Design Principles of Liquid Nebulization Devices Currently in Use

Joseph L Rau PhD RRT FAARC

Liquid nebulization is a common method of medical aerosol generation. Nebulizers are of 2 types: jet (or pneumatic) small-volume nebulizer, and ultrasonic nebulizer. Jet nebulizers are based on the venturi principle, whereas ultrasonic nebulizers use the converse piezoelectric effect to convert alternating current to high-frequency acoustic energy. Important variables for both types of nebulizer are treatment time required, particle size produced, and aerosol drug output. There are several advantages to jet nebulization, including that effective use requires only simple, tidal breathing, and that dose modification and dose compounding are possible. Disadvantages include the length of treatment time and equipment size. Design modifications to the constant-output nebulizer have resulted in breath-enhanced, open-vent nebulizers such as the Pari LC Plus and the dosimetric AeroEclipse. Ultrasonic nebulizers generally have a higher output rate than jet nebulizers, but a larger average particle size. Ultrasonic nebulizers can also substantially increase reservoir solution temperature, the opposite of jet nebulizer cooling. Drug concentration in the reservoir does not increase with ultrasonic nebulization, as it does with jet nebulization. Ultrasonic nebulizers have the same advantages as jet nebulizers. Ultrasonic nebulizers are more expensive and fragile than jet nebulizers, may cause drug degradation, and do not nebulize suspensions well. Neither type of nebulizer meets the criteria for an ideal inhaler: efficient and quick dose delivery with reproducibility, cost-effectiveness, and no ambient contamination by lost aerosol. *Key words: nebulization, jet nebulizer, aerosol, ultrasonic.* [Respir Care 2002;47(11):1257–1275]

Introduction

The term "nebulizer" derives from the Latin "nebula," meaning "mist," and reportedly was first used in 1872, followed by an 1874 definition as "an instrument for converting a liquid into a fine spray, especially for medical purposes."[1] The appealing logic of creating a vapor or aerosol for the inhalation treatment of lung disease is at least as old as written records of medicine. The Ayurvedic tradition of medicine in India, which dates back perhaps

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4,000 years or more, used inhaled substances for managing asthma.[2] Although inhalation devices were described in the 19th century, the modern precursors of small-volume nebulizer devices appeared with the glass and hand-bulb "atomizers" introduced for asthma treatment in the 1930s, such as the DeVilbiss No. 40 glass nebulizer.[1] The Collison nebulizer became available in the late 1940s; it used a baffle to filter out large particles, thus distinguishing a "nebulizer" from an "atomizer."[3] The Wright nebulizer, which appeared in the 1950s, was engineered from ebonite and perspex; it was much more compact than the Collison and more closely resembled today's pneumatically powered nebulizers.[4] A different method of creating liquid aerosols, the ultrasonic nebulizer, was introduced in the 1960s. It relies on high-frequency sound waves to aerosolize the solution. Today the term "nebulizer," as used clinically in respiratory care, encompasses both gas-powered jet nebulizers and ultrasonic nebulizers. This review considers the physical principles, designs, advantages, disadvantages, and factors affecting performance of jet and ultrasonic nebulizers that are in current clinical use.

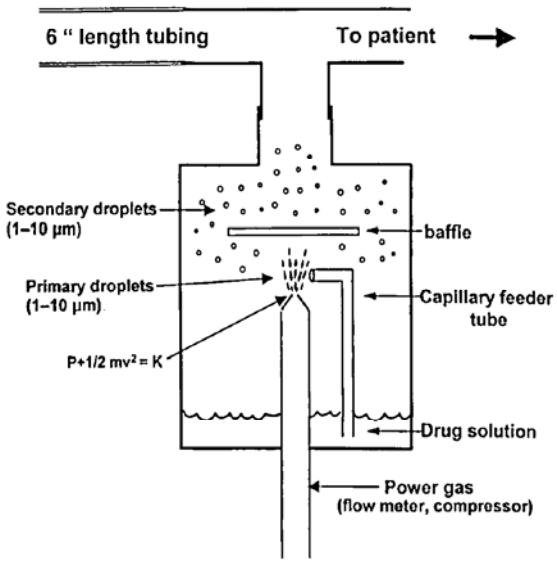

Fig. 1. The major elements of a jet (pneumatically powered) small-volume nebulizer. m = mass. v = velocity. P = pressure. K = constant.

Jet Nebulizers

Principle of Operation

Small-volume jet (pneumatic) nebulizers are 2-fluid atomizers. The basic principle of operation involves compressed gas directed through a narrow orifice, with entrainment of liquid through one or more capillary feeder tubes. The narrow-orifice gas nozzle has traditionally been termed a "venturi," with liquid entrainment based on the Bernoulli principle. In laminar flow, and keeping height constant, Bernoulli's equation[5] for an incompressible fluid states:

$$\tfrac{1}{2}\, mv^2 + P = \text{constant}$$

in which m = mass, v = velocity, P = pressure, and $\tfrac{1}{2}\, mv^2$ represents kinetic energy. For a gas in laminar flow through a tubing system, an increase in velocity, such as can occur at a restriction in the tubing, leads to a decrease in the lateral pressure. If kinetic energy increases, pressure energy must decrease, based on conservation of mass and energy. A "venturi" is based on Bernoulli's equation and uses the pressure drop to entrain a second fluid. The lower pressure causes drug solution to be drawn up to the gas jet through capillary or feeder tubes that lead down to the liquid reservoir. The entrainment is also attributed to momentum transfer between the power-gas molecules and air or liquid in the feeder tubes.[6] The high-velocity gas meeting the liquid causes primary generation of large droplets, typically 40–60 µm, but with a possible range of 15 to > 500 µm.[7,8] Droplets produced by primary generation are impacted onto baffles within the nebulizer, producing a secondary generation of aerosol with particles of 1–10 µm, with typical sizes of 4.0 and 5.0 µm.[7] During that second stage of aerosol generation the larger particles are baffled, coalesce, and drain back into the reservoir (Figure 1).

Aerosol droplet size depends on the geometry of the nozzle and baffles, nozzle diameter, gas velocity, mass flow of gas, and the physical constants of the power-gas and drug solution. Jet nebulizers produce a range of particle sizes, which is a distribution termed "polydisperse" or "heterodisperse," in contrast with "monodisperse" aerosols.[9] The mass median aerodynamic diameter (MMAD) is the median droplet size of the cloud of aerosol particles. Particles of 1–5 µm diameter have a higher probability of reaching the lower respiratory tract than do larger particles.[9] However, there is a trade-off between particle size and drug amount. With spherical particles, the mass of drug varies directly as the third power of the particle radius. An increase in particle size gives an exponential increase in drug mass, but the converse is also true. With aqueous solutions the extremely large surface area created by aerosol particles and a dry power-gas cause considerable evaporation and substantial cooling of the nebulizer, because of latent heat of vaporization, to approximately 10° C below ambient temperature, within minutes.[10] Higher power-gas flows can increase the amount of temperature drop in some nebulizers.[11] The amount of temperature drop differs among nebulizer brands,[11] and the amount of temperature drop is less with a partially humidified power-

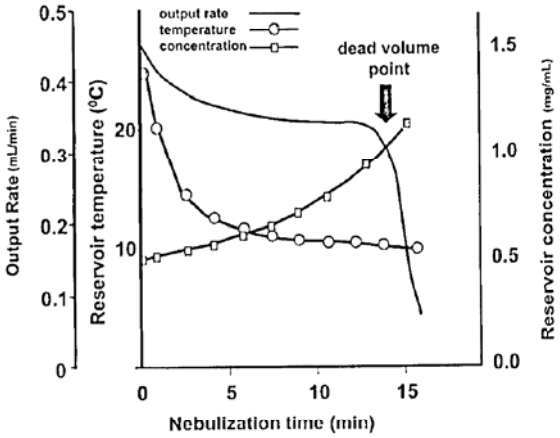

Fig. 2. Functioning of a small-volume jet nebulizer with respect to output rate, solution temperature, and concentration of solute in the solution during nebulization. The data are hypothetical and not based on actual measurements of a particular brand of nebulizer.

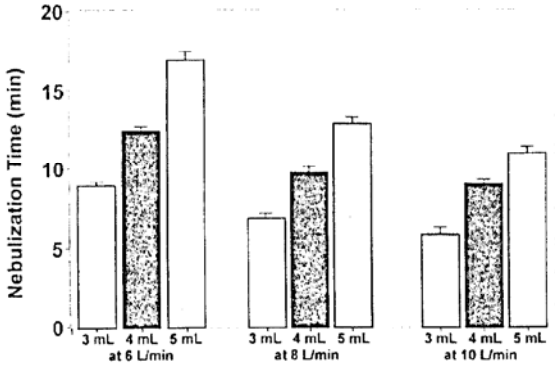

Fig. 3. Nebulization time is a function of both the power-gas flow rate and the fill volume. Lower flow rates and higher fill volumes increase the nebulization time. The graph shows pooled data from 17 nebulizers. (From Reference 17, with permission.)

gas, such as from a compressor, than with a drier gas, such as from a cylinder or wall outlet.[12] The evaporation also increases the solution's drug concentration during the time of operation.[10,13,14] Dennis et al found an increase from 1% to 3% using 5 mL of a solution of sodium fluoride in a Wright nebulizer—a 200% increase in concentration.[15] Concentration increases ranging from 5% to over 37% have been found with other jet nebulizers, using albuterol solution.[16] Figure 2 shows a generic illustration of output rate, temperature, and solution concentration for a typical small-volume jet nebulizer. In the first minutes the output rate falls as the solution temperature drops and viscosity and surface tension increase.[10] A plateau is then reached in both output and temperature, until a point at which output decreases precipitately; this is usually the point at which the level of liquid in the reservoir falls below the bottom of the capillary feeder tube. At that point, gas is drawn up with the liquid, the nebulizer begins to sputter, and aerosol creation is intermittent. Tapping the nebulizer can cause baffled droplets to coalesce, run down the walls of the reservoir, increase the solution level, and temporarily restore aerosolization. Ultimately nebulization ceases, although the nebulizer contains some residual solution on the apparatus walls, baffles, and at the bottom of the reservoir chamber. The amount of that remaining liquid is termed the "dead volume," which in most small-volume nebulizers is approximately 1 mL.[10] The fact that most nebulizers cannot aerosolize well below 1 mL is the reason that a bland diluent of saline or water is added to a 0.5 mL drug dose; for example, albuterol from a multi-use bottle of 0.5% solution. Addition of the diluent is not to weaken the drug solution, but is in fact needed if any aerosol is to be produced, and increases the amount of drug emitted by the nebulizer.[17]

Variables of Nebulizer Performance

Several variables describe the nebulizer performance, including the time required for nebulization, droplet size produced, and drug output.

Nebulization Time. The time required is directly proportional to the volume of solution placed in the reservoir and inversely proportional to the power-gas flow (Fig. 3).[11,17]

Determination of nebulization time in studies differs because it is difficult to decide when aerosolization has ceased. The nebulization time depends on how the end point of nebulization is defined. Kradjan and Lakshminarayan defined 3 possible end points for nebulization: sputtering time, total time, and clinical time.[18] Sputtering is the point when aerosolization becomes erratic, as noted by seeing and hearing. Total time is when production of aerosol ceases. Clinical time is between sputtering and total time, and approximates the point when a patient or therapist typically stops a treatment. With a 3 mL volume, averaged over 5 nebulizer brands, the sputtering, clinical, and total times were measured as 7.3, 9.9, and 12.8 min, respectively, by Kradjan and Lakshminarayan.[18] Nebulization time may also be defined as the point 30 seconds after sputter, with or without tapping, although this can introduce greater subjectivity in the measurement. Regardless of the end point chosen, it is important that studies define the end point clearly, in order to allow comparisons.

There is evidence to suggest that nebulization time varies directly with the viscosity of solutions. Antibiotic solutions can be more viscous than aqueous bronchodilator solutions and can require more powerful compressors (ie, higher power-gas flows) to keep nebulization times from being prolonged. Hess et al found that the average nebulization time pooled for 17 nebulizers, using albuterol,

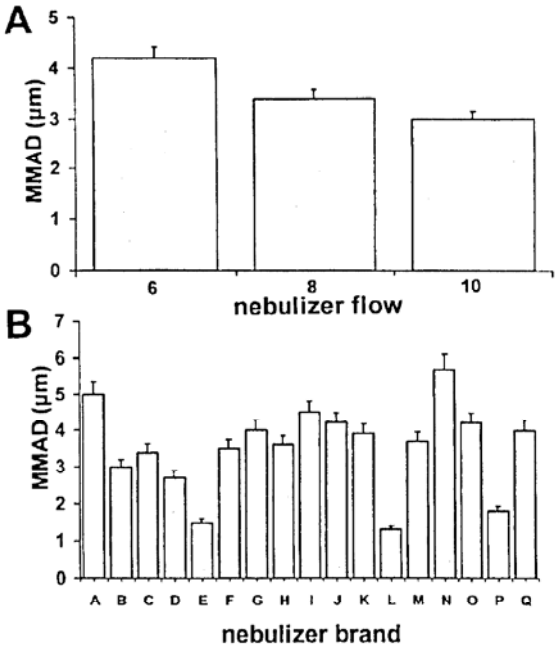

Fig. 4. A. Effect of power-gas flow rate on mass median aerodynamic diameter (MMAD), with smaller particle sizes at higher power-gas flow rates. The graph shows pooled data from 17 nebulizers. B. MMAD for 17 nebulizer brands, pooled for all power-gas flow rate settings. (From Reference 17, with permission.)

with 4 mL volume and 6 L/min power-gas flow, was approximately 13 min.[17] Newman et al investigated nebulized gentamicin solution with 4 different nebulizers and found that 4 mL (160 mg) at 6 L/min power-gas flow required between 17 and 25 min.[19] The approximate average time pooled for the 4 nebulizers was 20 min. That study recommended flows of 10–12 L/min or a high-flow compressor for nebulization of antibiotic solutions.

Particle Size. Particle size is a major factor influencing the probability of drug particles reaching the various levels of airway generation.[20] Particle size produced by a small-volume jet nebulizer is inversely proportional to power-gas flow (or compressor pressure). Hess et al found that the MMAD varied inversely with power-gas flow rates between 6 and 10 L/min (Fig. 4A).[17] In that study the percentage of 1–5 μm particles increased with higher power-gas flow rates. Similar data were reported from the United Kingdom by Clay et al for 4 disposable jet nebulizers.[21] Increasing the power-gas flow rate produced smaller particles and reduced nebulization time. Particle size is also affected by the physical characteristics of the drug solution, such as surface tension and viscosity.[19,22] Hess et al found that the MMAD produced by 17 nebulizers differed significantly (see Fig. 4B),[17] and the percentage of 1–5 μm particles ranged from slightly over 30% to 60%. Clay et al found an inverse relationship between the MMAD and the geometric standard deviation, indicating that the MMAD was smaller but the aerosol was more heterodisperse at higher flow rates.[21]

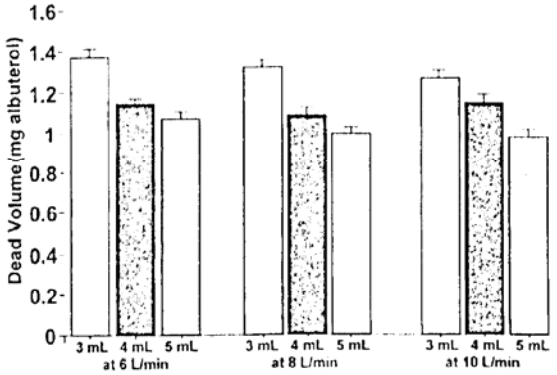

Fig. 5. Effect of power-gas flow rate (6, 8, or 10 L/min) and fill volume (3, 4, or 5 mL) on amount of drug remaining in the dead volume. The graph shows pooled data from 17 nebulizers. (From Reference 17, with permission.)

Aerosol Drug Output. The primary factors affecting the amount of aerosolized drug released from a jet nebulizer are the fill volume and, secondarily, the type of nebulizer. Increasing the fill volume results in lower concentrations of drug remaining in the dead volume of the nebulizer, when nebulization ceases. This is based on the following relationship:

Dead volume drug (mg) = dead volume (mL)

× concentration (mg/mL)

With a theoretical dead volume of 1.0 mL and assuming no increase in concentration of the residual solution due to evaporation, a 2 mL fill volume would leave at least half of the drug in the dead volume. A 4 mL fill volume would only leave a quarter of the drug in the dead volume. In reality, evaporation increases the concentration of the solution remaining in the nebulizer.[15] Increasing the fill volume therefore reduces or "dilutes" the concentration of drug in the dead volume, but also increases nebulization time (Fig. 5).[17] In the case of a 2.5 mg dose of nebulized albuterol, fill volumes of 3, 4, and 5 mL decrease the amount of drug left in the dead volume from approximately 1.4 mg to approximately 1.15 mg and 1.1 mg, respectively.[17] Determination of aerosol output, dead volume, and remaining drug amount depends on the definition of "end of nebulization."

The type of nebulizer can also affect the amount of drug available for inhalation. Devadason et al compared 4 neb-

ulizer systems (Acorn, Acorn plus Mizer, Ventstream, and Pari LC) and found significant differences in the delivery of albuterol to inspiratory filters, ranging from 9.35% to 19% of the nominal dose.[23] Barry et al compared outputs of a nebulized corticosteroid (budesonide) from the Ventstream, the Pari LC Plus, and the Pari LC Star, using the compressors specified for each. The nebulizers differed in both the rate of output (7.3–14.5 μg/min) and the total output of drug collected on inspiratory filters (32.3–91.9 μg), using simulated conditions of breathing.[24]

The physical properties of the power-gas and the solution to be nebulized also affect nebulizer output. Substituting heliox for air decreased particle size and inhaled drug mass significantly, using albuterol.[25] Nebulized albuterol availability was greater from a solution containing the preservative benzalkonium chloride, because of the lower surface tension produced by the preservative (35.0 ± 0.5 millinewtons per meter with preservative vs 70.5 ± 0.5 millinewtons per meter without).[22] The foaming seen with the lower surface tension from the preservative resulted in more return of liquid to the reservoir and a smaller dead volume than with the preservative-free solution, with which large droplets adhered to the nebulizer walls and increased the dead volume. Coates et al also found that nebulizer output of aerosolized tobramycin was greater with the addition of albuterol containing benzalkonium chloride, which lowered the surface tension.[26]

Advantages and Disadvantages of Jet Nebulizers

Table 1 lists the advantages and disadvantages of small-volume jet nebulizers. Chief among the advantages is the simple, tidal breathing pattern used. Complex breathing maneuvers or coordination of breathing with device function is not needed. Drug delivery to the airway is over a period of minutes, with 60–90 breaths, rather than dependent on 1 or 2 carefully timed inspirations with particular flow rates, as with a metered-dose inhaler (MDI) or dry powder inhaler (DPI). A second major advantage is the ability to nebulize various solutions and to modify solution concentration and thereby the amount of drug delivered. Many of the drugs currently used in the United States for inhalation treatment of pulmonary disease are available as nebulizer solutions, and some of these drugs, such as dornase alfa (Pulmozyme) and inhaled tobramycin (TOBI) are only available in solution form for nebulization. In the United States the use of nebulizers in home therapy is paid for by Medicare, whereas other inhaled drug formulations such as MDI and DPI are not, since drug therapy for nonhospitalized patients is not generally covered by Medicare at this time. This provides an additional economic advantage to nebulized drug therapy for a certain sector of patients.

Table 1. Advantages and Disadvantages of Small-Volume Jet (Pneumatic) Nebulizers

Advantages
• Patient hand-breathing coordination not required
• Effective when used with normal tidal breathing patterns, with no breath-hold
• Effective with low inspiratory flows or volumes
• Ability to aerosolize many drug solutions
• Ability to aerosolize drug mixtures (> 1 drug), assuming suitable testing of drug activity
• Drug concentrations can be modified and high doses are possible
Disadvantages
• Expense of equipment
• Equipment is cumbersome and lacks portability
• Treatment times are lengthy and include set-up and cleaning time
• Variability in performance characteristics
• Possible patient auto-contamination with inadequate cleaning
• Wet, cold spray is produced, which is unpleasant with face-mask delivery
• Need for an external power source (electricity and/or compressed gas)

The chief disadvantages of small-volume jet nebulizers are the size of the equipment (which requires a power source), the inconveniently long treatment time, and the equipment set-up and cleaning. In addition to the lack of portability and slow dosing, disposable jet nebulizers vary in performance among samples of the same brand and among different brands. Hollie et al showed both intranebulizer and internebulizer variability in output and respirable-range output (the "fine particle fraction") for the DeVilbiss 646 jet nebulizer.[27] Alvine et al examined 8 disposable jet nebulizer models, from 6 manufacturers, and found that 4 of the 8 models showed visual signs of malfunction, which included spraying of large, visible droplets, leaking of solution, and air leaks that prevented nebulization completely. Variability of the nebulization rate within a specific model ranged from 57% to 129%.[28] The studies by Hollie et al and Alvine et al attributed the lack of reliability in performance to poor quality control by manufacturers.

Design Variations in Traditional Jet Nebulizers

Although the basic design of jet nebulizers has remained the same over the last 40–50 years, within the last 10 years there have been modifications aimed at reducing device loss and exhaled loss and improving drug availability to the patient. These modifications are in current clinical use, although newer developments in nebulization of liquids are also occurring. Investigational developments are not reviewed herein.

Dennis conceptualized 3 categories of jet nebulizer: constant-output, breath-enhanced, and dosimetric.[13] Figure 6

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