Expert Opinion

Effective inhaled drug administration to mechanically ventilated patients

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Inhaled therapy is commonly employed in mechanically ventilated patients with chronic obstructive pulmonary disease or asthma. The efficacy of inhaled drugs is comparable to that achieved with systemic routes of administration, but the dose of drug required to achieve a therapeutic effect is generally much smaller. Moreover, limited systemic absorption of inhaled drugs minimises systemic side effects. Aerosol administration to ventilated patients differs from that in ambulatory patients in several respects. Optimal techniques for using pressurised metered-dose inhalers and nebulisers in ventilator circuits have been developed. With these techniques, the efficiency of inhaled drug delivery in mechanically ventilated patients is now comparable to that in ambulatory patients. Pressurised metered-dose inhalers are chiefly used to deliver bronchodilator and corticosteroid aerosols, and are more efficient and convenient to use than nebulisers for routine therapy in ventilated patients. However, nebulisers are more versatile and are employed to generate aerosols of bronchodilators, corticosteroids, antibiotics, prostaglandins, surfactant and mucolytic agents. Improvements in drug formulations and the design and efficiency of aerosol generating devices have led to increasing application of inhaled therapies in mechanically ventilated patients.

Keywords: aerosol, bronchodilator, inhalation therapy, mechanical ventilation, metered-dose inhaler, nebuliser, prostanoid, surfactant

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1. Introduction

Inhaled drug therapy is routinely employed in ventilated patients, especially in those with acute exacerbations of asthma or chronic obstructive pulmonary disease (COPD). In addition to bronchodilator and corticosteroid aerosols, prostanoids, surfactant, mucolytics and antibiotics are administered to mechanically ventilated patients by the inhalation route. In ambulatory patients, pressurised metered-dose inhalers (pMDIs), nebulisers and dry powder inhalers are the aerosol-generating devices of choice for inhalation therapy. As in ambulatory patients, aerosol delivery during mechanical ventilation also depends to a great extent on the type of aerosol-generating device employed; however, only pMDIs and nebulisers have been adapted for clinical use during mechanical ventilation. Inhaled drug delivery in ventilated patients is complicated by deposition of the aerosol particles in the ventilator circuit and endotracheal tube (**Figure 1**). Moreover, several factors governing pulmonary deposition of aerosol in ventilated patients differ from those in spontaneously breathing patients. Nevertheless, when a proper administration technique is employed, inhaled drug therapy is safe, convenient and effective in patients receiving mechanical ventilation [1].

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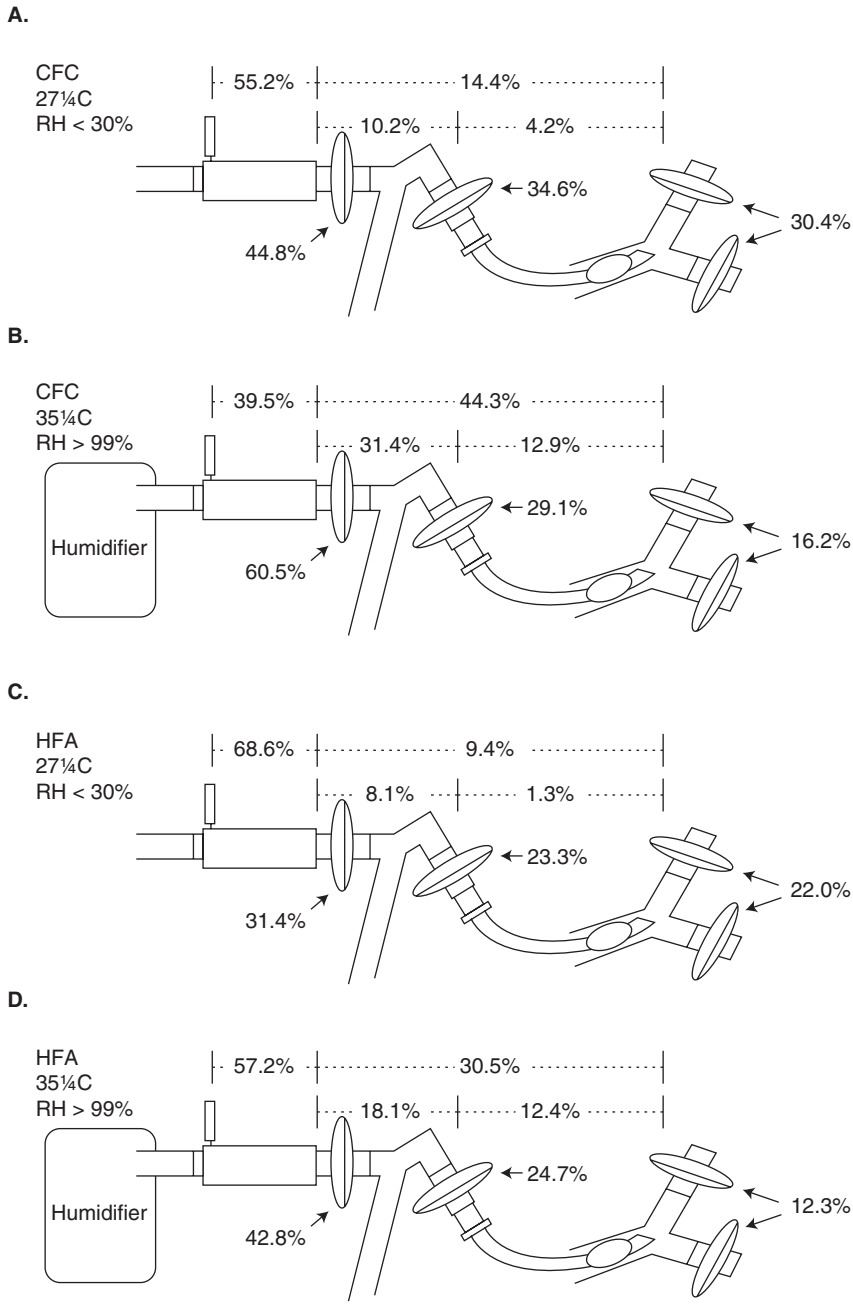

Figure 1. Drug deposition, expressed as a percentage of nominal dose of albuterol from a CFC-propelled pMDI, in the spacer chamber, the ventilator circuit, the endotracheal tube and on filters at the bronchi under dry and humidified conditions during controlled mechanical ventilation. A. Under dry conditions, 30.4% of the dose from a CFC-pMDI was deposited at the bronchi. **B.** The presence of humidity in the circuit reduced the delivery at the same site to 16.2%. **C.** With an albuterol HFA-propelled pMDI under dry conditions, 22.0% of the drug was delivered at the bronchi. **D.** The presence of humidity in the circuit reduced the delivery at the same site to 12.3%. Under both dry and humidified conditions drug delivery to the bronchi with the albuterol HFA-propelled pMDI was lower than that with the CFC-propelled pMDI.

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CFC: Chlorofluorocarbon; HFA: Hydrofluoroalkane; pMDI: Pressurised metered-dose inhaler; RH: Relative humidity.

Box 1. Inhaled medications during mechanical ventilation.

- Bronchodilator
  β-agonist (albuterol, metaproteronol, fenoterol)
  Anticholinergic (ipratropium bromide)
- Prostaglandin (alprostadil, prostacyclin, iloprost, treprostonil)
- Mucolytics (acetylcysteine)
- Proteins (dornase α)
- Surfactant (colfosceril palmitate)
- Antibiotics
  Antibacterial (aminoglycosides)
  Antiviral (ribavirin)
  Antifungal (amphotericin)
- Miscellaneous
- Corticosteroids (beclomethasone, budesonide)

2. Goals of inhalation therapy

The response to an inhaled drug depends on the amount of drug deposition in the lower respiratory tract [1,2]. Adequate amounts of the drug need to deposit in the lung to produce clinical effects. In addition, the precision, reliability and consistency of dosing are other important factors that influence the response to treatment. For precision of lung dosing, drug losses in the upper respiratory tract, or ventilator tubing and endotracheal tube in mechanically ventilated patients should be minimised, and drug deposition targeted to specific regions of the respiratory tract (e.g., 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 (e.g., 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 dry powder inhaler). Adequate understanding of the factors governing lung deposition of aerosols is essential to achieve these goals. In recent years, remarkable progress has been made towards increasing the efficiency of drug delivery to the lung due to the impressive gains in our knowledge and understanding of aerosol deposition in the lung, and with the availability of modern aerosolised drug delivery devices [1,3].

A variety of drugs are administered as aerosols in mechanically ventilated patients (**Box 1**). Among them, bronchodilator drugs are the most commonly employed, and several key issues regarding inhalation therapy have been elucidated with bronchodilator aerosols. However, the underlying scientific principles are also applicable to therapy with other aerosolised drugs.

3. Aerosol-generating devices

3.1 Pressurised metered-dose inhalers

The pMDI canister contains a pressurised mixture of propellants, surfactants, preservatives, flavouring agents and active drug; the latter comprising ~ 1% of the total contents [4]. 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. Previously, most pMDIs used chlorofluorocarbon (CFC) propellants, but newer-generation pMDIs contain hydrofluoroalkane (HFA) propellants [5]. In the US, CFC-pMDIs will be phased out by the year 2008. The formulation, metering-valve and actuator design of HFA-pMDIs differ from those in CFC-pMDIs [3,5]. For a pMDI to be connected in the ventilator circuit, the canister must be removed from the plastic actuator. A variety of adapters and spacers allow the canister to be connected in-line during mechanical ventilation (**Figure 2**). The cylindrical spacers have been shown to have a higher efficiency of drug delivery than connectors that attach directly to the endotracheal tube [6].

Aerosol particle size has a major influence on the quantity and site of drug deposition within the lung. A higher proportion of drug particles in the 1 – 5 μm range (respirable fraction) deposits in the lung, compared with particles with a size of 0.1 – 1.0 μm or those > 10 μm. The particle size of the aerosol produced by a pMDI depends on the vapour pressure of the propellant mixture, ambient temperature, design of the valve stem and actuator orifices, and drug concentration [7,8]. High vapour pressure propellants produce finer aerosol sprays, whereas increasing the drug concentration increases aerosol particle size.

3.2 Nebulisers

Nebulisers convert liquids into small droplets that can be inhaled into the lower respiratory tract [9]. Two types of nebulisers: jet and ultrasonic, are employed for inhalation therapy in ventilated patients.

3.2.1 Jet nebulisers

A jet of compressed air or oxygen under high pressure passes through a narrow opening near the tip of a capillary tube whose base is immersed in the drug solution to be nebulised [9,10]. The low pressure created by the expansion of the jet draws the liquid up the capillary tube. The shearing force of the jet stream produces a liquid film that breaks up into small droplets secondary to surface-tension forces. Larger particles deposit on a baffle placed upstream of the aerosol stream and on the walls of the nebuliser, whereas the smallest droplets leave the nebuliser. Droplet splashing from the primary and secondary baffles in a jet nebuliser also contributes to their splitting into smaller droplets that are more likely to penetrate deeper into the respiratory tract after inhalation by the patient [11].

Nebuliser design, solution characteristics (density, viscosity, surface tension), volume, gas pressure, flow, baffle design, and ratio of liquid to gas flow influence aerosol particle size [12-14]. Droplet size decreases when gas flow increases, whereas droplet size increases with the ratio of liquid to gas flow. A certain volume of solution (dead or residual volume) cannot be nebulised in jet nebulisers. The residual volume varies between 1 and 3 ml; it can be reduced by using a nebuliser with a conical

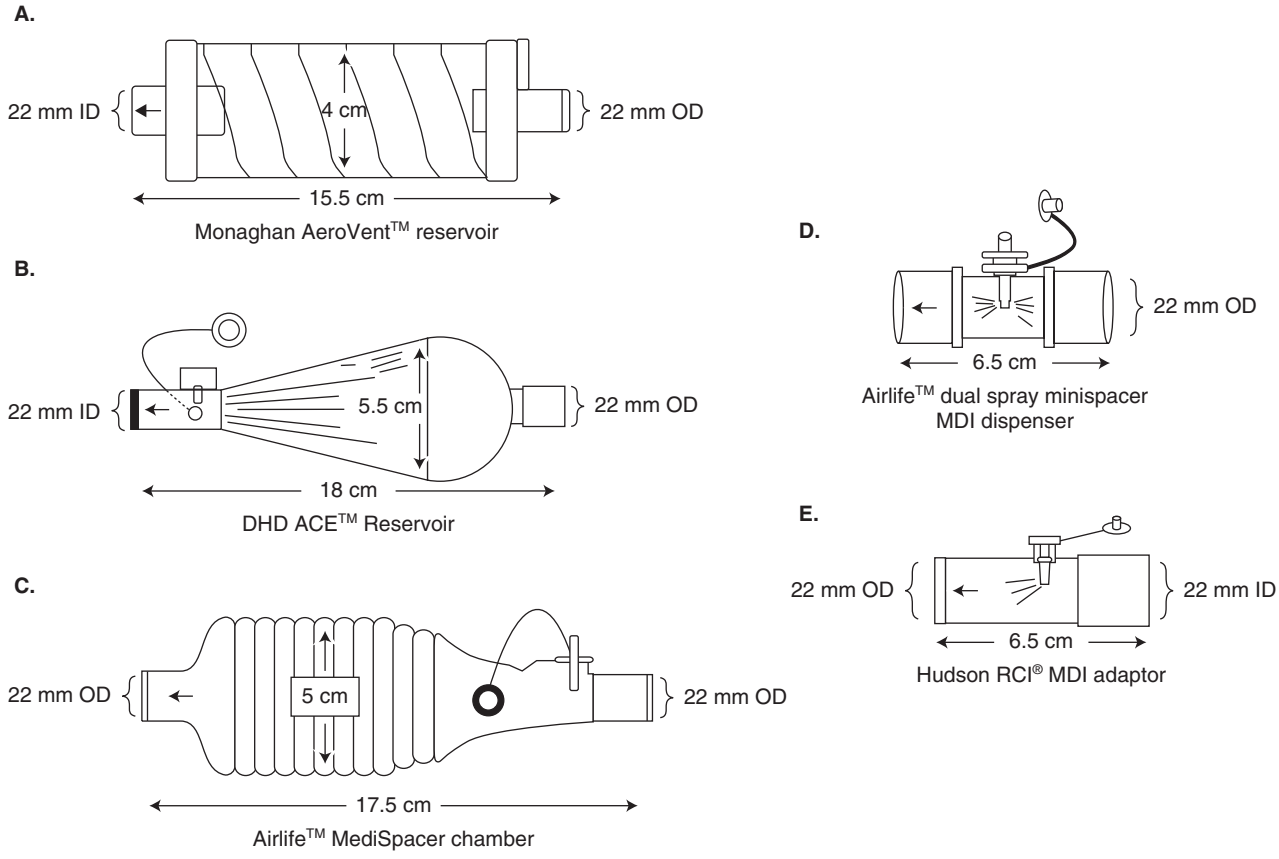

Figure 2. Commercially available spacers/adapters that are used to connect a metered-dose inhaler canister in the ventilator circuit. A. Collapsible spacer chamber. **B.** Aerosol cloud enhancer, wherein the aerosol flume is directed away from the patient. **C.** Non-collapsible spacer chamber. **D.** Bidirectional actuator (mini spacer). **E.** In-line adapter.

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ID: Inner diameter; MDI: Metered-dose inhaler; OD: Outer diameter.

shape, improving the wetness of the plastic surfaces, and reducing the internal surface area of the nebuliser [9,10].

During operation of a jet nebuliser, the solution concentration increases and its temperature decreases secondary to evaporative losses. The increased solution concentration and cooling both influence nebuliser output and particle size [9-13]. Moreover, nebuliser drug output markedly decreases after it starts sputtering. Significant disadvantages of jet nebulisers are the requirement for a power source, inconveniently long treatment time, need for equipment set up and cleaning, and significant variations in the performance of various nebulisers, both within the same brand and across different brands [15].

3.2.2 Ultrasonic nebulisers

These devices transmit sound waves generated by vibrating a piezo-electric crystal at high frequency (> 1 MHz) to the surface of the drug solution. Standing waves are created and droplets breaking free from the crest of these waves produce an aerosol [9,16]. Baffles remove larger droplets within the aerosol and a fan blows the aerosol to the patient. The source and flow of the gas used to carry the aerosol to the patient can influence droplet size and drug concentration. Low flow rates produce smaller particles and higher concentration of aerosols, whereas high flow rates yield larger droplets and lower aerosol concentrations. In some ultrasonic nebulisers, the solution to be nebulised is placed directly over the transducer, whereas in others, there is a water couplant chamber between the transducer and the medication chamber [16]. In ultrasonic nebulisers, the aerosol particle size is inversely proportional to the piezo-electric crystal vibration frequency, and drug output is directly proportional to amplitude of crystal vibration [9,16]. Similar to jet nebulisers, the drug solution becomes more concentrated during operation; however, in contrast to jet nebulisers the solution temperature increases by 10 – 15°C after 10 min of ultrasonic nebulisation [13,17]. Most ultrasonic nebulisers have a higher rate of nebulisation and require a shorter time of operation than jet nebulisers. Generally, the aerosol particle size is larger with ultrasonic nebulisers compared with jet nebulisers. The cost and bulk of ultrasonic nebulisers and their relative inefficiency in nebulising drug

suspensions are major limitations to their use, although smaller ultrasonic nebulisers have been employed during mechanical ventilation [18].

3.2.3 *Methods to assess efficiency of aerosol-generators during mechanical ventilation*

In the past, the efficiency of drug delivered during mechanical ventilation was reported to vary widely: for pMDIs, it varied between 0.3 and 97.5%, and for nebulisers between 0 and 42% [6]. These variations in drug delivery underscore the need for optimising the techniques of administration with each device. Both *in vitro* and *in vivo* studies have helped in understanding the complex factors governing aerosol delivery during mechanical ventilation (**Figure 3**), and these have been extensively reviewed in previous publications [1,2,6,19]. Several factors, such as the type of ventilator, the ventilatory parameters, the type of ventilator circuit, the configuration and position of the device in the ventilator circuit, that influence aerosol delivery during mechanical ventilation differ from those influencing delivery of aerosols in the ambulatory setting.

Bench studies with simulated models of mechanical ventilation, scintigraphy with radiolabelled aerosols, and pharmacokinetic studies in patients have been employed to optimise techniques of administration with various aerosol generators. With a standardised administration technique, ~ 11% of the nominal dose from a pMDI and spacer chamber deposits in the lower respiratory tract of ventilated patients [20]. This value is remarkably close to values observed with the optimal use of a pMDI without a spacer (10 – 14%) in ambulatory patients [21].

Drug delivery from nebulisers also shows discrepancy between values obtained with bench models versus those obtained by gamma scintigraphy. Miller *et al.* found that accounting for circuit humidity and breath-actuated nebulisation could reconcile most observed differences [22]. With an optimal administration technique, an estimated 6 – 10% of the nominal dose placed in the nebuliser would be inhaled by a patient breathing through a humidified ventilator circuit [22]. A significant proportion of the inhaled mass deposits in the endotracheal tube and a smaller proportion is exhaled. Thus, the efficiency of drug deposition in the lower respiratory tract of ventilated patients is lower with nebulisers than with pMDIs. Higher drug doses are employed with nebulisers to offset their reduced efficiency. The total amount of drug depositing in the lower respiratory tract with jet nebulisers is probably comparable to that achieved with smaller drug doses employed with a pMDI.

4. Clinical aspects of aerosol therapy in mechanically ventilated patients

4.1 Bronchodilators

4.1.1 *Indications*

Bronchodilators are among the most commonly used drugs in ventilator-supported patients with asthma or COPD. Patients with acute exacerbations of asthma or COPD account for 12 – 13% of patients receiving mechanical ventilation [23,24]. As shown in **Box 2**, ventilator-supported patients with a variety of illnesses could benefit from bronchodilator administration [25,26]. The goals of bronchodilator therapy are to reverse bronchoconstriction, decrease the work of breathing, and/or relieve dyspnoea. A response to bronchodilator administration has been observed after administration of either aerosolised β-adrenergic [27,28] or anti-cholinergic bronchodilators [29] (**Table 1**). The combination of fenoterol and ipratropium bromide was more effective than ipratropium alone in a group of ventilator-supported patients with COPD [30].

4.1.2 *Bronchodilator efficacy*

Most mechanically ventilated patients with COPD demonstrate an improvement in respiratory mechanics following bronchodilator administration with a pMDI or a nebuliser [27,28]. A fall in inspiratory resistance or intrinsic positive end-expiratory pressure follows bronchodilator administration, and such reductions are often used to determine bronchodilator responsiveness in stable, mechanically ventilated patients [1,6,27,28,30]. In more acutely bronchoconstricted patients, clinical effects such as improvement in wheezing and reductions in tachycardia and tachypnoea are noted after bronchodilator administration. The use of a spacer with a pMDI and synchronisation with the onset of inspiration are important to obtain the best results with bronchodilator therapy in ventilator-supported patients [1,6,31]. With careful attention to the administration technique, a bronchodilator response can be expected in most mechanically ventilated patients with asthma or COPD.

4.1.3 *Bronchodilator dosing*

In mechanically ventilated patients, significant bronchodilator effects occur after administration of albuterol with a standard nebuliser [28,31] or four puffs (400 µg) with a pMDI [27,28] (**Figure 4**). Minimal therapeutic advantage was gained by administering higher doses, whereas the potential for side effects was increased [27,31]. In certain clinical settings, higher doses of bronchodilators may be needed in patients with severe airway obstruction or if the administration technique is not optimal. With a carefully executed administration technique, most stable, mechanically ventilated patients with COPD achieve near maximal bronchodilation following administration of four puffs of albuterol with a pMDI or 2.5 mg with a nebuliser [27,28] (**Figure 4**).

4.1.4 *Duration of effect*

The duration of bronchodilator response in stable, mechanically ventilated patients with COPD seems to be shorter than that in ambulatory patients (2 – 3 h versus 4 – 6 h, respectively) [28,32]. Thus, ventilated patients require scheduled administration of short-acting β-agonist bronchodilator (albuterol) every 3 – 4 h.

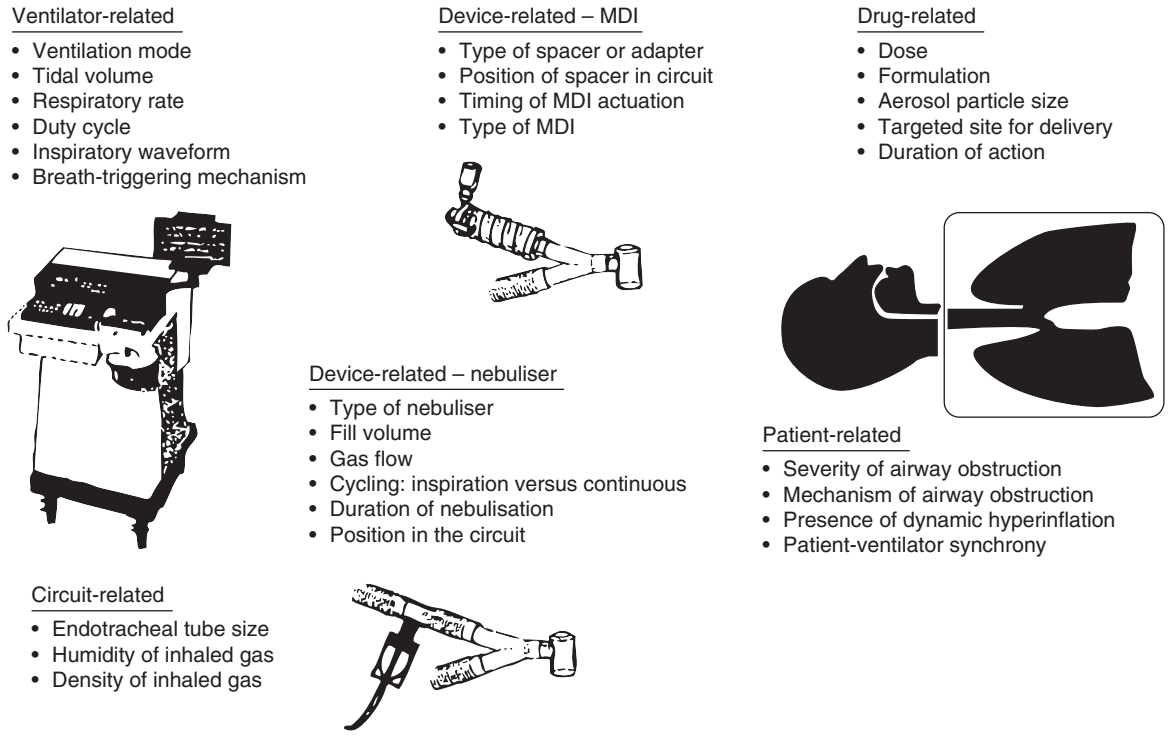

Figure 3. Factors influencing aerosol delivery in mechanically ventilated patients.
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MDI: Metered-dose inhaler.

4.1.5 Toxicity

Administration of higher doses of β-agonists is associated with an increased risk of serious arrhythmias and hypokalaemia, but no serious adverse effects have been reported after bronchodilator administration in ventilator-supported patients. Episodes of supraventricular tachycardia and ventricular ectopy have occurred following administration of 3- to 6-times the normal nebulised dose of albuterol [31], but no arrhythmias were observed following administration of 4 to 10 puffs of albuterol with a pMDI [27]. When pMDIs are used in very high doses, or when pMDI aerosol is delivered directly beyond the endotracheal tube by attaching a catheter to the canister nozzle, propellants in the pMDI formulation could cause local ulceration and they may precipitate serious cardiac arrhythmias [33,34].

A variety of agents, such as prostanoids, surfactant, antibiotics, mucolytic agents and corticosteroids, are administered by inhalation to ventilated patients.

4.2 Prostanoids

In contrast to intravenous administration [35,36], aerosolised vasodilators selectively increase blood flow to well-ventilated, but poorly perfused lung regions in mechanically ventilated patients with acute respiratory distress syndrome (ARDS), thereby improving oxygenation while decreasing pulmonary artery pressures [37]. Inhaled prostacyclin and prostaglandin E_1 are selective pulmonary vasodilators at doses < 10 ng/kg/min, but higher doses produce systemic vasodilation. In ventilator-supported patients with ARDS, inhaled prostacyclin and prostaglandin E_1 are as effective as nitric oxide in improving oxygenation and haemodynamics [38-40]. Likewise, in patients with severe pneumonia requiring mechanical ventilation, inhaled prostacyclin produces significant improvement in oxygenation and pulmonary haemodynamics in those patients without prior interstitial lung disease [41]. In mechanically ventilated patients, lower doses (< 10 ng/kg/min) of prostacyclin are well tolerated, but bronchospasm has been reported with higher doses.

Iloprost, a stable analogue of prostacyclin, has a longer half-life than prostacyclin (20 – 30 min versus ~ 3 min), and it produces pulmonary vasodilatation for 30 – 90 min. Haemodynamic effects of inhaled iloprost are similar to those of inhaled NO and inhaled prostacyclin [42-44]. Inhaled iloprost was recently approved for use in the US for treatment of patients with chronic pulmonary hypertension. In ambulatory patients, the drug is delivered by either of two pulmonary drug delivery devices: I-neb™ Adaptive Aerosol Delivery (AAD®; Respironics) system or the Prodose® AAD system (Respironics). The dose of inhaled iloprost is 2.5 – 5.0 mg, administered six to nine times daily during waking hours, depending on the individual need and tolerability. The combination of inhaled iloprost with oral sildenafil enhanced and prolonged the pulmonary vasodilator effect of iloprost, without affecting systemic arterial pressure or oxygenation [45].

Box 2. Indications for bronchodilator therapy in patients receiving mechanical ventilation.

- Asthma
- Chronic obstructive pulmonary disease
- Acute bronchospasm or wheezing
- Elevated airway resistance
- Dynamic hyperinflation
- Difficulty in weaning
- Chronic ventilator-dependence

Treprostonil – another prostacyclin analogue – is an effective pulmonary vasodilator when administered by inhalation to patients with chronic pulmonary hypertension. A single inhalation of the drug (15 mg) produced a prolonged vasodilator effect (> 180 min) [46]. The prolonged duration of action allowed the drug to be successfully used in two patients on a scheduled four-times-daily inhalation for over 3 months. Thus, inhaled iloprost or treprostonil could be employed for treatment of acute pulmonary hypertension in mechanically ventilated patients, without the need for continuous aerosolisation. Because the occurrence of pulmonary hypertension is an adverse prognostic factor in patients with ARDS [47], trials with inhaled prostanoids are needed to determine their influence on the outcomes of these critically ill patients. Before undertaking such trials, investigators will need to determine the efficiency of various aerosol generators to deliver inhaled prostanoids in ventilated patients.

4.3 Surfactant

Endogenous surfactant is a complex mixture of proteins and lipids that lines the alveolar surface and reduces alveolar surface tension, especially at low lung volumes. Alterations in endogenous lung surfactant contribute to abnormal respiratory mechanics in patients with ARDS [48]. Surfactant replacement therapy has been evaluated in an attempt to correct a deficiency of functional surfactant in neonates and adults with acute lung injury [48]. Exogenous surfactants employed for surfactant replacement therapy are mixtures of synthetic phospholipids alone (colfosceril palmitate) or lipids and peptides (e.g., sinapultide). Modified natural surfactants are obtained from minced animal lung or alveolar lavage extracts, and they consist of phospholipids combined with surfactant proteins B and C (e.g., beractant), or they are based on recombinant surfactant protein C (e.g., lusupultide). These exogenous surfactants lack surfactant protein A and D and differ from natural surfactants with respect to their functional and morphological properties [49].

Current techniques of exogenous surfactant delivery include liquid bolus instillation through the endotracheal tube, followed by a brief period of manual ventilation [50], instillation via a bronchoscope [51], instillation via an intratracheal catheter [52] or by aerosol delivery using a nebuliser system [53,54]. Aerosolised surfactant produces fewer bolus effects and more uniform dispersion in the lung compared with bolus instillation. Delivery of smaller quantities of surfactant to the parenchyma may be sufficient to lower surface tension and improve lung function when it is administered as an aerosol, compared with bolus instillation. However, the viscosity of exogenous surfactants makes them difficult to aerosolise, and they tend to foam and form stable bubbles during nebulisation. As a result, nebuliser delivery of surfactant to the lower respiratory tract is inefficient and most of the aerosol is lost in the delivery system and the ventilator circuit. Moreover, exhaled aerosol may deposit and interfere with the function of valves and monitoring devices of the ventilator. This complication can be avoided by placing filters in the expiratory limb of the circuit to trap any aerosol before it reaches the ventilator.

Inhaled surfactant administered to animals with non-homogenous lung injury is preferentially deposited in well ventilated and less injured lung regions [55]. As the pattern of injury in ARDS is not uniform, the more severely affected lung regions may not receive adequate amounts of surfactant. Two prospective multi-centre randomised trials evaluated the efficacy of inhaled surfactant (colfosceril palmitate) in patients with sepsis-induced ARDS [53,54]. In both trials, there were no improvements in oxygenation, duration of mechanical ventilation, length of stay in the intensive care unit or survival [53,54]. Improvements in the design of exogenous surfactants and better delivery systems are needed for aerosolised surfactant to become an effective treatment for ARDS.

4.4 Antibiotics

Inhalation of aerosolised antibiotics is appealing because it allows administration of a greater antibiotic concentration to the airways than could be achieved by other routes of delivery, whilst maintaining a low incidence of systemic side effects and toxicity.

In spontaneously breathing patients with cystic fibrosis, inhaled aminoglycosides improve pulmonary function, reduce symptoms and decrease the frequency of pulmonary infections so that fewer hospitalisations are needed [56]. Inhaled tobramycin is now routinely employed by patients with cystic fibrosis [57]. In contrast, the efficacy of inhaled antibiotic therapy in mechanically ventilated patients is controversial and less well defined [58,59]. Feeley *et al.* observed an increase in mortality after administration of inhaled polymyxin to patients admitted to the ICU, associated with a greater incidence of polymyxin-resistance organisms [58]. Antibiotic resistant isolates disappeared following discontinuation of inhaled therapy [58]. Since the publication of this study, there has been a great deal of skepticism regarding the role of inhaled antibiotic therapy. However, more recent work suggests that aerosolised aminoglycosides could be used in a select group of mechanically ventilated patients. The use of aerosolised antibiotics should be reserved for treatment of patients with multiresistant organisms, in patients with severe pneumonia not responding to conventional therapy, or in patients who develop tracheo-bronchitis following long-term mechanical ventilation [59].

Table 1. Bronchodilators administered by pressurised metered-dose inhaler in mechanically ventilated patients*.

Bronchodilator	Formulation	Dose (µg)	Recommended dose and frequency‡
β-adrenergic			
Albuterol	CFC	100	4 – 6 puffs every 3 – 4 h
Albuterol sulfate	HFA	100	4 – 6 puffs every 3 – 4 h
Levalbuterol tartarate	HFA	59	2 – 4 puffs every 3 – 4 h§
Anti-cholinergic			
Ipratropium bromide	CFC	18	4 – 6 puffs every 4 – 6 h
Combination			
Albuterol sulfate + ipratropium bromide	CFC	100/18	4 – 6 puffs every 4 – 6 h

*Commonly employed bronchodilator aerosols administered by pMDI to mechanically ventilated patients in the US 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. Additional doses may be needed for breakthrough symptoms.

§The efficacy of levalbuterol pMDI has not been determined in ventilated patients.

CFC: Chlorofluorocarbon; HFA: Hydrofluoroalkane; pMPI: Pressurised metered-dose inhaler.

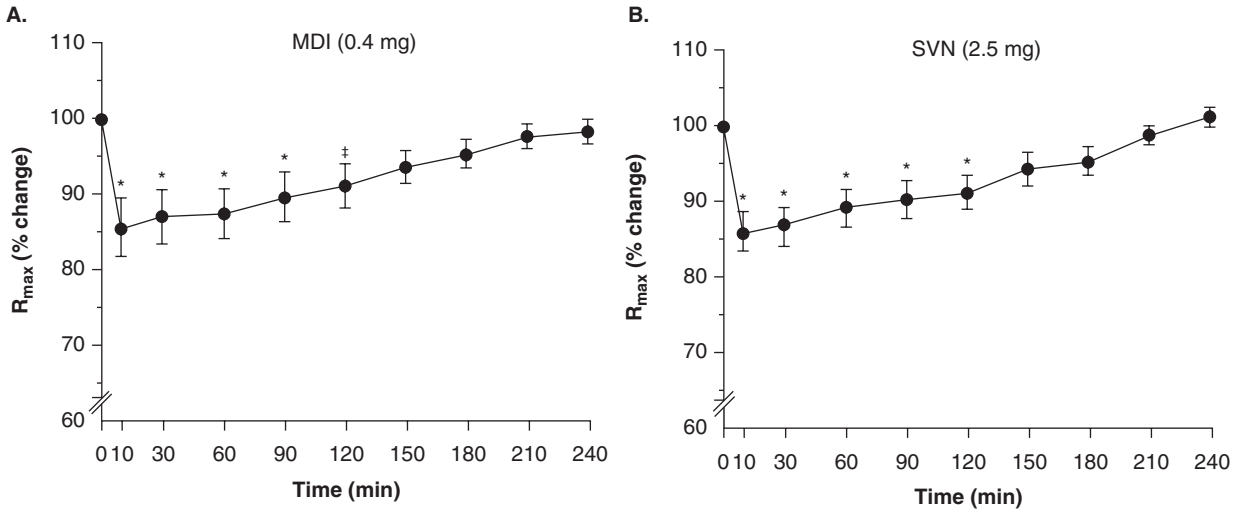

Figure 4. Effect of albuterol on maximum inspiratory airway resistance in stable, mechanically ventilated patients with COPD. There was a decrease in airway resistance from baseline values within 10 min of albuterol administration. **A.** Change in airway resistance from baseline (time 0) after four doses of albuterol from a pMDI. **B.** Change in airway resistance from baseline (time 0) after albuterol 2.5 mg given by nebuliser. Significant reductions in airway resistance were sustained for 2 h and returned to baseline by 4 h. The response to albuterol administered by pMDI (0.4 mg) was comparable to that achieved with 2.5 mg administered by nebuliser. Bars represent s.e.m.

Adapted with permission from DUARTE AG, MOMII K, BIDANI A: Bronchodilator therapy with metered-dose inhaler and spacer versus nebulizer in mechanically-ventilated patients: comparison of magnitude and duration of response. *Respir. Care* (2000) **45**:817-823.

*$p < 0.01$; ‡$p < 0.05$.

COPD: Chronic obstructive pulmonary disease; MDI: Metered-dose inhaler; R_{max}: Maximum inspiratory airway resistance; SVN: Small volume nebuliser.

In mechanically ventilated neonates and infants with respiratory syncytial virus infection, delivery of aerosolised ribavirin for up to 7 days resulted in a decrease in the duration of mechanical ventilation [60]. However, special precautions are needed to avoid crystallisation of the drug in respiratory equipment.

Inhaled antibiotic therapy in the mechanically ventilated patient seems promising, but must still be regarded as investigational, pending further studies examining inhaled versus intravenous routes of delivery, drug distribution within the respiratory tract, emergence of antibiotic resistance and local toxicity.

4.5 Mucolytics

Retention of airway secretions is associated with a high risk of pneumonia. Mechanical suctioning – the currently employed

method to clear secretions in mechanically ventilated patients – is painful and could lead to tracheal injury. Acetylcysteine is often employed to enhance secretion clearance by reducing sputum viscosity. The occurrence of an increase in inspiratory airway resistance after administration of mucolytic agents by aerosol [61] or bolus instillation [62] is a problem with the routine use of these agents. Recombinant human DNase was shown to improve mucus clearance in ventilator-supported patients with spinal cord injury and recurrent atelectasis refractory to conventional treatment [63]. Due to cost constraints, dornase α (a solution of recombinant human DNase) cannot be recommended for routine use in the management of ventilator-dependent patients with inspissated secretions. To the authors' current knowledge, systematic investigations of the use of mucolytic agents given by aerosol during mechanical ventilation have not been reported, but there may be a role for mucolytic agents in preventing lung collapse and hypoxaemia in ventilated patients with thick inspissated secretions who are refractory to other forms of treatment.

4.6 Miscellaneous

The use of inhaled corticosteroids has been recommended for use in neonates and infants with bronchopulmonary dysplasia [64]. However, aerosolised budenoside did not reduce the duration of mechanical ventilation in preterm babies, compared with infants receiving placebo inhalation [64]. Similarly, inhaled beclomethasone did not decrease the frequency of bronchopulmonary dysplasia compared with placebo in mechanically ventilated premature infants [65]. Inhaled corticosteroids probably have a limited role in the treatment of ventilator-supported premature infants.

The inhaled route of drug delivery is also being evaluated for a variety of anti-inflammatory and immuno-regulatory agents, and for gene therapy. In the near future, some of these therapies may be employed for treatment of patients receiving mechanical ventilation.

5. Expert opinion

5.1 Administration technique

The variations in the efficiency of pMDIs and nebulisers to deliver aerosol to the lung in mechanically ventilated patients underscore the need for carefully controlling the administration technique. The recommended techniques of administration with pMDIs, and nebulisers are shown in **Boxes 3** and **4** [66], respectively. When using pMDIs, the key steps are to employ an in-line chamber spacer and to synchronise the actuation of the pMDI with onset of inspiratory airflow from the ventilator. When using nebulisers, a device that produces an aerosol with most of the drug contained in particles < 3 μm is ideal. Intermittent operation of the nebuliser and placement at a distance from the patient also enhance drug deposition in the lung [1,2,6,19].

5.1.1 *Selection of aerosol delivery device*

Traditionally, pMDIs have been prescribed for out-patient treatment of airway obstruction, whereas nebulisers have been widely used during in-hospital visits. This has led to the erroneous belief that nebulisers are preferred for bronchodilator delivery in critically ill patients. In fact, bronchodilator therapy with either pMDIs or nebulisers produces similar therapeutic effects in ventilator-supported patients [6,28,67,68].

pMDIs are preferred for routine bronchodilator therapy in ventilator-supported patients, due to several problems associated with the use of nebulisers. The rate of aerosol production, aerosol particle size and delivery efficiency vary considerably between different nebuliser brands and also among different batches of the same brand [15]. Moreover, nebuliser solutions can become contaminated and lead to nosocomial pneumonia [69]. In addition, the costs of routine bronchodilator therapy in ventilated patients could be reduced by employing pMDIs rather than nebulisers [70]. For routine bronchodilator therapy in mechanically ventilated patients, pMDIs are now the aerosol-generators of choice. However, only a few drug formulations are available as pMDIs and nebulisers have the advantage that they could be employed for drug delivery in a variety of settings in ventilator-dependent patients.

5.1.2 *Effect of pMDI formulation on drug delivery*

In a mechanically ventilated lung model, Rau *et al.* found that the delivery of flunisolide from a CFC-pMDI was lower with all of the actuators tested compared with the values achieved with the albuterol pMDI [71]. These authors highlight the importance of matching the pMDI canister with a suitable adapter for optimal efficiency.

5.1.3 *CFC versus HFA-pMDIs*

Because HFA-propellants are not compatible with most surfactants, some of the HFA-pMDIs have been reformulated as solutions, resulting in a finer aerosol spray with greater peripheral lung deposition and improved efficacy compared with the CFC-pMDIs [72,73]. In bench models of mechanical ventilation, albuterol HFA-pMDIs employed with an Aerovent® spacer (Monaghan Medical) provide drug delivery that is lower than that with CFC-pMDIs [20]. Contrarily, beclomethasone HFA-pMDIs employed with an Aerochamber® HC MV spacer (Monaghan Medical) had a higher efficiency of drug delivery than the beclomethasone CFC-pMDI [74]. The differences in the results of the studies could be explained by differences in the pMDI formulation and types of spacers employed by the two groups of investigators. The beclomethasone HFA-pMDI is formulated as a solution and produces an extra fine aerosol (Mass Median Aerodynamic Diameter of 1.2 μm), whereas the albuterol HFA-pMDI is a suspension with aerosol particle size comparable to that of the albuterol CFC-pMDI. Moreover, the size of the canister stem is different for each pMDI, and the efficiency of drug delivery depends on how well the canister stem fits into the actuator. To

Box 3. Optimal technique for drug delivery by pressurised metered-dose inhaler in ventilated patients.

- Review order, identify patient, and assess need for bronchodilator
- Suction endotracheal tube and airway secretions
- Shake pMDI and warm to hand temperature
- Place pMDI in space chamber adapter in ventilator circuit
- Remove HME, do not disconnect humidifier
- Coordinate pMDI actuation with beginning of inspiration
- Wait at least 15 s between actuations; administer total dose
- Monitor for adverse response
- Reconnect HME
- Document clinical outcome

HME: Heat and moisture exchanger; pMDI: Pressurised metered-dose inhaler.

Box 4. Optimal technique for drug delivery by jet nebuliser in ventilated patients.

- Review order, identify patient, and assess need for bronchodilator
- Suction endotracheal and airway secretions
- Place drug in nebuliser to fill volume of 4 – 6 ml
- Place nebuliser in the inspiratory line 46 cm from the patient wye connector
- Turn off flow-by or continuous flow during nebuliser operation
- Remove HME from circuit (do not disconnect humidifier)
- Set gas flow to nebuliser at 6 – 8 l/min; use a ventilator if it meets the nebuliser flow requirements and cycles on inspiration, or use continuous flow from external source
- Adjust ventilator volume or pressure limit to compensate for added flow
- Tap nebuliser periodically until nebuliser begins to sputter
- Remove nebuliser from circuit, rinse with sterile water and run dry, store in safe place
- Reconnect humidifier or HME, return ventilator settings and alarms to previous values
- Monitor patient for adverse response
- Assess outcome and document findings

HME: Heat and moisture exchanger.
Adapted from [66].

improve drug delivery with HFA-pMDIs in the setting of mechanical ventilation, the actuators required to connect them in ventilator circuits need to be matched to the size of the pMDI canister stem. No commercially available actuator is equally efficient with all pMDIs, and HFA-pMDIs will need to be matched with suitable actuators to optimise their efficiency during mechanical ventilation.

5.2 Humidity in the ventilator circuit

The gas in the ventilator circuit is heated and humidified to prevent drying of the airway mucosa. Humidification leads to an increased loss of aerosol in the ventilator circuit [1,6,22,75] and several investigators have found that drug delivery to the lower respiratory tract from both MDIs and nebulisers is reduced by ≥ 40% or more in a humidified compared with a dry circuit [1,6,22]. Humidity was thought to retard propellant evaporation in a humidified environment [6,75], such that the droplet size did not decrease as rapidly after discharge from a pMDI as it would in dry air. However, further investigations were unable to demonstrate a reduction in the rate of propellant evaporation in humid versus dry air [76]. An alternative hypothesis is that propellant evaporation produces a drop in temperature that allows condensation nuclei to form in a humid atmosphere, which leads to a transient increase in particle size. However, subsequent droplet evaporation occurs if the relative humidity in the surrounding air is < 100%, and the effects of the initial water condensation may be largely negated by this phenomenon [77]. These observations could explain the enhanced efficiency of drug delivery that occurs following the use of a cylindrical spacer with a pMDI and placement of the pMDI at a distance from the endotracheal tube [1,6]. Although circuit humidity reduces drug delivery, bypassing the humidifier is not recommended for routine inhalation therapy in ventilator-supported patients. Such a practice would require reconnecting the circuit for each treatment and waiting several minutes for the circuit to dry. Treatment with a MDI can be completed in a few minutes, whereas the treatment interval may be 45 – 60 min with some nebulisers, and inhaling dry gas for extended periods could have detrimental effects on the tracheal mucosa. Moreover, with careful attention to the administration technique, the impact of humidity on drug delivery can be overcome by delivering a somewhat higher drug dose [27,28,31,32]. A dry circuit could be employed for delivery of those agents that are very expensive or those agents for which the amount of drug deposition is critical (e.g., surfactant). When a dry circuit is employed, drug administration should be achieved within a short period (< 10 min) to minimise the effects of dry gas on the airway mucosa.

5.3 Newer aerosol generators

5.3.1 Vibrating mesh nebulisers

Newer-generation nebulisers employ a vibrating mesh or plate with multiple apertures to produce an aerosol [78]. These devices can be operated either with a battery pack or electrical source, and they are portable and less noisy than conventional jet nebulisers. Moreover, these devices have higher drug output because their residual volume is negligible. The Aeroneb Pro® (Aerogen) is specifically designed as an in-line nebuliser; a breath-synchronised version of the Aeroneb Pro (Pulmonary Drug Delivery System [PDDS]) has been developed (**Figure 5**). The control module of the PDDS is microprocessor driven and

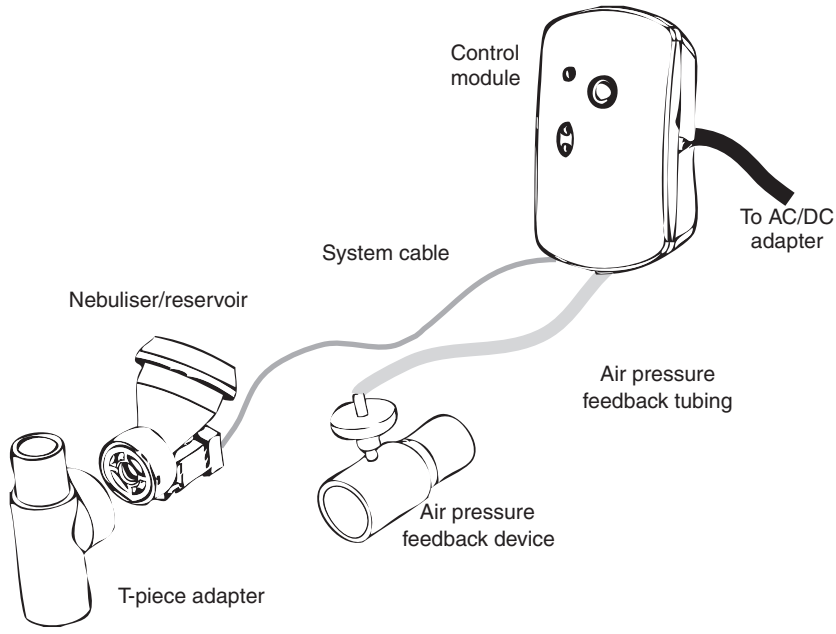

Figure 5. Components of the Pulmonary Drug Delivery System. The PDDS incorporates Aerogen's onQ™ Aerosol Generator. A pressure transducer monitors airway pressure and identifies inspiratory time. The control module of the PDDS is microprocessor driven.
Reprinted with permission from Nektar Therapeutics.
PDDS: Pulmonary Drug Delivery System.

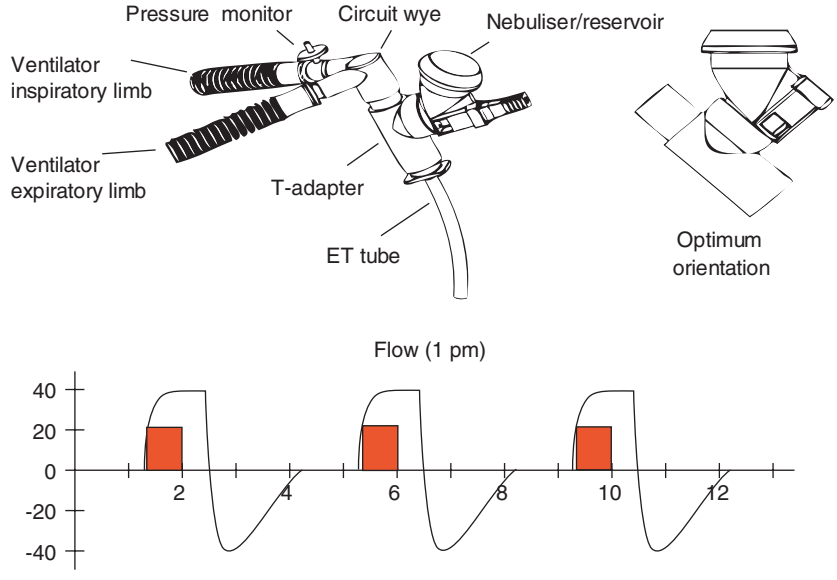

Figure 6. The Pulmonary Drug Delivery System device connected in a ventilator circuit is shown in the top panel. The aerosol generator connects to a low volume adapter that is, in turn, connected to the patient's airway between the circuit wye and endotracheal tube. The optimum orientation of the device is shown. The bottom panel shows that aerosol of a specific size is generated only during a specific portion, as indicated by the dark bar, of the inspiratory cycle. By these techniques, aerosol delivery to the lower respiratory tract can be optimised in mechanically ventilated patients.
Reprinted with permission from Nektar Therapeutics.
ET: Endotracheal; PDDS: Pulmonary Drug Delivery System.

utilises a pressure transducer to monitor changes in airway pressure and identify inspiratory time. The microprocessor delivers aerosol only during the first 75% of inspiration (**Figure 6**). The PDDS generates a fine particle aerosol that delivers inhaled amikacin with a high-efficiency (~ 60% of the nominal dose) in ventilated patients [79].

The vibrating mesh nebulisers have a high rate of nebulisation, and drug output is 2- to 3-times higher than with jet nebulisers [78]. Unlike ultrasonic nebulisers, the temperature of the solution does not change during operation of the vibrating mesh nebulisers, and proteins and peptides can be nebulised with minimal risk of denaturation. The vibrating mesh nebulisers have many advantages over jet nebulisers and they are likely to find increasing use for delivery of specific (non-bronchodilator) aerosols in ventilator-dependent patients.

5.3.2 *Intratracheal catheter*

The intracorporeal nebulising catheter (Aeroprobe®; Trudell Medical International) is a novel device that produces an aerosol in the trachea [80]. A central lumen transmits the solution to be nebulised and compressed gas is forced under high pressure (100 psi) at a variable flow rate (0.1 – 3.0 l/min) through several additional lumens that surround the central lumen. Droplets of drug solution form at the tip of the catheter and aerosol is formed by the pressurised gas breaking up the liquid droplets. The catheter produces an aerosol continuously or intermittently when a pulsed gas flow is employed. The pressure and flow rate of the gas determine the aerosol particle size. Preliminary data suggest that lung deposition is improved with the use of the catheter, compared with more conventional forms of aerosol administration [81]. The use of the intratracheal catheter holds considerable promise as a means of targeting inhalational delivery of a variety of therapeutic agents and genes in ventilated patients to the site of disease in the lung.

5.4 The future

The addition of dose counters with newer pMDIs could be a hindrance to their use in ventilated patients, because the dose counter would not permit removal of the canister from the actuator. For such pMDIs, the actuator itself would have to fit an adapter in order for the combination to be connected in the ventilator circuit. At present, the efficiency of such a delivery system is unknown. Alternatively, pMDIs for ventilated patients would have to be marketed without dose counters. However, the use of pMDIs in ventilated patients is only a small fraction of their total use, and it is unlikely that a separate pMDI for use in ventilated patients would be economically feasible.

Most nebulisers for use in ventilated patients have been stand-alone devices that were adapted for use during mechanical ventilation. Ventilators with in-built nebulisers are now available and their use will facilitate reproducible and consistent dosing with a variety of agents in ventilated patients.

5.5 Conclusion

Bronchodilator therapy with inhaled β-agonist and anticholinergic agents is commonly employed in mechanically ventilated patients. Inhaled bronchodilator therapy in patients receiving mechanical ventilation is complex: many factors influence the amount of drug de-position in the lower respiratory tract, and the administration technique needs to be carefully controlled. Optimal techniques for employing pMDIs and nebulisers have been developed as a result of a better understanding of the factors influencing aerosol delivery to the lower respiratory tract of ventilator-dependent patients. With a proper administration technique, drug deposition in the lower respiratory tract of ventilator-supported patients is comparable to that achieved in ambulatory patients. For routine therapy, a somewhat higher dose than that used in ambulatory patients is recommended in mechanically ventilated patients, to compensate for the effects of humidity in the ventilator circuit. Specific therapeutic applications require testing the efficiency of the delivery system under simulated conditions of clinical use, before they are employed in patients. There is a growing interest in the use of a variety of inhaled therapies in mechanically ventilated patients, and the availability of highly efficient delivery devices will lead to rapid progress in this field.

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