

Aerosol Delivery During Continuous Nebulization*

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Background and objectives: Continuous administration of aerosolized β_2 -agonists has been suggested as an effective treatment for severe reversible airways disease. To facilitate continuous therapy and avoid a feed system for small-volume nebulizers (SVNs), a large-volume medication nebulizer (Vortran HEART) was developed. The goal of this study was to determine actual drug delivery of the HEART and conventional SVNs for both adult and pediatric breathing patterns.

Design: Output studies were conducted on comparable samples of CIS-US AeroTech II and Hospitak PowerMist SVNs and Vortran HEART large-volume continuous nebulizers. To duplicate clinical aerosol delivery via an aerosol mask, drug particles were inhaled through the mouth of a model of a human face for two test breathing patterns (adult=tidal volume (VT) of 500 mL, 20 breaths/min, duty cycle of 40%; pediatric=VT of 100 mL, 35 breaths/min, duty cycle of 40%), generated by a ventilator. Radiolabeled particles of saline solution, confirmed to behave identically to albuterol, were collected on absolute filters at the mouth of the face to measure the actual mass of albuterol particles delivered to the airway opening.

Results: The AeroTech II and PowerMist SVNs delivered 5.14 and 3.74 mg/h, respectively, for the adult breathing pattern and 2.97 and 2.48 mg/h, respectively, for the pediatric breathing pattern. Drug delivery rates of the HEART were a function of drug concentration and ranged from 0.87 to 3.48 mg/h for the adult breathing pattern. For the pediatric breathing pattern, drug delivery rate was a function of drug concentration and inspired minute ventilation and ranged from 0.41 to 1.83 mg/h.

Conclusion: Our data demonstrate that drug delivery to the patient, expressed as inhaled mass over time, is similar for continuous nebulization (HEART system) and intermittently filled SVNs. In addition, for all nebulizers, the influence of the pediatric breathing pattern needs to be considered. Continuous nebulization permits the redistribution of health-care personnel and may reduce the costs of therapy. (CHEST 1997; 111:1200-05)

Key words: aerosol delivery; aerosol mask; asthma; β -agonist; breathing pattern; continuous nebulization; face mask; radiolabeled aerosols

Abbreviations: CN=continuous nebulizer, continuous nebulization; MMAD=mass median aerodynamic diameter; SVN=small-volume nebulizer; $^{99m}\text{Tc}/\text{NS}$ =technetium/normal saline solution; TTL=training test lung; σ_g =geometric SD

Continuous nebulization (CN) therapy evolved from frequent small-volume nebulizer (SVN) treatment with aerosolized β_2 -agonists (eg, albu-

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Manuscript received May 14, 1996; revision expected December 2.

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terol, terbutaline). Treatments every 20 min have been described as "nearly continuous"¹ and characterized as effective and safe treatment for acute bronchospasm.^{1,2} However, because high-frequency intermittent aerosol therapy has been perceived as highly labor intensive, true CN therapy with bronchodilators has been recommended as an effective alternative.^{3,4}

The earliest CN system, described by Moler and colleagues,³ consisted of a medication nebulizer (Raindrop; Nellcor-Puritan Bennett; Carlsbad, Calif) that had been modified by inserting an 18-gauge hypodermic needle through its top cap. A continuous IV pump and calibrated mixing chamber was attached to the needle, and its flow rate adjusted to keep the nebulizer filled during operation. Forty

milligrams of terbutaline was added to 60 mL of normal saline solution to create a bulk solution concentration of 0.4 mg/mL in a total volume of 100 mL. Based on the concentration of drug placed in the nebulizer and its liquid nebulization rate, the authors stated that the drug delivery rate was 4 mg of terbutaline per hour.

Another CN system, reported by Voss and associates,⁵ relied on interfacing a modified aerosol therapy mask and Whisper Jet medication nebulizer (Marquest Medical Products; Englewood, Colo) with a volumetric infusion pump and burette to continuously deliver a stock albuterol solution to the nebulizer. The drug delivery rate was stated to be 10 mg/h.

Still another approach to CN therapy was described by Colacone and colleagues.⁶ They administered albuterol continuously via a large-volume jet nebulizer designed for airway hydration. They claimed a drug delivery rate of 10 mg of albuterol over 2 h. However, all of these devices were adaptations of existing equipment designed for other purposes and none were specifically marketed or available for CN therapy with bronchodilators.

The Vortran High Output Extended Aerosol Respiratory Therapy (HEART) large-volume medication nebulizer (No. 100609; Vortran Medical Technologies; Sacramento, Calif) was developed specifically to facilitate CN therapy. This device has been described by Chipps and associates⁷ as a simple, safe, and cost-effective delivery system for continuously nebulized albuterol or terbutaline. Owing to its 200-mL reservoir and 8- to 10-h maximum operating time, it avoids the continuous feed system employed with SVN's. The manufacturer's package literature provides instructions for a "target dose" of 5, 10, 15 and 20 mg/h of albuterol. Examination of the package insert suggests that these drug delivery rates are calculated from knowledge of the amount of drug plus diluent placed in the reservoir and the measured liquid nebulization rate. Thus, in the Chipps et al⁷ study, terbutaline delivery was assumed to be 4 mg/h.

In the clinical studies mentioned above, which measured effects on patients,¹⁻⁷ no measure of actual dose was made. Further, the wide variation in reported rates of "drug delivery" from 4 to 20 mg/h raises questions regarding the possibility of overdose or toxicity.⁸ Using principles first developed for aerosolized antibiotics,^{9,10} we determined drug delivery to both adult and pediatric patient populations utilizing a bench protocol that attempted to duplicate a therapeutic session as closely as possible.

Selection of Nebulizers

Because our group has previously reported that disposable plastic nebulizers may vary significantly in output within the same manufacturing lot,^{10,11} we used the "standing cloud" technique¹²⁻¹⁴ to pretest 12 HEART, six AeroTech II (No. CA-1200A; CIS-US; Bedford, Mass), and six PowerMist nebulizers (No. 3759; Hospitak; Lindenhurst, NY), all from the same manufacturer's lot, to determine their comparability and to enable selection of similar nebulizers for subsequent experiments. The AeroTech II and PowerMist nebulizers were included to represent typical SVN's currently in routine clinical use in our hospital for administration of antibiotics (AeroTech II) and bronchodilators (PowerMist). The AeroTech II has been studied extensively in this laboratory and the methods and results previously reported.^{9,10,15} The PowerMist had not been previously studied. The HEART nebulizer was chosen for study because it is the only commercially available CN system on the market (to our knowledge). We elected not to test any kind of continuous-fill device for the SVN's because a standardized commercial device did not exist and the experimental modifications described in the literature may not be replicated accurately.

From pretesting with the standing cloud technique, the coefficients of variation were 15.2%, 3.5%, and 16.9%, respectively, for the HEART, AeroTech II, and PowerMist nebulizers. Six HEART nebulizer outliers were discarded, thereby leaving six "matched" samples with a coefficient of variation of 4.7% for use in further experiments.

Correlation of Radioactivity With Albuterol

To establish a correlation between the radiolabeled saline solution and albuterol output, two HEART nebulizers were charged with 80 mg of albuterol (Proventil; Schering; Kenilworth, NJ) in 120 mL of normal saline solution (NS) mixed with 11.0 to 16.9 mCi of technetium (^{99m}Tc). The nebulizer was operated at a flow rate of 10 L/min with a filter connected to the nebulizer outlet port via a 3-foot length of standard corrugated aerosol hose. During the first 2.5 min of nebulizer operation (early phase), filters were changed at predetermined intervals such that aerosol was permitted to accumulate on filter 1 for 30 s, filter 2 for 60 s, filter 3 for 90 s, filter 4 for 120 s, and filter 5 for 150 s in order to render a series of filters with progressively greater concentrations of both technetium and albuterol. After 3 h of nebulizer operation (late phase), aerosol was once again collected on filters for the same periods of time as before. These experiments were performed in duplicate.

Two AeroTech II and two PowerMist SVN's were charged with a 3.0-mL unit dose (2.5 mg) of albuterol sulfate inhalation solution (Dey Laboratories; Napa, Calif) to which 3.8 to 7.5 mCi of ^{99m}Tc in 0.25 mL of NS was added. These nebulizers were operated at a flow rate of 10 L/min with an absolute filter connected directly to the nebulizer outlet port. Filters were changed at intervals such that aerosol was permitted to accumulate on filter 1 for 60 s, filter 2 for 120 s, and filter 3 for 180 s.

After correction for decay, the radioactivity on all filters was expressed as a percentage of the technetium (percent ^{99m}Tc) in the nebulizer charge. Albuterol was recovered from each filter by vortexing it with 0.1N NaOH, and assaying the resulting fluid by spectrophotometry at a wavelength of 243 nm.¹⁶ The albuterol assayed on each filter was expressed as a percentage of the albuterol (percent albuterol) in the nebulizer charge.

As shown in Figure 1, the relationship of percent ^{99m}Tc nebulized to percent albuterol nebulized for both HEART early and late phases plus the AeroTech II and PowerMist nebulizers

is described by the following linear regression equation: $y = -0.0105 + 0.979x$ with a correlation coefficient (r^2) of 0.991 ($p = 0.0002$). This correlation demonstrated that technetium accurately represents albuterol at both early and late phases of prolonged large-volume nebulizer operation and SVN operation and permitted the use of $^{99m}\text{Tc}/\text{NS}$ as a convenient marker in place of albuterol in bench studies.

Test Bench Setup for Output Studies

To conduct the output studies under simulated but realistic clinical conditions, a special test bench setup was designed to reproduce CN into a conventional aerosol mask, in contrast to previous studies with nebulizers utilizing a mouthpiece.^{10,17} An aerosol mask is an open system, owing to the lack of a tight fit and the presence of large holes intentionally placed in the “cheeks” of the mask to facilitate ventilation. We constructed a model of the human face using a modified semirigid plastic costume mask to which an absolute filter was attached distal to the “mouth” (Fig 2). To generate a spontaneous breathing pattern at the mouth of the face, a mechanical model of spontaneous breathing, similar to that described by Banner and associates,¹⁸ was developed using a dual bellows training test lung (TTL) (Michigan Instruments; Grand Rapids, Mich) and a ventilator. The filter was connected by a short piece of rigid tubing to the right bellows of the TTL. The top plate on the left bellows to the TTL was fitted with a lift bar that rested underneath the top plate of the right bellows. A ventilator (Hamilton Veolar Ventilator; Hamilton Medical; Reno, Nev), set for volume-controlled ventilation with a sinusoidal inspiratory flow pattern, was used to inflate the left bellows. Thus, as the left bellows was inflated under positive pressure, its lift bar raised the top plate of the right bellows, thereby causing it to inflate while a negative pressure was created within it. By connecting the right bellows with tubing to the absolute filter, sinusoidal inspiratory airflow was created at the mouth to “inhale” aerosol as it was delivered to the aerosol therapy mask. Inhaled

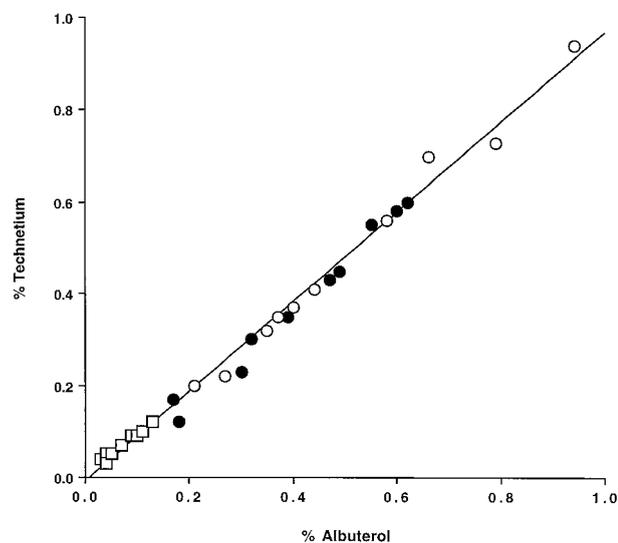


FIGURE 1. Output of HEART nebulizer and SVN's charged with radiolabeled (^{99m}Tc) albuterol shows excellent correlation between percent technetium (ordinate) and percent albuterol deposited on an absolute filter (abscissa); $y = -0.0105 + 0.979x$; $r^2 = 0.991$; $p = 0.0002$. Solid circles = early phase HEART nebulizer; open circles = late phase HEART nebulizer; open squares = AeroTech II and PowerMist SVN's. See text for details.

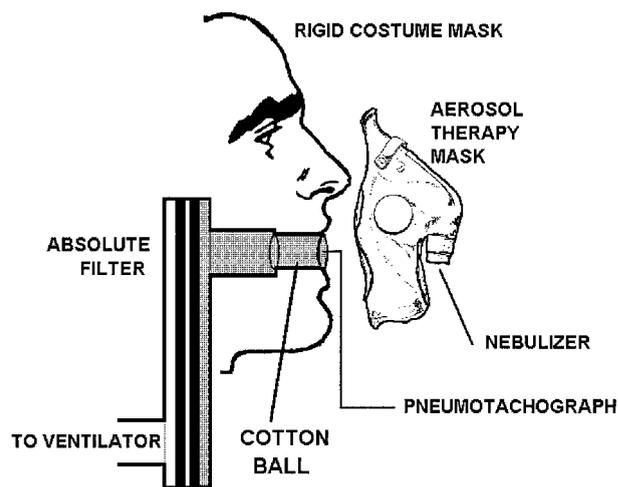


FIGURE 2. Aerosol mask test bench setup. A round plastic universal adapter (15 mm inner diameter \times 22 mm outer diameter) was fixed into the mouth of a costume mask with silicone sealant. The posterior end of the universal adapter was connected to an absolute filter. The aerosol mask was placed over the nose and mouth in the conventional manner. A ventilator attached to the absolute filter provided a to-and-fro breathing pattern as verified with a pneumotachograph (Fig 3). The shaded area represents the deadspace proximal to the filter media. Its influence on inhaled mass measurements conducted with the pediatric breathing pattern was eliminated by collecting radioaerosol on cotton balls²⁰ inserted into the mouth of the model.

aerosol particles (inhaled mass) were captured on the absolute filter.¹⁹ Tidal volume, respiratory rate, and duty cycle (inspiratory time percent) were controlled by manipulating ventilator settings affecting the inflation of the left bellows of the TTL.

The simulated “adult” breathing pattern consisted of a rate of 20 breaths/min, tidal volume of 500 mL, and a duty cycle of 40% while the simulated “pediatric” pattern was a rate of 35 breaths/min, tidal volume of 100 mL, and a duty cycle of 40%. The breathing pattern was confirmed using a respiratory monitor (Bicore Model CP-100; Bicore Monitoring Systems; Irvine, Calif) whose pneumotachograph was temporarily inserted into the mouth of the model (Fig 2). Typical tracings are shown in Figure 3.

The AeroTech II and PowerMist SVN's were attached directly to the inlet port of the aerosol therapy mask while the large-volume HEART nebulizer was connected to the aerosol therapy mask via a piece of standard 6-foot-long, 22-mm-diameter corrugated aerosol tubing. However, a single experiment with 3-foot-long aerosol tubing connecting the HEART nebulizer to the aerosol mask was conducted for the adult breathing pattern to determine the effect of tubing length on aerosol delivery. The SVN's were charged with a fill volume of 3 mL of radiolabeled saline solution and run at a flow rate of 10 L/min. The HEART nebulizers were charged with 120 mL of radiolabeled saline solution and run at 10 L/min, a typical setting according to the product literature. Aerosol particles could be visualized entering the mouth of the model during the inspiratory phase. Filters were measured and changed at intervals of every 1 to 2 min for the AeroTech II and PowerMist nebulizers and every 30 min over 4+ h for the HEART nebulizers. Filter media was placed in a radioisotope calibrator (CRC-10R; Capintec; Montvale, NJ) to determine radioactivity. The inhaled mass of radioactivity on the filter was then expressed as albuterol delivered in milligrams, and was plotted against time of nebulization to determine rate of albuterol delivery. The inhaled mass measurement accounts for

RESULTS

Output Studies (Albuterol Delivery)

The AeroTech II and PowerMist nebulizers nebulized a 3-mL charge in a mean time of 10 min. The HEART nebulizers with a 120-mL charge ran dry in a mean of 240 min in the adult breathing pattern and 270 min in the pediatric breathing pattern.

Table 1 summarizes the measured data. The two SVNs, AeroTech II and PowerMist, both emptied in 10 min and delivered an inhaled mass of 0.86 mg and 0.62 mg, respectively, for the adult breathing pattern. Significant differences were noted for the pediatric breathing pattern, with 0.49 mg and 0.41 mg delivered, respectively, for the SVNs. Inhaled mass for the HEART nebulizer was 13.92 mg delivered over 240 min for the adult breathing pattern. For the pediatric breathing pattern, inhaled mass was reduced to 8.22 mg over a delivery time of 270 min. Not shown in the table, when a 3-foot-long aerosol tubing was substituted for the standard 6-foot-long tubing on the HEART with the adult breathing pattern, the inhaled mass increased from 13.92 to 14.72 mg.

Figure 4 shows inhaled mass of albuterol for the different nebulizers displayed as albuterol delivered (milligrams) plotted against time. The data for the AeroTech II and PowerMist nebulizers represent the drug delivery rates from Table 1 that would occur if the SVNs were refilled intermittently every 10 min over 4 h. The data for the HEART nebulizers correspond to the actual measurements that were made at 30-min intervals over 4 h. The effect of the difference between breathing patterns is also shown in Figure 4.

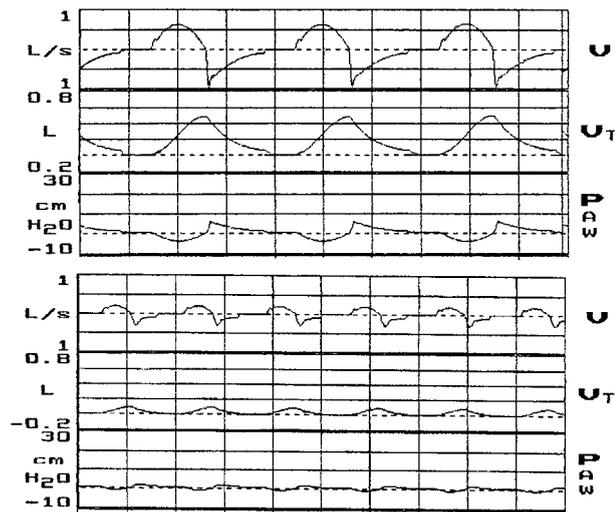


FIGURE 3. Examples of adult (*top*) and pediatric (*bottom*) breathing patterns obtained with the Bicore CP-100 pneumotachograph inserted into the airway opening of the aerosol mask test bench setup. Scales: V denotes flow rate, -1 to +1 L/s; VT denotes tidal volume, -0.2 to 0.8 L; PAW denotes pressure at the airway opening, -10 to +30 cm H₂O.

the combined effects of nebulizer function (liquid nebulization rate and particle size distribution) and the influence of the breathing pattern (duty cycle and total minute volume).^{10,19}

Deadspace in the proximal filter housing was shown, in preliminary experiments, to be approximately 70 mL, as measured by water displacement. This deadspace represents 14% of the tidal volume used in the adult breathing pattern and 70% of the tidal volume used in the pediatric breathing pattern. Preliminary experiments also showed that accuracy of inhaled mass measurements during the pediatric breathing pattern was compromised by the high filter deadspace. To eliminate this problem during the actual inhaled mass measurements, cotton balls, inserted into the mouth of the model, were used as filters²⁰ during the pediatric studies to eliminate virtually all deadspace. For technical reasons, cotton balls could not be used as filters during the adult breathing pattern, but the 14% deadspace to tidal volume ratio was not considered to be a significant source of error. Previous studies in animals and patients have shown that these filters accurately determine deposition for adult breathing patterns.^{10,21}

Particle Distribution

Particle size distribution was measured on two randomly selected samples of each brand of nebulizer as they were being operated with radiolabeled saline solution under the conditions previously described. A 22-mm-diameter T-piece was inserted into the inlet port on the aerosol therapy mask, and its free limb was connected to a 10-stage cascade impactor (GS-1 Cascade Impactor; California Measurements; Sierra Madre, Calif) sampling at a rate of 1.0 L/min for 2 min. The particle distribution was determined by measuring the cumulative radioactivity on successive cascade impactor stages and plotting the values on probability paper. The resulting data were approximated by a straight line representing a log-normal distribution. The mass median aerodynamic diameter (MMAD) was read from the ordinate at the point where the straight line intersected the 50% value on the abscissa.

Table 1—Measured Data Comparing Output Characteristics of Two SVNs With the HEART CN

Nebulizer	Adult	Pediatric
CIS-US AeroTech II		
Nebulizer charge, mg albuterol	2.5	2.5
Inhaled mass, mg albuterol	0.86	0.49
Treatment time, min	10	10
Albuterol delivery rate, mg/h*	5.14	2.97
Hospitalak PowerMist		
Nebulizer charge, mg albuterol	2.5	2.5
Inhaled mass, mg albuterol	0.62	0.41
Treatment time, min	10	10
Albuterol delivery rate, mg/h*	3.74	2.48
Vortran HEART [†]		
Nebulizer charge, mg albuterol	80	80
Inhaled mass, mg albuterol	13.92	8.22
Treatment time, min	240	270
Albuterol delivery rate, mg/h	3.48	1.83

*Assumes nebulizer refilled when empty.

[†]Manufacturer's 20-mg/h "target dose" setup concentration.

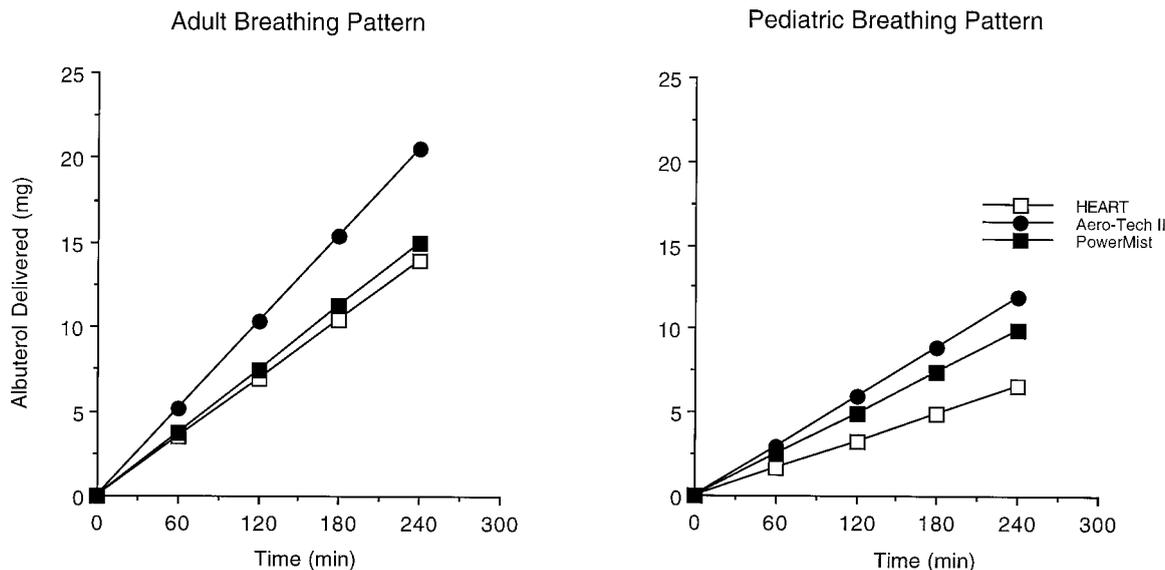


FIGURE 4. Inhaled mass data expressed as albuterol delivery vs time. Data for the AeroTech II and PowerMist SVNs express delivery rates that would occur if the nebulizers were refilled with a 2.5-mg albuterol unit dose every 10 min. The HEART nebulizer data are from the manufacturer's maximum recommended target dose (20 mg/h).

Particle Distributions

The MMADs ($\pm\sigma$, the geometric SD) for the AeroTech II and the PowerMist nebulizers were $0.65\ \mu\text{m}$ (σ , 2.24) and $1.00\ \mu\text{m}$ (σ , 2.30), respectively. For the HEART nebulizer, MMAD was $2.10\ \mu\text{m}$ (σ , 2.47) during the first hour of operation and $2.10\ \mu\text{m}$ (σ , 2.30) during the fourth hour of operation.

DISCUSSION

Our studies, as summarized in Table 1 and Figure 4, demonstrate that, under conditions simulating patient therapy with both adult and pediatric breathing patterns, a wide range in aerosolized albuterol can be inhaled over time with different nebulizers. But, with some attention paid to the drug concentration in the nebulizer, similar quantities will be inhaled using all devices. Further, as shown in Figure 4 for the adult breathing pattern, the HEART CN approaches a typical SVN at its highest recommended target dose (20 mg/h) in the adult breathing pattern. In the present study, the HEART nebulizer, operating at a fill volume of 120 mL and a flow rate of 10 L/min for an adult breathing pattern, had albuterol delivery rates of up to 3.48 mg/h for the adult breathing pattern and 1.83 mg/h for the pediatric breathing pattern. Therefore, when operated at the highest manufacturer's recommended target dose, the HEART is capable of providing drug

delivery equivalent to the PowerMist SVN (3.48 vs 3.74 mg/h). This would be consistent with clinical observations from patient studies¹⁻⁷ that CN is effective and yields bronchodilation similar to SVNs. Greater drug delivery (5.14 mg/h) was provided by the AeroTech II nebulizer in the adult breathing pattern, but its use for routine bronchodilator therapy is limited due to its high cost (approximately \$7 to \$8 each).

The pediatric data exemplify the effect of breathing pattern (*ie*, small tidal volume, rapid respiratory rate) on drug delivery, with a maximum of 1.83 mg/h of albuterol delivered by the HEART. Inhaled mass (aerosol delivered) can be a function of inspiratory time. The duty cycle, which defines the period of inspiration, was equal for the adult and pediatric breathing patterns and the total amount of time available per minute for inspiring aerosol was the same ($0.40 \times 60\ \text{s} = 24\ \text{s}$). Therefore, differences in duty cycle were not responsible for differences in drug delivery between adult and pediatric breathing patterns. We believe the relatively high nebulizer flow rate was the determining factor behind our observations for the pediatric breathing pattern. The HEART nebulizer was operated at the manufacturer's suggested flow rate of 10 L/min for all studies. Our adult breathing pattern (20 breaths/min and tidal volume of 500 mL) generated an inspired minute ventilation of 10 L/min, which was equal to the total flow rate of the HEART. Thus, all particles generated during inspiration would be inhaled.

However, the pediatric breathing pattern (35 breaths/min and tidal volume of 100) generated an inspired minute ventilation of only 3.5 L/min, which is significantly less than the HEART nebulizer's flow rate. During inspiration, a large fraction of the nebulizer output is unable to be inhaled, and particles are lost through the vent holes in the facemask. Thus, aerosol delivery with the HEART system, as expressed by the inhaled mass, is related to both nebulizer efficiency and breathing pattern as a function of total flow rate of the nebulizer.

A variety of studies,^{2,8,22,23} using clinical measures, have examined the possibility of toxic reactions during frequent intermittent and continuous bronchodilator therapy and have concluded that it is safe and that significant toxic reactions do not occur. Moler et al,⁸ in a 1995 study, measured serum terbutaline levels during continuous and intermittent nebulization with SVN's in children with acute asthma. They found no differences in plasma concentrations and cardiovascular responses. Our data would predict their observation because we found that bronchodilator delivery with both types of devices is similar, despite implications that CN delivers high dosages. The similarity of drug delivery between CN and high-frequency intermittent SVN therapy suggests that economic factors will determine the true potential of CN.

ACKNOWLEDGMENT: Lorraine Morra, BS, performed the albuterol assay.

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