Medication Nebulizer Performance*

Effects Of Diluent Volume, Nebulizer Flow, and Nebulizer Brand

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Background: **Medication nebulizers are commonly used to delivery aerosolized medications to patients with respiratory disease. We evaluated output and respirable aerosol available to the patient (inhaled mass) for 17 medication nebulizers using a spontaneous breathing lung model.**
Methods: **Three nebulizer fill volumes (3, 4, and 5 mL containing 2.5 mg of albuterol) and 3 oxygen flows (6, 8, and 10 L/min) were evaluated using the 17 nebulizers. A cotton plug at the nebulizer mouthpiece was used to trap aerosol during simulated spontaneous breathing. Following each trial, the amount of albuterol remaining in the nebulizer and the amount deposited in the cotton plug were determined spectrophotometrically. Aerosol particle size was determined using an 11-stage cascade impactor.**
Results: **Increasing fill volume decreased the amount of albuterol trapped in the dead volume ($p<0.001$) and increased the amount delivered to the patient ($p<0.001$). Increasing flow increased the mass output of particles in the respirable range of 1 to 5 μm ($p=0.004$), but the respirable mass delivered to the patient was affected to a greater extent by nebulizer brand ($p<0.001$) than flow. Although 2.5 mg of albuterol was placed into the nebulizers, less than 0.5 mg in the respirable range of 1 to 5 μm was delivered to the mouthpiece.**
Conclusions: **The performance of medication nebulizers is affected by fill volume, flow, and nebulizer brand. When they are used for research applications, the nebulizer characteristics must be evaluated and reported for the conditions used in the investigation.** ***(CHEST 1996; 110:498-505)***

Key words: aerosol therapy; inhaled bronchodilator administration; nebulizers

Abbreviations: GSD=geometric standard deviation; MMAD=mass median aerodynamic diameter

Despite the common use of metered-dose inhalers and the availability of dry powder inhalers, aerosolized medications are still frequently administered by nebulizer. Nebulizers are commonly used for inhaled bronchodilator administration to patients with reactive airways, including the perioperative and postoperative treatment of these patients. Advantages of nebulizers include the ability to use them with patients who cannot coordinate the use of a metered-dose inhaler[1] and the ability to conveniently administer a large (or continuous) dose into the lungs.[2] Important characteristics of nebulizer performance include the drug output, the aerosol particle size generated, the nebulization time, and the amount of drug delivered to the patient. Factors that have been shown to affect nebulizer performance include device construction (*ie,* manufacturer), fill volume, flow, temperature, and humidity of the driving gas.[1]

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A common feature of nebulizers is dead volume, which is the volume of solution that remains in the nebulizer cup after aerosol production ends. Previous studies have typically evaluated dead volume by serial weighing.[3-5] This method does not adequately characterize drug output and amount of drug in the dead volume due to reconcentration in the nebulizer cup.[6,7] Reconcentration occurs because of evaporation owning to the low relative humidity of the gas powering the nebulizer. Nebulizer output should be determined more appropriately by measuring the amount of medication that remains after aerosol production is complete.

Particle size is an important characteristic of nebulizer performance. Particles too large do not reach the

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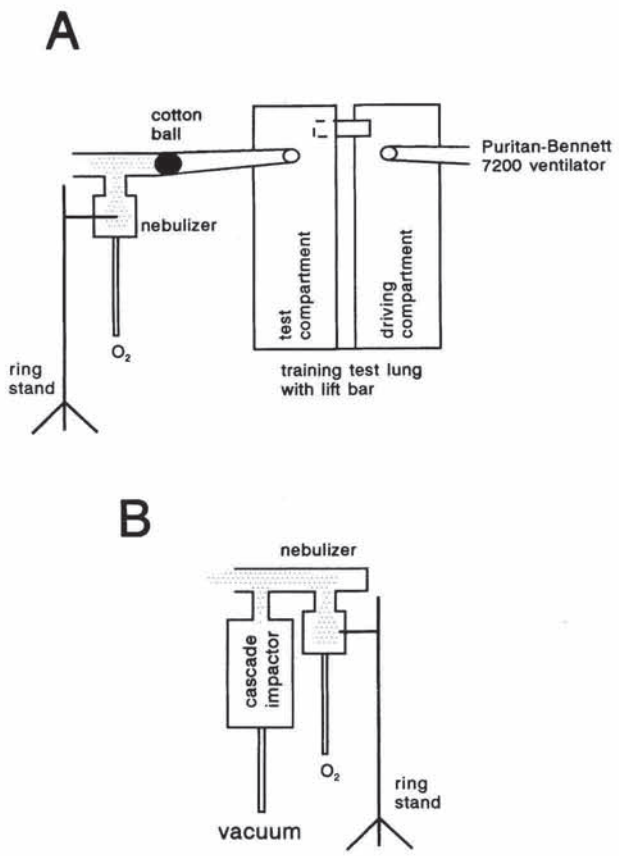

FIGURE 1. *Top, A:* experimental setup used to evaluate nebulizer output and inhaled mass. *Bottom, B:* experimental setup to evaluate aerosol particle size output of the nebulizer.

lower respiratory tract, whereas particles too small are exhaled.[8] It has been shown that smaller particles are produced at higher nebulizer flows.[9] Methods that determine particle sizes from nebulizers should classify them according to aerodynamic diameter and not physical diameter. A cascade impactor, unlike the optical laser particle counter, allows quantification of drug delivery in terms of aerodynamic size characteristics of the aerosol.[10] Aerodynamic diameter accounts for the density and irregular shape of drug particles and more accurately predicts the behavior of the aerosol as it is delivered to the patient.

Loffert et al[4] introduced the concept of respirable rate, which combines the effects of nebulizer output, nebulization time, and percent of particles in the respirable range. However, they determined nebulizer output by serial weighing rather than measurement of the amount of nebulized medication. A more useful index of nebulizer function might be respirable mass—the amount of aerosolized drug in the respirable range. In this study, we extended the concept of Loffert et al[4] by quantifying not only the respirable aerosol mass from the nebulizer, but also the respiratory

Table 1—*Nebulizer Brands Evaluated*

	Nebulizer Brand; Manufacturer; Location
A.	Whisper Jet Nebulizer System; Marquest Medical Products Inc; Englewood, Colo
B.	Ava-Neb Nebulizer; Hudson Respiratory Care Inc; Temecula, Calif
C.	Raindrop Medication Nebulizer; Puritan-Bennett; Lenexa, Kan
D.	Vix One Nebulizer; Westmed Inc; Tucson, Ariz
E.	Sidestream Nondisposable; Inspired Medical Products; Pagham, West Sussex, UK
F.	T-Updraft II Neb-U-Mist Nebulizer; Hudson Respiratory Care Inc; Temecula, Calif
G.	Fan Jet Nebulizer; Westmed Inc; Tucson, Ariz
H.	One-No 8900 TG; Salter Labs; Arvin, Calif
I.	Airlife Misty Neb; Baxter Healthcare Corp; Valencia, Calif
J.	Hospitak; Lindenhurst, NY
K.	T Up-Draft; Hudson Respiratory Care Inc; Temecula, Calif
L.	Sidestream Disposable; Inspired Medical Products; Pagham, West Sussex, UK
M.	Intertech Inspiron; Intertech Resources Inc; Lincolnshire, Ill
N.	Betamist$_2$ Medication Nebulizer; Professional Medical Products Inc; Greenwood, SC
O.	Micro-Mist; Hudson Respiratory Care Inc; Temecula, Calif
P.	Ventstream; Inspired Medical Products; Pagham, West Sussex, UK
Q.	B & F Medical Products Inc; Toledo, Ohio

It has been suggested that nebulizers be characterized by the amount of medication that is delivered to the patient. Smaldone[11] introduced the term *inhaled mass,* which he defined as that mass of drug actually delivered by a given nebulizer for a defined breathing pattern and period of time. Inhaled mass is affected not only by the performance of the nebulizer, but also by the breathing pattern chosen. For a given breathing pattern, inhaled mass should allow comparison of the quantity of drug delivered by different nebulizer systems and adjustment of the drug dose accordingly. To our knowledge, evaluation of inhaled mass has not been reported for nebulizers designed primarily for delivery of bronchodilators.

We conducted this study to evaluate medication nebulizer performance addressing those issues described above. Dead volume, the amount of drug remaining in the dead volume, nebulization time, and aerosol available to the patient (inhaled mass) were evaluated for 17 nebulizers, 3 fill volumes, and 3 flows. We also evaluated particle size for 3 flows with the 17 nebulizers at a single fill volume.

MATERIALS AND METHODS

Nebulizers Evaluated

We evaluated 17 commercially available nebulizers (Table 1). Nebulizers were provided by their manufacturers. All units were from the same lot number and the same packaging case. The nebulizers were provided by the manufacturer from their saleable stock;

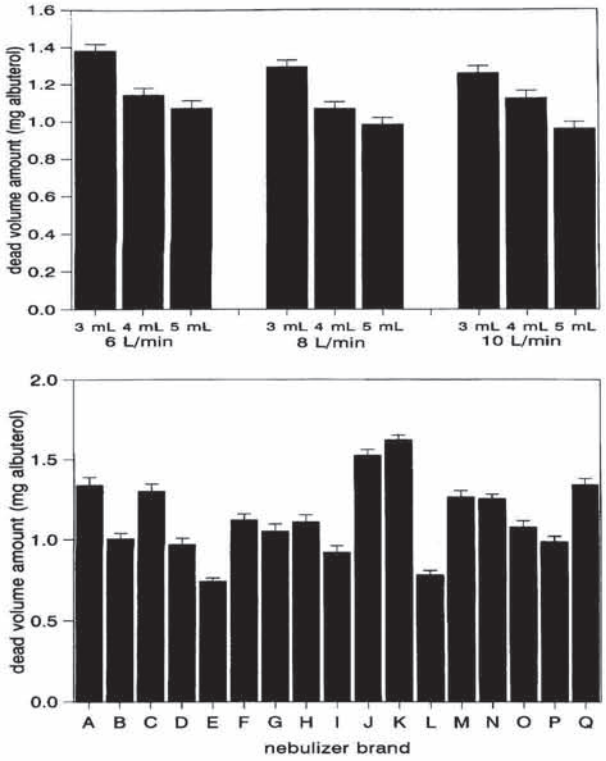

FIGURE 2. *Top:* effect of volume ($p<0.001$) and flow ($p=0.02$) on amount of albuterol trapped in the dead volume. Data are pooled from all nebulizers for each flow and volume setting. *Bottom:* effect of nebulizer brand on amount of albuterol trapped in dead volume ($p<0.001$). Data for each nebulizer brand are pooled from all volume and flow settings.

Evaluation of Dead Volume and Aerosol Available to the Patient

The experimental system is shown in Figure 1. The nebulizer was placed in a clamp and attached to a ring stand in the vertical position. A double-sided test lung (Michigan Instruments; Grand Rapids, Mich) was used to simulate spontaneous breathing. One side of the test lung was attached to a ventilator (Puritan-Bennett 7200 ventilator; Puritan-Bennett; Carlsbad, Calif) and that side of the test lung lifted the contralateral side to simulate spontaneous breathing. The lung model was set to simulate breathing at 12 breaths/min, fraction of total respiratory cycle inspiration (Ti/Ttot) approximately 0.4, peak inspiratory flow approximately 0.3 to 0.4 L/s with a sine wave pattern, and tidal volume approximately 0.45 to 0.5 L. A pilot evaluation showed that this closely simulated the breathing pattern of a normal volunteer breathing through a mouthpiece without nose clips (imitating mouthpiece breathing with a nebulizer).

The mouthpiece of the nebulizer was replaced with a step-down adapter and a cotton plug was placed into the adapter to trap aerosol. Pilot testing using several cotton plugs showed that a single plug was 100% effective as a filter of aerosol from the nebulizer. The test chamber of the lung model (simulating a spontaneously breathing patient) was attached to the adapter containing the cotton plug.

Saline solution diluent volumes of 2.5, 3.5, and 4.5 mL and 2.5 mg (0.5 mL of 0.5%) of albuterol (Proventil; Schereing; Kenilworth, NJ) were placed into the nebulizer cup to produce fill volumes of 3, 4, and 5 mL. Saline solution and albuterol were precisely measured using calibrated syringes. Oxygen flows of 6, 8, and 10 L/min were used from a calibrated flowmeter (Timeter; Lancaster, Pa) connected to the hospital bulk oxygen supply. Three new nebulizers were used for each flow and volume setting. Trials were performed at ambient room temperature (approximately 22°C) and humidity (approximately 40 to 50% relative humidity).

The nebulizer was tapped periodically during each trial. Nebulization time was determined by a stopwatch and was considered complete when there was no visible or audible evidence of nebulization for a period of 30 s. The nebulizer was weighted empty (Ohaus 311 Cent-O-Gram Balance; Carolina Biological; Burlington, NC), after it was filled with medication and diluent, and at the end of the trial. The percentage of solution that was nebulized was calculated from these mass values.

At the end of each trial, the amount of drug remaining in the nebulizer cup was determined by washing the inside of the nebulizer cup with 10 mL of saline solution and spectrophotometrically determining the amount of albuterol remaining in the nebulizer cup. The drug present in the cotton plug was extracted using 20 mL of saline solution and gentle agitation by vortex. The resulting solution was centrifuged at 5,000 *g* for 10 min to remove all cotton fibers from the solution and the amount of albuterol was then determined spectrophotometrically. As with other studies using methods similar to ours, we assumed that all albuterol was extracted from the cotton.[12,13]

Particle Size Determination

The experimental setup used to determine particle size is shown in Figure 1. During evaluation, the nebulizer was placed in a clamp and attached to a ring stand in the vertical position. Albuterol (0.5 mL of 0.5%) was placed into the nebulizer cup and diluted with 2.5 mL of saline solution. Particle sizes were determined at oxygen flows of 6, 8, and 10 L/min. Three new nebulizers of each type were evaluated at each oxygen flow.

Aerosol particle size produced by the nebulizer was determined using an 11-stage cascade impactor (Intox; Albuquerque, NM) with cutoff stages of 12, 9.52, 7.56, 6, 5, 4, 3, 1.8, 1, 0.4, and 0.25 µm. Aerosol was sampled 5 cm from the outlet of the nebulizer at a flow of 2 L/min to the impactor for 2 min. The albuterol deposited on each stage of the impactor was collected on plates, washed with saline solution, and the amount of albuterol was determined spectrophotometrically. The cascade impactor was calibrated by the manufacturer and used per manufacturer's specifications. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were determined from the calibration curves provided by the manufacturer. Cumulative deposition data were plotted against stage cutoff diameter, and fitted with a logarithmic regression curve to determine the particle size at 50% of the accumulated deposition (MMAD). This relationship was unimodal for all nebulizers and R^2 for this relationship is typically greater than 0.9 in our laboratory. GSD was calculated as the MMAD divided by the particle size at 16% deposition. In addition to MMAD and GSD, the percentage of particles in the respirable range of 1 to 5 µm was determined. Although both larger and smaller particles may have clinical benefit, we defined respirable particles as 1 to 5 µm for purposes of describing nebulizer performance in the laboratory. The same particle size range (1 to 5 µm) has been used by others to describe nebulizer performance.[4]

Respirable Mass

We also calculated respirable mass to combine the effects of drug output and the percentage of particles in the respirable range. Drug output was calculated by subtracting the amount of medication in the dead volume from the amount of medication placed into the nebulizer at the beginning of the trial (2.5 mg). Respirable mass output of the nebulizer was then calculated by multiplying the drug output times the percentage of particles in the respirable range of 1 to 5 µm. Respirable mass available to the patient was calculated

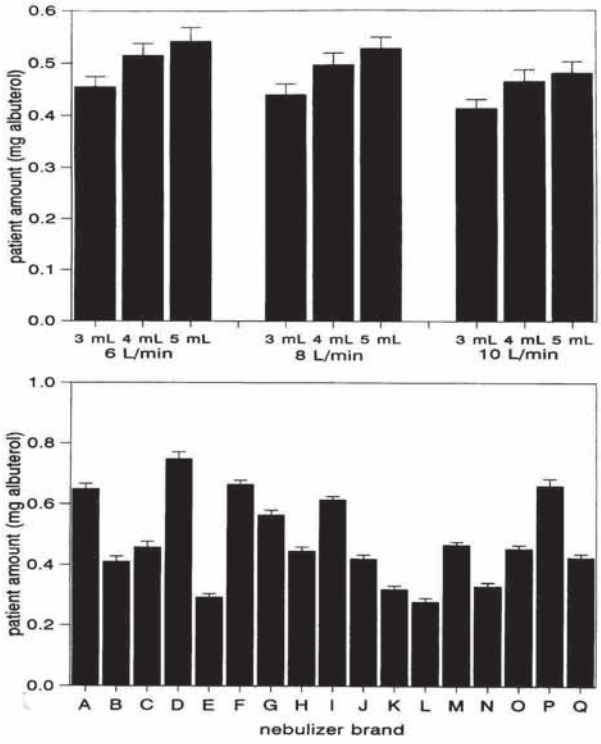

FIGURE 3. *Top:* effect of volume ($p<0.001$) and flow ($p=0.02$) on amount of albuterol delivered to the patient. Data are pooled from all nebulizers for each flow and volume setting. *Bottom:* effect of nebulizer brand on amount of albuterol delivered to the patient ($p<0.001$). Data or each nebulizer brand are pooled from all volume and flow settings.

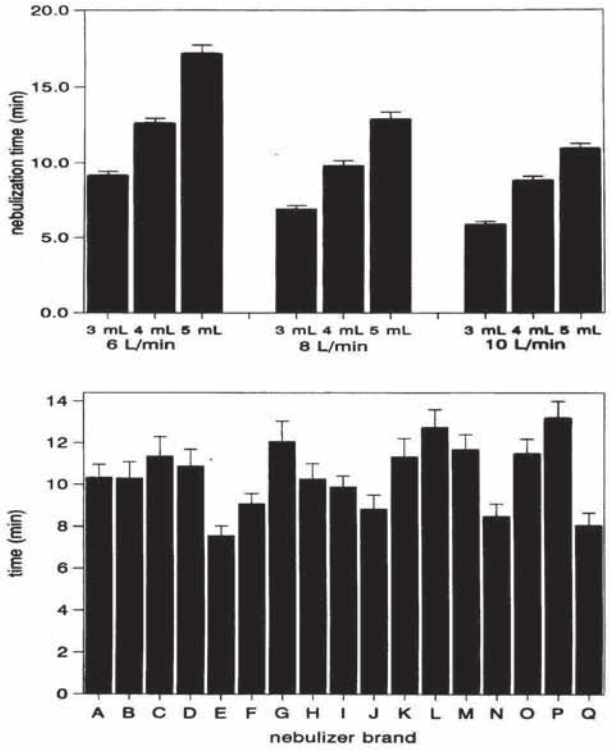

FIGURE 4. *Top:* effect of volume ($p<0.001$) and flow ($p<0.001$) on nebulization time. Data are pooled from all nebulizers for each flow and volume setting. *Bottom:* effect of nebulizer brand on nebulization time ($p<0.001$). Data for each nebulizer brand are pooled from all volume and flow settings.

lizer described the aerosol production of the device, whereas *respirable mass available to the patient* described aerosol available at the mouthpiece of the device. Because particle size was determined only for a single nebulizer volume, these calculations were conducted only for a nebulizer volume of 3 mL.

Spectrophotometric Analysis of Albuterol

A stock solution of albuterol (0.05 mg/mL) was prepared from powdered drug (Sigma; St. Louis) and a standard curve was constructed from serial dilutions. An absorbance peak was found at 278 nm and all absorbance measurements were made at this wavelength. Our spectrophotometric scan of the reference drug solution agreed well with published spectral properties of albuterol.[14] The spectrophotometer absorbance was adjusted to zero with a saline solution solvent (or saline solution solvent treated with cotton as appropriate) before each measurement was made. The amount of drug in test solutions was determined from the standard curve.

Statistical Analysis

Summary statistics are reported and mean±SE. Differences between groups were determined by one-way and multifactorial analysis of variance as appropriate. *Post hoc* analysis was conducted using the Scheffé procedure. Statistical significance was set at $p<0.05$.

RESULTS

Dead Volume

cantly less than that determined by measuring the amount of drug remaining in the dead volume (spectrophotometric method) (0.81±0.01 mg vs 1.14±0.01 mg; $p<0.001$). The effects of flow, diluent volume, and nebulizer brand on dead volume are shown in Figure 2. There was a small but significant ($p=0.02$) decrease in dead volume amount with an increase in flow from 6 to 10 L/min. There was no significant difference ($p>0.05$) between 8 and 10 L/min and 6 and 8 L/min. With an increase in diluent volume, there was a significant decrease in dead volume amount ($p<0.001$); this effect was significant among all levels of diluent volume. There were also significant differences in dead volume among nebulizer brands ($p<0.001$).

Aerosol Mass Available to the Patient (Inhaled Mass)

The effects of flow, fill volume, and nebulizer brand on the amount of aerosol available at the mouthpiece are shown in Figure 3. There was a small but significant ($p=0.02$) decrease in the amount of drug delivered to the mouthpiece (and thus available to the patient) with an increase in flow from 6 to 10 L/min. There was no significant difference ($p>0.05$) between 8 and 10 L/min and 6 and 8 L/min. There was a significantly

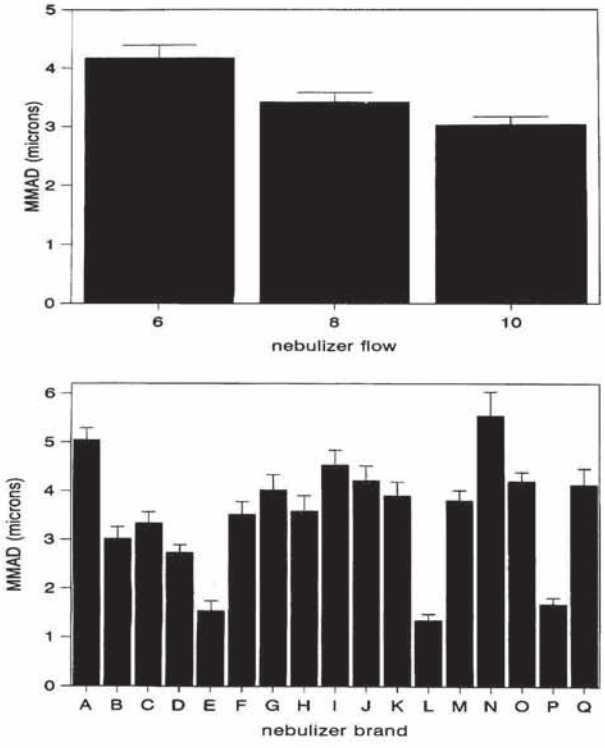

FIGURE 5. *Top:* effect of flow on MMAD ($p<0.001$). Data are pooled from all nebulizers for each flow. *Bottom:* effect of nebulizer brand on MMAD ($p<0.001$). Data for each nebulizer brand are pooled from all flow settings.

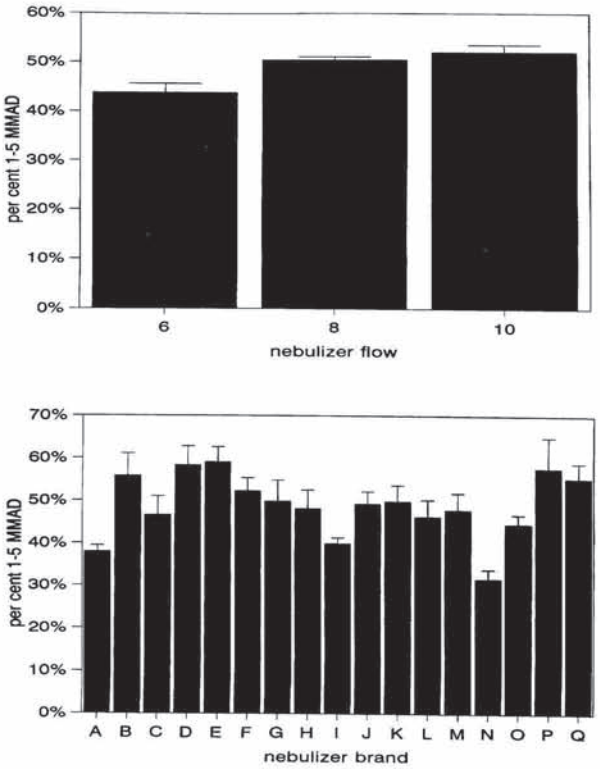

FIGURE 6. *Top:* effect of flow on percentage of particles in the respirable range of 1 to 5 μm ($p=0.004$). Data are pooled from all nebulizers for each flow. *Bottom:* effect of nebulizer brand on percentage of particles in the respirable range of 1 to 5 μm ($p<0.001$). Data for each nebulizer brand are pooled from all flow settings.

mL and from 3 to 5 mL. However, there were significant differences in albuterol delivered to the mouthpiece between 4 and 5 mL. There were also significant differences among nebulizer brands in the amount of drug delivered to the mouthpiece ($p<0.001$).

Nebulization Time

The effects of flow, fill volume, and nebulizer brand on nebulization time are shown in Figure 4. There was a significant increase in nebulization time with an increase in volume or a decrease in nebulizer flow ($p<0.001$ in each case). These differences were significant between all levels of volume and nebulizer flow ($p<0.05$ by Scheffé analysis). There were also significant differences in nebulization time among nebulizer brands ($p<0.001$).

Particle Size

The effects of flow and nebulizer brand on particle size are shown in Figure 5. There was a significant decrease in MMAD with an increase in nebulizer flow ($p<0.001$). There were also significant differences in MMAD among nebulizer brands ($p<0.001$). As shown in Figure 6, there was a small, but significant ($p=0.004$) increase in the mass of particles in the respirable range with an increase in nebulizer flow. There were signif-

Scheffé *post hoc* analysis, there was a significant difference in both MMAD and particles in the respirable range between flows of 6 and 8 L/min and between 6 and 10 L/min, but no difference between 8 and 10 L/min.

Respirable Mass

Respirable mass output of the nebulizers and respirable mass available to the patient is shown in Figure 7. With an increase in flow, there was a small but insignificant increase in respirable mass output ($p=0.07$) and respirable mass available to the patient ($p=0.43$). For nebulizer brands, there were significant differences in respirable mass output and respirable mass available to the patient ($p<0.001$ in each case). There was significantly more respirable aerosol mass output from each nebulizer than was available to the patient ($p<0.001$).

DISCUSSION

In this study, we have demonstrated that medication nebulizer function is affected by diluent volume, flow, and nebulizer brand. Increasing diluent volume decreased the amount of albuterol trapped in the dead

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