Aerosol Delivery and Modern Mechanical Ventilation

In Vitro/*In Vivo* Evaluation

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Aerosol delivery via a mechanical ventilator remains unregulated with no standards for drug delivery to intubated patients. Bench models predicting drug delivery have not been validated *in vivo*. For modern ventilator designs, we chose to identify, on the bench, the most important variables affecting aerosol delivery and to correlate *in vitro* predictions of aerosol delivery with *in vivo* end points independent of patient response. Test aerosols of albuterol and antibiotics were compared. Bench measurements of inhaled mass (percentage of nebulizer charge, mean ± SEM) ranged from 5.7 ± 0.5% to 37.4 ± 1.6%, with breath-actuated nebulization and humidity identified as the most important factors determining aerosol delivery. In patients, sputum levels of deposited antibiotics varied from 1.10 to 19.6 μg/ml/mg. Variation in sputum levels correlated with predictions from the *in vitro* model. Aerosol delivery in ventilated patients can be efficient and reproducible only if defined ventilator parameters are tightly controlled. Key parameters can be determined via *in vitro* bench testing defining delivery standards for clinical trials of drugs with narrow therapeutic/toxicity ratios.

Keywords: aerosolized antibiotics; nebulizers; bronchodilators; humidification; sputum

Modern ventilator design does not include standards that relate to aerosol delivery. Bench models predicting nebulized drug delivery during mechanical ventilation have not been validated *in vivo*. Previous studies have measured patient- and ventilator-related factors affecting aerosol generation and inhalation for nebulizers on the bench (1–4). A few studies have measured deposition of nebulized drugs in ventilated patients, but they did not relate actual deposition to bench predictions (5–7).

Besides the variables already studied *in vitro* (e.g., humidity, nebulizer type), newer ventilator designs may further complicate predictions of drug delivery. For example, the use of constant flow in the ventilator tubing (e.g., bias flow) during all phases of ventilation may increase aerosol losses. Indeed, adult ventilator systems are becoming similar in design to neonatal ventilators, which are known to be inefficient in aerosol delivery (8). Breath-actuated nebulization, an important factor in spontaneously breathing patients (9), is not a feature of all modern ventilators.

In vivo effects of conventional aerosols can be difficult to relate to aerosol delivery and deposition. For example, responsiveness to bronchodilators may vary between patients, and in the absence of a deposition measurement, changes in airway resistance will not differentiate between patient-related factors and differences in drug delivery.

The purpose of our study was to detail the most important variables affecting aerosol delivery via nebulizer on the bench for modern ventilators employing the newer flow regimes with and without breath actuation and the effects of humidity. For the major variables defined *in vitro*, predictions of aerosol delivery were correlated to measured levels of antibiotic in suctioned sputum from intubated patients. Sputum levels were chosen as an *in vivo* end point to the present study because unlike bronchodilators they are independent of patient responsiveness. Some of the results of these studies have been previously reported in the form of an abstract (10).

METHODS

In Vitro Bench Model

The bench model is diagramed in Figure 1. The test ventilator was connected to a test lung (M.I.I. VentAid TTL; Michigan Instruments, Inc., Grand Rapids, MI) via an endotracheal tube (inside diameter = 8.0 mm). Aerosols were sampled just distal to the endotracheal tube with an inhaled mass filter (Pari GmbH, Starnberg, Germany) and a filter in the expiratory line. Aerosols were generated by nebulization with the device located in the inspiratory line 12 inches from the Y piece.

For the *in vitro* study, we decided to use albuterol (2.5 mg in 3 ml of normal saline) labeled with technetium as the test solution, as it was previously characterized in our laboratory. Activity of albuterol aerosol has been shown to correlate with technetium when measured by cascade impaction (11). This allowed for a comparison with previous studies defining important parameters influencing aerosol generation and delivery (1, 2, 12).

The breathing pattern was fixed at a tidal volume of 750 ml, a respiratory rate of 15, a peak flow of 70 L/minute, an inspiratory time of 0.9 seconds, and an inspiratory:expiratory ratio of 1:3.4. For the T-Bird ventilator, bias flow was set at 10, 15, and 20 L/minute.

Ventilatory parameters were monitored with the Bicore, Pulmonary Monitor CP 100 (VIASYS Healthcare, Critical Care, Conshohocken, PA). For experiments using humidification, a Hudson RCI Concha III humidifier (Hudson Respiratory Care Incorporated, Temecula, CA) was set at 35°C. This device was turned off and bypassed for experiments without added humidity.

Aerosol particle distribution was sampled via a cascade impactor (GS 1 IMPAQ; California Measurements, Inc., Sierra Madre, CA) with the device located distal to the endotracheal tube. Aerosols were sampled over a 4-minute period. Radioactivity on the cascade stages was measured by a collimated ratemeter (Ludlum Measurements Inc., Sweetwater, TX) and the distribution plotted on log probability paper. Activity at the median defined the mass median aerodynamic diameter (MMAD).

Aerosol production was quantified by measuring radioactivity on the filters via a well counter (CRC-10; Capintec, Inc., Montvale, NJ), and all activity (filters plus nebulizer) was summed in a "mass balance" designed to trace aerosol losses.

The experimental configurations are outlined on Figure 2. There were multiple configurations/combinations that were designed to test major variables. These included the ventilator type, nebulizer brand, form of nebulizer activation (continuous versus breath actuation), and presence of humidification and magnitude of bias flow. Some devices could not perform all functions; for example, the Evita ventilator does not have adjustable bias flow, and the T-Bird ventilator does not have nebulizer breath actuation.

Ventilators were chosen based on properties that may affect aerosol delivery.

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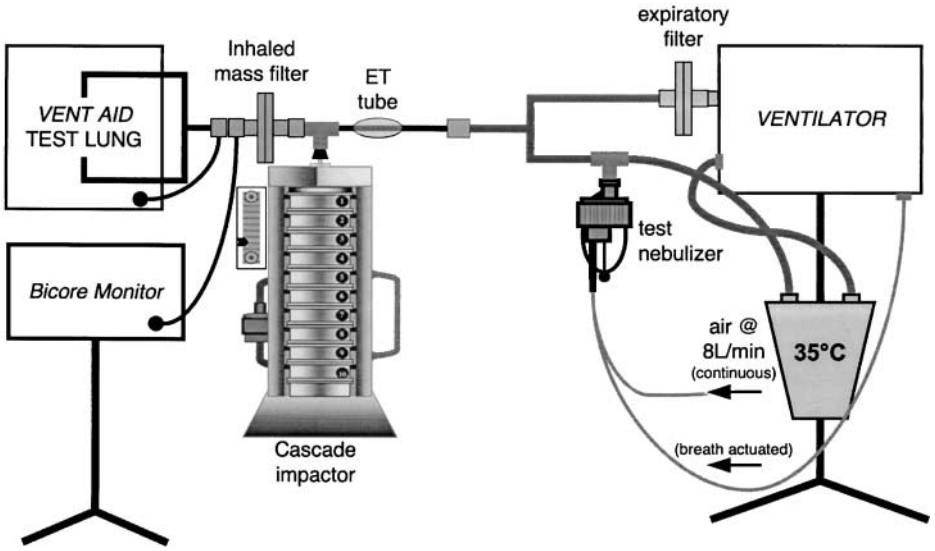

Figure 1. Diagram of experimental apparatus. The test nebulizer was placed in the inspiratory line 12 inches before the Y piece and either triggered by breath actuation or powered continuously by a separate pressure source. Aerosol was captured just distal to the endotracheal (ET) tube (inhaled mass filter). For particle sizing experiments, a cascade impactor was placed between the ET tube and the inhaled mass filter. The Bicore monitor confirmed the breathing pattern during nebulization.

- PB 7200 (Puritan Bennett, Pleasanton, CA): breath-actuated nebulization, no bias flow, previously tested in our laboratory
- Evita 4 (Drager Inc., Critical Care Systems, Telford, PA): newer, breath-actuated nebulization
- T-Bird (VIASYS Healthcare, Inc., Conshohocken, PA); no breath actuation, mandatory bias flow

The nebulizers that were tested included the AeroTechII Aerosol Delivery System (CIS-US, Bedford, MA), which was previously tested in our laboratory, and the Portex Small Volume Medication Nebulizer Kit (SIMS Portex, Inc., Fort Myers, FL), which is a nebulizer that was used for routine aerosol therapy in our hospital. Nebulizers, run to dryness, were driven directly by the ventilator (breath actuation) or continuously via compressed air or wall oxygen at a flow of 8 L/minute (continuous nebulization).

The variables evaluated for each configuration were as follows:

- Humidified versus nonhumidified ventilator circuit (heated wire circuits were not used)
- Breath-actuated nebulization versus continuous nebulization
- Bias flow set at flow rates of 10, 15, and 20 L/minute
- Nebulizer brand

Parameters measured for each of the variables evaluated were as follows:

- Inhaled mass (%), the amount of drug on the filter as a percentage of the nebulizer charge
- Mass balance (percentage of recovery), the sum of both filters plus remnant activity in the nebulizer
- MMAD

Data obtained from the configurations listed in Figure 2 were combined by the test parameter when reported in the results. For example, "breath-actuated humidification" included data from all devices that satisfied that specific criteria.

In Vivo Model

Based on our bench data, the effects of major parameters predicting aerosol delivery were tested *in vivo* by measuring sputum levels of aerosolized antibiotics sampled from intubated patients. Patients were participating in a parallel protocol designed to measure the effectiveness of aerosolized antibiotics. The routine consent for the institutional review board–approved antibiotic protocol was modified to allow variation in the mode and conditions of nebulization, that is, breath actuated or continuous as well as humidified or nonhumidified. Institutional review board approval was obtained for these modifications. For these parameters, paired data for each patient were obtained for sputum suctioned from the proximal airways 1 hour after aerosol therapy with an antibiotic. The protocol incorporated a standardized suction routine (13) and avoidance of instilled saline. Patients were treated with Gentamicin, Amikacin, or Vancomycin via the AeroTech II nebulizer (the clinical "dose" or nebulizer charge was 80 mg for Gentamicin, 400 mg for Amikacin, and 120 mg for Vancomycin). Sputum was sampled after ventilator parameters were set for 24 hours (humidification was maintained throughout except as noted later here). The antibiotic treatment regimen consisted of aerosolized antibiotics given three times using an every 8 hours regimen. It is important to note that for the "nonhumidified" treatment regimen, the humidifier was turned off and bypassed only during the actual nebulizer

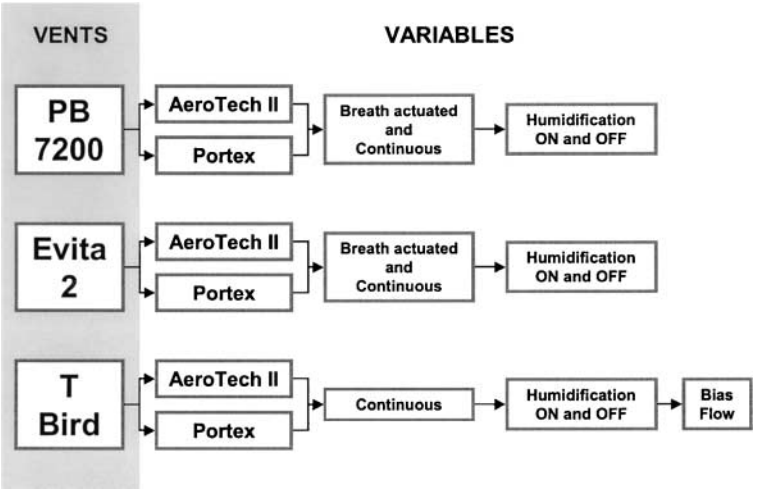

Figure 2. Outline of bench protocol.

TABLE 1. INHALED MASS PERCENTAGE* (MEAN ± SEM) EFFECTS OF BREATH-ACTUATED NEBULIZATION AND HUMIDIFICATION

	Inhaled Mass %					
Nebulization Mode	Nonhumidified	n	Humidified	n	NH/H	p Value
Breath-actuated nebulization†	37.4 ± 1.6	8	9.6 ± 1.0	19	3.84	< 0.0001
Continuous nebulization‡	10.4 ± 0.8	21	5.7 ± 0.5	17	1.81	< 0.0001
All ventilators	17.9 ± 2.4	29	7.7 ± 0.7	36	2.09	< 0.0001

Definition of abbreviation: NH/H = ratio of nonhumidified to humidified values.
* Value of inhaled mass reported as a percentage of nebulizer charge.
† Ventilator type used for breath-actuated nebulization was PB 7200 and Drager Evita 4.
‡ Ventilator type used for continuous nebulization was T-Bird.

treatment (approximately 1 hour). After the 24-hour test period, sputum was obtained for the 1-hour period between 1 and 2 hours after an aerosol treatment. The sample was weighed, and the volume was standardized with normal saline to 4.0 ml and centrifuged at 40,000 rpm for 60 minutes at 4°C. The supernatant phase was diluted 1:100 for Gentamicin and Vancomycin and 1:1,000 for Amikacin to allow analysis within the reference range of the assay (Roche Integra; Roche Diagnostics, Somerville, NJ). Results are reported in micrograms per milliliter sputum per milligram of drug placed in the nebulizer.

Statistical Analysis

Results are reported as mean ± SE. The Mann-Whitney and unpaired *t* tests were used in the statistical analysis of the *in vitro* data. *In vivo* data were analyzed as pairs using the Wilcoxin signed rank test and paired *t* tests (Stat View 4.5; Abacus, Inc., Berkley, CA). When the n was small, the nonparametric p values were reported.

RESULTS

In Vitro Bench Study

Table 1 lists the values of inhaled mass affected by breath-actuated nebulization and humidity. Data are presented as the percentage of nebulizer charge. On average, for all ventilators tested, turning off and bypassing the humidifier significantly increased aerosol delivery. The ratio of inhaled mass for nonhumidified gas to humidified gas was 2.09:1 ($p < 0.0001$), indicating a doubling of delivery when the humidifier was turned off and bypassed. When controlled for the presence of breath-actuated nebulization, there was an even greater effect of humidity with the ratio increasing to 3.84:1 ($p < 0.0001$). Continuous nebulization was the least efficient delivery method under all circumstances.

The effect of bias flow on inhaled mass percentage is shown in Table 2. Although values of inhaled mass ranged from 3.08 ± 0.8 to 10.0 ± 0.7%, much of the effect was explained by the influence of humidity. When the circuit humidifier was turned off and bypassed, the effects of bias flow were small.

TABLE 2. EFFECT OF BIAS FLOW ON INHALED MASS PERCENTAGE (MEAN ± SEM)

	Inhaled Mass %			
Bias Flow (*L/min*)	Nonhumidified	n	Humidified	n
10	10.0 ± 0.7	7	5.3 ± 0.4	9
15	8.3 ± 1.0	12	5.3 ± 0.5	15
20	8.6 ± 0.7	10	3.8 ± 0.8	5

All experiments were preformed with the T-Bird ventilator.

TABLE 3. INHALED MASS PERCENTAGE (MEAN ± SEM) FOR DIFFERENT NEBULIZERS, EFFECT OF HUMIDIFICATION

	Inhaled Mass %				
Ventilator Mode	AeroTech II	n	Portex	n	p Value
Nonhumidified	20.8 ± 3.0	19	12.3 ± 3.6	10	0.0929
Humidified	10.7 ± 1.3	13	6.1 ± 0.5	23	0.0003

TABLE 4. CASCADE IMPACTION DATA (MASS MEDIAN AERODYNAMIC DIAMETER, MEAN ± SEM) FOR DIFFERENT NEBULIZERS

	MMAD (μm)				
Ventilator Mode	AeroTech II	n	Portex	n	p Value
Nonhumidified	1.2 ± 0.1	16	1.9 ± 0.2	8	0.0065
Humidified	2.3 ± 0.3	13	2.2 ± 0.2	8	0.6435

Definition of abbreviation: MMAD = mass median aerodynamic diameter.

Aerosol delivery was not a strong function of the brand of nebulizer. As shown in Table 3, differences in inhaled mass were found between devices, but because of variability in the data, results were statistically significant for experiments only when the system was humidified.

The aerodynamic behavior of the particles is summarized in Table 4. Differences in MMAD between nebulizers were small and statistically significant only for the nonhumidified condition. The addition of humidity to the circuit increased the size of the particles presented to the patient (cascade impactor placed at distal tip of endotracheal tube) presumably by hygroscopic growth. Although MMAD increased from 1.5 ± 0.1 to 2.3 ± 0.2 μm ($p = 0.0006$, all data humidified vs. nonhumidified, $n = 45$), total aerosol delivery decreased with humidification (Table 2), suggesting greater particle impaction in the ventilator tubing.

Tubing losses with added humidity were also suggested by the recovery data. When the humidifier was turned off and bypassed, the sum of filters plus residual nebulizer activity averaged 88.2 ± 0.9% ($n = 29$). With humidification, recovery dropped to 73.9 ± 1.8% ($n = 36$).

In summary, under typical clinical conditions of aerosol delivery, for example, continuous nebulization in a humidified circuit, only 5.7 ± 0.5% of the nebulizer charge was delivered. On the other hand, an optimized system (breath-actuated nebulization, nonhumidified) delivered 37.4 ± 1.6% to the filter (Table 1).

In Vivo Clinical Study

Six patients were studied. Diagnoses, ventilators, settings, endotracheal and tracheostomy tube sizes, and peak airway pressures are listed in Table 5. Paired sputum samples for each are also shown with the mean data for each patient. Depending on the drug, individual levels ranged from 86 ± 10 μg/ml for gentamicin to 5,790 ± 2,140 μg/ml for amikacin (68-fold variation). Two major factors accounted for this variability: The first was the variation in nebulizer charge (the clinical "dose" of 80 mg for Gentamicin, 400 mg for Amikacin, and 120 mg for Vancomycin); the second was the differences in aerosol delivery. Normalizing the levels for the nebulizer charge assessed the latter factor. When listed as μg/ml/mg nebulizer charge, the range decreased (0.66 to

19.6), a 20-fold variation. These data are analyzed for ventilator-related parameters in Table 6. Average levels varied from 0.83 ± 0.11 to 12.57 ± 1.80 μg/ml/mg. In general, nonhumidified aerosol delivery was more effective in raising sputum levels than the conventional humidified condition, with levels averaging 3.63 times higher in sputum from nonhumidified circuits ($p = 0.0002$). When the mode of nebulization was considered, levels after breath-actuated nebulization were superior to those after continuous nebulization. The 20-fold range in sputum levels appeared to be accounted for by the combined effects of breath-actuated nebulization and reduced humidification.

When compared with the bench data, there were similarities as well as systematic differences between the predicted aerosol delivery (Table 1) and *in vivo* sputum levels (Table 6). The relative effects of humidity predicted on the bench were reflected in the *in vivo* levels of antibiotics (predicted ratios of nonhumidified to humidified values breath actuation and continuous nebulization 3.84 and 1.81; ratio of nonhumidified to humidified values observed 3.89 and 2.20, respectively). However, breath-actuated nebulization compared with continuous nebulization was more effective in raising sputum levels *in vivo* than predicted on the bench. In the bench study, depending on humidification, inhaled mass was 1.7 to 3.6 times higher for breath actuation compared with continuous nebulization (Table 1). *In vivo* levels of sputum antibiotics were four to seven times higher (Table 6), indicating that other *in vivo* factors were important (*see* Discussion).

TABLE 6. SPUTUM LEVELS OF DEPOSITED ANTIBIOTICS (MEAN ± SEM)

		Sputum levels (μg/ml/mg)			
Nebulizer Activation	n	Nonhumidified	Humidified	NH/H	p Value
Breath actuation	14	12.6 ± 1.8	3.2 ± 0.5	3.89	< 0.001
Continuous	10	1.8 ± 0.3	0.8 ± 0.1	2.20	0.0005
All ventilators	24	8.1 ± 1.5	2.2 ± 0.4	3.63	0.0002

Definition of abbreviation: NH/H = ratio nonhumidified to humidified.

DISCUSSION

The present study illustrates the major factors affecting aerosol delivery to intubated patients via conventional nebulization. The bench model predicted that breath-actuated nebulization and humidification would be the major determinants of drug delivery. In patients, after inhalation of antibiotics, sputum values ranged over an order of magnitude, but much of this variability was explained when the data were normalized for breath actuation and humidification. Sputum levels of deposited antibiotics provided a direct index of drug delivery (as opposed to an indirect index such as a change in airway resistance). When reported as absolute values, antibiotic levels were high (e.g., a mean gentamicin level of 12.6 μg per ml of sputum per mg of drug multiplied by 80 mg = 1,008 μg per ml of sputum) if the humidifier was turned off and bypassed. These results are consistent with previously reported values (5). However, if a clinical response were dependent on drug level, the simple addition of humidification would reduce the average gentamicin level to 258 μg per ml of sputum.

The recovery data coupled with the changes seen in MMAD suggest hygroscopic growth of particles and losses via tubing impaction in the presence of humidification of inspired gases. The humidifier supersaturates the ventilator gas and promotes rainout as the humid air cools. Aerosol particles can serve as nuclei and losses are enhanced.

Early studies from our group suggested that nebulizer type may be important (12, 14), but later bench studies showed that running the nebulizer to the point of sputtering (loosely termed "dryness" in the literature) reduced device-related variability (2). The present protocol ran the devices to dryness (run time of approximately 60 minutes). When the data were corrected for breath actuation and humidification, the AeroTechII was more efficient than the Portex device (Table 3).

The bench model predicted that breath-actuated nebulization and humidification would have the greatest effects *in vivo*. Bench predictions for humidity effects appeared to be the most accurate. However, the bench model seemed to underestimate the effects of breath-actuated nebulization. As presented in the Results, the *in vivo* levels of antibiotic between breath actuated and continuous nebulization were approximately twice as high as predicted. We believe that these observations can be explained by the differences in the concepts of inhaled mass versus actual aerosol deposition. In a bench model, it is possible to measure variables that affect the quantity of aerosol presented to the patient and "inhaled," that is, the "inhaled mass." Once the particles are inhaled, a certain fraction of the inhaled particles are deposited (the "deposition fraction"), and sites of deposition are determined by the breathing pattern, airway geometry, and the MMAD. Although we did not

TABLE 5. DETAILS OF *IN VIVO* STUDY

		Ventilator			Tube		No. of	Sputum Levels (μg/ml)		Sputum Levels (μg/ml/mg)		PIP	
Case No.	Diagnosis	Type	Mode	Setting	I.D.	Antibiotic	Pairs	Humidified	Nonhumidified	Humidified	Nonhumidified	Before	After
1	Respiratory failure/ Quadraplegia	T-Bird*	AC	12 500 40%	8.0†	Amikacin	6	263 ± 46	553 ± 108	0.66 ± 0.12	1.38 ± 0.27	26	28
2	Pneumonia	T-Bird*	AC	10 600 50%	8.0†	Gentamicin	4	86 ± 10	200 ± 34	1.08 ± 0.12	2.51 ± 0.43	29	29
3	Severe COPD/ Pneumonia	Bear 3	IMV	6 700 35%	8.0†	Amikacin	4	1,777 ± 519	5,790 ± 2,140	4.44 ± 1.30	14.48 ± 5.35	28	30
4	Pneumonia	PB-7200	AC	14 700 50%	7.5	Gentamicin	4	133 ± 21	734 ± 99	1.66 ± 0.27	9.18 ± 1.24	30	30
5	Pneumonia	PB-7200	AC	15 450 40%	7.5	Vancomycin	1	132	2,352	1.10	19.60	24	24
6	Pancreatitis	PB-7200	PC	18 450 30%	7.5	Amikacin	5	1,576 ± 280	4,947 ± 941	3.94 ± 0.70	12.37 ± 2.35	36	36

Definition of abbreviations: AC = assist control; COPD = chronic obstructive pulmonary disease; I.D. = inside diameter (mm); IMV = intermittent mandatory ventilation; PC = pressure control; PIP = peak inspiratory pressure.

* Bias flow = 10 L/min.

† Tracheostomy.

Settings: rate/tidal volume/% O_2.

Aerosolized antibiotics were delivered via continuous (T-Bird) or breath-actuated nebulization (Bear and Puritan Bennett ventilators); sputum levels are reported as mean ± SEM.

TABLE 7. MASS MEDIAN AERODYNAMIC DIAMETER (MEAN ± SEM) FOR AEROTECH II NEBULIZER AS A FUNCTION OF ACTUATION MODE AND HUMIDIFICATION

	MMAD			MMAD		
Mode	n	Nonhumidified	p Value	n	Humidified	p Value
Breath actuated	9	1.5 ± 0.1	0.0006	7	3.0 ± 0.2	0.0177
Continuous	7	0.9 ± 0.1		6	1.6 ± 0.5	

Definition of abbreviation: MMAD = mass median aerodynamic diameter.

measure actual deposition in our patients, we did control many of the parameters that affect the deposition of inhaled particles. For example, all of our *in vivo* experimental conditions were paired, except for changes in nebulizer actuation and humidification. In our clinical study using aerosolized antibiotics, only the AeroTechII nebulizer was used. A comparison of the data between Tables 1 and 6 suggests that for breath-actuated nebulization, either the deposition fraction was increased or particle deposition was more central than during treatment with continuous nebulization. A parameter linked to increases in both deposition fraction and central deposition is the MMAD. To isolate this factor, we returned to our bench studies. Table 7 summarizes experiments with the AeroTechII in which MMADs were measured as a function of nebulizer actuation and humidification. MMADs were always significantly greater during delivery via breath-actuated nebulization. With all other things being equal, increases in MMAD will result in increases in deposition and/or greater deposition in central airways. We cannot distinguish between the two possibilities, as suctioned sputum levels are related primarily to centrally deposited particles (15). Further studies are necessary to determine the extent that these processes account for the observed differences in sputum levels.

Our findings have important implications for clinical trials. Future studies will be needed to define the safety and efficacy of a given drug and mode of delivery (such as using a nonhumidified circuit). For drugs such as antibiotics, control of dose requires strict control of the aerosol delivery protocol. Failure to specify the ventilator type, the presence or absence of humidity, and/or breath actuation will prevent control of drug dosing and may affect the assessment of clinical effects.

For commonly used drugs (bronchodilators), the lowest doses delivered in this study exceed those given in clinical trials (16), and thus, potent safe drugs should still be effective in most patients even under conditions that promote inefficient aerosol delivery (e.g., continuous nebulization and added humidification); however, the potential remains that with efficient delivery toxic levels can be achieved and with inefficient delivery some patients (e.g., those with severe asthma) may be undertreated.

In clinical situations different from those studied with our model, there may be important differences in drug delivery. Aerosol delivery is notoriously difficult during neonatal ventilation primarily because of high bias flow (8). In adults, the use of other modes of ventilation may have an impact on delivery. If important to the investigator, bench studies under clinically relevant conditions will help in understanding and controlling potential confounding factors.

In conclusion, bench models can determine factors important in aerosol delivery to intubated patients. Clinical trials of aerosolized drugs require strict control of the ventilator and conditions of nebulization if the dose to the patient is important in assessing clinical response.

Conflict of Interest Statement: D.D.M. has no declared conflict of interest. M.A.M. has no declared conflict of interest. L.B.P. is a co-inventor of patents held by SUNY in the use of antibiotics in intubated patients. None of the data or support for this study are related to those patents or to the money received from Nektar. A.R.S. has no conflict of interest. G.C.S. is a co-inventor of patents held by SUNY in the use of antibiotics in intubated patients. None of the data or support for this study are related to those patents or to the money received from Nektar.

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