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Real-Time *In Vitro* Assessment of Aerosol Delivery During Mechanical Ventilation

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Abstract

Background: A new real-time method for assessing factors determining aerosol delivery is described.
Methods: A breath-enhanced jet nebulizer operated in a ventilator/heated humidifier system was tested during bolus and continuous infusion aerosol delivery. ^{99m}Tc (technetium)/saline was either injected (3 or 6 mL) or infused over time into the nebulizer. A shielded gamma ratemeter was oriented to count radioaerosol accumulating on an inhaled mass (IM) filter at the airway opening of a test lung. Radioactivity measured at 2–10-minute intervals was expressed as % nebulizer charge (bolus) or % syringe activity per minute infused. All circuit parts were measured and imaged by gamma camera to determine mass balance.
Results: Ratemeter activity quantitatively reflected immediate changes in IM: 3 and 6 mL bolus IM% = 16.1 and 18.8% in 6 and 14 minutes, respectively; infusion IM% = 0.64 + 0.13 (run time, min), R^2 0.999. Effect of nebulizer priming and system anomalies were readily detected in real time. Mass balance (basis = dose infused in 90 minutes): IM 39.2%, breath-enhanced jet nebulizer residual 35.5%, circuit parts including humidifier 23.4%, and total recovery 98.1%. Visual analysis of circuit component images identified sites of increased deposition.
Conclusion: Real-time ratemeter measurement with gamma camera imaging provides operational feedback during *in vitro* testing procedures and yields a detailed analysis of the parameters influencing drug delivery during mechanical ventilation. This method of analysis facilitates assessment of device function and influence of circuit parameters on drug delivery.

Keywords: continuous drug delivery, inhalation administration, mechanical ventilators

Introduction

Inhaled drug delivery to the intubated patient can be predicted *in vitro* with a ventilator system and appropriate test lung or respiration simulator.[1] With most experimental models, delivery is measured as aerosol deposited on filters and reported as a single data point at the end of the experiment.[1–4] Aerosolized drugs are typically analyzed using chemical assay and albuterol inhalation solution is often used as a surrogate for other drugs. This approach can be difficult and time consuming, particularly for assessing the effects of ventilator changes and the influence of circuit components. To expedite device testing, our group has often used radioactive labeling of nebulizer solution for analysis, which is more convenient than chemical analysis. However, a single data point at the end of an experimental run may not

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reveal information regarding transients that can occur during the experiment, for example, changes in nebulizer output, effects of ventilator settings, and so on, that can be important in a clinical situation. Measuring real-time, instantaneous aerosol delivery may provide a greater understanding of these complex systems that, combined with regional scintigraphic deposition data, allows a better understanding of device function. The present article describes in detail a method for determining the minute-by-minute measurement of inhaled mass (IM) or delivered dose. Two aerosol delivery protocols were tested: bolus treatments (e.g., unit-dose vials) and continuous infusion of solution into the nebulizer with an infusion pump. This method, combined with a detailed scintigraphic mass balance, illustrated during the more-complex infusion procedure, provided a comprehensive analysis of the contributions of all of the circuit components to drug delivery and facilitates the assessment of new aerosol delivery systems.

Materials and Methods

An experimental model for testing nebulizers during mechanical ventilation, based upon typical clinical protocols, is shown in Figure 1. In this example, the gas outlet of the mechanical ventilator was connected to the inlet port of a prototype breath-enhanced jet nebulizer (*i-AIRE*; InspiRx, Inc., Somerset, NJ). The outlet port of the *i-AIRE* nebulizer was connected via an 18-inch length of corrugated tubing to the inlet port of the heated humidifier chamber (MR-850; Fisher & Paykel Healthcare, Ltd., Auckland, New Zealand). The humidifier was operated in its invasive mode (for mechanical ventilation via an artificial airway) with default settings and the temperature was maintained throughout the procedure at 37°C ± 1°C, representing the gas delivery temperature at the patient-Y connector of the ventilator circuit. The inspiratory tubing of the Fisher & Paykel dual-limb heated wire ventilator circuit was connected from the heated humidifier outlet port to the patient-Y connector, which was, in turn, connected to a pair of 1-L neoprene rubber test lungs via a closed-system suction (CSS) device and a 7.5-mm ID endotracheal tube (ETT). The CSS device was included in the experimental setup to render a more clinically accurate model of mechanical ventilation inasmuch as its tee-piece assembly is situated in the inspiratory pathway and may be a site for aerosol deposition proximal to the airway opening. The pair of rubber test lungs in parallel simulate nonelastic (airway resistance) and elastic (lung compliance) forces that the ventilator must overcome to deliver assisted breaths and are not adversely affected by the increased humidification in the circuit. The IM filter (Pari,

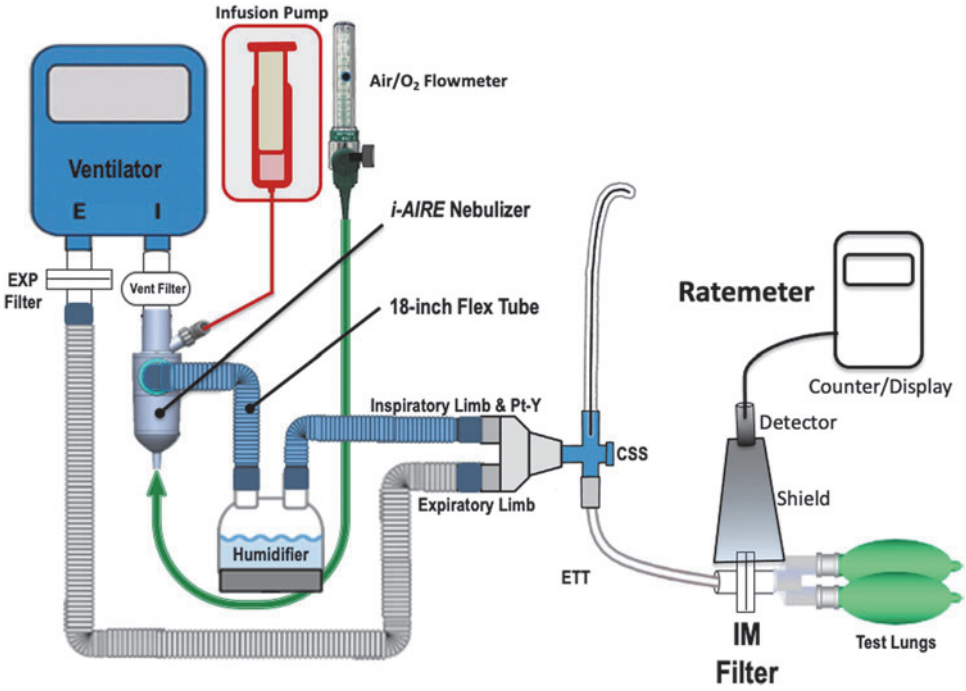

FIG. 1. Schematic diagram of experimental test setup illustrating the mechanical ventilator circuit and typical components, connection of a breath-enhanced jet nebulizer to the ''dry'' or inlet side of the heated humidifier, and a programmable infusion pump connected by delivery tubing to infuse solution into the dual medication port of the *i-AIRE* nebulizer. The IM filter is shown distal to the CSS device and ETT and immediately proximal to the test lungs. The ratemeter system consisting of an electronic counter/display device, gamma detector, and lead shield[8] is shown with the detector directed toward the IM filter. For experiments representing bolus treatments, in which the nebulizer would be filled from a unit-dose ampule or syringe, the infusion system was removed and the bolus dose of ^{99m}Tc-NS was injected directly into the i-AIRE nebulizer through its dual medication port adapter (Fig. 2). ^{99m}Tc, technetium; CSS, closed-system suction; ETT, endotracheal tube; IM, inhaled mass; NS, normal saline.

Starnberg, Germany) was interposed between the distal tip of the ETT and the test lungs. The distal end of the ventilator circuit expiratory limb tubing was connected to a similar aerosol collection filter (EXP filter) attached to the expiratory channel inlet connector of the ventilator.

Technetium (^{99m}Tc) pertechnetate dissolved in normal saline (NS, 0.9% NaCl) was used as a tracer and surrogate for albuterol and other drugs.[5–7] Preparation of the surrogate nebulizer solutions plus deposition of ^{99m}Tc-NS on collection filters and other parts of the ventilator circuit was quantified by direct measurement in a radioisotope calibrator (AtomLab 100; Biodex, Inc., Shirley, NY) or regionally in the ventilator circuit using a calibrated gamma camera (Maxi Camera 400; General Electric, Horsholm, Denmark, Model 604/150/D; Power Computing, Austin, TX, Nuclear MAC OS, Version 4.2.2; Scientific Imaging, Inc., Thousand Oaks, CA).

A portable ratemeter (Model 2200 Scaler Ratemeter; Ludlum Measurements, Sweetwater, TX) was used to allow real-time measurement of the radioactivity accumulating on the IM filter during the test run.[8] Ratemeter counts per minute were calibrated against quantitative units (millicuries [mCi] or microcuries [μCi]) of ^{99m}Tc activity with the gamma camera. After a room background radiation measurement coincident with the start of nebulization, the investigator triggered 1 minute counts of radioactivity on the IM filter at desired intervals.

To illustrate the real-time observations possible with this technique, two bolus nebulization experiments using unit-dose volumes of 3 and 6 mL were conducted to demonstrate basic principles of the method. In addition, four different continuous infusion experiments were also conducted: the first two experiments assessed the effect of priming the nebulizer (''Prime vs. No Prime''); the third was an uninterrupted test run for 90 minutes for a mass balance determination, while the fourth test run was deliberately perturbed by intentional interruptions (air flow disconnect, infusion pump failure) to illustrate how the ratemeter technique reveals real-time operational patterns and potential anomalies with drug delivery experiments. While the ratemeter counts alone allowed monitoring of experiments in real time, the counts were converted to quantitative units (μCi) and analyzed by linear regression to reveal the rate of increase in IM over time.

The complete mass balance determination carried out at the end of the uninterrupted 90 minutes infusion experiment demonstrated distribution of the aerosol across the circuit. The mass balance technique is fundamentally similar for bolus treatments and continuous infusion, particularly with respect to the gamma camera measurement of activity on the component parts of the ventilator system. The only major difference is that the initial charge for the bolus treatment is known before the experiment commences. For the bolus treatment, the radioactivity added to the nebulizer is measured before commencing the experiment after the dose has been added to the nebulizer. For continuous infusion aerosol delivery, the amount of radioactivity infused into the nebulizer is determined after the experiment has concluded and the infused volume is read off the infusion pump.

Bolus nebulization

For determinations of aerosol delivery during bolus nebulization, a few drops of ^{99m}Tc pertechnetate were titrated into a syringe containing 3 or 6 mL of NS to achieve activity of $\sim$1200 to 1500 μCi as measured on the radioisotope calibrator. In separate experiments, the 3 or 6 mL bolus was injected into the nebulizer through the dual medication port adapter (Fig. 2). Immediately thereafter, the residual activity in the syringe was measured by the radioisotope calibrator and subtracted from the full syringe activity to render the initial nebulizer charge (nominal dose) in μCi. Next, the nebulizer was placed on the gamma camera to determine the initial nebulizer charge in counts per minute. These measurements allow the calculation of a calibration factor for the gamma camera (μCi/counts/min) pertinent to the specific experiment for use in subsequent calculations. At the same time as the gamma camera initial charge measurement, the ratemeter was triggered to make a measurement of room background radiation and the actual time was recorded and designated as t_0 so that future measurements could be decay-corrected for the Δt that elapsed beyond t_0.

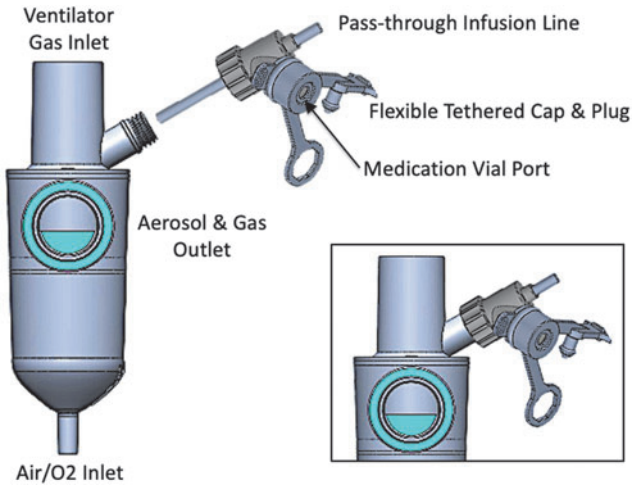

FIG. 2. Prototype *i-AIRE* breath-enhanced jet nebulizer with dual medication port adapter allowing continuous infusion and/or instillation of medication into the nebulizer. The adapter is attached via a threaded connector to the nebulizer body to allow the tip of the infusion line to be positioned inside the nebulizer. Medications contained in a syringe or unit-dose vial can be added to the nebulizer through the medication vial port which is capped and plugged by a flexible tethered device when not in use.

To start the experiment, the *i-AIRE* nebulizer was connected into the ventilator circuit (Fig. 1) and powered with medical air at 3.5 L/min and 50 psig. The ventilator was set to provide a constant flow breathing pattern with a rate of 20 breaths per minute, tidal volume of 650 mL, positive end-expiratory pressure (PEEP) of 5 cm H_2O, bias flow of 2 L/min, and duty cycle (DC, inspiratory time fraction) of 0.34. A stopwatch was used to time the experiment. The ratemeter was triggered at 2-minute intervals throughout nebulization of the bolus and the measured activity (counts/μCi) on the IM filter was used to monitor the progress of the experiment and define the run time (cessation of nebulization). Measurement of the IM filter on the gamma camera at the conclusion of the test run was used to calibrate the procedure and define total drug delivery. The nebulizer residual activity plus the activity on the EXP filter was measured by gamma camera at the conclusion of the bolus test runs.

Continuous nebulization

For continuous infusion aerosol delivery experiments, a few drops of ^{99m}Tc pertechnetate from a 30 mCi source syringe were added to a beaker containing 65 mL of NS solution, mixed thoroughly, and then measured on the gamma camera. This process was repeated, as necessary, until the gamma camera measured activity ranging between ~1.0 and 1.5 million counts per minute in the beaker. Next, 60 mL of the ^{99m}Tc-NS solution was drawn into the empty 60 mL infusion pump syringe, which was then capped and measured within 1 minute by both the radioisotope calibrator (activity in μCi) and the gamma camera (activity in counts/min). These measurements allow the calculation of a calibration factor for the gamma camera (μCi/counts/min), and the concentration of radioactivity in the infusion pump syringe (μCi/mL), to be used in subsequent calculations. At this point, the ratemeter was also triggered to make a measurement of room background radioactivity and the actual time was recorded and designated as t_0 so that future measurements could be decay-corrected for the Δt that has elapsed since t_0.

Nebulizer filling protocols for continuous nebulization. To assess nebulizer behavior per minute from t_0, the influence on IM of priming the nebulizer was initially tested. In one experiment, the nebulizer was primed, and in the other, the nebulizer was not primed. The transient behavior due to nebulizer priming could be important in defining initial patient response to continuous nebulization. At the start of these experiments, the nebulizer was dry, empty, free of radioactivity, and already installed in the ventilator circuit. The infusion syringe and its delivery tubing were installed on the programmable infusion pump (BD Alaris Pump Module; Becton, Dickinson and Company, Franklin Lakes, NJ). For both experiments, the infusion set delivery tubing was primed with 4 mL from the infusion syringe to displace all air and clamped to allow controlled connection to the dual medication port adapter on the *i-AIRE* nebulizer (Fig. 2). For the ''Primed'' experiment, after priming the delivery tubing, the infusion pump was set to prime exactly 2 mL of solution into the nebulizer immediately before starting the timed experiment. For the ''No Prime'' experiment, the delivery tubing was primed before starting the timed experiment, but the nebulizer was not. For both experiments, the infusion pump was set to deliver ^{99m}Tc-NS to the nebulizer continuously at a rate of 5 mL/hr and was started simultaneously with the gas flow to the *i-AIRE* nebulizer (3.5 L/min medical air at 50 psig), and run for 60

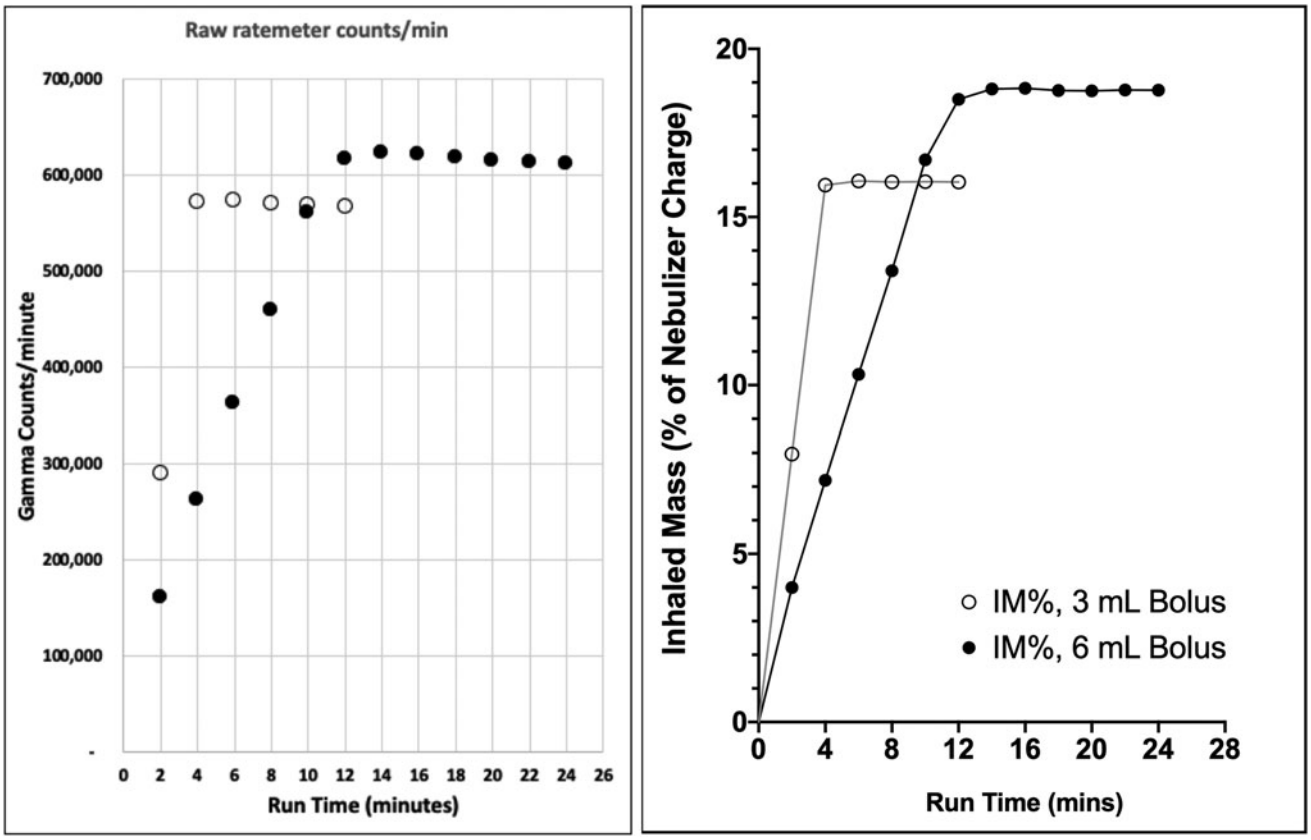

FIG. 3. Completion of two bolus treatment experiments at different nebulizer fill volumes but same ventilator breathing pattern and duty cycle. Open circles are 3 mL bolus data, closed circles are 6 mL bolus data. Left: nondecay corrected ratemeter counts per minute versus run time, as would be displayed in real time by the MS-Excel spreadsheet program (Microsoft Corporation, Redmond, WA) and seen by the investigator as the experiment is conducted. Right: final ratemeter data after having been adjusted for room background, corrected for decay from the time elapsed since t_0, converted from ratemeter counts per minute to μCi, and expressed as IM (% of nebulizer charge) versus run time in the GraphPad Prism statistics and graphing program. The 3 mL bolus reached cessation of aerosol output, as indicated by the onset of a plateau, at 6 minutes with an IM of 16.1% while the 6 mL bolus required 14 minutes to achieve an IM of 18.8%. μCi, microcuries.

minutes. For the ''No Prime'' experiment, the ratemeter was triggered to perform a 1 minute count of radioactivity on the IM filter at 1 minute intervals until the nebulizer began to emit aerosol, as evidenced by increasing counts on the IM filter, and then at 15 minutes intervals thereafter. For the ''Primed'' experiment, the ratemeter was triggered to perform counts at 5, 10, and 15 minutes intervals during the experiment. Both experiments were terminated at 60 minutes.

Steady state experiments. Two different continuous infusion experiments were conducted. The first experiment was run for 90 minutes and a complete mass balance determination was conducted at the termination of the test run. The ventilator was set to provide a constant flow breathing pattern with a rate of 20 breaths per minute, tidal volume of 650 mL, PEEP of 5 cm H_2O, bias flow of 2 L/min, and DC (inspiratory time fraction) of 0.34. Infusion pump flow for these experiments was 10 mL/min and a 2 mL prime was delivered to the nebulizer immediately before starting the test run. At timed intervals during the run, the ratemeter was triggered to perform a 1 minute count of radioactivity accumulating on the IM filter. The measurements were performed at 2-minute intervals for the first few minutes of the procedure and were lengthened to every 5 minutes for the balance of the experiment. At the conclusion of the 90 minutes test run, a final 1 minute ratemeter count of the IM filter was made, followed by a 1 minute scan of the IM filter by the gamma camera to calibrate the ratemeter and to determine the IM% for each data point. Thereafter, all the component parts of the nebulizer/ventilator system, including the nebulizer residual, were individually scanned on the gamma camera to determine their radioactivity for the mass balance determination.

For the second continuous infusion experiment, the 50 psig, 3.5 L/min gas flow to the nebulizer was interrupted at 40 minutes for 35 minutes and then restored; and later the infusion pump flow was paused at 75 minutes for 30 minutes and then restored. Ratemeter measurements were obtained and graphed at intervals as before. A mass balance determination was not conducted on this run.

Analysis. At the conclusion of each experiment, ratemeter activity (counts/min − background activity) over time was decay-corrected to t_0 and converted to μCi by using the final decay-corrected measurement of radioactivity of the IM filter on the gamma camera. This represents the dose of drug delivered to the IM filter over time. For bolus experiments, radioactivity on the IM filter was converted to μCi and graphed against time as IM (% of initial charge), where initial charge = the amount of radioactivity (μCi) added to the nebulizer at the beginning of the run. For the uninterrupted continuous infusion experiment, radioactivity on the IM filter was graphed against time as a percentage of the radioactivity used (μCi) to initially fill the infusion syringe: IM (% of infusion syringe activity/min) and analyzed by linear regression (GraphPad Prism 9.0.1 for Mac OS; GraphPad Software, San Diego, CA).

Mass balance determination for the 90 minutes infusion. All component parts of the ventilator circuit were laid directly on the surface of the gamma camera for measurement. Filters (filter holder plus filter media) were placed in a plastic sandwich bag to protect against leakage, stood on end, and placed individually in the center of the field. Nebulizers were stood upright in a thin plastic cup and placed individually in the center of the field. The ETT and CSS device were placed in a plastic tub and set directly on the camera surface. Ventilator tubing was coiled and placed in a plastic tub to contain it within the camera field. Left-right orientation of parts placed on the camera field was standardized and the text insertion feature of the gamma camera software was often used to identify parts and orientation. Gamma counts for each component were acquired individually and adjusted by subtracting room background and corrected for the time elapsed since the initial syringe charge was determined at t_0. Regions of interest were not drawn for this type of analysis because the camera counts and background images included the entire camera field. No adjustment for component thickness was required because a parallel hole collimator was used, which is insensitive to distances from the camera face.

The amount of radiolabeled aerosol deposited in each circuit component was expressed as a percentage wherein the numerator was the radioactivity delivered to the filter or circuit component, and the denominator was the nominal

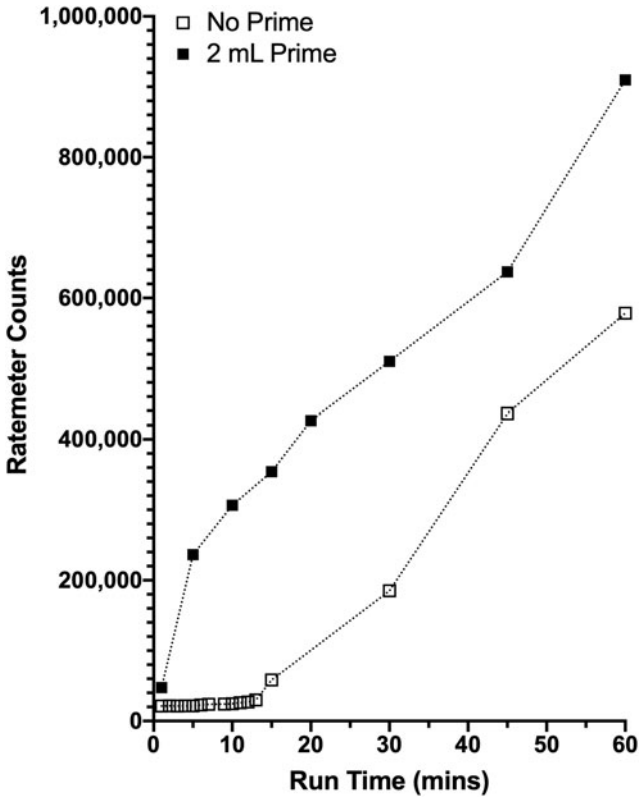

FIG. 4. Influence of nebulizer priming before continuous infusion. These experiments with a ventilator duty cycle of 0.34 and an infusion pump flow of 5 mL/h illustrate the effect of nebulizer priming. The open squares represent the ''No Prime'' condition where ~13 minutes was required for the nebulizer to accumulate sufficient solution to begin operating. The closed squares represent 2 mL of nebulizer prime immediately before commencing the experiment. The ''primed'' experiment demonstrates an immediate rise in radioactivity on the IM filter as the prime volume is nebulized.

dose (initial charge) of radioactivity available for delivery, that is, the activity infused into the nebulizer during the test run. The amount of radioactivity (μCi) infused into the nebulizer during the test run was calculated as Volume Infused (mL) × Syringe Radioactivity Concentration (μCi/mL). Once the radioactivity infused was calculated and decay-corrected, the percentage of initial charge on the filters and various circuit parts was calculated for the mass balance determination and analyzed as ''parts of a whole'' by GraphPad Prism.

Results

Ratemeter activity over time for the two bolus nebulization runs is shown in Figure 3 (nondecay corrected ratemeter counts, and the decay-corrected IM as a percentage of the nebulizer charge (nominal dose). Activity was detected shortly after the start of nebulization and increased linearly until all of the solution added to the nebulizer was effectively nebulized and emitted, at which point ratemeter measurements indicated a plateau (no further increase in activity). The line graph demonstrates an IM of 16.1% of nebulizer charge in 6 minutes for the 3 mL bolus, and 18.8% of nebulizer charge in 14 minutes for the 6 mL bolus. Visual inspection of both the ratemeter and IM graphs indicate that the nebulizer output was linear over time and it delivered a constant quantity of aerosol for both bolus fill volumes until the nebulizer ceased emitting aerosol, as indicated by the line having plateaued.

Figure 4 demonstrates the startup behavior of the jet nebulizer during continuous infusion. When the nebulizer

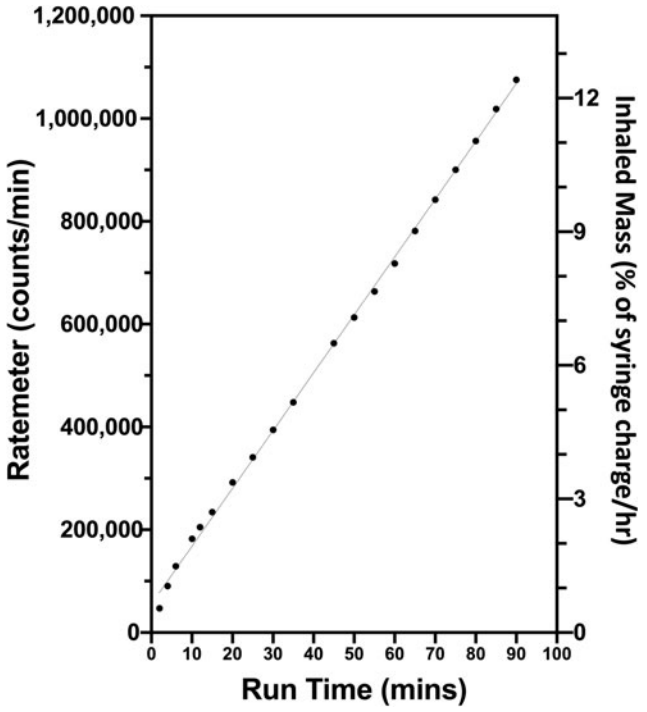

FIG. 5. Uninterrupted continuous infusion aerosol delivery experiment. The dual Y-axis line graph demonstrates the raw, real-time ratemeter counts of the IM filter at intervals during the experimental run, with run time (min) on the abscissa and ratemeter counts per minute on the left ordinate. The right ordinate, IM%, shows the IM calculated as the decay corrected percentage of the radioactivity of the initial infusion syringe charge. At the onset of the experimental run, the ratemeter count was triggered at 2, 4, 6, 10, and 12 minutes to show the initial response of the nebulizer to the prime. From 15 minutes on, ratemeter counts were triggered at 5 minutes intervals (with the exception of the missed measurement at the 40 minutes mark).

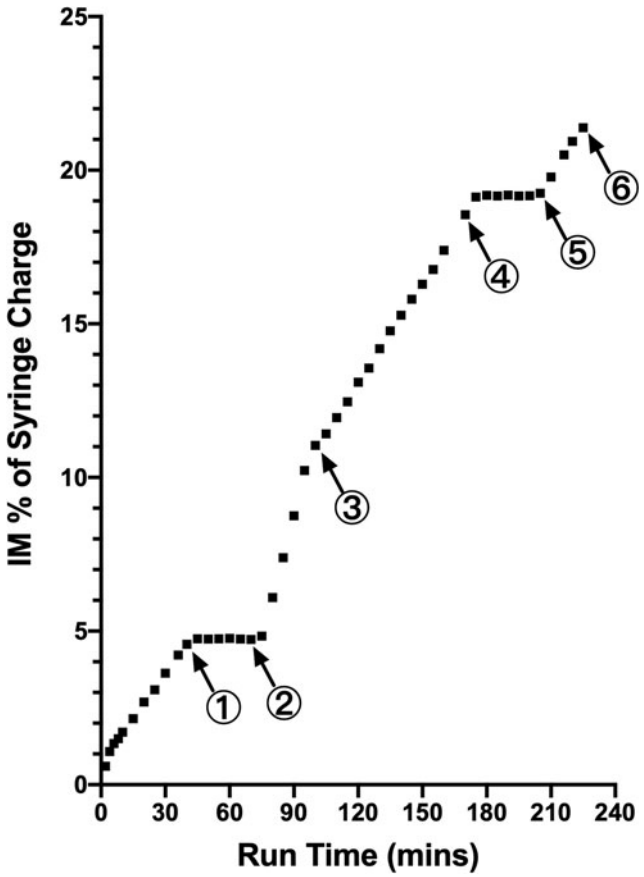

FIG. 6. Deliberately interrupted continuous infusion aerosol delivery experiment. The line graph shows the real-time ratemeter counts of the IM filter converted to decay-corrected μCi and presented as a percentage of the initial radioactivity in the infusion syringe (syringe charge). The circled numbers indicate intentional interventions that were performed to assess the sensitivity of the ratemeters response to acute changes in system parameters. At Event 1 the air flow powering the breath-enhanced jet nebulizer was disconnected, thereby causing aerosol output to cease. Air flow was reconnected at Event 2. The steep slope occurring immediately after Event 2 represents the increased nebulizer output due to 5.8 mL volume [Pump Flow (mL/h)/60*35 minutes] of radioactive solution that accumulated during the period of air flow disconnection. At Event 3, the system achieved a steady state again after the excess nebulizer solution was aerosolized and the slope of the line approximates the original slope. At Event 4, the infusion pump was paused, and within 2 minutes, aerosol output ceased because the nebulizer cup was no longer being continually replenished by the infusion pump. At Event 5, the infusion pump was restarted and aerosol output from the nebulizer immediately resumed with the slope of the line approximating the former slope. At Event 6 the experiment was terminated.

was primed, aerosol was immediately generated at a rapid rate over the first few minutes, which then slowed to a steady state reflecting the infusion rate of 5 mL/min. When the nebulizer was not primed, aerosol was not produced immediately; the nebulizer retained volume until a sufficient amount of solution accumulated and nebulization began. After 15 minutes, steady state nebulization was reached.

For the 90 minutes continuous infusion run shown in Figure 5, ratemeter activity was detected shortly after the start of nebulization and increased linearly until the end of the observation period. Regression analysis defined the rate of increase of activity on the IM filter as IM% = 0.64 + (0.13 × Run Time, minutes), $R^2 = 0.999$. The slope component of the regression equation plus its coefficient of determination (R^2) indicates that the nebulizer delivered a constant quantity of aerosol over time. The sudden termination of the line shows that the experiment was deliberately concluded at 90 minutes.

The second continuous infusion aerosol delivery experiment is shown in Figure 6 when two different interventions were deliberately applied to perturb the system. The nebulizer was primed with 2 mL from the infusion syringe immediately before starting the test run. After a steady state was reached, the nebulizer gas flow was disconnected at 40 minutes and restored at 75 minutes. There was a rapid onset of nebulization immediately detected on the IM filter. The slope of this line represents the maximum output of the nebulizer as it was filled with 5.8 mL saline by the infusion pump during the period of gas flow interruption. Further into the run, the infusion pump was paused, resulting in a flat line, and later restarted, resulting in resumption of nebulization at the previous rate. The sudden termination of the line, rather than a plateau as seen in the bolus experiments, shows that the experiment was intentionally concluded.

Gamma camera scans of the different components of the aerosol delivery system and ventilator circuit following the uninterrupted continuous infusion experiment are shown in Figure 7, illustrating the distribution of deposited aerosol particles as they transited the ventilator circuit from the nebulizer to the IM filter and through the expiratory limb to the EXP filter. Quantitative measurements of each component were made for the mass balance determination shown in Figure 8. The radioactivity of each component was expressed as a percentage of the radioactivity infused into the nebulizer. The total recovery, the sum of the individual components, was 98.1% of the activity infused. Of the nominal dose delivered to the nebulizer by the infusion pump over 90 minutes, 35.5% remained in the nebulizer as residual, while 39.2% was delivered to the IM filter.

Discussion

Use of a radioactive tracer coupled with the gamma camera provides a detailed assessment of inhaled drug delivery in a mechanical ventilation circuit.[7,9–11] However, in previous studies, analysis of an experiment could not begin until after it was completed, and IM separately measured. Nebulizer function and aerosol output of some nebulizers in a ventilator circuit may be difficult to observe, and if aerosol output differs from that expected, the question always remained ''did the nebulizer function?'' The effect of anomalies on the veracity of the experiment

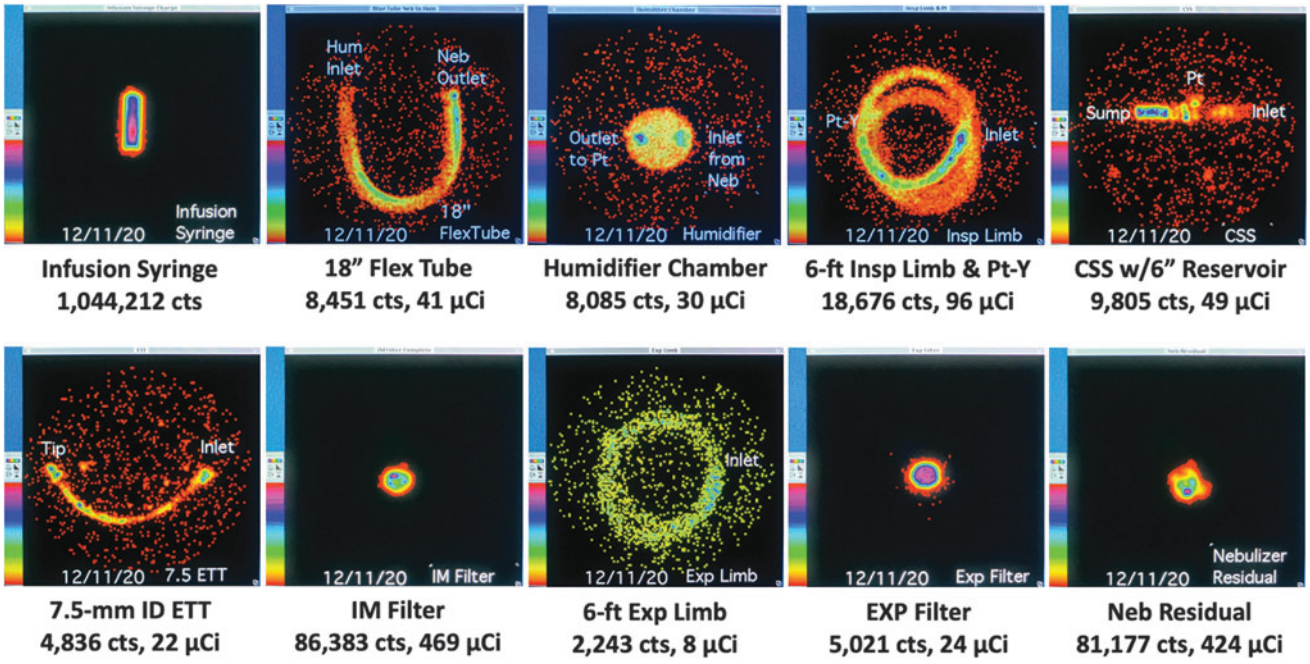

FIG. 7. Gamma camera images of individual components of the experimental circuit. Images correspond to the measured components for the complete Mass Balance: flex tube from the nebulizer to the humidifier, the humidifier chamber, the 6-foot inspiratory tubing limb with patient-Y connector, the CSS device (with a deliberately added ''sump'' flex tube to collect circuit condensate), the 7.5 mm ID ETT, the IM filter, the 6-foot expiratory limb, the expiratory (EXP) filter and, finally, the nebulizer residual measured at the conclusion of the experiment. The raw gamma counts (cts) and the decay-corrected quantitative radioactivity determination (μCi) are listed below each image. The color spectrum for each image is shown.

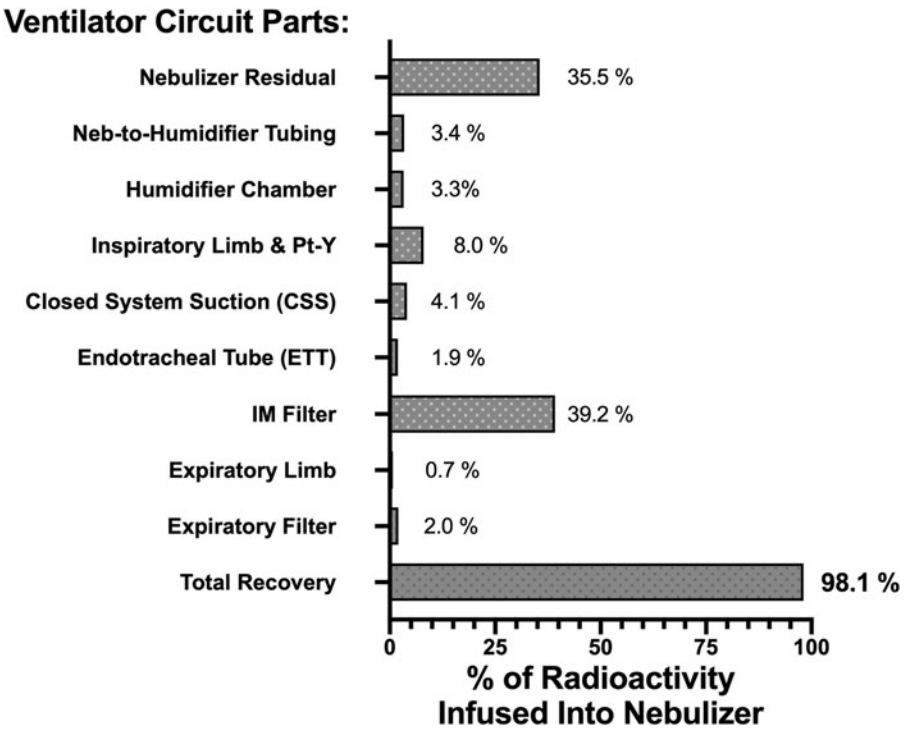

FIG. 8. The Mass Balance data, shown graphically, demonstrates the fate of the radioactive solution that was infused into the nebulizer. The nebulizer residual (35.5%) is radioactivity that remained in the nebulizer. The amount of radioactivity that was emitted from the nebulizer is distributed throughout the different components of the ventilator circuit as shown in Figure 7. The ''inhaled dose'' delivered to the simulated patient (IM filter) is 39.2% of the total amount of the radioactivity infused into the nebulizer during the 90 minutes test run. The horizontal bar at the bottom of the graph shows the sum of all the individual components (Total Recovery), indicating a technically acceptable study.

often could not be determined in real time. The addition of the ratemeter allows precise confirmation of aerosol delivery to the IM filter during the experiment, while anomalies with the nebulizer, ventilator, or infusion pump can be readily detected. Nebulizer run time for bolus experiments, plus the effects of ventilator parameters and the influence of priming on continuous nebulization, can be determined by the ratemeter signal over time and, with calibration, quantified.

The addition of the mass balance determination enables a more complete analysis with respect to aerosol transit through, and deposition within, the circuit. For example, it has been reported that the ETT serves as a major barrier to aerosol delivery.[12] However, that did not occur with this nebulizer and test conditions as the mass balance demonstrates that the nebulizer residual was the major determinate of losses and maneuvers to influence ETT deposition would be futile in affecting delivery. Other nebulizers may behave differently. Similarly, with this particular nebulizer, the heated humidifier did not present as a significant barrier to aerosol delivery as has been shown in other studies.[7,9,10] The mass balance is therefore an important aspect of *in vitro* aerosol delivery assessment because (i) it accounts for all the drug or tracer placed initially or infused into the nebulizer over time, and (ii) its distribution has the potential to vary depending on several factors, alone and in combination.

Only one experiment of each condition has been described; no replicates are reported. The experiments and results shown in this article are examples that illustrate the application of the equipment and methods described. This article serves as a detailed template for future studies.

In vitro bench studies are limited because the laboratory is not a true hospital environment and patient related factors are not assessed. However, in past studies using older technology, our group found that *in vitro* measurements of IM predicted aerosol delivery *in vivo* that were correlated with measured drug concentrations in patient secretions[1] and measured deposition of antibiotics in the lungs.[13,14] Delivery systems are now more sophisticated. Ventilators and humidifiers are different, and drugs are now aerosolized continuously as life-saving interventions in critically ill patients. The challenge to understanding device function under these circumstances is far more complex than giving a simple bronchodilator treatment. The real-time ratemeter technique lends itself well to the assessment of more complex aerosol delivery methods, devices, and protocols facilitating a more precise assessment of factors that is important in controlling drug delivery.

Authors' Contributions

M.M.: Study design, data collection, data analysis, literature search, and article preparation. J.A.L.: Study design, data collection, data analysis, and article review. A.D.C.:

Study design, data collection, data analysis, and article review. G.C.S.: Study design, data analysis, and article review.

Author Disclosure Statement

Dr. Smaldone is a consultant to InspiRx and is a member of the Advisory Board; Ms. Cuccia serves as a consultant to InspiRx, Inc.; Mr. McPeck and Dr. Lee have no conflicts.

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