# Special Problems in Aerosol Delivery: Artificial Airways

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## Introduction

Intubation of the trachea is often required for effective mechanical ventilation. The provision of an artificial airway helps to maintain airway patency, prevent aspiration, and deliver high concentrations of oxygen. Moreover, cuffed artificial airways allow application of positive airway pressure and facilitate suctioning of the airways. Artificial airways may also be used for drug delivery either by instillation of drug solutions or by administration of drug aerosols. Aerosol therapy via artificial airways is a routine practice in mechanically ventilated patients.

Two types of artificial airways are commonly used for long-term airway management. Endotracheal tubes are preferred for initial airway management in most mechanically ventilated patients, and they are passed into the trachea through the mouth or nose. For patients requiring long-term mechanical ventilation, or in special circumstances that preclude the use of endotracheal tubes, a tracheostomy tube is passed through a surgically created stoma in the anterior wall of the trachea. Endotracheal and tracheostomy tubes each have some standard features, but a number of variations to this basic design are found among artificial airways used in clinical practice.[1]

The presence of an artificial airway influences extrathoracic dead space, air flow turbulence, and airway resistance. The normal extrathoracic dead space (~75 mL) is decreased by approximately 60 mL when a 25-cm-long endotracheal tube with an internal diameter of 8 mm is used.[2] The artificial airway is the narrowest portion of the ventilator circuit and thus the site of the highest resistance to air flow.

Figure 1 shows the relationship of the pressure drop across endotracheal tubes of various diameters with gas flow. The slope of the graph of pressure versus flow is the resistance. The dramatic rise in resistance at high flows is characteristic of turbulent air flow.[3] Under conditions of laminar air flow, airway resistance is proportional to $1/r^4$, where r is the radius of the airway, whereas it is proportional to $1/r^5$ when air flow is turbulent.[3] Thus, the resistance of a 6 mm internal diameter endotracheal tube is 4.2 times higher than that of an 8 mm internal diameter endotracheal tube. The narrow diameter of endotracheal tubes, compared to the normal upper airway, and the high inspiratory air flows typically employed during mechanical ventilation predispose to turbulent air flow and higher airway resistance in intubated than in nonintubated patients.

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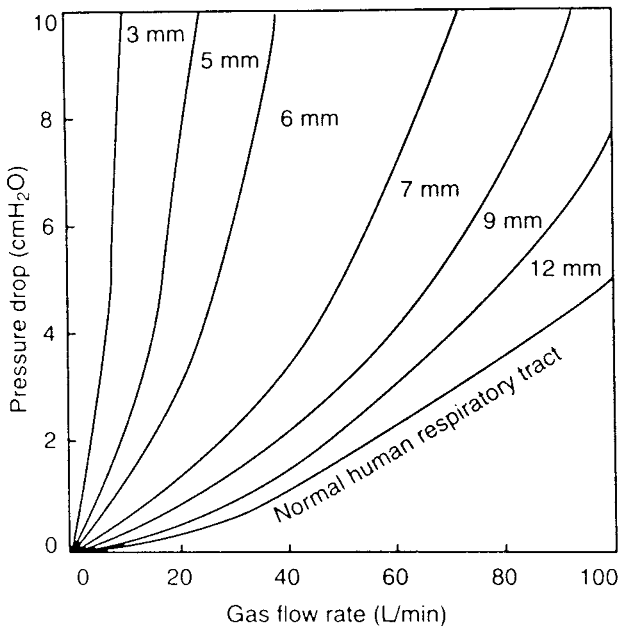


Fig. 1. Pressure drop across various sizes of endotracheal tube versus gas flow. (From Reference 3, with permission.)

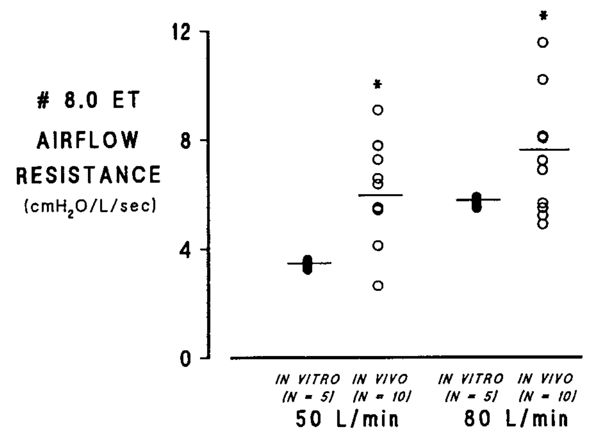


Fig. 2. Endotracheal tube resistance (average of inspiratory and expiratory resistance) at inspiratory flows of 50 and 80 L/min. The endotracheal tube resistance measured in vivo was higher than that measured in vitro, at both inspiratory flows. (From Reference 9, with permission.)

Both these factors are known to have a significant influence on aerosol deposition in the lung.

In spontaneously-breathing normal subjects, aerosol delivery to the lung is significantly lower at an inspiratory flow of 120 L/min than at 30 L/min.[4] Similarly, narrowing of the airways in patients with obstructive airways disease results in a greater aerosol deposition in the central airways.[5,6] In intubated, mechanically ventilated patients, endotracheal tubes produce significant airway resistance,[7] and the endotracheal tube resistance is dependent on inspiratory air flow.[8] Airway resistance due to endotracheal tubes in intubated patients may be higher than that measured in vitro with tubes of similar diameter.[9] Wright et al found that the mean air flow resistance with an endotracheal tube of internal diameter 8 mm was approximately 2.0–2.5 cm $H_2O$/L/s higher in vivo than the corresponding in vitro measurements (Fig. 2).[9] In view of the effects of an endotracheal tube on air flow resistance and turbulence, significant aerosol loss within the endotracheal tube is to be expected during mechanical ventilation.

MacIntyre et al found that only 2.9 $\pm$ 0.7% of nebulized $^{99m}$technetium-labeled diethylenetriamine pentaacetic acid deposited in the lungs of mechanically ventilated patients,[10] whereas 1.6 $\pm$ 1.1% deposited in the distal 25–33% of the endotracheal tube. The values for pulmonary deposition were significantly lower than the values (10–14%) for pulmonary deposition reported for ambulatory patients.[11,12] On the basis of the ground-breaking study by MacIntyre et al, as well as other investigations, aerosol delivery in mechanically ventilated patients was thought to be significantly lower than in nonintubated patients.[13] The decreased efficiency of aerosol delivery during mechanical ventilation was largely attributed to the effects of the endotracheal tube, alluded to above. However, recent research has highlighted that several factors interact to influence aerosol deposition in intubated patients (Fig. 3).[14] The effects of aerosol deposition within artificial airways on aerosol delivery during mechanical ventilation need to be viewed in light of this new information.

Table 1 lists the factors that could influence aerosol deposition within artificial airways. One group of investigators who compared pulmonary deposition of $^{99m}$technetium-labeled fenoterol administered via metered-dose inhaler (MDI) with spacer (4 puffs) found no difference in aerosol delivery between tracheostomy and endotracheal tubes (6.1 $\pm$ 2.8 vs 4.6 $\pm$ 3.0%, respectively, $p < 0.12$).[15] Although response to bronchodilators administered via endotracheal or tracheostomy tubes has not been directly compared, obvious differences have not been observed in clinical studies, and fewer patients are ventilated with tracheostomy tubes than with endotracheal tubes. Therefore, most of the data regarding the influence of artificial airways on aerosol delivery pertain to endotracheal tubes.

## Factors Influencing Aerosol Delivery through Endotracheal Tubes

The characteristics of the tube and other factors that influence aerosol deposition in mechanically ventilated patients[14] interact in determining drug deposition within an artificial airway. Minimizing aerosol losses within artificial airways could lead to greater pulmonary deposition of drug in mechanically ventilated patients.

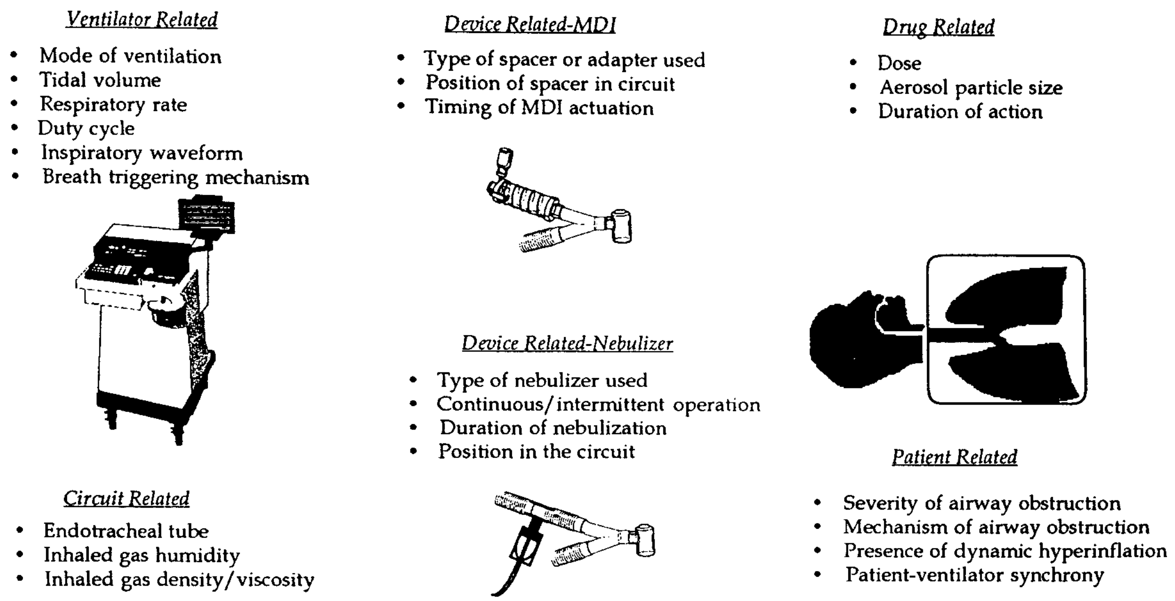


Fig. 3. Factors influencing aerosol deposition in mechanically ventilated patients. (From Reference 14, with permission.)

## Endotracheal Tube Size

Several investigators have attempted to determine the influence of endotracheal tube size on aerosol delivery. Ahrens et al compared aerosol delivery with two nebulizers through endotracheal tubes of internal diameter 3, 6, and 9 mm.[16] They used continuous air flows (rather than cyclic flows) of 7.5, 10, 22.5, and 50 L/min through a simulated ventilator circuit. Table 2 summarizes their results with air flows of 22.5 and 50 L/min. This investigation is often quoted in support of the view that aerosol deposition is higher in endotracheal tubes of smaller diameter. However, it is obvious that the inspiratory air flow and particle distribution within the aerosol had a greater influence on aerosol delivery than the size of the endotracheal tube per se.

Another group of investigators identified several factors that influence aerosol delivery from nebulizers during mechanical ventilation.[17] They noted that aerosol delivery through an endotracheal tube of internal diameter 7 mm did not differ significantly from that observed with a 9 mm tube (Table 3). Once again, the type of nebulizer used had a much greater influence on aerosol delivery than the size of the endotracheal tube.[17] In an infant model of mechanical ventilation (endotracheal tube diameter 3.5 mm), 0.7 ± 0.1% and 0.4 ± 0.2% of the nominal dose placed in a nebulizer deposited in the endotracheal tube at inspiratory flows of 5 and 8 L/min, respectively, whereas the losses in the inspiratory tubing were 34.7 ± 0.7% and 43.7 ± 4.9%, respectively.[18]

Table 1. Factors Influencing Aerosol Deposition through Artificial Airways

| |
|---|
| Type: endotracheal or tracheostomy tube |
| Material: polyvinylchloride (PVC), silicone, or metal |
| Size |
| Electrostatic charge |
| Aerosol generator: metered-dose inhaler or nebulizer |
| Ventilator settings: tidal volume, breathing frequency, duty cycle |
| Ventilator circuit: humidity, temperature, density of inhaled gas |

Table 2. Influence of Endotracheal Tube Size and Air Flow on Aerosol Delivery via Nebulizer

| Device | Air Flow (L/min) | ET diameter (mm) | % Deposition* in ET | % Deposition* in Lung |
|---|---|---|---|---|
| Fan Jet† | 22.5 | 3 | 10.3 | 8.8 |
| | | 6 | 30.9 | 25.0 |
| | | 9 | 25.0 | 54.4 |
| | 50 | 6 | 22.1 | 17.6 |
| | | 9 | 19.1 | 30.9 |
| Ultravent‡ | 22.5 | 3 | 14.7 | 76.5 |
| | | 6 | 1.5 | 94.1 |
| | | 9 | 0 | 99.0 |
| | 50 | 6 | 7.4 | 85.3 |
| | | 9 | 1.5 | 92.6 |

ET = endotracheal tube
*Percent of nebulizer output (not nominal dose).
†Fan Jet mass median aerodynamic diameter = 3.95 $\mu$m.
‡Ultravent mass median aerodynamic diameter = 0.54 $\mu$m.
Nebulizers operated with flow of 7.5 L/min.
(Data from Reference 16.)

Table 3. Influence of Endotracheal Tube Size on Pulmonary Delivery and Aerosol Characteristics

| Device | $V_T$ (mL) | % Deposition* | | MMAD (GSD) | |
|---|---|---|---|---|---|
| | | ET (7 mm) | ET (9 mm) | ET (7 mm) | ET (9 mm) |
| Aerotech II | 1,000 | 37 | 32 | 1.1 (1.6)† | 1.1 (1.6) |
| | 700 | 26 | 25 | — | 1.1 (1.6)† |
| Power Mist | 1,000 | — | 11 | 1.3 (2.0)† | 1.1 (1.7) |
| Twin Jet | 1,000 | 18 | — | — | 0.6 (1.9) |

*These are the highest/near highest values of "lung" delivery obtained with each device after operation for 20 minutes. Aerosol delivery was negligible with the Respirgard II.
MMAD = mass median aerodynamic diameter. GSD = geometric standard deviation. $V_T$ = tidal volume. ET = endotracheal tube.
†Volume fill 3 mL; other tests with a volume fill of 2 mL.
Controlled mechanical ventilation: respiratory rate = 20 breaths/min, inspiratory flow = 40 L/min, ratio of inspiratory time to total time = 0.5, dry circuit.
(Data from Reference 17.)

With MDIs, one group of investigators found that differences in aerosol deposition depended on the size of the endotracheal tube,[19] whereas another group did not[20] (Table 4). Both groups of investigators used a swivel adapter connected to the endotracheal tube to actuate the MDI. Despite seemingly similar methods of aerosol delivery and analysis, significant differences in the delivery across 6 mm endotracheal tubes were observed (see Table 4). Clearly, the size of the endotracheal tube influences aerosol deposition, but the effect is variable, and other factors appear to have a greater impact on overall aerosol delivery.

## Endotracheal Tube Material/Design

Endotracheal tubes may be made of polyvinylchloride (PVC) or silicone, whereas tracheostomy tubes are made of PVC, silicone, or silver. The material used to manufacture artificial airways is likely to alter aerosol deposition on the inner walls of the tube. However, to the best of my knowledge, the influence of the tube material/design on aerosol deposition within artificial airways has not been investigated.

Table 4. Influence of Endotracheal Tube Size on Aerosol Delivery with Metered-Dose Inhalers

| Air Flow (L/min) | ET (mm) | % Deposition* | |
|---|---|---|---|
| | | Filter | ET |
| 30† | 3 | 2.5 | 45.7 |
| | 5 | 10.7 | 43.7 |
| | 6 | 12.3 | 40.1 |
| 20‡ | 6 | 4.0 | 52.0 |
| | 9 | 10.0 | 30.0 |
| 60‡ | 6 | 5.0 | 57.0 |
| | 9 | 11.0 | 40.0 |

ET = endotracheal tube.
*Percent of nominal dose (by weight) of metaproterenol[19] or albuterol[20] administered with a swivel adapter connected to the ET. Metered-dose inhaler actuated into a continuous flow of air.
†Data from Reference 20.
‡Data from Reference 19.

## Endotracheal Tube Electrostatic Charge

Artificial airways in common clinical use are made of PVC. These tubes are rigid initially, to facilitate insertion, but they become softer at body temperature. The electrostatic charge on the inner walls of PVC tubes attracts aerosol particles. Preliminary investigations in our laboratory (Fink JB, unpublished data, 2000) were carried out with albuterol delivered via MDI and cylindrical spacer (Aerovent) placed 15 cm from the endotracheal tube (the usual setup for administration of bronchodilator aerosols). Washing the endotracheal tube with soap increased aerosol delivery to the distal end of the endotracheal tube, compared to a dry tube (28.3 ± 1.6 vs 33.5 ± 1.0% of the nominal dose in dry and washed conditions, respectively). Reduction of electrostatic charge on the inner walls of the tube is expected to decrease aerosol deposition in the endotracheal tube, but this was not determined directly. Further investigations are needed to determine the extent of aerosol loss due to electrostatic charge within endotracheal tubes.

## Aerosol Generator

The type of aerosol generator used, whether a nebulizer or MDI, influences aerosol delivery during mechanical ventilation.[21] Fuller et al administered 4 puffs of fenoterol radiolabeled with $^{99m}$technetium pertechnate via MDI and cylindrical spacer placed in the inspiratory limb of the ventilator circuit of 7 patients. Another group of 9 patients were randomized to receive fenoterol solution containing $^{99m}$technetium sulfur colloid. A Bennett Twin-jet nebulizer was used to nebulize the solution during the inspiratory phase, for a total of 15 minutes. Pulmonary deposition with the MDI and spacer (5.65 ± [SE] 1.1%) was significantly greater than that with the nebulizer (1.22 ± 0.4%).

Table 5. Aerosol Delivery from Nebulizers Versus Metered-Dose Inhalers with Holding Chambers

| Device | Position (cm) | Radiolabel | % Deposition | | Device |
|---|---|---|---|---|---|
| | | | Filter | ET | |
| MDI + large chamber | 22 | fenoterol with $^{99m}TcO_4$ | 30.3 ± 7.4 | NA | NA |
| MDI + small chamber | 22 | fenoterol with $^{99m}TcO_4$ | 27.7 ± 5.1 | 5.9 ± 2.0 | NA |
| Bennett nebulizer | 70 | $^{99m}$Tc-sulfur colloid in saline | 4.6 ± 2.1* | 2.3 ± 1.0 | 58.7 ± 9.6 |
| Ultravent nebulizer | 70 | $^{99m}$Tc-sulfur colloid in saline | 1.3 ± 0.4* | NA | 80.9 ± 1.4 |

Values are means ± SD of 8–11 experiments.
ET = endotracheal tube. MDI = metered-dose inhaler. $^{99m}TcO_4$ = $^{99m}$technetium pertechnate. NA = not available. $^{99m}$Tc-sulfur = $^{99m}$technetium-labeled sulfur colloid.
*$p < 0.05$, compared to MDI with chamber.
Controlled mechanical ventilation: tidal volume = 700 mL, respiratory rate = 12 breaths/min, inspiratory flow = 50 L/min, humidified circuit at 31–33°C, ET = 8 mm.
(Data from Reference 22.)

The absolute values for deposition reported in this study have been debated, but higher pulmonary deposition of aerosol with MDI and spacer than with jet nebulizer was corroborated by most subsequent investigations. For example, Fuller et al determined the amount of radioactivity depositing on a filter in a bench model of mechanical ventilation.[22] They found a significantly higher deposition of radioactivity on the filter with the MDI and spacer than with the nebulizer (Table 5). Moreover, the lower deposition with the nebulizer could not be explained by increased aerosol loss in the endotracheal tube. On the other hand, Diot et al reported equivalent delivery of albuterol aerosol with a jet nebulizer and MDI with spacer.[23] In a dry ventilator circuit, the amount of drug delivered with optimal use of an Aerotech II nebulizer was equal to that delivered by an MDI and cylindrical spacer. However, Marik et al found that the systemic bioavailability of albuterol delivered by an MDI and spacer to mechanically ventilated patients was 2.5 times higher than that observed with a jet nebulizer.[24] Since the endotracheal tube precludes gastrointestinal deposition in these patients, the quantity of drug recovered in the urine indirectly reflects its pulmonary deposition.

Therefore, at the present time, the consensus is that the MDI and spacer is more efficient than the jet nebulizer for aerosol delivery to mechanically ventilated patients. Both devices achieve comparable pulmonary drug delivery, because the dose of drug placed in the nebulizer is much higher than that administered by an MDI.

## Endotracheal Tube Deposition of Aerosol from Metered-Dose Inhalers

The method of delivering aerosol with an MDI in a ventilator circuit influences the amount of aerosol depositing in the endotracheal tube and that delivered to the lower respiratory tract. Because of the complexity of studying aerosol deposition in mechanically ventilated patients, most studies were performed with bench models of mechanical ventilation. When the MDI canister was connected to the endotracheal tube with a swivel adapter, approximately 90% of the drug in the aerosol deposited in the adapter and endotracheal tube.[25] This amount could be significantly reduced by actuating the MDI in a reservoir, particularly by placing the reservoir at a distance from the endotracheal tube (Table 6).

Our investigations reveal that only a small fraction of the aerosol deposits in the endotracheal tube when the MDI is actuated into a spacer chamber in a dry ventilator circuit (Figs. 4 and 5).[26] In contrast, a higher proportion of aerosol is lost in the tube in a humidified ventilator circuit. Moreover, the amount of aerosol lost in the endotracheal tube with a hydrofluoroalkane-propelled MDI (12.4%) was similar to that with the chlorofluorocarbon-propelled MDI (12.9%), although the amount of drug exiting the spacer was significantly lower with the hydrofluoroalkane-propelled MDI than with the chlorofluorocarbon-propelled MDI (42.8 vs 60.5% in humid conditions, respectively) (see Figs. 4 and 5). Closer examination of these data reveal that similar amounts of drug entered the endotracheal tube

Table 6. Effect of the Placement of the MDI and Actuator on the Site of Aerosol Deposition

| Method of Actuation | Site of Deposition | % Deposition* | |
|---|---|---|---|
| | | Circuit | Filter |
| MDI on ET | Adapter and ET | 92.7 | 7.3 |
| MDI + spacer on ET | Spacer, circuit Y | 67.2 | 32.1 |
| | ET | 0.7 | |
| MDI + spacer in inspiratory limb | Spacer | 65.2 | 29.0 |
| | ET | 5.9 | |

MDI = metered-dose inhaler.
ET = endotracheal tube.
*Percent of albuterol deposited at each site as a percent of the nominal dose.
Controlled mechanical ventilation: tidal volume = 800 mL, respiratory rate = 12 breaths/min, sine wave flow, dry circuit, ET = 8 mm.
(Data from Reference 25.)

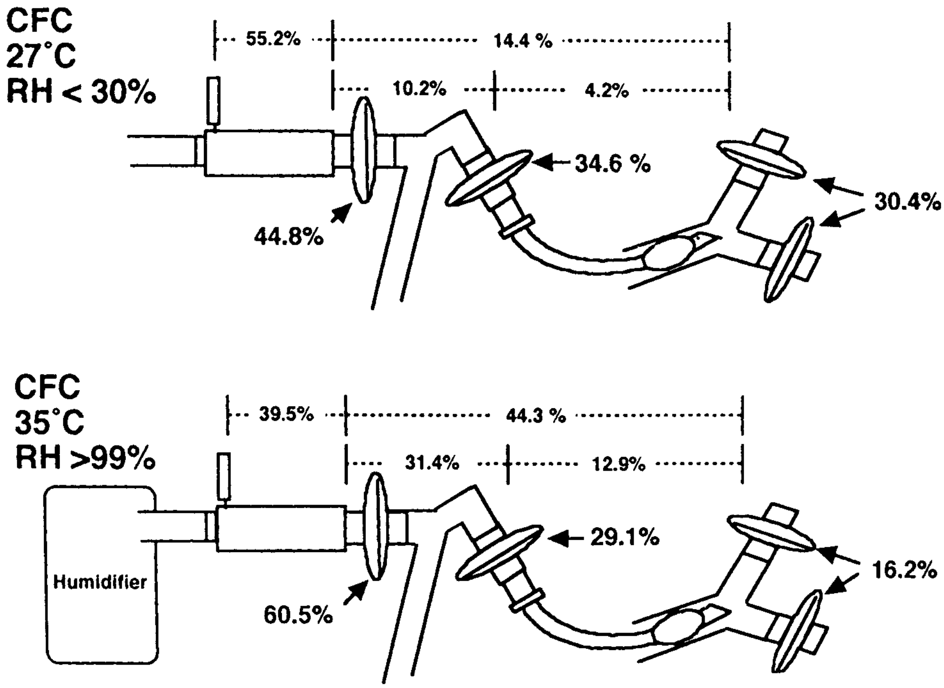


Fig. 4. Albuterol delivery, expressed as percent of the nominal dose, from a chlorofluorocarbon-propelled metered-dose inhaler was measured on filters placed distal to the spacer chamber, proximal to the endotracheal tube, and at the ends of the bronchi. Drug deposition in the spacer chamber, ventilator circuit, endotracheal tube, and tracheobronchial model was calculated under dry conditions (top panel) and humidified conditions (bottom panel). Aerosol deposition in the endotracheal tube was greater in humidified than in dry conditions (12.9% in humidified vs 4.2% in dry). (From Reference 26, with permission.)

in dry and humid conditions (34.6% and 29.1%, respectively). Therefore, aerosol loss in the endotracheal tube (4.2% in dry and 12.9% in humid conditions, a difference of ~8.5%) contributed significantly to the ~14% difference in aerosol delivery to filters placed at the ends of the bronchi (30.4% in dry and 16.2% in humidified circuits). These findings suggest that a significant proportion of the aerosol delivered by an MDI deposits within a humidified ventilator circuit. Methods to decrease aerosol loss within the ventilator circuit and endotracheal tube could substantially improve pulmonary deposition of aerosol given via MDI with spacer in mechanically ventilated patients.

## Endotracheal Tube Deposition of Aerosol from Jet Nebulizers

The efficiency of aerosol generation differs among nebulizer brands.[17] Nebulizers may be operated continuously or only during the inspiratory phase (intermittent operation). Continuous aerosol generation requires a pressurized gas source (either a wall outlet, pressurized gas cylinder, or compressor), whereas intermittent operation requires a separate line to conduct inspiratory air flow from the ventilator to the nebulizer. The aerosol generated by the nebulizer is entrained in the gas flowing through the ventilator circuit. Although the gas flow provided by the ventilator during intermittent operation is similar to that during continuous operation, the driving pressure provided by most ventilators to the nebulizer (< 15 psi) is much lower than the pressure from compressed gas sources or wall outlets (> 50 psi). Reduction in driving pressure is likely to reduce the efficiency of aerosol generation by nebulizers and also to increase the distribution of aerosol particle size. Once a critical operating pressure is achieved, intermittent operation of nebulizers is more efficient for aerosol delivery than is continuous operation, because aerosol waste during the expiratory phase is minimized.[27] Similar to MDIs, placing the nebulizer at a distance from the endotracheal tube also enhances aerosol delivery.[27]

In contrast to MDIs, deposition of nebulized aerosol within endotracheal tubes is quite low. O'Doherty et al reported the effect of various ventilator settings on aerosol delivery with a System 22 Acorn jet nebulizer.[28] The fraction of aerosol depositing on a filter placed beyond the endotracheal tube varied from 5.4% to 17.4% of the nominal dose, but the differences in tube deposition ranged from 0.6% to 2.2% (Table 7). Similarly, placing the neb-

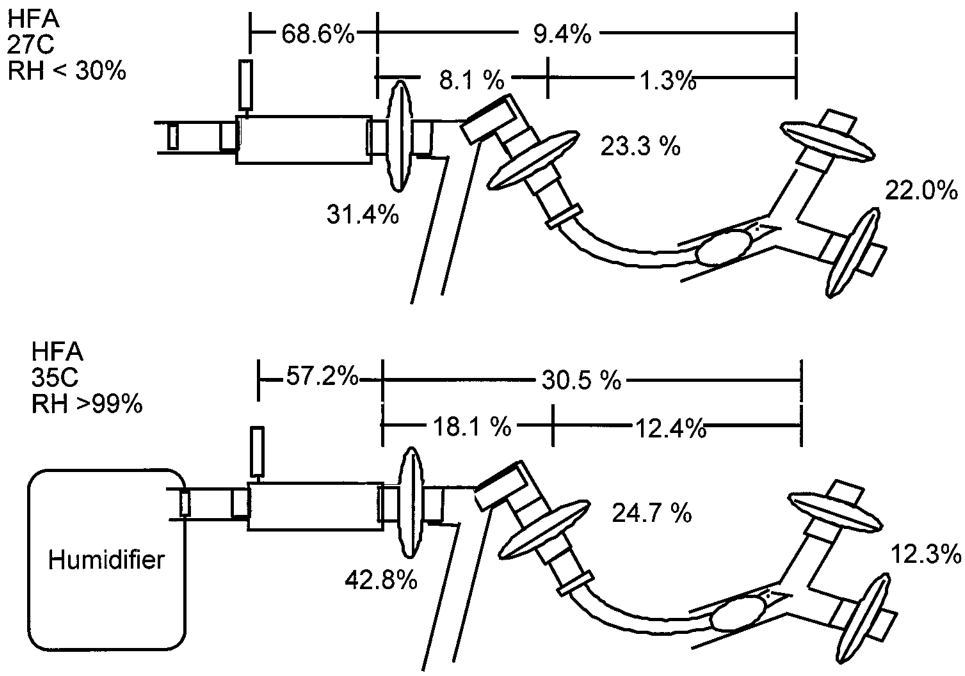


Fig. 5. Albuterol delivery, expressed as percent of the nominal dose, from a hydrofluoroalkane-propelled metered-dose inhaler was measured on filters placed distal to the spacer chamber, proximal to the endotracheal tube, and at the ends of the bronchi. Drug deposition in the spacer chamber, ventilator circuit, endotracheal tube, and tracheobronchial model was calculated under dry conditions (top panel) and humidified conditions (bottom panel). Aerosol deposition in the endotracheal tube was greater in humidified than in dry conditions (12.4% in humidified vs 1.3% in dry). (From Reference 26, with permission.)

ulizer close to the endotracheal tube produced minimal losses of aerosol within the endotracheal tube (Table 8).

Nebulization within a 600 mL spacer connected in the ventilator circuit increased pulmonary delivery of aerosol, despite a marginal increase in aerosol losses within the endotracheal tube (see Table 8). The in vitro observations were supported by subsequent investigations that showed a low (1–3% of nominal dose) deposition of nebulized aerosol within the trachea or endotracheal tube in mechanically ventilated patients.[29,30] The low deposition in the

Table 7. Effect of Ventilator Settings on Aerosol Delivery with a Nebulizer*

| Ventilator Settings: Rate (breaths/min) | $\dot{V}_E$ (L/min) | $T_I$ (%) | Deposition %: Filter | Deposition %: Trachea/ET | MMAD |
|---|---|---|---|---|---|
| 10 | 9 | 25 | 8.3 ± 0.8† | 0.6 ± 0.1 | 2.99 ± 0.42 |
| 12 | 9 | 25 | 11.2 ± 1.6† | 1.5 ± 0.1 | 3.02 ± 0.56 |
| 15‡ | 9 | 25 | 5.4 ± 0.2 | 1.9 ± 0.2 | 3.20 ± 0.40 |
| 15 | 6 | 25 | 9.9 ± 0.9† | 2.2 ± 0.5 | 3.48 ± 0.20 |
| 15 | 12 | 25 | 5.8 ± 0.3 | 2.1 ± 0.5 | 3.34 ± 0.29 |
| 15 | 9 | 20 | 5.0 ± 0.8 | 2.1 ± 0.5 | 3.54 ± 0.30 |
| 15 | 9 | 33 | 13.3 ± 0.1† | 2.2 ± 0.7 | 3.28 ± 0.20 |
| 15 | 9 | 50 | 17.4 ± 0.4† | 1.9 ± 0.5 | 3.07 ± 0.19 |

*System 22 Acorn jet nebulizer: 3 mL fill volume, pause time 10%, ET 9 mm, $^{99m}$technetium-HSA in water.
Values are expressed as mean ± standard error.
$\dot{V}_E$ = minute volume. $T_I$ = inspiratory time, percent of total breath duration. ET = endotracheal tube. MMAD = mass median aerodynamic diameter.
†$p < 0.05$, compared to default setting.
‡Default setting.
(Data from Reference 28.)

Table 8. Effect of Nebulizer Position and Spacer on Aerosol Delivery via Nebulizer

| Position | % Deposition | |
|---|---|---|
| | Filter | Trachea/ET |
| After circuit Y | 5.4 ± 0.2 | 1.9 ± 0.2 |
| Before circuit Y | 8.0 ± 0.9 | 2.6 ± 1.4 |
| With spacer* | 10.3 ± 1.3 | 3.3 ± 0.7 |

Values are expressed as mean ± standard error.
ET = endotracheal tube.
*600 mL storage chamber placed in the inspiratory limb of the ventilator circuit.
(Data from Reference 28.)

endotracheal tube may reflect the low efficiency of aerosol generation by nebulizers or may be due to the experiments being conducted in dry ventilator circuits. However, careful examination of the pattern of aerosol deposition with nebulizers produced somewhat contradictory findings. O'Riordan et al used a mass balance technique to determine the deposition of nebulized aerosol at various sites in the ventilator circuit.[31] As shown in Table 9, approximately 10% of the nominal dose from a nebulizer deposited in the tracheostomy tube of mechanically ventilated patients, with the majority of the aerosol deposition occurring during the exhalation phase of the breathing cycle (~7%).[31] Since this is the only study that evaluated aerosol deposition in the artificial airway during exhalation, it is possible that a significant proportion of the aerosol inhaled, as determined by in vitro tests, is exhaled by the patient. Further investigations are needed to assess the extent of aerosol loss in the artificial airways during exhalation, and to develop methods to minimize this loss.

## Endotracheal Tube Deposition of Aerosol with Ultrasonic Nebulizers

With ultrasonic nebulizers, a significant fraction of the aerosol generated deposits in the endotracheal tube.[32,33] The higher aerosol loss with the ultrasonic nebulizer than with the jet nebulizer occurs despite placement of the ultrasonic nebulizer at a distance of > 35 cm from the endotracheal tube (Table 10).[33]

## Influence of Gas Density on Aerosol Deposition within the Endotracheal Tube

The use of helium-oxygen mixtures, which have lower gas density than air or oxygen, are believed to reduce air flow turbulence through narrowed airways. In previous studies using various helium-oxygen mixtures, Fink et al found that aerosol delivery via MDI showed a linear increase with the decrease in gas density within the ventilator circuit.[34] The use of an 80% helium-20% oxygen mixture in a dry ventilator circuit caused a 50% increase in the amount of drug delivered to the lower respiratory tract, compared to that observed with 100% oxygen (46.1 vs 30.4%, respectively) (unpublished data). The increase in aerosol delivery with the helium-oxygen mixture was accompanied by a decrease in aerosol deposition within the endotracheal tube. Therefore, mechanical ventilation with gas mixtures having lower density than air could reduce aerosol loss within artificial airways.

## Summary

Several factors interact in influencing aerosol deposition during mechanical ventilation. Among these factors, the artificial airway is a significant barrier for aerosol deposition. Earlier studies overemphasized the impediments created by the artificial airway to aerosol delivery, because the aerosol generator was placed adjacent to the endotracheal tube or was connected to it. When the aerosol generator is placed away from the endotracheal tube, the fraction that deposits within the tube is reduced and greater aerosol deposition occurs in the lungs. The type of aerosol generator used and the ventilator settings have a greater effect than the size of the tube on the amount of aerosol that deposits in the artificial airway. To minimize aerosol loss within artificial airways, an endotracheal tube of the appropriate size should be selected. "Priming" the tube with a few doses of aerosol before use decreases the elec-

Table 9. Pattern of Deposition of Nebulized Aerosol During Mechanical Ventilation*

| Inhalation Filter | Tracheostomy Tube | | | Expiratory Filter | | | Inhaled by Patient |
|---|---|---|---|---|---|---|---|
| | Total* | Inspiration | Exhalation | Total* | Leakage | Exhaled by Patient | |
| 28.0 ± 6.0 | 9.6 ± 4.9 | 2.6 ± 0.5 | 7.0 ± 5.2 | — | — | 5.8 ± 5.4 | 15.3 ± 9.5 |

Values are means ± SE as a percent of the nominal dose of $^{99m}$technetium-human serum albumin placed in the nebulizer.
The proportion of aerosol that bypassed the tube (leakage) to deposit on the exhalation filter was not stated.
*Determined during radiolabeled aerosol administration to patients; the remaining values were obtained by in vitro testing.
Intermittent nebulization with Aerotech II placed 30 cm from the Y-piece: tidal volume = 500–1200 mL, respiratory rate = 10–16 breaths/min, ratio of inspiratory time to total time = 0.25 ± 0.09, dry circuit.
(Data from Reference 31.)

Table 10. Site of Deposition of Nebulized Aerosol during Mechanical Ventilation

| Site of Deposition | % Deposition | | |
|---|---|---|---|
| | Nebulizer* | Nebulizer + Spacer† | Ultrasonic‡ |
| Lungs | 2.3 ± 0.8 | 3.0 ± 0.8 | 5.3 ± 1.4 |
| Trachea/ET | 0.9 ± 0.5 | 1.5 ± 0.9 | 11.6 ± 3.9 |
| Exhalation filter | 11.1 ± 2.7 | 15.5 ± 1.5 | 7.5 ± 1.7 |
| Nebulizer retention | 51.5 ± 8.1 | 47.2 ± 1.0 | 29.6 ± 4.4 |
| Unaccounted (in tubing)§ | 33.7 ± 9.0 | 30.7 ± 1.5 | 40.1 ± 3.5 |

Mean ± SD of values obtained in mechanically-ventilated patients.
ET = endotracheal tube.
*Data from Reference 29 (nebulizer at Y-piece).
†Data from Reference 30 (nebulizer 12 cm from Y-piece).
‡Data from Reference 33 (nebulizer 35 cm from Y-piece).
§Values are approximations.

trostatic charge on its walls and may reduce aerosol deposition within the tube. Similarly, using a spacer with the MDI, and placement of the combination in the inspiratory limb at a distance of at least 15 cm from the endotracheal tube reduces aerosol loss within the endotracheal tube. Use of nebulizers that produce submicronic aerosols, and placing them closer to the ventilator instead of closer to the patient also decreases aerosol impaction in the artificial airway. Use of a low inspiratory flow (30–60 L/min in adults), higher duty cycle ($>$ 0.3), and helium-oxygen mixture instead of air or oxygen are other measures to reduce aerosol loss in the airway and thereby improve aerosol delivery to the lower respiratory tract of mechanically ventilated patients.

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