Nebulizers: Principles and Performance

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Introduction

Nebulizers are used to convert liquids into aerosols of a size that can be inhaled into the lower respiratory tract. The process of pneumatically converting a bulk liquid into small droplets is called atomization. Pneumatic nebulizers have baffles incorporated into their design so that most of the droplets delivered to the patient are within the respirable size range of 1–5 μm. Ultrasonic nebulizers use electricity to convert a liquid into respirable droplets.

Although the first choice of aerosol generator for the delivery of bronchodilators and steroids is the metered-dose inhaler,[1,2] nebulizers remain useful for several reasons. First, some drugs for inhalation are available only in solution form. Second, some patients cannot master the correct use of metered-dose inhalers or dry powder inhalers. Third, some patients prefer the nebulizer over other aerosol generating devices. The physiologic benefits of metered-dose inhalers and nebulizers are virtually equivalent,[3,4] and the choice of device is often based on clinician or patient preference rather than clear superiority of one approach over the other. Although cost savings have been suggested with the use of metered-dose inhalers compared to nebulizers, these benefits may be overestimated.[3]

The purpose of this paper is to review the performance characteristics of nebulizers. Both pneumatic and ultrasonic nebulizer designs will be considered.

Pneumatic Nebulizers

Nebulizers are the oldest form of aerosol generation. Although they have been commonly used for many years, their basic design and performance has changed little over the past 25 years. Nebulizers are most commonly used for bronchodilator administration, and it is well established that nebulized bronchodilators produce a physiologic response. Because bronchodilators are relatively inexpensive, there is little market pressure to improve nebulizer performance. In fact, the market generally prefers an inexpensive nebulizer rather than a high-performance neb-

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Table 1. Factors Affecting Penetration and Deposition of Therapeutic Aerosols Delivered via Jet Nebulizer

Technical Factors
Manufacturer of nebulizer
Gas flow used to power nebulizer
Fill volume of nebulizer
Solution characteristics
Composition of the driving gas
Designs to enhance nebulizer output
Continuous versus breath-actuated
Patient Factors
Breathing pattern
Nose versus mouth breathing
Composition of inspired gas
Airway obstruction
Positive pressure delivery
Artificial airway and mechanical ventilation

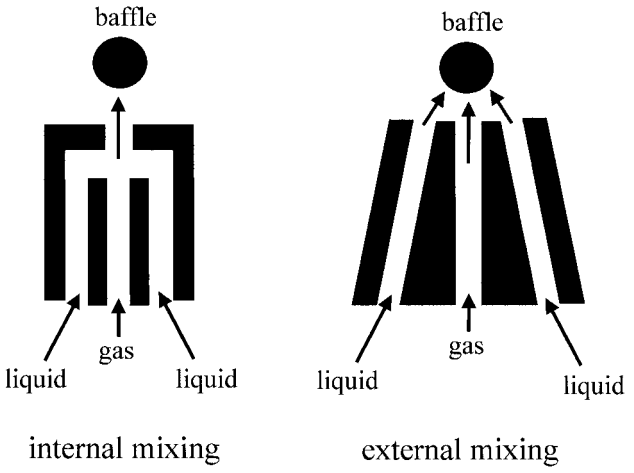

Fig. 2. Internal mixing and external mixing nebulizer designs. (Adapted from Reference 5.)

ulizer for bronchodilator administration. However, there are newer drugs available for inhalation that are expensive and for which precise dosing may be important. These include dornase alfa, tobramycin, and pentamidine. Nebulizer performance is affected by both technical and patient-related factors (Table 1).

Principle of Operation

The operation of a pneumatic nebulizer requires a pressurized gas supply as the driving force for liquid atomization (Fig. 1).[5–10] Compressed gas is delivered through a jet, causing a region of negative pressure. The solution to be aerosolized is entrained into the gas stream and is sheared into a liquid film. This film is unstable and breaks into droplets because of surface tension forces. A baffle is placed in the aerosol stream, producing smaller particles and causing larger particles to return to the liquid reservoir. More than 99% of the particles may be returned to the liquid reservoir.[8] The aerosol is delivered into the inspiratory gas stream of the patient. Before delivery into the patient's respiratory tract, the aerosol can be further conditioned by environmental factors such as the relative humidity of the carrier gas.[11–14]

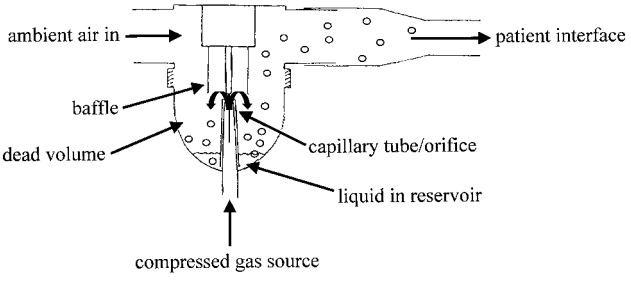

Fig. 1. Basic components of the design of pneumatic nebulizers. (Adapted from Reference 6.)

Nebulizer nozzles are of two types (Fig. 2).[15] With the internal mixing design, gas flow interacts with the solution prior to leaving the exit port. With external mixing, gas and the solution interact after both leave the nozzle. Modifications on these designs are used by nebulizer manufacturers, without clear superiority of one approach over the other.

Determinants of droplet size produced by nebulizers include the characteristics of the solution (density, viscosity, surface tension), the velocities of the gas and solution, and the flow rates for the gas and the solution.[5,15] The most important factors are gas velocity and the ratio of liquid to gas flow.[5] An increase in gas velocity decreases droplet size, whereas an increase in the ratio of liquid to gas flow increases particle size. It is interesting to note that gas velocity affects the flow rates for both the gas and the solution. Thus, it is impossible to separately control the primary factors affecting droplet size from nebulizers.

An important consideration in the use of nebulizers is the dead volume of the device. Dead volume refers to the amount of solution that is trapped inside the nebulizer and is thus not made available for inhalation. The dead volume is typically in the range of 1 to 3 mL. Dead volume is minimized by using a conical shape of the nebulizer, by decreasing the surface area of the internal surface of the nebulizer, and by improving the wetness of the plastic surface of the nebulizer.[5,15] To reduce medication loss due to dead volume, clinicians and patients may tap the nebulizer periodically during therapy, which has been shown to increase nebulizer output.[16] Therapy may also be continued past the point of inconsistent nebulization (sputtering) in an attempt to deliver medication from the dead volume, but this has been reported to be unproductive.[17]

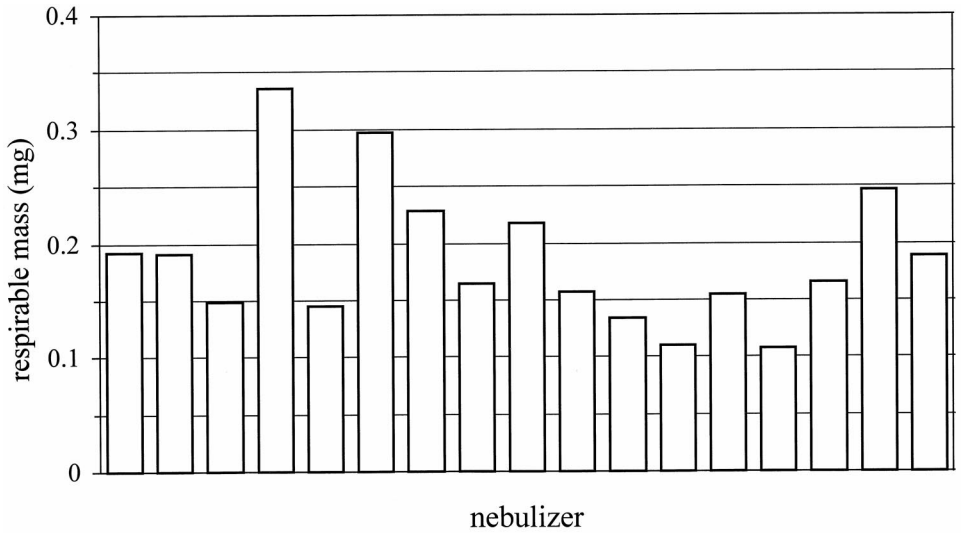

Fig. 3. Comparison of the output of 17 commercially available pneumatic nebulizers. Respirable mass = particles 1–5 μm delivered to mouthpiece with simulated spontaneous breathing; 2.5 mg albuterol placed into nebulizer cup. (Adapted from Reference 25.)

Due to evaporative water loss, the solution in the nebulizer becomes increasingly concentrated during the nebulization time.[18–20] For this reason, gravimetric methods underestimate nebulizer output.[21,22] Due to the evaporative effects, the nebulizer solution cools.[18] Solution temperature affects nebulizer output, with output varying directly with temperature.[15,23] The droplet size produced by the nebulizer also varies directly with temperature.[18]

Clinically Important Characteristics of Nebulizer Performance

The most important characteristic of nebulizer performance is the respirable dose provided for the patient. The respirable dose is determined by the mass output of the nebulizer and the size of the droplets that are produced. The droplet size should be 2–5 μm for airway deposition and 1–2 μm for parenchymal deposition.[24] Droplet size is usually reported as mass median aerodynamic diameter (MMAD), which is the diameter around which the mass of the aerosol is equally divided. Note that MMAD is used to characterize the population of droplets produced; it does not refer to the size of individual droplets. Because the volume, and hence the mass, of the droplet is determined by the cube of the radius (volume = $4/3\ \pi\ r^3$), most of the particles will be smaller than the MMAD. The respirable dose is sometimes reported as respirable mass, which is the output of droplets from a nebulizer in the respirable range of 1–5 μm.[25,26]

Other important characteristics of nebulizer performance include nebulization time, cost, ease of use, and requirements for cleaning and sterilization. Nebulization time is important for patient compliance in the outpatient setting and clinician supervision for hospitalized patients. A short nebulization time that delivers an effective dose is desirable. Many nebulizers are low-cost, mass-produced, single-patient-use devices. This results in variability in performance among devices,[25–28] which might not be important for bronchodilator delivery, but which could be important for delivery of other inhaled medications.

Technical Factors Affecting Nebulizer Performance

Several studies have reported performance differences between nebulizers from different manufacturers.[23,25–27,29–36] Performance differences among nebulizers from the same manufacturer have been reported.[37–39] Hess et al[25] evaluated the performance of 17 nebulizers, using a model of spontaneous breathing. They reported a respirable mass available to the patient that was severalfold greater from some nebulizers than from others (Fig. 3). Performance differences between nebulizers may have clinical implications.[37,40–43] In healthy subjects, Hardy et al[42] reported aerosol deposition from some pneumatic nebulizers that was twice that of others. In subjects with chronic stable asthma, Johnson et al[43] reported differences in bronchodilation between nebulizers from different manufacturers.

Because of cost considerations, disposable single-patient-use nebulizers are typically used for many treatments. The effects of repetitive use and cleaning were evaluated by Standaert et al.[44] In that study, nebulizers were found to function correctly for 100 repeated uses, provided they were properly maintained. Proper maintenance consisted of washing with soapy water, rinsing, and air drying after each use. Each nebulizer was also subjected to a daily 30-minute soak in 2.5% acetic acid. In the same study,[44] it

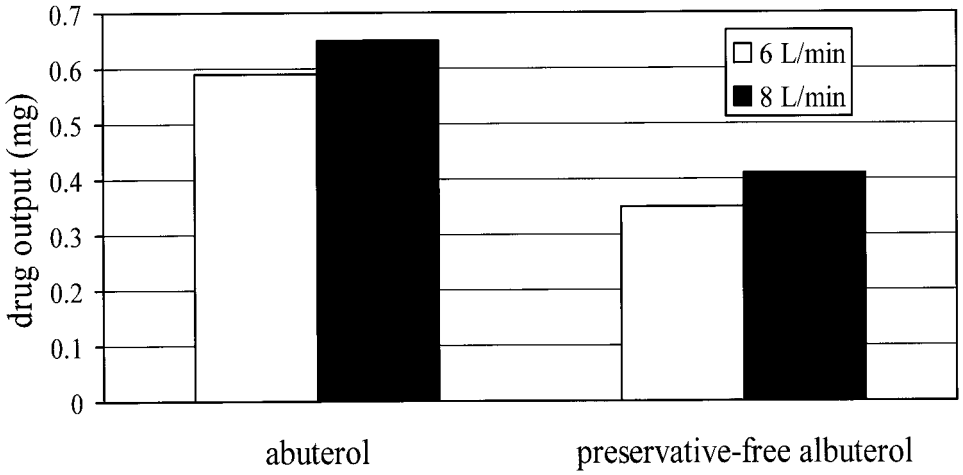

Fig. 4. Comparison of albuterol output of a pneumatic nebulizer, using two formulations of albuterol. (Drawn from data in Reference 38.)

was reported that the nebulizers started to fail after 40 uses if they were not cleaned after each use.

Several studies have reported greater output from pneumatic nebulizers when the fill volume is increased.[23,25,33,34,45] This is probably because nebulizers have a fixed dead volume, and thus an increase in fill volume reduces the proportion of dead volume within the nebulizer. Although nebulizer output increases with a greater fill volume, there is also an increase in nebulization time.[25] The nebulization time can be reduced when a larger fill volume is used by increasing the flow to power the nebulizer.[23,25] A nebulizer fill volume of 4–5 mL is recommended.

Output increases with an increased flow to power the nebulizer.[23,25,33] An increase in flow also decreases the droplet size produced by nebulizers.[25,39,46–48] A flow of 8 L/min is recommended. Flows lower than this result in decreased nebulizer performance. A flow greater than this may result in increased drug loss during the expiratory phase, which offsets the effect of greater flow on nebulizer output.[25]

It is not commonly appreciated that the drug formulation can affect nebulizer performance. MacNeish et al[38] reported differences in nebulizer output with two formulations of albuterol. Nebulizer output was significantly greater with the formulation containing the preservative benzalkonium chloride, probably because of its surface activity (Fig. 4). Large droplets were seen to adhere to the walls of the nebulizer with the preservative-free formulation, whereas foaming was seen to occur with the preservative-containing formulation. Others have also reported effects of drug formulation on nebulizer output.[39,49] It is interesting to note that metered-dose inhalers have always been tested and approved as a drug-delivery-system combination. Newer drug solutions have also been approved for a specific nebulizer (eg, pentamidine, ribavirin, dornase alpha, tobramycin).

The density of the gas powering the nebulizer affects nebulizer performance. Hess et al[50] reported the effect of heliox (80% helium, 20% oxygen) on nebulizer function. The inhaled mass of albuterol was significantly reduced when the nebulizer was powered with heliox, and there was a greater than twofold increase in nebulization time with heliox. An increased flow with heliox produced a respirable mass output similar to that produced when the nebulizer was powered with air. These results are explained by Bernoulli's principle, which predicts that the decreased density of heliox increases the velocity at which the gas leaves the jet orifice and produces less negative pressure to entrain drug solution.[50]

Patient Factors Affecting Nebulizer Performance

The breathing pattern of the patient affects the amount of aerosol deposited in the lower respiratory tract. This partially explains differences in aerosol deposition between children and adults. To improve aerosol penetration and deposition in the lungs, the patient should be encouraged to use a slow and deep breathing pattern.[51] Because of the effect of breathing pattern on drug delivery from nebulizers, in vitro evaluations of nebulizer performance should be conducted in a manner that simulates the breathing pattern of a patient.[52]

Inhaled aerosols can be administered using a mouthpiece or a face mask.[53–57] Bronchodilator responses occur with both techniques, and some have argued that the selection of interface should be based on patient preference.[53] However, it should be appreciated that the nasal passages effectively filter droplets delivered from the nebulizer. Everard et al[54] reported a nearly 50% reduction in aerosol

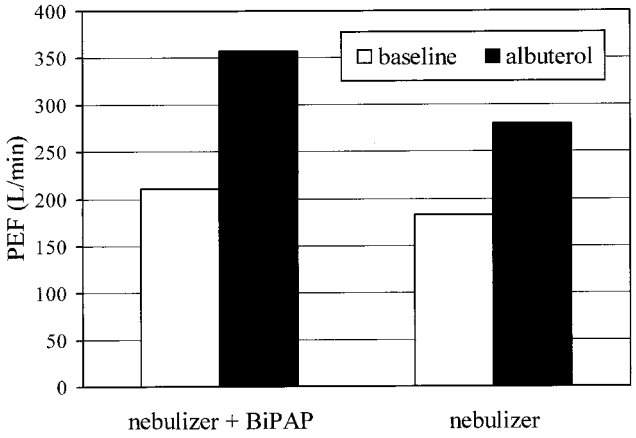

Fig. 5. Peak expiratory flow (PEF) responses with albuterol delivery by nebulizer with bilevel positive airway pressure (BiPAP) or by nebulizer alone. (Drawn from data in Reference 68.)

delivery to the lungs with nasal inhalation. Whether a mouthpiece or a face mask is used, it is important to instruct the patient to inhale through the mouth. Use of a mouthpiece may encourage oral breathing.[54] It is interesting to note that asthmatic patients switch their breathing route from the nasal route to the oronasal route during acute exacerbations and, even when not acutely bronchoconstricted, switch to oronasal breathing when wearing a face mask.[58]

Airway caliber affects lung delivery of nebulized bronchodilators.[59–61] Lipworth et al[61] reported lower plasma albuterol concentrations and attenuated bronchodilator responses in patients with severe asthma than in normal subjects or those with mild asthma. It is ironic that the air flow obstruction that produces the need for inhaled bronchodilator therapy also decreases the effectiveness of that therapy.

Several studies have reported greater pulmonary penetration of aerosols in patients with stable asthma and with acute airway constriction during heliox breathing.[62–66] Because of the lower density and greater viscosity of heliox, gas flow becomes less turbulent, which theoretically improves the transport of aerosols through constricted airways to more peripheral lung regions. Henderson et al[67] reported no significant advantage of heliox-driven nebulizer therapy over oxygen-driven nebulizer therapy. However, they[67] did not account for the effect of heliox on nebulizer function,[50] and this may have contributed to their negative findings.

Nebulizer therapy has been used in combination with noninvasive ventilation. Pollack et al[68] randomized patients with acute asthma to receive either bronchodilator therapy with a nebulizer and face mask or with a nebulizer, nasal mask, and BiPAP (bi-level positive airway pressure system made by Respironics). The BiPAP settings were: inspiratory pressure 10 cm H_2O, expiratory pressure 5 cm H_2O. The patients who received bronchodilator therapy with BiPAP had a greater improvement in peak flow (Fig. 5). Although these results are intriguing, further positive reports are needed before widespread acceptance of this practice. Interestingly, this approach to nebulizer therapy is reminiscent of intermittent positive-pressure breathing, which was abandoned many years ago as a method for delivery of inhaled bronchodilators to patients with asthma.

Nebulizer therapy is commonly used in mechanically ventilated patients, and this topic has been reviewed in detail elsewhere.[69–73] A number of factors are known to affect aerosol delivery from nebulizers during mechanical ventilation (Table 2).[12] There are disadvantages of nebulizer use during mechanical ventilation, such as circuit contamination,[74] decreased ability of the patient to trigger the ventilator[75] (if the nebulizer is not powered by the ventilator), and increases in the delivered tidal volume and airway pressure[76] (if the nebulizer is not powered by the ventilator). The nebulizer is less efficient than the metered-dose inhaler during mechanical ventilation, but the nebulizer delivers a greater dose to the lower respiratory tract.[77]

Designs to Enhance Nebulizer Performance

In recent years, several nebulizer designs have become available to decrease the amount of aerosol lost during the expiratory phase.[78] These include reservoir bags to collect aerosol during the expiratory phase, the use of a vented design to increase the nebulizer output during the inspiratory phase (breath-enhanced nebulizers), and nebulizers that only generate aerosol during the inspiratory phase (breath-actuated nebulizers). Because these designs improve drug delivery to the patient, they have the potential to reduce treatment time, which should improve patient compliance with nebulizer therapy.

Use of Reservoir Bags to Collect Aerosol During the Expiratory Phase

For many years, it has been a common practice to use a T-piece and corrugated tubing as a reservoir for small-

Table 2. Factors Affecting Aerosol Delivery from Nebulizers During Mechanical Ventilation

Endotracheal tube size
Position of nebulizer placement in the circuit
Type of nebulizer and fill volume
Humidification of the inspired gas
Treatment time
Duty cycle (I:E ratio)
Ventilator brand

I:E ratio = ratio of inspiratory time to expiratory time.

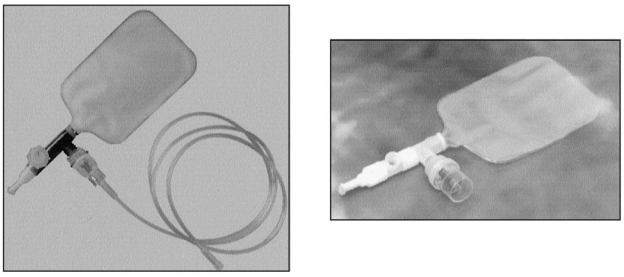

Fig. 6. Two designs of nebulizer device that use a reservoir bag. Circulaire (left) and AeroTee (right).

volume nebulizers.[79] In the late 1980s and early 1990s, there were reports of increased aerosol delivery to the lower respiratory tract when a plastic chamber was used with the nebulizer to capture aerosol during the expiratory phase, and provide that to the patient during the subsequent inspiration.[80,81] In the United States, a similar concept was incorporated into the Circulaire and AeroTee designs (Fig. 6). Both of these designs use a 750 mL bag to store aerosol during exhalation, but differ in how they prevent rebreathing. The Circulaire uses a one-way valve to prevent exhaled gas from entering the reservoir bag, whereas the AeroTee allows some exhaled gas to enter the bag.[82] These designs also decrease environmental contamination with the aerosol that is generated. The Circulaire incorporates a variable inspiratory/expiratory resister that is set to maximize inspiration from the reservoir bag, and to provide a positive expiratory pressure effect.

Mason et al[83] reported an MMAD of 0.51 μm with the Circulaire. Compared with a conventional nebulizer, they also reported better lung deposition, less gastrointestinal deposition, and less drug loss to the environment (Fig. 7). However, there are several important observations about these results. First, of 9 normal subjects, 2 actually had decreased pulmonary deposition with the Circulaire. This illustrates why caution must be exercised when applying group data to individual patients. Second, the conventional nebulizer used by Mason et al[83] does not perform as well as the nebulizer incorporated into the Circulaire. Thus, it is unclear whether the results were the effect of the reservoir bag or the nebulizer. The MMAD reported by Mason et al[83] for the Circulaire is not ideal. For maximal pulmonary deposition of bronchodilators, an MMAD of 1–5 μm is more desirable.

In another study by Mason et al,[84] the Circulaire was compared to a conventional nebulizer for bronchodilator delivery in patients with chronic obstructive pulmonary disease. In that study, the pulmonary deposition and therapeutic effect were similar for the Circulaire and the conventional nebulizer. Hoffman et al[85] compared the Circulaire to a conventional nebulizer for bronchodilator delivery in patients with acute bronchospasm presenting to an emergency department. They reported a greater improvement in bronchospasm (measured by peak flow) in the Circulaire group. In this study,[85] like those by Mason et al,[83,84] the nebulizer used with the Circulaire may have been superior to the conventional nebulizer that was used and, thus, the study may have compared the performance of nebulizers rather than the effect of the reservoir bag.

Breath-Enhanced Nebulizers

The traditional nebulizer design incorporates the nebulizer sidestream to the air flow of the patient. Some newer nebulizers use a mainstream design with valves. In this valved open-vent design, the patient breathes through the nebulizer during inspiration, which enhances the nebulizer output. During the expiratory phase, a one-way valve directs patient flow away from the nebulizer chamber (Fig. 8).

This design has been evaluated in several studies, which have reported greater pulmonary deposition with this design than with a conventional nebulizer.[86–88] A potential advantage of the open-vent nebulizer design is an improvement in nebulizer output with an increase in inspiratory flow. Coates et al[31] reported a greater output of tobramycin with increased inspiratory flow, using an open-vent nebulizer, whereas changes in inspiratory flow did not affect the output of the conventional nebulizer (Fig. 9). As with conventional nebulizers, performance differences between breath-enhanced nebulizers have been reported.[88,89]

Breath-Actuated Nebulizers

Aerosol waste during the expiratory phase can be eliminated if the nebulizer is only active during the inspiratory phase. Methods to manually actuate the nebulizer during the inspiratory phase have been available for many years.[45,90] It is also of interest to note that this design is commonly used in mechanical ventilator-actuated designs.[91,92] Both pneumatically and electronically controlled breath-actuated nebulizers have recently become commercially available. Their role in clinical application is yet to be determined.

Continuous Nebulization

Since the late 1980s, there has been considerable clinical and academic interest in the use of continuous aerosolized bronchodilators for the treatment of acute asthma[93–106] (Table 3). These studies suggest that this therapy is safe, at least as effective as intermittent nebulization, and may be superior to intermittent nebulization in patients with the most severe pulmonary function.

Several configurations have been described for continuous nebulization.[107] These include frequent refilling of

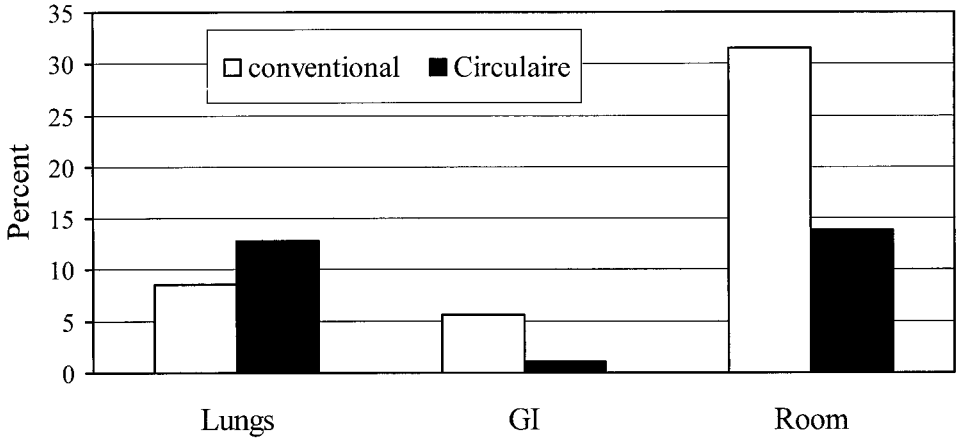

Fig. 7. Percent of drug delivery to the lungs, gastrointestinal (GI) tract, and room using a Circulaire nebulizer system. (Drawn from data in Reference 83.)

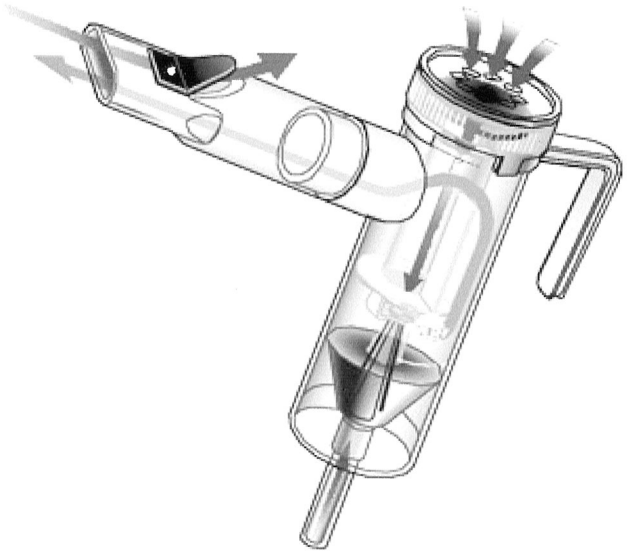

Fig. 8. Schematic representation of the function of a breath-enhanced nebulizer. Courtesy of Pari Respiratory Equipment.

the nebulizer,[93,101,104,106] use of a nebulizer and infusion pump (Fig. 10),[94,96,99,102,103,108] and use of a large-volume nebulizer.[95,97,98,106,109] Berlinski et al[110] reported a consistent and adequate aerosol production by a large-volume nebulizer over a 4-hour period of operation. Reisner et al,[111] however, reported a more consistent aerosol delivery with a small-volume nebulizer attached to an infusion pump than with a large-volume nebulizer. A commonly used large-volume nebulizer for this therapy is the High-output Extended Aerosol Respiratory Therapy (HEART) nebulizer. Raabe et al[112] reported a detailed evaluation of the performance of the HEART nebulizer. At a flow of 10–15 L/min, the aerosol output was 38–50 μL of aerosolized drug per liter of gas flow, and the solution output was 30–56 mL/hr.

McPeck et al[113] compared the HEART nebulizer to a conventional small-volume nebulizer in a model of adult and pediatric breathing. With the adult breathing pattern they reported similar aerosol delivery from the HEART nebulizer and small-volume nebulizer. For the pediatric breathing pattern the aerosol delivery from the small-volume nebulizer was greater than from the HEART. Both Raabe et al[112] and McPeck et al[113] reported an MMAD of about 2 μm with the HEART nebulizer. An important finding of McPeck et al[113] was that the albuterol delivery from the HEART nebulizer was significantly less than the target dose from the manufacturer's recommended setup.

Nebulizers for Specific Applications

Specially constructed small-volume nebulizers should be used when contamination of the ambient environment with the aerosolized drug needs to be avoided.[35,114,115] The most common example is aerosolized pentamidine.[116] The nebulizer is fitted with one-way valves and filters to prevent gross contamination of the environment. Examples of these devices include the Cadema Aero-Tech II and the Respirgard II. These devices produce a very small particle size, with an MMAD of about 1–2 μm, which is necessary to improve alveolar deposition of the drug.

The Small-Particle Aerosol Generator is used specifically to aerosolize ribavirin (Virazole).[117–119] The device consists of a nebulizer and a drying chamber. The drying chamber reduces the MMAD of particles to about 1.3 μm. There are concerns about the potential adverse effects of this drug on health care workers when ribavirin is used. For this reason, a scavenging system should be used when ribavirin is administered.[120–122] This is a double-enclosure system, with a ribavirin administration hood or mask inside a tent. Two high-flow vacuum scavenging systems

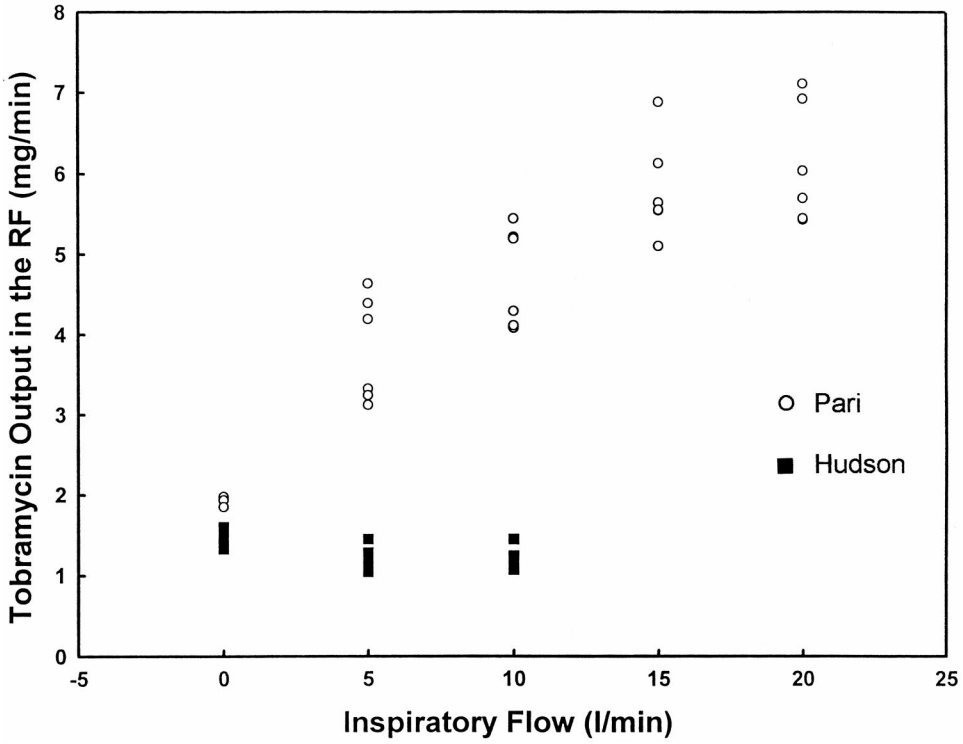

Fig. 9. Tobramycin output from a conventional nebulizer (Hudson) and a breath-enhanced nebulizer (Pari) with changes in inspiratory flow. RF = respirable fraction. (From Reference 31, with permission.)

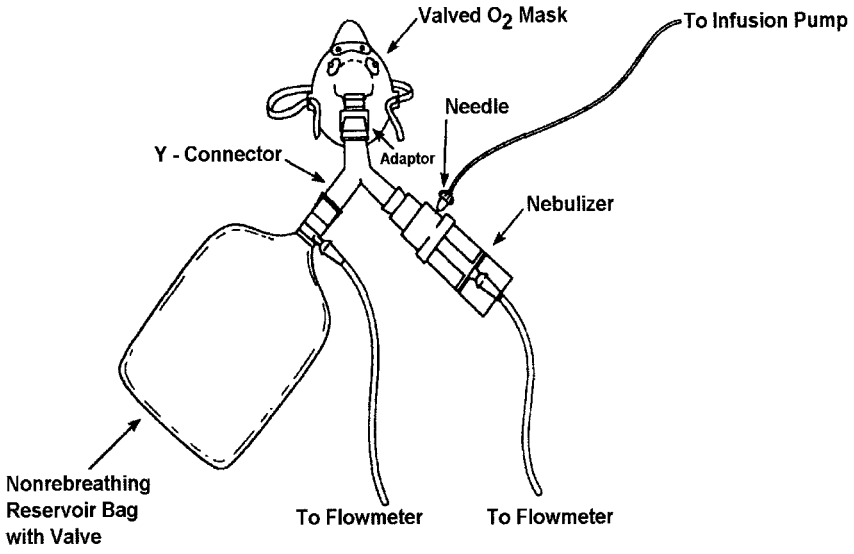

Fig. 10. System for continuous bronchodilator administration using a conventional nebulizer and an infusion pump. (From Reference 103, with permission.)

aspirate ribavirin from the system through high-efficiency particulate air filters.

Ultrasonic Nebulizers

Ultrasonic nebulizers have been clinically available since the 1960s.[123,124] Small-volume ultrasonic nebulizers are commercially available for delivery of inhaled bronchodilators.[125–131] Although several studies reported greater bronchodilator response with ultrasonic nebulizers than with other aerosol generators,[127,128] this has not been confirmed in other studies.[129–131] Large-volume ultrasonic nebulizers are used to deliver inhaled antibiotics in patients with cys-

Table 3. Summary of Studies Reporting Use of Continuous Nebulization

Author	Study Population	Drug	Research Design	Continuous Nebulizer Design	Major Finding
Portnoy[93]	Children with severe asthma	Terbutaline; 1–12 mg/h	Case series	Frequent refilling of conventional nebulizer	Continuously nebulized terbutaline safe and effective for treatment of severe asthma.
Moler[103]	Children with severe asthma	Terbutaline; 4 mg/h	Case series	Conventional nebulizer with infusion pump	Continuously nebulized terbutaline is an effective therapy for severe asthma.
Calcacone[95]	Adults with acute asthma	Albuterol; 10 mg over 2 h	Randomized controlled trial	Large volume nebulizer	Continuous nebulization was as effective as intermittent nebulization.
Chipps[109]	Children with bronchospasm	Terbutaline; 4 mg/h	Case series	HEART nebulizer	18 of 23 cases showed significant improvement with continuous nebulization.
Papo[96]	Children with status asthma	Albuterol; 0.3 mg/kg/h	Randomized controlled trial	Conventional nebulizer with infusion pump	Continuous nebulization was safe and resulted in more rapid improvement than intermittent nebulization.
Lin[97]	Adults with acute asthma	Albuterol; 30 mg over 110 min	Randomized controlled trial	HEART nebulizer	Continuous nebulization most beneficial in patients with $FEV_1 < 50\%$ predicted.
Rudnitsky[98]	Adults with acute asthma	Albuterol; 10 mg over 70 min	Randomized controlled trial	HEART nebulizer	Continuous nebulization may be of benefit for patients with peak flow < 200 L/min.
Lin[99]	Adults with acute asthma	Albuterol; 0.4 mg/kg/h for 4 h	Case series	Conventional nebulizer with infusion pump	High dose continuous nebulization can result in markedly elevated serum albuterol levels and potential cardiac stimulation.
Katz[100]	Infants and children with bronchospasm	Albuterol; 3 mg/kg/h	Case series	Not reported	Continuous albuterol safe and without significant evidence of cardiotoxicity.
Olshaker[101]	Adults with acute asthma	Albuterol; 7.5 mg over 1 h	Case series	Frequent refilling of conventional nebulizer	Continuous nebulization was safe and effective.
Baker[105]	Adults with acute asthma	Albuterol; 10 mg/h	Retrospective case control	Conventional nebulizer with infusion pump	Continuous and intermittent nebulization were similar in terms of safety, morbidity, and mortality.
Reisner[111]	Adults with acute asthma	Albuterol; 7.5 mg/h	Randomized controlled trial	Conventional nebulizer with infusion pump	Continuous nebulization was as safe and effective as intermittent nebulization.
Moler[103]	Children with acute asthma	Terbutaline; 16 mg over 8 h	Randomized controlled trial	Conventional nebulizer with infusion pump	Continuous nebulization produced similar plasma terbutaline levels and cardiovascular effects as intermittent nebulization.
Shrestha[104]	Adults with acute asthma	Albuterol; 2.5 mg or 7.5 mg over 2 h	Randomized controlled trial	Frequent refilling of conventional nebulizer	The standard dose continuous nebulization group had the greatest improvement with the fewest side effects.
Weber[106]	Adults with acute asthma	Albuterol at 10 mg/h; ipratropium at 1 mg/h	Randomized controlled trial	HEART nebulizer	There was no significant difference in outcomes for patients receiving continuous albuterol alone or continuous albuterol with ipratropium.

Table 4. Advantages and Disadvantages of Ultrasonic Nebulizers

Advantages
Little patient coordination required
Small dead volume
Quiet
Aerosol accumulates during exhalation
High doses possible
No chlorofluorocarbon release
Fast drug delivery
Disadvantages
Expensive
Contamination possible
Prone to electrical and mechanical breakdown
Not all drug formulations available
Drug preparation required

tic fibrosis (eg, tobramycin).[132–135] Ultrasonic nebulizers have also been used during mechanical ventilation,[136–139] where they have an advantage in that they do not augment tidal volume, as occurs with pneumatic nebulizers.

Table 4 lists advantages and disadvantages of ultrasonic nebulizers for medication delivery. Table 5 lists factors affecting output from ultrasonic nebulizers.[140] A potential issue with the use of ultrasonic nebulizers is the possibility of drug inactivation by the ultrasonic waves,[141] although this has not been shown to occur with commonly-used nebulized medications.

The ultrasonic nebulizer uses a piezoelectric transducer to produce ultrasonic waves that pass through the solution and aerosolize it at the surface of the solution. The ultrasonic nebulizer creates particle sizes of about 1–6 μm MMAD, depending on the manufacturer of the device.[140] The volume output of the ultrasonic nebulizer is about 1–6 mL/min, depending on the manufacturer of the device.[140]

An ultrasonic nebulizer has 3 components: the power unit, the transducer, and a fan. The power unit converts electrical energy to high-frequency ultrasonic waves at a frequency of 1.3–2.3 megahertz.[140] The frequency of the ultrasonic waves determines the size of the particles, with an inverse relationship between frequency and particle size. The frequency is not user adjustable. The power unit also controls the amplitude of the ultrasonic waves. This is user adjustable, with an increase in amplitude resulting in an increase in output from the ultrasonic nebulizer. The transducer vibrates at the frequency of the ultrasonic waves applied to it (piezoelectric effect). The transducer is found in two shapes, concave (focused) and flat (unfocused).[140] Concave transducers produce a higher output but require a constant level of solution for proper operation. The conversion of ultrasonic energy to mechanical energy by the transducer produces heat, which is absorbed by the solution over the transducer.

Table 5. Factors Affecting Output from Ultrasonic Nebulizers

Fluid characteristics: density, viscosity, surface tension, vapor pressure
Piezoelectric transducer: frequency of vibration, amplitude of vibration, configuration (focused or flat)
Coupling of medication chamber to transducer
Medication chamber: size, baffles
Flow from fan

In some ultrasonic nebulizers, the solution to be nebulized is placed directly over the transducer. In others, the solution to be nebulized is placed into a nebulization chamber and a water couplant chamber is placed between the transducer and the medication chamber. A fan is used to deliver the aerosol produced by the ultrasonic nebulizer to the patient, or the aerosol is evacuated from the nebulization chamber by the inspiratory flow of the patient.

Summary

Nebulizers have been used clinically for many years. Despite the increasing use of metered-dose inhalers and dry powder inhalers, it is likely that nebulizers will continue to be used in selected patients. A number of factors affect nebulizer performance, and these should be appreciated by clinicians who use these devices. Several new designs have recently become available that improve the performance of the nebulizer, but their cost-effectiveness remains to be determined.

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