

# Inhalation Therapy With Metered-Dose Inhalers and Dry Powder Inhalers in Mechanically Ventilated Patients

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### **Summary**

Pressurized metered-dose inhalers (pMDIs) are commonly employed for administering bronchodilator aerosols to mechanically ventilated patients. Although it is feasible to employ dry powder inhalers in ventilator circuits, the presence of humidity in the ventilator circuit could reduce their efficiency. A complex array of factors influence drug delivery from pMDIs during mechanical ventilation, and subtle differences in the method of administration can markedly alter aerosol deposition in the lower respiratory tract. However, when the technique of administration is optimized, the efficiency of drug delivery from pMDIs in mechanically ventilated patients is comparable to that in ambulatory patients. Significant bronchodilator effects are observed with as few as 4 puffs from a pMDI and cylindrical spacer. In mechanically ventilated patients, pMDIs are a cost-effective, convenient, and safe method for delivering bronchodilator aerosols. *Key words: mechanical ventilation, drug delivery, aerosol, metered-dose inhaler, dry powder inhaler, bronchodilator, corticosteroids, endotracheal tube.* [Respir Care 2005;50(10):1331–1344. © 2005 Daedalus Enterprises]

## **Introduction**

Inhaled drug therapy in mechanically ventilated patients differs from that in ambulatory patients with respiratory disorders. In ambulatory patients, the major aerosol-generating devices that have been employed include pressurized metered-dose inhalers (pMDIs), nebulizers, and dry

powder inhalers (DPIs). Similarly to ambulatory patients, aerosol delivery during mechanical ventilation also depends to a great extent on the type of aerosol-generating device employed. Only pMDIs and nebulizers have been adapted for clinical use during mechanical ventilation. While it is feasible to employ DPIs during mechanical ventilation (see below), their efficacy has not been dem-

onstrated in the clinical setting. On the other hand, pMDIs are convenient and cost-effective and they are widely employed for bronchodilator therapy in patients receiving mechanical ventilation. This review, therefore, focuses heavily on pMDI use in mechanically ventilated patients.

### Goals of Inhalation Therapy

The concept of drug dose in inhaled drug delivery is complicated<sup>1,2</sup> by the fact that only a small portion of the nominal dose of drug in a pMDI deposits in the lung. For example, when a pMDI or a DPI is employed in the ventilator circuit, a variable amount of the drug deposits in the actuator, the ventilator circuit, and the endotracheal tube (ETT) (Fig. 1).<sup>3,4</sup> The amount of drug reaching the distal end of the ETT is available for deposition in the lung; a small proportion of this drug is exhaled and a variable amount is systemically absorbed. The remainder of the drug deposits in the lung (the lung dose) and is responsible for the pharmacologic effects. Several investigators have shown that the response to an inhaled drug depends on the amount of drug deposition in the lower respiratory tract.<sup>5-7</sup> Thus, clinicians need to be more concerned with the lung dose from a given device rather than the nominal dose. To achieve the goals of inhalation therapy, 3 essential variables need to be considered: *precision*, *reliability*, and *consistency* of the lung dose. *Precision* of lung dosing requires consideration of limiting drug losses in the upper respiratory tract and also targeting the drug to specific regions of the respiratory tract (eg, larger airways versus more peripheral airways and lung parenchyma). For drug dosing to be *reliable*, uniform amounts of drug should be deposited in the lung under a variety of conditions (eg, in various age groups, smokers, and patients with airways obstruction). *Consistency* of dosing requires uniformity in drug deposition across the life of a device (multi-dose pMDI or DPI). Adequate understanding of the factors governing lung deposition of aerosols is essential to achieve these goals. Re-

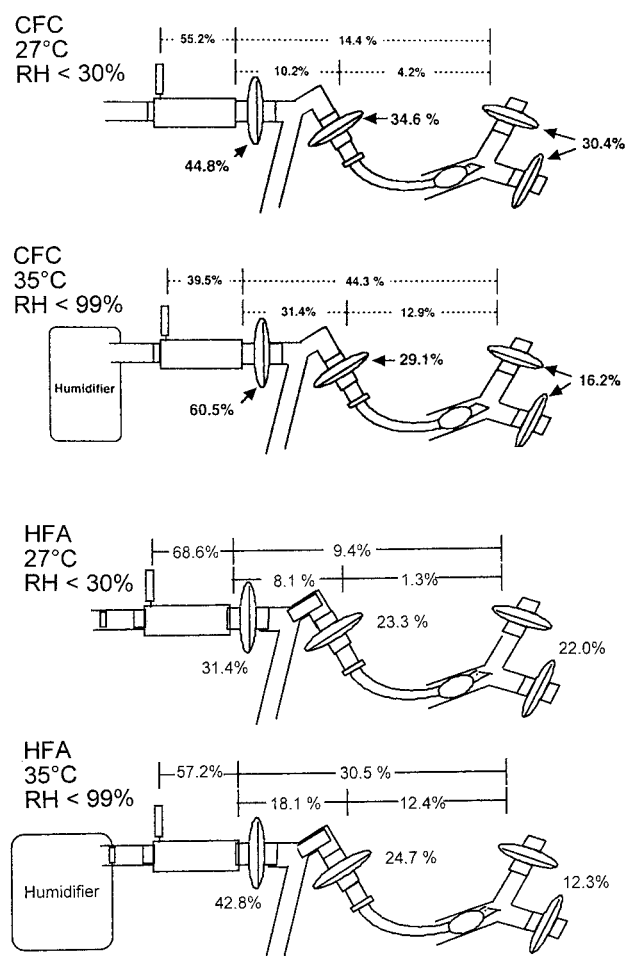


Fig. 1. Drug deposition, expressed as percent of nominal dose of albuterol from a chlorofluorocarbon (CFC) propelled metered-dose inhaler (MDI), in the spacer chamber, the ventilator circuit, the endotracheal tube, and on filters at the bronchi, under dry and humidified conditions during controlled mechanical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

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markable progress has been made in recent years toward achieving these goals because of the impressive gains in our knowledge and understanding of aerosol deposition in the lung, and with the availability of high-efficiency delivery devices.<sup>8</sup>

### Dry Powder Inhalers

DPIs create aerosols by drawing air through a powder that contains aggregates of micronized particles. The mi-

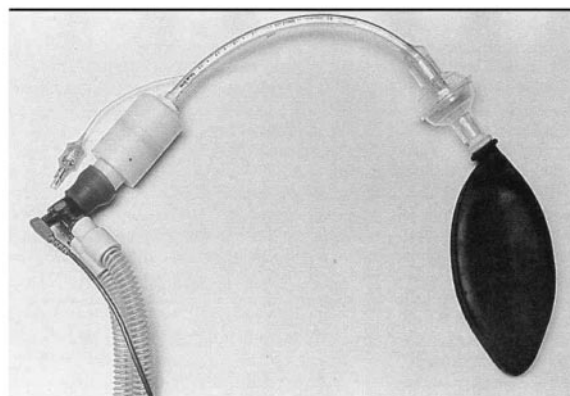
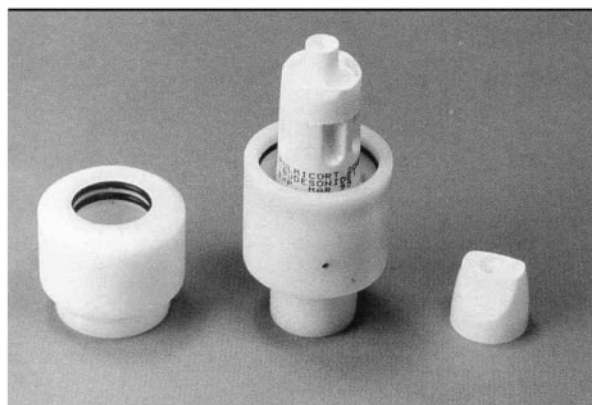


Fig. 2. A budesonide Turbuhaler was modified by cutting back the outer covering. The Turbuhaler was then enclosed in a chamber which allowed air to flow through the device and which connected to the proximal end of the endotracheal tube. The modified Turbuhaler was connected between the circuit Y-piece and the endotracheal tube. (From Reference 4, with permission.)

ronized particles are either in the form of loose aggregates or they are bound to larger carrier particles (usually lactose or glucose).<sup>9</sup> Each DPI has 3 essential elements: drug formulation, metering system, and dispersion mechanism. Thus, the properties of the drug and the aerodynamic and flow properties of the inhaler device determine the performance and characteristics of the aerosol generated.

Most DPI systems in current use are passive systems; that is, they require the energy from inhalation to generate an aerosol. On the other hand, active DPIS employ an impeller or other mechanical device to generate inspiratory airflow.

### DPI Use During Mechanical Ventilation

DPIS could be employed in-line in ventilator circuits, either by employing the ventilator's inspiratory airflow to generate an aerosol or by first producing an aerosol from the DPI and then entraining the drug particles in the airflow from the ventilator. Everard and colleagues<sup>4</sup> modified the Turbuhaler for use in a ventilator circuit. These investigators removed the outer covering of the Turbuhaler and enclosed the inner cylinder containing the spiral disaggregation channels in a chamber (Fig. 2). Once the device was loaded, air flowing through the chamber carried the aerosol beyond the ETT (see Fig. 2). The system employed by Everard and coworkers<sup>4</sup> was reported to deliver approximately 20% of the nominal dose to a filter placed at the distal end of the ETT (Table 1):<sup>10</sup> values that are comparable to those achieved with pMDIs and spacers. Moreover, Everard and colleagues employed a dry ventilator circuit, and humidity is well known to reduce drug delivery from DPIS.<sup>11</sup> Drug losses are likely to be higher when a DPI is employed in a ventilator circuit. Once the drug enters the lower respiratory tract, humidity may not

Table 1. Efficiency of a Modified DPI for Use in a Ventilator Circuit\*

Device	Total in MSLI	Particles < 6.8 $\mu\text{m}$	Total on Filter With ETT
DPI ( $\mu\text{g}$ )	142.6 $\pm$ 16.4	91.2 $\pm$ 8.9	—
DPI With ETT ( $\mu\text{g}$ )	60.4 $\pm$ 4.8	46.8 $\pm$ 3.2	41.1 $\pm$ 3.7
Nominal Dose (%)	29.6	23.0	20.0

\*Values are mean  $\pm$  SD  
 DPI = dry powder inhaler  
 MSLI = multistage liquid impinger  
 ETT = endotracheal tube  
 (Data from Reference 4.)

be a major influence on drug efficacy, as Lindsay and colleagues<sup>12</sup> did not find any difference in the clinical effect of albuterol given via Turbuhaler from that observed after the same drug was given via pMDI in a hot and humid region. Because mechanically ventilated patients routinely receive warm and humidified gas, the feasibility of administering dry powders in a humid environment needs further evaluation.

### Pressurized Metered-Dose Inhalers

The MDI canister contains a pressurized mixture of propellants, surfactants, preservatives, flavoring agents, and active drug, the latter comprising approximately 1% of the total contents.<sup>13,14</sup> This mixture is released from the canister through a metering valve and stem, which fits into an actuator boot, designed and extensively tested by the manufacturer to work with that specific formulation.<sup>13,14</sup> Previously, most pMDIs used chlorofluorocarbon (CFC) propellants, but newer-generation pMDIs contain hydrofluoroalkane (HFA) propellants.<sup>15</sup> The formulation, metering-valve, and actuator design of HFA pMDIs differ from those in CFC pMDIs.

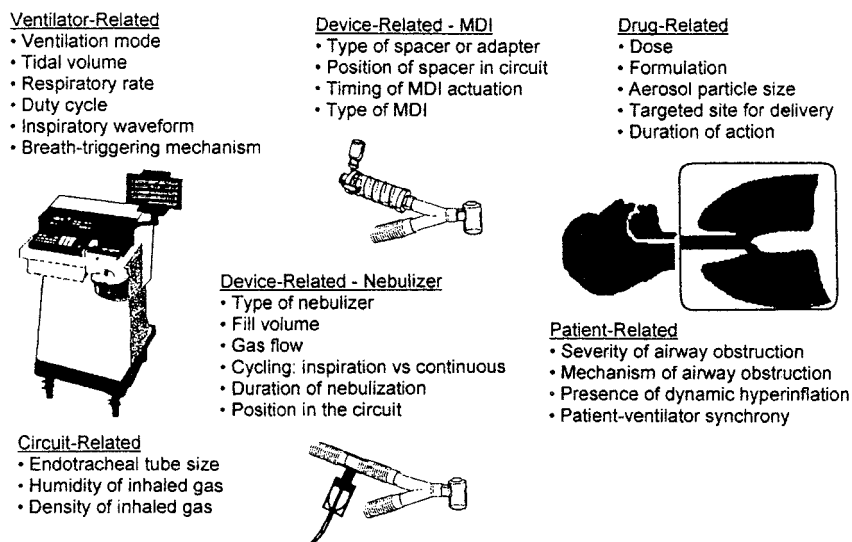


Fig. 3. Factors that influence aerosol delivery in mechanically ventilated patients. MDI = metered-dose inhaler. (From Reference 20, with permission.)

The particle size of the aerosol produced by a pMDI depends on the vapor pressure of the propellant mixture, ambient temperature, design of the valve stem and actuator orifices, and drug concentration.<sup>15–18</sup> High-vapor-pressure propellants produce finer aerosol sprays, whereas increasing the drug concentration increases aerosol particle size. Initially, drug particles emerging from the pMDI actuator are coated by a mixture of surfactant and propellant. When the propellant completely evaporates before inhalation, the diameter of the droplets decreases and drug particles coated by surfactant are inhaled into the respiratory tract. If the propellant does not evaporate completely, the particle diameter does not decrease as rapidly, greater amounts of drug are lost during transit to the lower respiratory tract, and the patient is exposed to propellant vapor.

### Use of pMDIs in Ventilator Circuits

Several factors related to the MDI itself, the type of adapter/actuator employed, type of ventilator, ventilator settings, circuit conditions, the type of drug employed, and the condition of the patient could impact drug delivery from a pMDI during mechanical ventilation (Fig. 3).<sup>19,20</sup>

### In Vitro Studies of Drug Delivery With pMDIs

#### Effect of pMDI Formulation on Drug Delivery

In a mechanically ventilated lung model, Rau and colleagues<sup>21</sup> found that the type of pMDI formulation influenced the efficiency of drug delivery. They compared drug delivery from an albuterol CFC MDI and a flunisolide CFC MDI with a variety of adapters. The delivery of

Table 2. Effect of the Type of MDI and Spacer on Efficiency of Drug Delivery (% nominal dose)

	Hudson	MiniSpacer	Aerovent	ACE	MediSpacer
Albuterol	12.0	17.2	17.7	30.0	31.8
Flunisolide	5.0	11.4	12.4	13.1	21.0

(Data from Reference 21.)

flunisolide was lower with all the actuators tested, compared to the values achieved with the albuterol MDI (Table 2).<sup>21</sup>

**CFC Versus HFA pMDIs.** Because HFA propellants are incompatible with surfactants, many of the HFA pMDIs have been reformulated as solutions, resulting in a finer aerosol spray, with greater peripheral lung deposition and improved efficacy, compared to the CFC pMDIs.<sup>6,7,22</sup> In bench models of mechanical ventilation, albuterol HFA pMDIs employed with an Aerovent spacer (Monaghan Medical, Plattsburgh, New York) provide drug delivery that is lower than that with CFC pMDIs.<sup>3</sup> Contrarily, beclomethasone HFA pMDIs employed with an Aerochamber HC MV spacer (Monaghan Medical, Plattsburgh, New York) had a higher efficiency of drug delivery than the beclomethasone CFC MDI.<sup>10</sup> The differences in the results of the studies could be explained by differences in the MDI formulation and types of spacers employed by the 2 groups of investigators. The beclomethasone HFA MDI is formulated as a solution and produces an extra-fine aerosol (mass median aerodynamic diameter 1.2  $\mu\text{m}$ ), whereas the albuterol HFA MDI is a suspension, with aerosol particle size comparable to that of the albuterol CFC MDI.

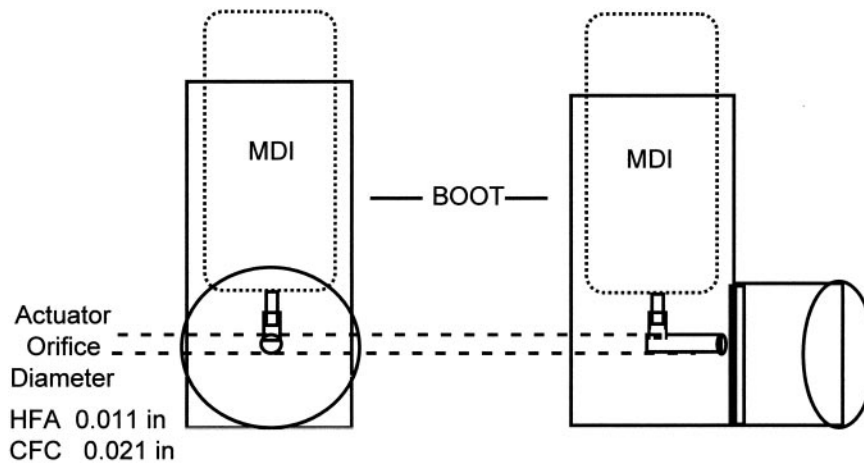


Fig. 4. Illustration showing that the size of the canister stem and pin hole for the actuator in an albuterol chlorofluorocarbon-propelled metered-dose inhaler (MDI) differs from the hydrofluoroalkane-propelled MDI. The actuator of the chlorofluorocarbon-propelled MDI cannot be used interchangeably with the actuator of a hydrofluoroalkane-propelled MDI, and vice versa. (Illustration courtesy of James B Fink, MSc, RRT, FAARC.)

Moreover, the size of the canister stem is different for each MDI, and the efficiency of drug delivery depends on how well the canister stem fits into the actuator (Fig. 4). To improve drug delivery with HFA pMDIs in the setting of mechanical ventilation, the actuators required to connect them in ventilator circuits need to be matched to the size of the pMDI canister stem.

**Effect of the pMDI Actuator.** The canister of the pMDI has to be removed from the manufacturer-supplied actuator and a different actuator is needed to connect the canister in the ventilator circuit. The choice of an appropriate adapter has an important bearing on the response to drug administration. Several types of adapters, including elbow adapters, in-line devices that may be uni-directional or bi-directional, and chamber or reservoir adapters, are commercially available (Fig. 5).<sup>20,23</sup> The elbow adapters connect to the ETT, whereas the in-line and chamber adapters are placed in the inspiratory limb of the ventilator circuit. Employing a chamber spacer with a pMDI in a ventilator circuit results in 4–6-fold greater aerosol drug delivery, compared with either an elbow adapter or a uni-directional in-line spacer.<sup>24–27</sup> A chamber spacer connected at a distance of approximately 15 cm from the ETT provides efficient aerosol delivery in mechanically ventilated patients and has been shown to elicit a significant response to bronchodilator administration via an MDI.<sup>28</sup> A bi-directional in-line spacer increases the volume of gas into which the aerosol is actuated and correspondingly produces a 1.5–2.5-fold increase in aerosol delivery, compared with the uni-directional in-line spacer.<sup>21</sup> The efficiency of aerosol drug delivery with an MDI and bi-directional in-line spacer was reported to be comparable to that achieved with chamber spacers;<sup>21</sup> however, the efficiency of the

bi-directional spacer has not been established in clinical studies.

### Synchronization of Actuation With Inspiratory Airflow

The actuation of a pMDI in a ventilator circuit must be synchronized with the precise onset of inspiratory airflow from the ventilator.<sup>29</sup> Even a 1–1.5-second delay between pMDI actuation and the ventilator breath can profoundly reduce the efficiency of drug delivery.<sup>27</sup> Unfortunately, the ventilator-supported patient is unable to self-administer the dose, and the respiratory therapist has to ensure that pMDI actuation is synchronized with the precise onset of inspiratory airflow from the ventilator. A practical method to achieve synchrony is to time the pMDI actuation with expansion of the ventilator tubing at the onset of a ventilator breath; delivery is improved when an MDI is synchronized with a simulated spontaneous breath, compared with a controlled mechanical ventilation breath of similar tidal volume.<sup>30</sup>

### Type of Ventilator and Ventilatory Parameters

The type of ventilator employed has not been shown to alter drug delivery from an MDI, but the ventilator settings have a significant influence on drug delivery. A tidal volume of 500 mL or more (in an adult) ensures that the dead space is cleared of aerosol and improves drug delivery to the lower respiratory tract.<sup>30</sup> A longer inspiratory time and slower inspiratory flow also improves aerosol delivery;<sup>30</sup> drug delivery is linearly correlated with a longer duty cycle.<sup>3,30</sup> In contrast to nebulizers, drug delivery is not influenced by the inspiratory waveform employed during



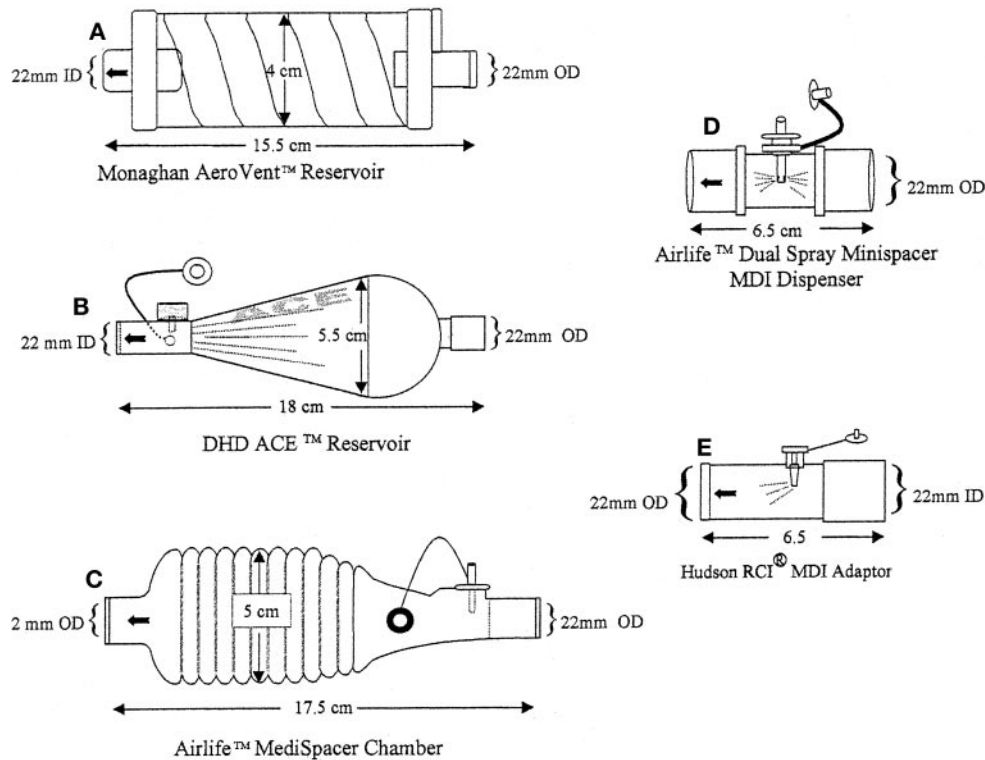


Fig. 5. Commercially available spacers/adapters that are used to connect a metered-dose inhaler (MDI) canister in the ventilator circuit. A: Collapsible spacer chamber. B: Aerosol cloud enhancer, wherein the aerosol plume is directed away from the patient. C: Noncollapsible spacer chamber. D: Bi-directional actuator (Mini Spacer). E: In-line adapter. (From Reference 21, with permission.)

pressure-controlled or volume-controlled ventilation.<sup>31</sup> The breath-triggering mechanism does not significantly influence drug delivery from an MDI.<sup>30</sup>

**Heat and Humidity in the Ventilator Circuit**

Heating and humidification of gas in the ventilator circuit is needed to prevent drying of the airway mucosa. Several investigators have found that drug delivery to the lower respiratory tract from pMDIs is reduced by 40% or more in a humidified (compared to a dry) circuit (Fig. 6).<sup>3,27,32,33</sup> Although circuit humidity reduces drug delivery, bypassing the humidifier is not recommended for routine inhalation therapy in ventilator-supported patients.

**Density of the Inhaled Gas**

The density of the inhaled gas influences deposition of aerosol in the lung.<sup>34,35</sup> High inspiratory airflows are often employed during mechanical ventilation. Such high flows are associated with turbulence, and inhalation of a less dense gas, such as helium-oxygen mixture, makes airflow less turbulent and more laminar. The use of helium-oxygen mixtures improves drug delivery in a pediatric model of mechanical ventilation.<sup>35</sup> In a bench model of adult

mechanical ventilation, drug delivery from an MDI was noted to be 50% higher with an 80% helium/20% oxygen mixture than with oxygen,<sup>36</sup> and drug delivery was inversely correlated with the density of the gas mixture (Fig. 7).

**Endotracheal Tube Size**

The ETT poses another impediment to drug delivery in mechanically ventilated patients. Earlier investigators over-emphasized the impediments created to aerosol delivery via the artificial airway, probably because the aerosol generator was placed too close to the artificial airway. Impaction of aerosol in the ETT is certainly of concern in neonatal and pediatric ventilator circuits, with whom the inner diameter of the artificial airway is 3–6 mm.<sup>37,38</sup> However, nebulizer efficiency with ETTs of inner diameter 7 mm was similar to that with ETTs of 9 mm inner diameter.<sup>39</sup> When the aerosol generator is placed at a distance from the ETT instead of being directly connected to it, drug losses in the ETT are minimized.<sup>40</sup> Overall, in adult mechanical ventilation the type of aerosol generator and the ventilator parameters have a greater influence on aerosol deposition within the ETT than the diameter of the ETT per se.<sup>40</sup> Some investigators attached a long catheter to the nozzle of an MDI and delivered aerosol directly into the trachea

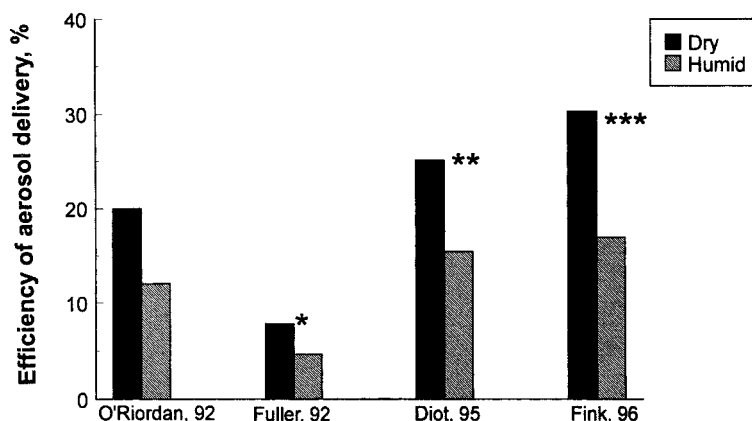


Fig. 6. Efficiency of aerosol delivery to the lower respiratory tract in bench models of mechanical ventilation with dry (dark shaded bars) and humidified (light shaded bars) ventilator circuits. The delivery of aerosol to the major airways is reduced by about 40% when the circuit is humidified. The numbers after the authors' names indicate the years of publication of the studies.<sup>27,30,32,39</sup> The study by O'Riordan and colleagues was conducted with a nebulizer, whereas the other investigators employed metered-dose inhalers (MDIs). Both nebulizers and MDIs were tested by Diot and coworkers. \*  $p < 0.05$ . \*\*  $p < 0.01$ . \*\*\*  $p < 0.001$ . (From Reference 20, with permission.)

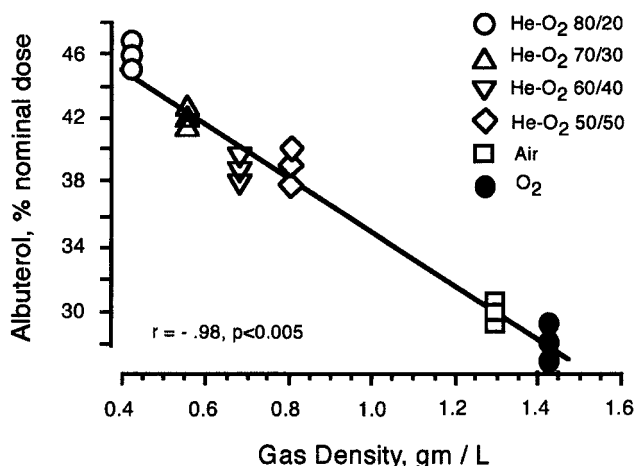


Fig. 7. Albuterol delivery from a metered-dose inhaler to filters placed at the ends of bronchi, as a function of gas density. Eight puffs (720  $\mu\text{g}$ ) of albuterol were administered into a chamber spacer during controlled ventilation in an unheated, dry ventilator circuit containing either air, oxygen, or one of several mixtures of helium and oxygen (80%/20%, 70%/30%, 60%/40%, 50%/50%). Values of albuterol delivered are expressed as a percent of the nominal dose. Albuterol delivery was inversely related to gas density in the ventilator circuit ( $r = -0.98$ ,  $p < 0.005$ ); the highest aerosol delivery occurred with the lowest density gas (ie, with the 80/20 helium-oxygen mixture). (From Reference 36, with permission.)

(ie, beyond the ETT).<sup>41</sup> With this delivery system, concerns have been raised about mucosal damage induced by propellants, surfactant, or other constituents of the MDI formulation.<sup>42</sup> The catheter also tends to become blocked after only a few actuations from an MDI.

On the basis of in vitro studies, the technique of administration of a pMDI in mechanically ventilated patients is shown in Table 3. When these techniques are employed, the variations in drug delivery<sup>3,10,21,25,27,30,41,43,44</sup> can be

Table 3. Optimal Technique for Drug Delivery via MDI in Mechanically Ventilated Patients

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

MDI = metered-dose inhaler  
HME = heat-and-moisture exchanger

minimized. Approximately 16% of the nominal dose of drug in an MDI could be delivered to the lower respiratory tract in a humidified ventilator circuit. Fink and colleagues reported that approximately 5% of the nominal dose of albuterol administered via MDI is exhaled by mechanically ventilated patients,<sup>3</sup> compared to  $< 1\%$  exhaled in ambulatory patients.<sup>45</sup> Thus, in vitro studies estimate that the lung dose of a drug administered from an MDI in a humidified ventilator circuit is approximately 11% of the nominal dose.

### In Vivo Studies of Drug Deposition From pMDIs

Gamma scintigraphy has been employed as a noninvasive method to assess total and regional lung deposition. Fuller and co-workers<sup>26,32</sup> estimated aerosol deposition in the lower respiratory tract in mechanically ventilated patients. About 6% of the dose was deposited in the lower

respiratory tract, a value significantly lower than that reported with an MDI and spacer in nonintubated ambulatory patients (10–20%).<sup>46,47</sup> However, quenching of radioactivity by the tissues of the chest wall<sup>26</sup> was not accounted for by these investigators. When a correction is made for this factor, deposition in the lower respiratory tract is also approximately 11%. Thus, in vitro data obtained with humidified ventilator circuits (see above) and in vivo gamma scintigraphic studies reveal comparable values for lung deposition (approximately 11%) after administration of the drug with a pMDI and spacer chamber in the setting of mechanical ventilation.

Drug pharmacokinetic studies with plasma and urine could be employed to estimate drug delivery to the lower respiratory tract of ventilator-dependent patients. Unlike nonintubated patients, direct deposition of aerosol in the oropharynx and subsequent enteral absorption cannot occur in mechanically ventilated patients. Therefore, estimation of plasma levels of drugs administered via MDI should reflect lower-respiratory-tract deposition, even though the site of aerosol deposition cannot be determined. Duarte and colleagues<sup>48</sup> found that administration of albuterol with an MDI and spacer produced peak serum levels in mechanically ventilated patients that were similar to those in healthy control subjects, although the area under the concentration-time curve was marginally lower in the patients than in the controls. Marik and colleagues<sup>49</sup> measured urinary albuterol excretion in 30 mechanically ventilated patients with normal renal function. They found that albuterol recovery in the urine was significantly influenced by the technique of drug administration. The highest recovery of albuterol (38%) occurred after administration with an MDI and chamber spacer, recovery after nebulizer administration (16%) was intermediate, and the lowest recovery (9%) was observed after albuterol administration with an MDI and right-angle port connected to the ETT.<sup>49</sup>

The findings from radionuclide studies and pharmacokinetic studies have verified the somewhat decreased efficiency of aerosol deposition in the lower respiratory tract of ventilator-supported patients; nevertheless, satisfactory deposition can be obtained when the technique of administration is carefully regulated.

### Therapeutic Use of pMDIs During Mechanical Ventilation

#### Bronchodilator Therapy

Bronchodilators are one of the most commonly used drugs in ventilator-supported patients with asthma or chronic obstructive pulmonary disease (COPD).<sup>50</sup> The use of MDIs to deliver bronchodilators has been steadily increasing over the past decade. One survey found that the majority of reporting centers (57%) were using MDIs for

Table 4. Bronchodilators Administered via pMDI in Mechanically-Ventilated Patients\*

Bronchodilator	Formulation	Dose (μg/puff)	Recommended Dose and Frequency†
<i>β-adrenergic</i>			
Albuterol	CFC	100	4–6 puffs every 3–6 h
Albuterol sulfate	HFA	100	4–6 puffs every 3–6 h
<i>Anti-cholinergic</i>			
Ipratropium bromide	CFC	18	4–6 puffs every 3–6 h
<i>Combination</i>			
Albuterol sulfate + Ipratropium bromide	CFC	100/18	4–6 puffs every 3–6 h

pMDI = pressurized metered-dose inhaler

\*Commonly employed bronchodilator aerosols administered via pMDI to mechanically-ventilated patients in the United States are shown

†The doses indicated are those employed in stable, mechanically-ventilated patients. Higher doses may be required for patients experiencing episodes of acute bronchoconstriction.

CFC = chlorofluorocarbon

HFA = hydrofluoroalkane

bronchodilator therapy in neonates, and the proportion of MDI use had steadily increased since 1988.<sup>51</sup> Similar data are not available for adults; however, the frequency of use of MDIs for bronchodilator therapy in adult mechanical ventilation is likely to be higher than that in neonates.

The goals of bronchodilator therapy are to reverse bronchoconstriction, decrease the work of breathing, and/or relieve dyspnea. A response to bronchodilator administration has been observed after administration of either aerosolized  $\beta$ -adrenergic<sup>23,28,52–66</sup> or anti-cholinergic bronchodilators.<sup>52,54,67,68</sup> Inhaled isoproterenol,<sup>52,69</sup> isoetharine,<sup>70</sup> metaproterenol,<sup>53</sup> fenoterol,<sup>62</sup> and albuterol<sup>23,55–61,63–66</sup> have been reported to produce significant bronchodilation when administered to mechanically ventilated patients. The combination of fenoterol and ipratropium bromide was shown to be more effective than ipratropium in a group of ventilator-supported patients with COPD.<sup>71</sup> In the United States, the various bronchodilator MDIs that are available for use in ventilator-dependent patients and their recommended doses are shown in Table 4. The combination MDI that contains albuterol sulfate and ipratropium bromide is commonly employed for bronchodilator therapy in ventilator-supported patients. Long-acting bronchodilators, such as salmeterol, have been employed in mechanically ventilated patients, but the MDI formulation of salmeterol is no longer available in the United States. Thus, at the present time, no long-acting bronchodilator is available for use in mechanically ventilated patients. Recently, the MDI formulation of levalbuterol was approved by the Food and Drug Administration; however, there are no published clinical studies on its use in mechanically ventilated patients.

**Selection of Patients.** Bronchodilator therapy is administered as a routine to most chronically ventilator-



Table 5. Indications for Bronchodilator Therapy in Patients Receiving Mechanical Ventilation

1. Asthma
2. Chronic obstructive pulmonary disease
3. Acute bronchospasm or wheezing
4. Elevated airway resistance
5. Dynamic hyperinflation
6. Difficulty in weaning
7. Chronic ventilator dependence

dependent patients (Table 5). Based on the response of ambulatory patients with asthma and COPD to bronchodilators, these patients are obvious candidates for bronchodilator therapy during mechanical ventilation. Patients with exacerbations of asthma and COPD often receive high-dose bronchodilator therapy. A significant decrease in airway resistance and intrinsic positive end-expiratory pressure (PEEP) occurs after administration of bronchodilators via pMDI to mechanically ventilated patients with COPD.<sup>23,28,54,57,58,61,63,65–68</sup> Bronchodilators have been successfully used to treat acute “bronchospasm” in the operating room,<sup>52,69,70</sup> and they are widely used in mechanically ventilated patients with severe asthma.<sup>72</sup> In addition, a heterogeneous group of mechanically ventilated patients, including some patients without a previous diagnosis of airway obstruction, have shown improvement in their expiratory airflow after bronchodilator administration.<sup>53</sup> Bronchodilators may also benefit patients with COPD who are having difficulty in weaning from the ventilator.<sup>56</sup>

**Technique of Administration.** Similarly to ambulatory patients, the technique of administration of MDIs in ventilator-supported patients requires careful execution of several steps in sequence. The steps involved in use of MDIs in mechanically ventilated patients are different from those employed in ambulatory patients. The optimal technique of administration of MDIs in mechanically ventilated patients is shown in Table 3. When this technique is employed, substantial drug deposition is achieved in the lung and a clinically meaningful response is observed.

**Bronchodilator Efficacy.** The response to bronchodilator administration depends on several variables, including the patient’s airway geometry, the degree of airway responsiveness, severity of disease, quantity of airway secretions, and counter-regulatory effects of airway inflammation and other drugs. The response to bronchodilator administration can be assessed by clinical variables (relief of dyspnea, reduction in respiratory rate or wheezing, improvement in hemodynamics, improved patient-ventilator synchrony, reduced pressure requirements for ventilation) and objective measurements of lung mechanics. Most in-

vestigators 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.<sup>73,74</sup> Similarly, airway occlusion at end-expiration results in an increase in airway pressure to a plateau value that signifies the amount of intrinsic PEEP (see Fig. 2).<sup>75</sup> Comparisons of the airway resistance and intrinsic PEEP prior to drug administration, with the post-bronchodilator values at 10–30 min after drug administration, are useful indices for assessing the therapeutic response.

Most mechanically ventilated patients with COPD demonstrate a decrease in airway resistance and intrinsic PEEP following bronchodilator administration with a pMDI.<sup>57,59,61,63</sup>

**Duration of Bronchodilator Response.** In stable mechanically ventilated patients with COPD, the bronchodilator effect of albuterol is sustained for 2–3 hours.<sup>23,66</sup> Thus, in contrast to the every-6-hours and as-needed albuterol dosing schedule in ambulatory patients, mechanically ventilated patients may require an every-3-to-4-hour dosing schedule with albuterol to sustain a bronchodilator response.

**Dose Response to Bronchodilator Administration in Mechanically Ventilated Patients.** Few investigators have examined the dose response to bronchodilators administered via MDI in mechanically ventilated patients.<sup>23,28,57</sup> In mechanically ventilated patients with COPD, we administered 4, 8, and 16 puffs of albuterol with an MDI and cylindrical spacer.<sup>28</sup> A significant decrease in airway resistance was observed after administration of 4 puffs, with no additional effect after cumulative doses of 12 and 28 puffs (Fig. 8). In a separate group of patients with COPD, the bronchodilator effect of a single dose of 4 puffs of albuterol was sustained for at least 60 min.<sup>29</sup> In a study with a randomized, crossover design, Duarte and co-workers<sup>23</sup> found that the response to 4 doses of albuterol with a pMDI was comparable to that obtained with 10 doses from a pMDI or 2.5 mg administered via nebulizer (Fig. 9). In summary, when the technique of administration is carefully executed, the majority of stable mechanically ventilated patients with COPD achieved near maximal bronchodilation following administration of 4 puffs of albuterol. Patients with exacerbations of asthma or COPD may require higher doses of inhaled bronchodilators, but further studies are needed to establish a dosing schedule in such patients.

**Drug Toxicity.** Higher doses of  $\beta$  agonists delivered via pMDI can cause adverse effects because of the systemic absorption of the drug or propellants. The potential for hypokalemia and atrial and ventricular arrhythmias must

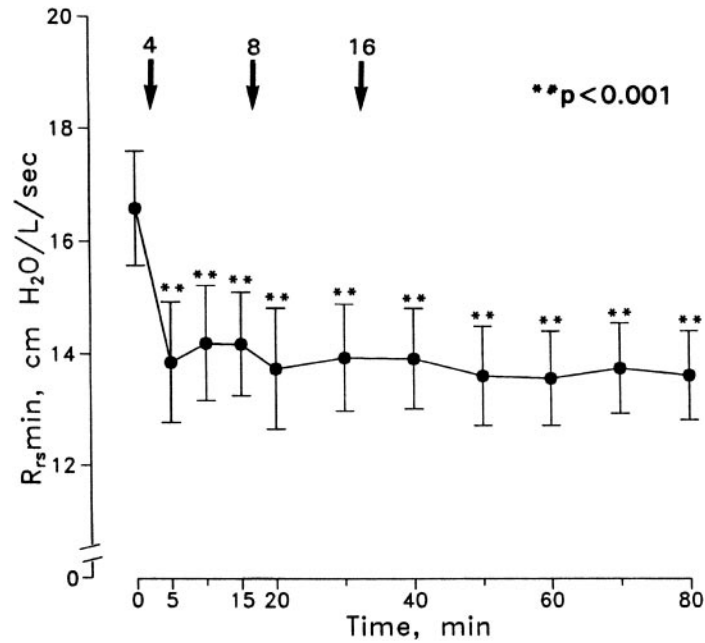


Fig. 8. Effect of albuterol on minimum inspiratory resistance ( $R_{rs\min}$ ) in 12 stable, mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). Significant decreases in  $R_{rs\min}$  occurred within 5 min of administration of 4 puffs of albuterol. The addition of 8 and 16 puffs (cumulative doses of 12 puffs and 28 puffs, respectively) did not achieve a significantly greater effect than 4 puffs ( $p > 0.05$ ). The error bars represent standard error of the mean. \*\*  $p < 0.001$ . (From Reference 20, with permission.)

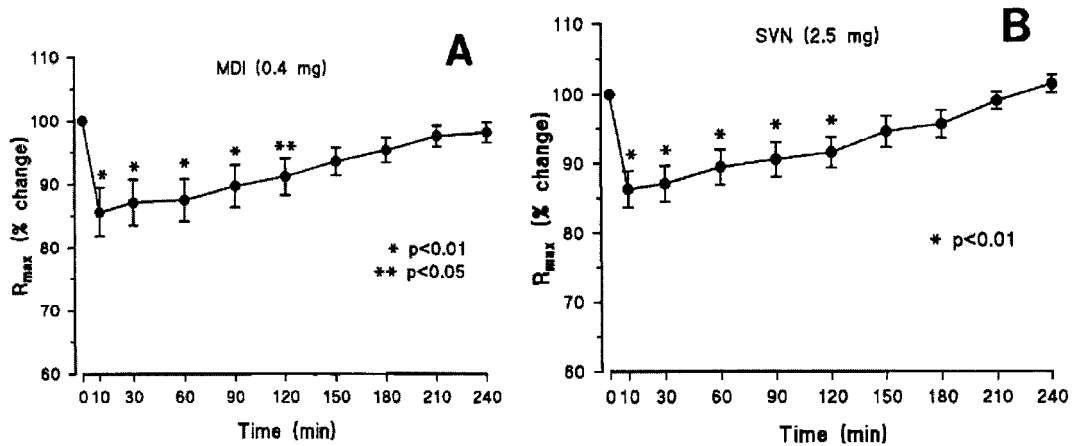


Fig. 9. Effect of albuterol on maximum inspiratory airway resistance ( $R_{\max}$ ) in stable, mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). There was a decrease in  $R_{\max}$  from baseline values within 10 min of albuterol administration. A: Change in  $R_{\max}$  from baseline (time 0) after 4 doses of albuterol from a metered-dose inhaler (MDI). B: Change in  $R_{\max}$  from baseline (time 0) after 2.5 mg of albuterol given via small-volume nebulizer (SVN). Significant reductions in  $R_{\max}$  were sustained for 2 h, and returned to baseline by 4 h. The response to albuterol administered via MDI (0.4 mg) was comparable to that achieved with 2.5 mg administered via nebulizer. The error bars represent standard error of the mean. (Modified from Reference 23, with permission.)

be borne in mind when high doses of  $\beta$  agonists are given in critically ill patients.<sup>76-78</sup> Most investigators have reported no adverse effects following administration of albuterol with an MDI.<sup>54,57,58</sup> A dose-dependent increase in heart rate, which became significant after administration of a cumulative dose of 28 puffs, has been reported.<sup>28</sup> Similarly, no significant arrhythmias or other serious cardiovascular adverse effects were observed in ambulatory

patients in an emergency department who were treated for acute asthma with up to 16 puffs each of albuterol or fenoterol administered via MDI attached to a holding chamber and face mask.<sup>79</sup> A few anecdotal reports have described cardiotoxicity due to CFCs, which are used as propellants in pMDIs.<sup>80</sup> Adverse cardiac effects are unlikely to occur with the doses recommended in clinical practice, particularly if there is a short interval between

successive doses, since CFCs have a short half life (< 40 s) in blood after administration of an MDI to healthy volunteers.<sup>81</sup> However, with a catheter connected to an MDI nozzle, a substantial portion of the total mass output of the MDI is delivered directly onto the tracheobronchial mucosa. Since CFCs constitute the majority of the total mass output of an MDI (eg, each puff of an albuterol MDI contains 100  $\mu\text{g}$  of albuterol and has a total mass of 85 mg), systemic concentrations of CFCs could reach toxic levels with this delivery system. With a catheter system, substantial quantities of oleic acid, a surfactant used in some MDI formulations, are also delivered to the respiratory tract; this may produce necrotizing inflammation and ulceration of the mucosa, as shown in mechanically ventilated rabbits.<sup>42</sup>

### Bronchodilator Therapy With pMDIs During Noninvasive Ventilation

Noninvasive positive-pressure ventilation (NPPV) is increasingly being employed for treatment of patients with acute and chronic respiratory failure.<sup>82</sup> Successful application of NPPV with a nasal or face mask can often obviate endotracheal intubation and mechanical ventilation.<sup>83–86</sup> Patients with acute or acute-on-chronic respiratory failure who are receiving NPPV often require inhaled bronchodilators for relief of airway obstruction. In a bench model, application of continuous positive airway pressure (10 cm H<sub>2</sub>O) was found to significantly reduce drug delivery from a jet nebulizer.<sup>87</sup> The ventilator settings and nebulizer position that achieved the maximum aerosol delivery with a nebulizer during NPPV was evaluated in a bench model by Chatmongolchart and colleagues.<sup>88</sup> There was a 5-fold variation (between 5% and 25% of the nominal dose) in the amount of albuterol delivered by a jet nebulizer, depending on the placement of the nebulizer in the circuit, the inspiratory and expiratory positive pressure settings, and the breathing frequency employed.<sup>88</sup> These investigators observed that the highest albuterol delivery (25%) occurred when the nebulizer was placed closer to the patient (ie, between the leak port and patient connection), the inspiratory pressure was high (20 cm H<sub>2</sub>O), and the expiratory pressure was set at a low (5 cm H<sub>2</sub>O) level.<sup>88</sup> Fauroux and colleagues<sup>89</sup> found that in children with cystic fibrosis, pulmonary deposition of radiolabeled aerosol was increased by the application of 10 cm H<sub>2</sub>O inspiratory pressure support. Patients with acute asthma exacerbations who received albuterol administered during bi-level positive airway pressure ventilation<sup>90</sup> were found to have greater improvement in peak expiratory flow than patients who received a similar dose of albuterol via nebulizer alone. The optimum settings required for maximum drug delivery with an MDI during NPPV have not been reported as yet. Nevertheless, a significant bronchodilator response was observed after albuterol was given via jet

nebulizer or via MDI to stable patients receiving NPPV with mask.<sup>87,91</sup> Both MDIs and nebulizers could be employed during NPPV, however, factors influencing drug delivery during NPPV are poorly understood and further work is needed to elucidate the optimal techniques for administering inhaled therapy during NPPV.

### Summary

Bronchodilator therapy is commonly employed in mechanically ventilated patients. Inhaled  $\beta$  agonist and anticholinergic bronchodilators are widely used in the ICU. Therapy with inhaled bronchodilators in patients receiving mechanical ventilation is complex, many factors influence the amount of drug deposition in the lower respiratory tract, and the technique of administration needs to be carefully controlled. Although DPIS could be employed in ventilator circuits, their efficiency may be reduced by the presence of humidity in the ventilator circuit. Optimal techniques for employing MDIs have been developed as a result of better understanding of the factors that influence aerosol delivery to the lower respiratory tract of ventilator-dependent patients. Important variables that influence aerosol delivery include the MDI formulation, actuation of an MDI into an in-line chamber spacer, timing of actuation, ventilator mode, tidal volume, circuit humidification, and duty cycle. With a proper technique of administration, drug deposition in the lower respiratory tract of ventilator-dependent patients is comparable to that achieved in ambulatory patients. A somewhat higher dose than that used in ambulatory patients is recommended in mechanically ventilated patients to compensate for the effects of humidity in the ventilator circuit. Typically, dose-response curves to bronchodilators in ventilator-supported patients are shallow and the duration of the drug effect is variable.

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## Discussion

**MacIntyre:** You say, “Don’t turn off the humidifier,” but you gave us a compelling argument that humidity decreases the deposition a lot, so why not turn off the humidifier? Also, how do I know what size boot I’ve got in my spacer device, to make sure to get the optimal dose? Are they labeled, or are the inches described, or is there some way I can pick the right boot? Or do manufacturers even make different-size boots for their in-line spacers?

**Dhand:** Both excellent points. The humidity aspect we say because we need humidification for these patients. Even if you were to shut off the humidifier, it would take a few minutes for the circuit to dry out. Especially with the nebulizers, the treatment might take a substantial amount of time, and we don’t want to keep giving gas that is under-humidified for a long period. At least with bronchodilators, I think it probably doesn’t matter; you can just use a higher dose. But with certain expensive drugs that will soon be employed, it might be reasonable to switch off the humidity, provided then that somebody remembers to switch it back on. I think that’s the bigger fear, that the patient might actually become constricted because their airways become really dry.

In answer to your second point, I think you have to test it out. You need to have data from in vitro studies that show that a canister and actuator are well matched and that there is a good drug output.

**MacIntyre:** Are they labeled?

**Dhand:** No, there is no labeling. But if you look at each canister, the size of the stem of the canister is different from albuterol and from flunisolide and so on. Each canister is different, and I don’t think that manufacturers are making actuators of different sizes.

**MacIntyre:** But as we go from CFC albuterol to HFA albuterol, are manufacturers of in-line adapters changing the boot size for us, or are we out of luck?

**Coppolo:**\* The MDI actuator receptacle has 2 steps, so that canisters with large and small valve stems can be accommodated

**MacIntyre:** But what about the HFAs?

**Coppolo:** Again, that has to be re-designed and redeveloped.

**Fink:** The HFAs have only been out about 5 years.

**Anderson:** I had the same question. We’re probably using the cheapest albuterol the hospital can get, which is a CFC product. What’s planned as far as actuators and cylindrical spacers for HFA albuterol? What do you recommend?

**Dhand:** I think that one of the reasons that CFCs didn’t go out right away is the mechanically ventilated and pediatric populations. As Dom Coppolo was saying, we would need to rede-

sign those actuators for that particular device.

**Smaldone:** The fact that you only need a few puffs to get the effect on a mechanically ventilated patient goes along with the overall observations for all devices that it doesn’t take a lot of drug to get an effect when you’re using a potent drug such as a bronchodilator in a mechanically ventilated patient. We’ve been doing a lot of work on humidification over the last couple of years, and we finally got a handle on this. There are humidifiers, and then there are humidifiers: just like everything else we’re dealing with.

For example, we found that the ability to transfer water to the patient’s lungs is greatly diminished if you use hot-wire humidification, versus non-hot-wire humidification. I think the *kind* of humidification profoundly affects aerosol delivery, and we’re just getting into this now. I think it’s very important for everybody to realize that jury-rigged systems are going to be unpredictable. In addition, I have no problem shutting the humidifier off for a period of time to give a treatment, to ensure that the drug gets to the patient. We’ve been administering aerosolized antibiotics with the humidifier off, with no problems.

Dean [Hess], I glanced at the paper that Rajiv [Dhand] flashed by, in which you did some comparisons using nebulizers and MDIs in different breathing modes,<sup>1</sup> and I think in that paper the nebulizers were not run to dryness, so the ventilator breathing mode, especially on a breath-actuated system, profoundly impacts the time it takes for a nebulizer to run dry. To me it’s no issue if you let the nebulizer run dry,

\* Dominic Coppolo, Monaghan Medical/Trudell Medical International, Plattsburgh, New York.

but if you don't do that, then it's obviously going to affect output. The conclusion of that paper was that when you are on pressure-controlled ventilation or something like that, then nebulizers fail to deliver. I think that's not true.

REFERENCE

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**Hess:** The issue there is that on pressure-controlled ventilation, depending on the lung mechanics, the flow to the patient stops partway through the inspiratory phase, at which point, with a nebulizer, drug can no longer be delivered to the patient.

**Smaldone:** That's correct.

**Hess:** Whereas with an MDI, it front-loads the delivery.

**Smaldone:** I agree completely with that statement. But the overall drug delivery with the nebulizer would still be markedly different if it was allowed to run. Any maneuver that reduces the duty cycle affects nebulizer treatment time if it is a breath-actuated system. If the treatment time as a variable is not addressed, then one might reach the wrong conclusion.

**Hess:** Correct, and I take your point.

**Fink:** In regards to turning off the humidifier, I think that when you are administering pMDIs of albuterol or ipratropium or other relatively inexpensive drugs, it makes more sense not to interrupt active humidification and increase the risk of bronchospasm. But when administering a more expensive drug, such as Tobi, that costs

\$100 a dose, I would probably turn off the humidifier to gain the additional 30% deposition.

**Dhand:** That's what I meant when I said that if you have more expensive drugs, then it might be appropriate to do that.

**Atkins:** Rajiv, that was a fascinating presentation. I had never really appreciated how MDIs were used in these systems. I think everyone should be aware that, essentially, albuterol CFC MDIs, either branded or generic, are all the same. They come from different suppliers but they're effectively the same formulation, valve, and actuator. The generic will be made with a proprietary actuator that differentiates the products.

But it will be dramatically different with the HFA products. There will be 3 or 4 albuterol HFA MDIs. They will have different actuator geometries. I think the Proventil has got the circular mouthpiece; the Glaxo product, and I believe the IVAX product, have the more oval-shaped actuator. The formulations are different, so characterization is going to be critical. Otherwise you may well be mis-serving patients.

**Martonen:** Regarding patient orientation, there is a collaborative study going on between my group, doing modeling, and Southampton General Hospital, doing experiments. We are addressing mechanical ventilation and we're looking at patient orientation. The work is in progress, but realizing that deposition depends on morphology, aerosol characteristics, and breathing parameters, what we've found is that deposition is markedly enhanced when the patient is lying down, compared to the upright position, which is expected from theoretical considerations.

**Fink:** As we come up with these new MDIs and aerosol devices that interface with the ventilator, the onus needs to be on the device manufacturers to fully characterize the range of drugs the devices should be used with.

**Amato:**<sup>†</sup> Regarding the changeover to HFA and the fact that the pharmaceutical companies are going to have to add dose-counting mechanisms where you won't be able to remove the can, obviously that's going to limit use of the appropriate drug and cause inability to service. There's no question that as we look toward the future—and the future is pretty well nailed, certainly for the next 12 months—it's going to be a completely different scenario. We'll be back where we were in a few years, needing new studies.

**Hess:** You didn't say anything about aerosol delivery during noninvasive ventilation.

**Dhand:** Actually, I took out those slides in the interest of time, but it will be in the paper. Certainly we haven't gotten anywhere near to understanding the *factors* that influence aerosol delivery in that population of patients, as far as I know. I know people are working on it. The current consensus appears to be that just by giving the therapy you can achieve substantial effects from bronchodilators with patients receiving mask ventilation. Certainly, we haven't gotten anywhere near to understanding the practices that influence aerosol delivery in that population of patients. I will cover that in the paper.

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