles of 0.5 to 12 μm MMAD are thought to be optimal for deposition in the distal airways. Experiments by Heyder suggest that in mouth-breathing patients, particles in the range of 0.5 to 2.0 μm penetrate to the alveoli and are deposited there by gravitational sedimentation. Particles smaller than 0.5 μm are largely exhaled with little airway or alveolar deposition. Particles ranging in size from 2.0 to 12.0 μm impact and deposit on predominantly larger airways, including trachea, large bronchi, and bronchioles.

2. Gas Velocity: The velocity of inspired gas is an important determinant of particle transport and deposition. Higher inspiratory flow rates increase turbulent flow leading to impaction of particles by inertial and other forces in more proximal airways. Interestingly, low-density gases such as heliox may reduce turbulent flow and could be employed to improve delivery of therapeutic aerosols.

3. Airway Geometry: Tubes of uniform size with smooth walls promote distal transport of particles. Tubes with irregular surfaces, with tapering diameters...

Figure 3. A common ultrasonic nebulizer system. Ultrasonic waves of 1 MHz are applied to a reservoir of drug and diluent, perturbing the liquid, leading to aerosolization and entrainment by the tidal volume going to the patient.
Table 1—Potential Determinants of Aerosol Delivery in Intubated, Mechanically Ventilated Patients

<table>
<thead>
<tr>
<th>Ventilator/circuit-related factors</th>
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<tr>
<td>Ventilator settings</td>
</tr>
<tr>
<td>1. Inspiratory flow rate</td>
</tr>
<tr>
<td>2. Respiratory rate</td>
</tr>
<tr>
<td>3. Tidal volume</td>
</tr>
<tr>
<td>4. Flow waveform</td>
</tr>
<tr>
<td>5. Ventilator cycling-volume vs pressure</td>
</tr>
<tr>
<td>6. Delivery by manual bag inflations</td>
</tr>
<tr>
<td>Circuit determinants</td>
</tr>
<tr>
<td>1. Characteristics of the delivery device</td>
</tr>
<tr>
<td>a. Nebulizer</td>
</tr>
<tr>
<td>1. Volume of fill</td>
</tr>
<tr>
<td>2. Frequency selection for ultrasonic devices</td>
</tr>
<tr>
<td>3. Specifications of the nebulizer device used, including MADD</td>
</tr>
<tr>
<td>4. Flow rates for jet nebulization</td>
</tr>
<tr>
<td>b. MDI</td>
</tr>
<tr>
<td>1. Timing of the actuation</td>
</tr>
<tr>
<td>2. Spacer device</td>
</tr>
<tr>
<td>3. Actuator</td>
</tr>
<tr>
<td>4. Intra-ETT catheters</td>
</tr>
<tr>
<td>2. Amount of drug administered</td>
</tr>
<tr>
<td>3. Humidification of inspired gases</td>
</tr>
<tr>
<td>4. Where in circuit MDI/nebulizer is administered</td>
</tr>
<tr>
<td>5. Length and diameter of ventilator tubing</td>
</tr>
<tr>
<td>6. Diameter and length of the ETT</td>
</tr>
<tr>
<td>7. Use of low-density gas (heliox)</td>
</tr>
<tr>
<td>Patient-determined factors</td>
</tr>
<tr>
<td>Airway determinants</td>
</tr>
<tr>
<td>1. Bronchoconstriction</td>
</tr>
<tr>
<td>2. Secretions</td>
</tr>
<tr>
<td>3. Mucosal function</td>
</tr>
<tr>
<td>Patient’s effects on gas flow</td>
</tr>
<tr>
<td>1. Spontaneous respiratory pattern</td>
</tr>
<tr>
<td>2. Generation of intrinsic PEEP</td>
</tr>
</tbody>
</table>

and with numerous bifurcations, as in human airways, impede the distal delivery of aerosolized particles by creating turbulent flow which increases the likelihood of the particle impacting and depositing on the side wall.11 Excessive mucus may also impede delivery of aerosols to more distal airways.12 Furthermore, the transport mechanism predominating at any given airway site is dependent on airway geometry. In the upper airways, gas travels at high velocities and inertial deposition is the predominant mechanism of particle delivery. In the most distal airways, gas velocities are low, favoring gravitational and diffusional mechanisms.11

Aerosol Delivery in Mechanically Ventilated Patients

From even a superficial overview of the principles governing aerosol transport and deposition, one might conclude that aerosol therapy during mechanical ventilatory support presents obstacles to drug delivery. Specifically, even if particle size is similar during treatment of spontaneously breathing and mechanically ventilated patients, the ventilator circuit, endotracheal tube, and ventilator-determined factors could substantially influence transport and deposition of a given agent13,14 (Table 1). Accordingly, we review pertinent clinical investigations of drug delivery and efficacy during mechanical ventilation in either lung models or patients. These investigations have generally attempted to quantitate drug deposition or measure a physiologic end point of drug effect.

Quantitative Studies: Conventional aerosol delivery systems deliver less aerosol in mechanically ventilated patients than in spontaneously breathing, nonintubated patients (Table 2). MacIntyre et al15 determined the delivery of nebulized radiolabeled penta-acetic acid in seven intubated, mechanically ventilated patients with a variety of disease processes. These particles of 1 to 5 μm were delivered by a positive-pressure system attached to the patient’s endotracheal tube. The “inspiratory pressure, sensitivity, and flow were adjusted to deliver tidal volumes similar to what the patient had been receiving on the volume ventilator,” but parameters were not discussed in detail. Only 2.9 percent of the dose was actually delivered to the patients undergoing mechanical ventilation as compared with 11 percent of a nebulized dose administered to nonintubated control subjects. The authors concluded that “aerosol delivery in mechanically ventilated patients is significantly reduced and that this is probably due to a combination of suboptimal breathing patterns, intrinsic airway disease, and the endotracheal tube functioning as both a site for aerosol deposition through impaction as well as a barrier to gastrointestinal absorption.”

O’Doherty et al16 studied the deposition of nebulized radioactive albumin in a ventilator-lung model. They used ventilators (Siemens Servo 900C) in volume control mode, with a heated water bath humidifier and attached the “Y” piece of the ventilator circuit to an endotracheal tube (ETT) leading to a filter that trapped nebulized drug. Three different nebulizer systems were assessed and each was tested at two different points in the ventilator circuit, placed just before the Y piece in the inspiratory limb and just after it. Flow rates of 8 L/min and 5.5 L/min, rates of between 10 and 20 bpm, and several nebulizer volumes of fill (amount of saline solution diluent) were studied. Drug delivery to the filter ranged from 3.1 to 5.4 percent of initial dose, depending on nebulizer model. Low flow rates, low respiratory rates, and higher inspiratory times improved delivery of the nebulized particles, the size of which were not measured. In addition, the greater the volume of fill of the nebulizer, the greater the aerosol delivery.

O’Riordan et al17 used a ventilator-lung model to examine the role of various parameters on aerosol
Table 2—Studies Examining the Delivery of Aerosols in Patients and Lung Models During Mechanical Ventilation∗

<table>
<thead>
<tr>
<th>Source</th>
<th>Model</th>
<th>Method of Delivery</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacIntyre et al15</td>
<td>Patients</td>
<td>RLP NEB via volume-cycled ventilation</td>
<td>2.9% of labeled dose was deposited in the lungs</td>
</tr>
<tr>
<td>O’Doherty et al16</td>
<td>Ventilator-lung model</td>
<td>RLP NEB via volume-cycled ventilation varying NEB devices, flows, rates, and NEB volume of fill</td>
<td>Lower flow and respiratory rates and higher volumes of fill had higher deliveries</td>
</tr>
<tr>
<td>O’Riordan et al17</td>
<td>Ventilator-lung model</td>
<td>RLP NEB by volume-cycled ventilation, varying flows, rates, and NEB volume of fill</td>
<td>Lower flows and respiratory rates had higher deliveries</td>
</tr>
<tr>
<td>Crogan and Bishop18</td>
<td>Ventilator-lung model</td>
<td>RLP NEB by continuous and pulsatile flows; different ETT sizes</td>
<td>Continuous flows and greater ETT sizes had higher deliveries</td>
</tr>
<tr>
<td>Fuller et al19</td>
<td>Patients</td>
<td>RLP NEB vs MDI with spacer via volume-cycled ventilation, 60 L/min, 7.5-mm ETT</td>
<td>1.2% NEB delivery vs 5.7% MDI delivery</td>
</tr>
<tr>
<td>Bishop et al20</td>
<td>Ventilator-lung model</td>
<td>MDI with and without spacer</td>
<td>Spacer MDI delivered 7 times as much aerosol as via swivel adapter</td>
</tr>
<tr>
<td>Rau et al22</td>
<td>Ventilator-lung model</td>
<td>MDI albuterol with and without spacer</td>
<td>MDI without spacer delivered 7% while spacer delivered 35%</td>
</tr>
<tr>
<td>Taylor and Lerman23</td>
<td>Ventilator-lung model</td>
<td>MDI salbutamol via varying ETT and intra-ETT catheters</td>
<td>MDI delivery was greater with larger ETT but greatest with intra-ETT catheter</td>
</tr>
<tr>
<td>Taylor et al24</td>
<td>Ventilator-lung model</td>
<td>MDI salbutamol via varying lengths and diameters of intra-ETT catheters during continuous flow</td>
<td>Longer thinner intra-ETT catheters had higher deliveries (nearly 100%)</td>
</tr>
<tr>
<td>Niven et al25</td>
<td>MDI-lung model</td>
<td>MDI albuterol via an intra-ETT catheter during continuous flow</td>
<td>20-30% delivery</td>
</tr>
</tbody>
</table>

∗RLP=radiolabeled particles; NEB=nebulizer.

delivery. They used a ventilator (Bear II) and four brands of nebulizer placed 30 cm from the Y piece in the inspiratory limb of the ventilator circuit. Respiratory rates of 12 and 20 bpm, flow rates of 40, 60, and 80 L/min, and volumes of fill between 2 and 6 ml were evaluated. They found that the amount of aerosol delivered varied widely (3 to 37 percent) between various brands of nebulizers. The amount of inhaled medication was proportional to the duty cycle (percentage of time spent in inspiration), so slower respiratory rates and lower flow rates improved delivery. Humidification of the inspired gas decreased delivery while endotracheal tube size did not affect delivery.

Crogan and Bishop18 delivered MDI through an adapter (Marquest) and ETT into a test lung during both continuous and pulsatile (postactuation) flows of 20 and 60 L/min. They measured drug (metaproterenol) at the end of the tube, finding that 3.0 percent of the initial dose was delivered through a size 6 mm ETT, while 6.5 percent was delivered through a 9 mm ETT; the remainder of the drug was deposited on the walls of the ETT. Delivery was higher with actuation into the continuous flow systems than when actuation occurred just before intermittent breaths.

Fuller et al19 compared the delivery of radiolabeled fenoterol by MDI with a spacer and nebulizer in 21 patients with "airflow limitation." Patients were receiving mechanical ventilation with volume-cycled ventilators (Bennett MA-1, MA-2, or Bear II). The MDI spacer was placed in the inspiratory limb 15 cm before the Y piece; a nebulizer (Bennett Twin-jet) was placed 70 cm before the Y piece in the inspiratory limb. Ventilator parameters varied between patients and were not reported. Lung deposition was 5.7 percent of the administered dose for MDI and 1.2 percent of the nebulized dose. Bishop et al20 found that the quantity and size of MDI particles delivered to a lung model (800 ml tidal volumes, 60 L/min, 7.5-mm ETT) were affected by the actuator device used. The use of an in-line spacing device delivered seven times more MDI than actuation into a Y piece swivel adapter.
### Table 3—Studies Examining the Physiologic Effects of Nebulized (NEB) and MDI-Delivered Bronchodilators to Intubated Mechanically Ventilated Patients*

<table>
<thead>
<tr>
<th>Source and Study Design</th>
<th>n</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>End Points</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold29</td>
<td>12</td>
<td>Heterogeneous</td>
<td>250 μg isoproterenol MDI by manual bag inflation</td>
<td>Peak airway pressure</td>
<td>Peak pressure decreased in all 12 patients</td>
</tr>
<tr>
<td>Sprague30</td>
<td>16</td>
<td>Bronchospastic</td>
<td>680 μg isetharine/140 μg phenylephrine MDI by Y-piece adapter, with inspiratory pause</td>
<td>Peak airway pressure</td>
<td>Peak pressure decreased in all 16 patients</td>
</tr>
<tr>
<td>MacIntyre et al35</td>
<td>7</td>
<td>Heterogeneous</td>
<td>NEB metaproterenol</td>
<td>Peak, static airway pressure, heart rate</td>
<td>No changes after NEB metaproterenol</td>
</tr>
<tr>
<td>Fuller et al19 (r/s)</td>
<td>21</td>
<td>“Airflow limitation”</td>
<td>MDI with spacer vs NEB fenoterol</td>
<td>Peak airway pressure</td>
<td>Neither MDI nor NEB decreased peak airway pressure</td>
</tr>
<tr>
<td>Gay et al31 (r/s/c)</td>
<td>18</td>
<td>“Suspected airflow obstruction”</td>
<td>3 puffs MDI by slow manual inflation vs 2.5 mg of NEB albuterol</td>
<td>Airway resistance by occlusion technique</td>
<td>Both NEB and MDI albuterol decreased airway resistance</td>
</tr>
<tr>
<td>Fernandez et al32 (r/c)</td>
<td>20</td>
<td>COPD</td>
<td>0.2 mg salbutamol vs 0.04 mg ipratropium by slow manual inflation and 10% inspiratory pause</td>
<td>Peak, static airway pressure, resistance</td>
<td>Both MDI drugs decreased airway resistance and pressure</td>
</tr>
<tr>
<td>Farhangfar et al33†</td>
<td>12</td>
<td>COPD</td>
<td>2 puffs of MDI (no spacer) vs 2.5 mg of NEB albuterol</td>
<td>Peak, static airway pressures</td>
<td>Both MDI and NEB improved resistive airway pressures</td>
</tr>
<tr>
<td>Gutierrez and Nelson34†</td>
<td>20</td>
<td>COPD</td>
<td>2 puffs of MDI (with spacer) vs 2.5 mg NEB metaproterenol</td>
<td>Peak, static, resistive pressures</td>
<td>Both MDI and NEB improved airway resistance</td>
</tr>
<tr>
<td>Hess et al35†</td>
<td>16</td>
<td>Heterogeneous</td>
<td>360 μg MDI (into ETT with inspiratory pause) vs 2.5 mg albuterol</td>
<td>Expiratory resistive pressure</td>
<td>Both MDI and NEB improved expiratory resistive pressure</td>
</tr>
<tr>
<td>Bakow et al36†</td>
<td>30</td>
<td>Heterogeneous</td>
<td>MDI vs NEB both in proximal and distal positions in the inspiratory limb (few specifics)</td>
<td>Peak and plateau airway pressures, Raw</td>
<td>? Equal improvement in both groups</td>
</tr>
<tr>
<td>Manthous et al37 (r/s/c)</td>
<td>10</td>
<td>Heterogeneous</td>
<td>100 puffs of MDI via adapter vs 2.5, 7.5, 15.0 mg NEB albuterol</td>
<td>Peak-static airway pressure (resistive pressure)</td>
<td>MDI had no effect; NEB reduced airway pressure at 2.5 and 7.5 mg with limited toxic reaction</td>
</tr>
<tr>
<td>Dhand et al38†</td>
<td>6</td>
<td>COPD</td>
<td>10 puffs of MDI via spacer</td>
<td>Peak, static airway pressures</td>
<td>MDI via spacer reduced resistive airway pressure</td>
</tr>
</tbody>
</table>

*For study design: r=randomized; s=single blind; c=crossover.
†Signifies that the data are reported in abstract form only.

In another investigation published in abstract form,21 less than 1 percent of drug was delivered when MDIs were actuated into an ETT adaptor. In contrast, 42 percent of MDI delivered into a spacing device in the inspiratory limb of the ventilator circuit cleared the end of the ETT in the same ventilator-lung model. The specifics of ventilator settings were not discussed. Rau et al22 examined the delivery of albuterol to a test lung by MDI actuated into an 8-mm ETT via an adapter and via a spacer (AeroVent).
placed before and after the Y piece of the ventilator circuit. A ventilator (Siemens Servo 900C) delivered 12 to 800 ml breaths per minute with a 20 percent inspiratory time. Actuation directly into the ETT adapter was associated with delivery of 7.3 percent of drug, while actuation into the spacing device led to about 35 percent delivery regardless of position in the circuit.

Taylor and Lerman\textsuperscript{33} studied the delivery of salbutamol by MDI through 3- to 6-mm ETTs and 19-gauge intra-ETT catheters during continuous gas flows. Delivery was greatest through the intra-ETT catheter (96 percent) and ranged from 2.5 to 12.3 percent increasing with the size of the ETT. Recently, Taylor et al\textsuperscript{24} examined delivery of salbutamol by MDI through a 6-mm ETT at constant (non-pulsatile) flows of 30 L/min delivered through an ETT swivel adapter or through varying lengths and diameters of intra-ETT catheters. Delivery of MDI was 50 times higher through the intra-ETT catheters than through the standard swivel adapter. These data suggest that all of any given actuation reaches the distal ETT through 22-cm-long, 14 to 22 standard wire gauge catheters placed through the center of the ETT. Niven et al\textsuperscript{35} have also demonstrated that 20 to 30 percent of MDI administered through 16- and 19-gauge intra-ETT catheters during constant gas flow reaches a lung model.

Studies Utilizing Physiologic End Points: Most physiologic studies of the efficacies of aerosol therapies in mechanically ventilated patients have been in treatment of bronchospasm with \(\beta\)-agonists. Abundant clinical physiologic and radiolabeled drug studies have been performed to show that both MDI and nebulized treatments are equally effective in the treatment of bronchospasm in nonintubated, spontaneously breathing subjects. However, there are few data comparing the physiologic efficacy of these very commonly used delivery systems in intubated, mechanically ventilated patients (Table 3).

Gay et al\textsuperscript{26} have validated the use of readily obtainable airway pressures to evaluate the response of bronchodilator therapy in mechanically ventilated patients. Pressure measured at the airway opening is displayed by most ventilators and is a useful parameter to assess respiratory system mechanics. Since peak airway pressure is the sum of static and resistive pressures, the difference between peak and static pressures reflects airway resistance at a given flow rate (Fig 4). In addition, the measurement of intrinsic positive end-expiratory pressure (PEEP) in airflow-obstructed patients is a measure of dynamic hyperinflation, and hence, indirectly, a reflection of airway resistance. Also, some ventilators possess or may be adapted to provide measurement of airway resistance by an interruptor technique.

The use of aerosol bronchodilators in intubated patients began in the 1960s.\textsuperscript{27} Fresoli et al\textsuperscript{28} treated eight bronchospastic patients undergoing anesthesia for a variety of reasons with 0.225 to 0.375 mg of isoproterenol by MDI finding that wheezing was reduced in seven. Gold\textsuperscript{29} treated 12 anesthetized patients with 250 \(\mu\)g of isoproterenol delivered by MDI actuation into a side-port adapter with manual bag inflation, finding that peak airway pressure decreased in all 12 by between 10 and 33 mm Hg. Sprague\textsuperscript{30} studied 16 anesthetized patients who developed bronchospasm while undergoing operative procedures finding that 680 \(\mu\)g of isoetharine per 140 \(\mu\)g of phenylephrine by MDI decreased peak inspiratory pressures in all patients with a mean reduction of 3.2 cm H\(\text{O}\).

Gay et al\textsuperscript{31} randomized 18 mechanically ventilated patients with "suspected airway obstruction" to crossover between albuterol delivered by MDI (3 puffs, 270 \(\mu\)g) or nebulizer (2.5 mg). The MDI canister and adapter were attached to a conduit with a balloon attached; actuation occurred into the reservoir balloon and was then delivered by slow manual inflation with end-inspiratory pause. Expiratory resistance was measured using an interruptor technique before and after treatments. They found that

**Figure 4.** Superimposed pressure and volume curves during mechanical ventilation. The addition of an end-inspiratory pause (shown in breaths 3 to 5) causes airway pressure to plateau at a level representing the pressure required to expand the lung and chest wall at the given tidal volume (static airway pressure). The difference between peak (dynamic) and static airway pressures is related to flow and airway resistance. In intubated patients, resistive pressure includes contributions from the ventilator circuit, the ETT, and the patient's airways. The fifth breath (in hashed lines) demonstrates the effects of increased airways resistance on mechanics: peak airway pressure increases while static pressure remains unchanged. In situations of inadequate expiratory time, trapped gas at end-expiration may lead to intrinsic positive end-expiratory pressure that increases peak pressure through increases in static pressure (figure provided by Richard Samel, M.D., using the Critical Concepts Inc Human Physiology Simulator).
both methods of delivery significantly reduced airway resistance. The study by Fuller et al.\textsuperscript{39} cited above, examined the effect of MDI (with a spacer) and nebulizers on peak airway pressures, finding that neither significantly reduced peak pressures. MacIntyre et al.\textsuperscript{15} (also cited above) showed that 1.25 mg of metaproterenol in 4 ml of normal saline solution via a nebulizer attached to the proximal ETT with flows of 8 to 10 L/min did not significantly alter pulmonary mechanics or heart rate.

Fernandez et al.\textsuperscript{32} studied 20 patients who required mechanical ventilation secondary to an exacerbation of COPD. Salbutamol (0.2 mg) or ipratropium bromide (0.04 mg) was given by MDI actuation into an intraendotracheal catheter coupled to slow bag ventilation, with 10 h of washout between treatments. Airway mechanics were measured 60 min after treatments. They found that both agents decreased airway pressures and resistance when delivered by this method.

Farhangfar et al.\textsuperscript{35} studied 12 patients with COPD randomized to receive two puffs of albuterol by MDI (two puffs, 180 µg) or jet nebulizer (2.5 mg) with a crossover to alternative delivery at 6 h. Both drug delivery systems reduced mean airway pressures as well as intrinsic PEEP and there was no statistically significant difference between the two techniques. Gutierrez and Nelson\textsuperscript{34} also studied 20 mechanically ventilated patients after delivery of 180 µg MDI or 2.5 mg of nebulized metaproterenol. Airway resistance was measured before and after using the “static mechanics function” on a ventilator (Puritan-Bennett 7200a). Airway resistances significantly decreased with each drug administration technique. Hess et al.\textsuperscript{35} evaluated 16 patients using a ventilator (Siemens Servo 900C) with inspiratory times of 25 percent and inspiratory pauses of 5 percent finding that both 360 µg of albuterol by MDI actuated into the ETT and 2.5 mg of nebulized albuterol reduced expiratory resistive pressure compared with placebo. Bakow et al.\textsuperscript{36} also observed similar results, though their methods were not well described. We recently reported a crossover study in which ten patients were randomized to receive increasing doses of either MDI (actuated into an ETT adapter) or nebulized albuterol. After 4 h, patients crossed over to the alternate method of administration. Cumulative doses of 100 puffs of MDI albuterol (9 mg) had no effect on resistive pressure, whereas cumulative doses of 2.5 and 7.5 mg of nebulized albuterol reduced resistive pressure.\textsuperscript{37} Dhand et al.\textsuperscript{39} studied six mechanically ventilated patients with COPD finding that ten puffs of MDI albuterol delivered via a spacer (Aerovent) in the inspiratory limb significantly reduced resistive airway pressure.

Atropine-like drugs, including ipratropium-bromide delivered by MDI and glycopyrrolate delivered by nebulizers, are frequently used to treat airflow obstruction in nonintubated patients. Despite the fact that these agents are also widely administered to intubated, mechanically ventilated patients, only one study in adults\textsuperscript{32} (described above) has demonstrated clinical efficacy in this setting. No studies in ventilated adults have determined whether anticholinergics provide equivalent or additive effects when compared with β-agonist alone.

The assumption that bronchodilator drugs may be delivered by aerosol in intubated patients with efficacy comparable to treatment of the nonintubated patient is likely true. However, insofar as aerosol delivery is affected by the presence of an ETT and by ventilator parameters, the following questions must be answered so that such therapies may be reliably and reproducibly administered in a safe and effective manner.

1. Are nebulized treatments effective? If so, what is the optimal method of nebulization, where in the ventilator circuit should the nebulizer be placed, and how much of each drug should be administered by this method? The studies cited above that evaluated drug nebulization did not assess the utility of continuous nebulization, an approach now favored in many intensive care units. This nebulization strategy should be formally evaluated with the techniques described above. When jet nebulizers are used, what is the optimal volume of fill?

2. Are MDIs effective? If so, where in the circuit should the MDI be actuated, during what period of the respiratory cycle, and in what doses should MDI be administered? Is a spacing chamber or intra-ETT catheter required for the delivery of MDI and if so, what is its optimal design and where should it be placed in the ventilator circuit? Lastly, even if a standardized effective method of MDI administration is determined, are they “doomed to extinction”\textsuperscript{39} because they emit polluting chlorofluorocarbons?

3. What are the optimal ventilator parameters for the delivery of nebulized aerosols to intubated patients and are the same parameters optimal for MDI delivery systems? The in vitro work by O’Doherty et al.\textsuperscript{16} is very important in beginning to address this issue; in vivo work should be performed to confirm their findings.

4. Are atropine-like drugs effective? Do they add any additional benefit when added to β\textsubscript{2}-agonists? Are there some patients who will respond to atropine-like drugs who will not respond to β\textsubscript{2}-agonists? Are any of these questions affected by whether a patient is intubated or not?

5. Would vehicles such as heliox, which enhance the delivery of aerosols in spontaneously breathing patients,\textsuperscript{16} be useful (and feasible) for intubated,
mechanically ventilated patients?

Since the delivery of these agents depends on numerous variables, studies must be performed to determine preferred, standardized methods of delivery to assure adequate safety and efficacy for the patient. We conducted an informal survey of Chicago-area teaching hospitals in September 1992, finding that both β2-agonists and atropine-like drugs are widely used both by MDI and nebulization in mechanically ventilated patients. Furthermore, some of these institutions used MDI delivery techniques that may not be effective.19,37 In a second informal poll at the 1993 American Thoracic Society meetings, 13 of 32 physicians (10 community-based and 22 university-based) delivered aerosols by MDI through a side-port adapter, 12 used an in-line spacer for MDI, and 7 used nebulizers exclusively. Of the 25 using MDI, 8 also used nebulization for some treatments.

Therapeutic Aerosols in Pediatrics

Compared with the literature regarding adult treatment, even fewer studies have examined the efficacy of therapeutic aerosols in mechanically ventilated infants and children. Based on the adult data presented above, various ventilator parameters (small tidal volumes) and the presence of small-diameter ETTs would be expected to hamper delivery of aerosols to children. Cameron et al40 compared deposition rates of aerosolized budesonide for five jet nebulizers and an ultrasonic nebulizer in a pediatric ventilator-lung model. Deposition varied between devices from a low of 0.15 percent to a high of 1.52 percent. Arnon et al41 found that 14.2 percent of a dose of budesonide could be delivered to a ventilator-lung model by MDI with spacer compared with only 0.68 percent by nebulized treatments. Data collected by Grigg et al42 suggest that MDI with spacer delivered only 1.7 percent compared with 1.3 percent for an ultrasonic nebulizer. Everard et al43 demonstrated that 1 to 5 percent of MDI sodium cromoglycate could be delivered via a spacer in a ventilator-lung model. In a separate series of experiments,44 they also demonstrated that nebulized drug was better delivered to a ventilator-lung model by higher tidal volumes, higher volumes of fill, and higher flow rates used to generate the nebulized agent. Flavin et al45 ventilated rabbits with an infant ventilator (Bourns LS 104T), finding that the deposition of nebulized radiolabeled particles was dependent on the brand of nebulizer used. Furthermore, the most efficient nebulizer system was a “nontraditional” device that created submicronic particles at higher than normal flow rates. However, Watterberg et al46 compared urine samples of nine infants after jet and submicronic nebulized cromolyn, finding that despite increased rates of delivery, no more cromolyn was recovered in the urine after submicronic therapy. This suggests that submicronic particles may be more likely to be exhaled.

We are aware of only one clinical study that has examined a physiologic end point after aerosol bronchodilator therapy in infants. Rio et al47 delivered isetharine by jet nebulizer to 13 preterm infants with respiratory distress syndrome. Airway resistance decreased in all patients and lung compliance tended to increase. To our knowledge, no similar physiologic studies have been performed to determine the efficacy of MDI in ventilated infants and children. Preliminary data concerning surfactant aerosol therapy in infants with respiratory distress syndrome, presented below, examine physiologic end points for efficacy of aerosol therapy but further studies are required to determine the optimal method of delivery to this patient population.

Other Drugs Delivered by Aerosol

Aerosolized steroids are commonly used in the treatment of nonintubated patients with asthma and COPD. Beclomethasone and triamcinolone are the steroids most commonly administered by aerosol. In severe acute asthma, systemic steroids are invariably used in lieu of inhaled steroids, since the aerosol delivery is likely compromised and dose requirements are likely higher. There may be critically ill patients in whom systemic steroids would be contraindicated but who would benefit from aerosolized steroids. Some in vitro data suggest that aerosolized steroids may be delivered through pediatric ETTs through an MDI spacer system.41,48 To our knowledge, no studies have evaluated aerosolized steroids in the treatment of bronchospasm in intubated patients.

Cromolyn sodium is another agent used in the outpatient management of asthma. Since cromolyn requires a significant duration of therapy before it is effective as an inhibitor of mast cell degranulation, it has not been believed to be useful in the course of critical illness.

The role of mucolytics in clinical practice is controversial. Although studies have shown that acetylcysteine, the commercially available aerosolized mucolytic, is effective in vitro in liquefying both mucoid and purulent secretions, clinical benefit of such therapy is not clear.49 This agent is used as adjunctive therapy for patients with tenacious secretions or for dissolution of bronchial plugs. One study has been performed in mechanically ventilated patients, which showed that acetylcysteine delivered by nebulizer caused bronchospasm; this study did not address its mucolytic activity.50 Therefore, there are no data (to our knowledge) to support use of this agent in mechanically ventilated patients.

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Aerosolized antibiotics have been studied for the treatment and prophylaxis of infections in nonintubated patients with cystic fibrosis (gentamicin), HIV-related disease (pentamidine for Pneumocystis carinii pneumonia), and immunocompromised states (amphotericin B for fungal infections). One of the main theoretic problems with such therapies is that delivery of aerosols to consolidated lung may be limited. Amphotericin B is not currently approved for aerosol therapies, although some animal data suggest that it may be effective for treatment of pulmonary fungal infections. Girard et al. examined plasma concentrations of pentamidine after ultrasonic aerosolization (4 mg/kg) in 8 intubated and 18 nonintubated patients. They found that plasma concentrations of pentamidine in intubated patients were double those of nonintubated patients and similar to levels observed after intramuscular injection of 4 mg/kg, although they did not examine actual lung deposition/delivery. Thus aerosolized pentamidine therapy for pulmonary infections in intubated patients remains experimental and must be validated in prospective trials with clinical end points. Aerosolized ribavirin has also been used for treatment of (viral) infections in intubated patients. After studies demonstrating safety, 28 infants with respiratory syncytial virus pneumonia requiring mechanical ventilation were prospectively randomized to receive 7 days of continuously nebulized ribavirin or placebo. Ribavirin decreased both days on the ventilator and days in hospital, but did not reduce overall mortality. To our knowledge, no similar studies have been performed in mechanically ventilated adults with viral pneumonitides.

Surfactant suspension has been delivered via ETTS in the management of infant respiratory distress syndrome and adult respiratory distress syndrome (ARDS). Experimental models of ARDS in animals suggested that aerosolized surfactant was at least as effective as instilled surfactant in attenuating lung injury as measured by pulmonary mechanics and oxygenation despite lower doses of drug in the lung. Reines et al. studied 49 patients with ARDS randomized to receive saline solution nebulization, intratracheal surfactant suspension, or surfactant nebulization for 5 days. Patients receiving surfactant by either modality had improved mortality and oxygenation compared with the group receiving saline solution. Nebulized surfactant was well tolerated except for two episodes of occlusion of the expiratory filters of the ventilator circuits. Weg et al. studied 52 patients comparing nebulized surfactant with saline solution over 5 days finding a trend toward improved survival and shunt in the surfactant-treated group. They observed filter occlusion as well, in one case leading to pneumothorax. A randomized placebo-controlled multicenter trial is currently underway to assess the effect of nebulized surfactant on the course of ARDS.

Recommendations

Based on this review of the literature, we suggest the following for the delivery of aerosols to intubated patients:

Which drugs? The only aerosolized medications that have been shown to be effective in intubated patients are β-agonist bronchodilators (in both adults and children) and ribavirin (in children). Use of other agents should be restricted to experimental protocols until further studies substantiate effectiveness and safety.

Which methods of delivery and how? Nebulized and MDI-delivered drugs should be titrated to physiologic effect until more conclusive studies determine standardized, reproducible methods of delivery, specifically noting the following:

1. When MDI bronchodilators are used, the clinician should be aware that adequate medication may not be reaching the airways of the patient. Further studies, using physiologic end points, are required to determine optimal dosing through and optimal positioning of spacer devices. Based on the available data, when MDIs are used they should be administered through an in-line spacing device, following airway mechanics for effect, until further studies are performed to determine whether actuation into the ETT can deliver adequate doses of medication. The use of intra-ETT catheters appears promising, but in vivo studies are required to validate this method of MDI delivery before it can be recommended for routine use in ventilated patients.

2. When jet nebulizers are used, we suggest using the largest possible volumes of fill. The clinician must be aware of the specifications of aerosol production for their particular ultrasonic and jet nebulizer (MMAD, optimal operating procedures).

What ventilator settings? Ventilators should be set at reduced inspiratory flows (40 to 50 L/min) and respiratory rates to maximize inspiratory time during aerosol administration. Of course, either maneuver could result in sufficient reduction of expiratory time to cause or worsen dynamic gas trapping, as indicated by the existence of intrinsic PEEP. If intrinsic PEEP exists, it should be minimized by ventilator settings that maximize expiratory time. The role of additional maneuvers, ie, the use of end-inspiratory pauses, remains to be illuminated, but it may be advisable based on the limited available data. When MDIs are used, slow bag inflation with an inspiratory pause may also be effective.

Future studies will determine the methods for maximal delivery of aerosolized medications. Yet the
multitude of patient and ventilator circuit-deter-
mined variables impacting on aerosol delivery sug-
gest that there will be no universally applicable
method of aerosol delivery or dose that serves all pa-
ients. Rather, we strongly urge that clinicians con-
sider these factors and titrate their therapies to effect
as is the practice with most other interventions in
critically ill patients.

CONCLUSIONS

Aerosols have been used widely in the treatment of
critically ill intubated patients. However, the data
supporting the physiologic effectiveness of such
therapies are currently incomplete. Instead, data
from the nonintubated patient population have been
used to justify similar techniques of administration to
intubated patients. The use of aerosol therapies in the
critical care unit has become a multimillion dollar
industry precisely because aerosol therapies are poten-
tially as useful in intubated patients as in nonin-
tubated patients. However, further studies are re-
quired to determine the optimal mode of adminis-
tration and appropriate dosing for each modality, to
fully realize the potential of aerosol therapies in me-
chanically ventilated patients.

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