Radioaerosol Pulmonary Deposition Using Mesh and Jet Nebulizers During Noninvasive Ventilation in Healthy Subjects

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BACKGROUND: In vivo deposition studies of aerosol administration during noninvasive ventilation (NIV) are scarce in the literature. The aim of this study was to compare radioaerosol pulmonary index and radioaerosol mass balance in the different compartments (pulmonary and extrapulmonary) of radio-tagged aerosol administered using vibrating mesh nebulizers and conventional jet nebulizers during NIV. METHODS: This was a crossover clinical trial involving 10 healthy subjects (mean age of 33.7 ± 10.0 y) randomly assigned to both treatment arms of this study: group 1 (NIV + vibrating mesh nebulizer, $n = 10$) and group 2 (NIV + jet nebulizer, $n = 10$). All subjects inhaled 3 mL of technetium-99m diethylenetriaminepentaacetic acid (25 mCi) and 0.9% saline solution via vibrating mesh and jet nebulizers during NIV through a face mask secured with straps while receiving positive inspiratory and expiratory pressures of 12 and 5 cm H_2O, respectively. Scintigraphy was performed to count radioaerosol particles deposited in the regions of interest to determine radioaerosol mass balance from the lungs, upper airways, stomach, nebulizer, ventilator circuit, inspiratory and expiratory filters, and mask as a percentage. RESULTS: Vibrating mesh nebulizers deposited 972,013 ± 214,459 counts versus jet nebulizer with 386,025 ± 130,363 counts ($P = .005$). In a determination of mass balance, vibrating mesh nebulizers showed a higher deposition of inhaled radioaerosol compared with jet nebulizers (23.1 ± 5.8% vs 6.1 ± 2.5%, $P = .005$) and a higher proportion of radioaerosol deposited into the lungs (5.5 ± 0.9% versus 1.5 ± 0.6%, respectively, $P = .005$). The residual drug volume was lower with vibrating mesh nebulizers (5.1 ± 1.5%) compared with jet nebulizers (41.3 ± 4.2%, $P = .005$). CONCLUSIONS: During NIV in healthy subjects, vibrating mesh nebulizers delivered > 2-fold more radiolabeled drug into the respiratory tract compared with conventional jet nebulizers. Additional studies are recommended in subjects with asthma, COPD, bronchiectasis, and cystic fibrosis to better understand differences in both aerosol delivery and response. (ClinicalTrials.gov registration NCT01889524.) *Key words: nebulizer; noninvasive ventilation; inhalation device; aerosol; pulmonary scintigraphy; radioaerosol.* [Respir Care 2015;60(9):1238–1246. © 2015 Daedalus Enterprises]

Introduction

Nebulization works to deposit drugs directly into the lungs of patients with acute and chronic pulmonary diseases, avoiding systemic adverse effects associated with other routes of administration.[1] Noninvasive ventilation (NIV) is commonly employed to reduce work of breathing and minimize respiratory discomfort in those patients whose exacerbations increase the work of breathing.[2-5] Many pa-

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tients requiring NIV may benefit from effective inhaled medication delivery.[6,7] Many factors influence the efficacy of aerosol delivery during NIV, such as ventilator type, ventilation mode, circuits, gas density, humidity, interfaces, aerosol generator type, particle size, aerosol generator position, and factors related to the patient (including type and severity of disease, respiratory pattern, and ability to tolerate a face mask).[8-12]

Historically, the jet nebulizer has been used frequently in emergency departments.[6,7,13,14] The vibrating mesh nebulizer consists of a membrane (or mesh) with thousands of funnel-shaped apertures that dictate the particles sizes according to the exit diameter of the apertures. A piezo element converts electricity to mechanical vibration of the mesh at 128 kHz (one-tenth frequency of ultrasonic nebulizers), creating a micro-pumping action that extrudes fluid through the small holes in the membrane, breaking fluid from the apertures into a stream of precise droplets.[11,15-18]

The vibrating mesh nebulizer has been associated with production of precise particle sizes without adding gas flow into the ventilator circuit and a low residual volume of drug remaining after nebulization is complete.[11,15] This type of nebulizer has been shown to be promising in providing greater inhaled and pulmonary deposition compared with jet nebulizers during conventional mechanical ventilation using both in vitro and animal models.[10,19-21]

Although pulmonary scintigraphy has been used to quantify radioaerosol pulmonary deposition generated by different types of aerosol generators under a number of conditions, we did not find any reports comparing aerosol deposition with vibrating mesh and jet nebulizers in healthy subjects during NIV. On the basis of previous in vitro and animal studies, we hypothesized that vibrating mesh nebulizers would deposit more aerosols into the lungs during NIV compared with jet nebulizers. The aims of this study were to analyze the radioaerosol deposition index in horizontal and vertical gradients and to determine the mass balance of aerosol, including the pulmonary and extrapulmonary compartments (deposition) of radio-tagged aerosols generated by vibrating mesh and jet nebulizers in healthy adult subjects during NIV.

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) is a standard of care for exacerbations of chronic lung disease. These patients often require aerosolized medications during NIV. Many factors influence the efficacy of aerosol delivery during NIV, including the type of ventilator, mode of ventilation, circuit configuration (fixed leak or exhalation valve), humidity, interface, type of aerosol generator, position of the aerosol generator, and respiratory pattern.

What this paper contributes to our knowledge

In a group of normal subjects without lung disease using a crossover study design, a vibrating mesh nebulizer delivered a 2-fold greater dose of radiolabeled drug to the respiratory tract than a conventional jet nebulizer. The study used a full face mask without humidification. Clinical studies to confirm these findings in subjects with lung disease are warranted.

Methods

Study Design and Sample

A randomized crossover clinical trial was performed in the Department of Nuclear Medicine and the Cardiorespiratory Laboratory of the Physiotherapy Department at the Universidade Federal de Pernambuco in association with Georgia State University. Healthy subjects of both sexes between 18 and 60 y of age recruited from the Hospital das Clínicas de Pernambuco and the Cardiorespiratory Laboratory were enrolled in this study. This protocol was approved by the human ethics committee, and all participants gave written informed consent after receiving complete protocol information.

Inclusion and Exclusion Criteria

Inclusion criteria included: healthy volunteers between 18 and 60 y of age, FVC or $FEV_1 \geq 80\%$ of predicted,[22] ability to understand verbal commands, and willingness to provide signed consent to participate in this study. Subjects were excluded if they had a smoking history or a history of lung or cardiovascular disease, were pregnant, or were unable to tolerate NIV.[23]

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Procedures and Measurements

We collected the subjects' anthropometric data: age, height, weight, and body mass index. Cardiopulmonary parameters were considered: breathing frequency, peripheral S_{pO_2}, systolic blood pressure, and diastolic blood pressure using pulse oximetry (ACTIVE, Ecafix, São Paulo, Brazil) and a manual pressure manometer (DS series, Welch Allyn, Beaverton, Oregon). In addition, spirometry data (MicroLoop 8, Cardinal Health, London, United Kingdom) were collected in accordance with the American Thoracic Society guidelines with a variance of < 0.2 L allowed between tests, and the average of 3 measurements was recorded.[24]

The inhalation protocol was divided into 2 arms: (1) NIV + jet nebulizer and (2) NIV + vibrating mesh nebulizer. The order in which nebulizers were tested was randomized with subjects acting as their own control, with a washout period of 1 week before the second administration was performed to eliminate risk of residual trace radiation and to avoid the possibility of bias.

Subjects inhaled technetium-99m diethylenetriaminepentaacetic acid with a radioactivity of 25 mCi.[25] Both nebulizers were charged with 2.5 mg of salbutamol, 0.25 mg of ipratropium bromide, and normal saline solution to a fill volume of 3 mL. The jet nebulizer (AirLife Misty Max, CareFusion, San Diego, California), with a particle mass median aerodynamic diameter of 5 μm (according to the manufacturer's information), was positioned in the circuit using a T-piece placed between the circuit leak and the mask and operated at an oxygen flow of 8 L/min. The vibrating mesh nebulizer (NIVO, Philips Respironics, Murrysville, Pennsylvania), with a mass median aerodynamic diameter of 3.4 μm, was placed in the elbow adapter at the mask. Both nebulizers were operated until 1 min after onset of sputter or until no visible aerosol was produced (whichever was observed first). Bi-level positive airway pressure (BPAP) was applied with a BiPAP Synchrony system (Philips Respironics) through an inspiratory filter and a passive 22-mm inner diameter, 72-inch circuit with a fixed orifice and attached to a face mask (ComfortFull 2, Philips Respironics). The ventilator was set to delivery 12 cm H_2O of peak inspiratory pressure and 5 cm H_2O of expiratory positive airway pressure. Subjects were acclimated to the mask and NIV before starting measurements, and the mask was secured using standard headgear and straps. Subjects were oriented to use a passive breathing pattern and exhaling slowly to avoid ventilator-patient asynchrony.[26] The setup used for NIV with aerosol delivery is shown in Figure 1.

Immediately after inhalation, subjects sat in a chair positioned 30 cm from midline to a gamma camera (STARCAM 3200, Healthcare, Madison, Wisconsin) to obtain radioactive counts from the posterior thorax for a period of 300 s on a matrix of 256 × 256. Subjects were then positioned to obtain anterior images of the face for 300 s. To measure radiation in the nebulizer, circuit, inspiratory filter, expiratory filter, and face mask, the device components were laid out on a vertical surface placed 30 cm below the face of the gamma camera and analyzed for 300 s. Count corrections for technetium decay were used. The results from analysis of deposition in pulmonary and extrapulmonary compartments was expressed as a per-

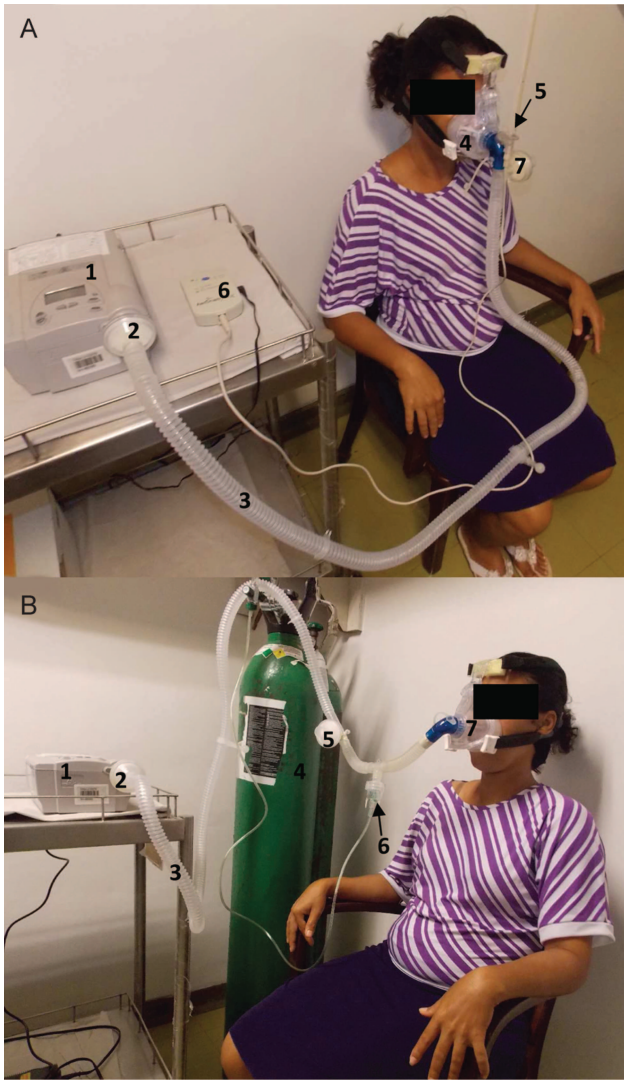

Fig. 1. Setup of the BiPAP Synchrony with an inspiratory filter and single-limb passive circuit, with the filter placed over the fixed leak to collect aerosol. A: setup with the ventilator (1), inspiratory filter (2), circuit (3), mask (4), NIVO placed at the elbow of the mask with the Aeroneb Pro controller attached by cable to the vibrating mesh nebulizer (5), nebulizer connector (6), and expiratory filter (7). B: setup with the ventilator (1), inspiratory filter (2), circuit (3), expiratory filter placed on a fixed leak (4), and oxygen cylinder with a regulator and flow meter with oxygen tubing (5) to drive the jet nebulizer (6) with a T-piece and 6 inches of 22-mm inner diameter tubing between the circuit and mask (7). An oxygen cylinder with a regulator and flow meter provided driving gas to the jet nebulizer.

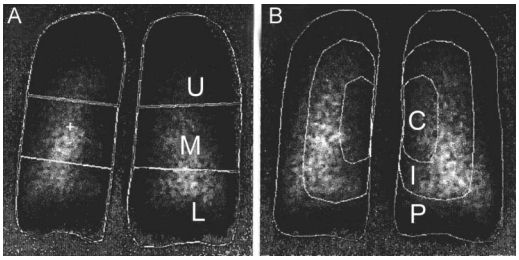

Fig. 2. Regions of interest analyzed in this study. A: vertical regions. U = upper third. M = middle third. L = lower third. B: horizontal regions. C = central region. I = intermediate region. P = peripheral region.

centage of the cumulative count in each compartment for each subject, representing the total radioaerosol mass. The inhaled radioaerosol was the sum of deposition into the upper airways, lungs, and stomach.[19] Regions of interest were delimited based on a previous protocol, and the radioaerosol deposition index was expressed as absolute values and calculated according to the counts generated from each region of interest (Fig. 2).[25]

Statistical Analysis

The sample size was calculated based on a pilot study involving 5 subjects to obtain an SD of repeated observations in the same individual and then an SD of the difference between 2 measurements in the same individual, considering percentage of lung deposition. A total of 10 healthy subjects were enrolled in this 2-treatment crossover study. The probability was calculated as 84% that the study would detect a treatment difference at a one-sided .01 significance level if the true difference between treatments is 1.19 units. It was based on the assumption that the within-subject SD of the response variable is 0.80. For the sample size calculation, we used the software developed by David Schoenfeld PhD (Harvard University, Boston, Massachusetts), support from the Massachusetts General Hospital Mallinckrodt General Clinical Research Center, and the JavaScript version developed by Ricky Morse (Harvard University, Boston, Massachussets).

The Primary outcome was the radioaerosol inhaled (radioaerosol deposition index) into the lungs. The secondary outcome was radioaerosol mass balance in the pulmonary, extrapulmonary, and device compartments. The Shapiro-Wilk test was performed to analyze normality, followed by the Wilcoxon test to compare deposition in the right and left lungs for each region of interest and to compare the percentages deposited in each compartment between devices. The Friedman test was performed to compare the counts deposited in the different regions of interest for each lung, and the Tukey test was performed as a post hoc analysis. The CI was 99% ($P < .01$) as determined with SPSS 20.0 (SPSS, Chicago, Illinois) and Prism 4.0 (GraphPad Software, San Diego, California).

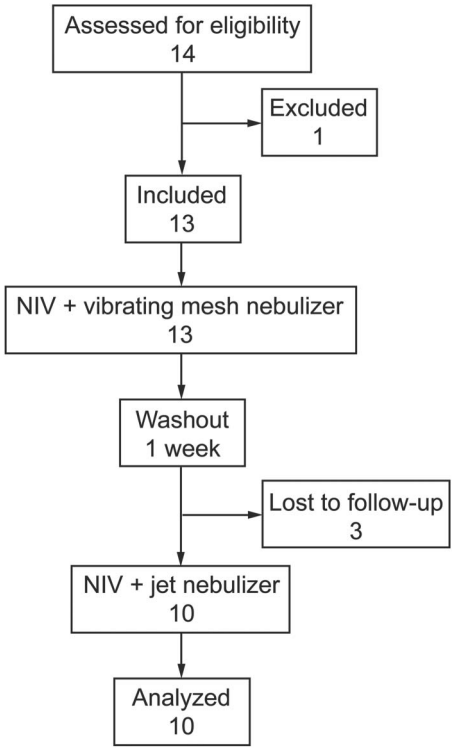

Fig. 3. Flow chart. NIV = noninvasive ventilation.

Results

Fourteen subjects were enrolled and consented to participate in this study, but only 10 (6 males and 4 females) completed the protocol. One subject declined to perform the protocols, 2 complained of claustrophobia using a face mask during NIV, and one did not meet the inclusion criteria. Thus, 10 subjects participated in the study and were randomly allocated to which type of nebulizer would be used first. The flow chart of the study is presented in Figure 3. Table 1 shows the anthropometric and spirometric data obtained from the subjects.

The total radioaerosol deposited into the lungs was higher in the NIV + vibrating mesh nebulizer group than in the NIV + jet nebulizer group (972,013 ± 214,459 counts vs 386,025 ± 130,363 counts, $P = .005$). Intergroup analysis of vertical and horizontal gradients demonstrated that the NIV + vibrating mesh nebulizer group had increased counts compared with the NIV + jet nebulizer group, as presented in Figure 4. Table 2 shows the results of intragroup analysis of each region of interest in the vertical and horizontal differences.

The percentage of radioaerosol inhaled was significantly higher in the NIV + vibrating mesh nebulizer group than

Table 1. Anthropometric and Cardiopulmonary Characteristics of Subjects

Variable	Values
Age, y	33.7 ± 10.04
Weight, kg	78.1 ± 17.50
Height, m	1.70 ± 0.09
BMI, kg/m^2	26.6 ± 2.70
Breathing frequency, breaths/min	15.5 ± 1.41
Heart rate, beat/min	78.1 ± 5.65
SBP, mm Hg	122.0 ± 10.6
DBP, mm Hg	78.5 ± 3.53
S_{pO_2}, %	97.1 ± 0.70
FEV_1, L	3.94 ± 0.69
FEV_1, % predicted	100.7 ± 3.36
FVC, L	4.47 ± 0.67
FVC, % predicted	95.3 ± 0.85
FEV_1/FVC	87.0 ± 2.23
FEV_1/FVC, % predicted	104.2 ± 5.21
PEF, L/min	9.15 ± 1.53
PEF, % predicted	92.3 ± 1.50

Values are mean ± SD.
BMI = body mass index
SBP = systolic blood pressure
DBP = diastolic blood pressure
PEF = peak expiratory flow.

in the NIV + jet nebulizer group. We observed that the vibrating mesh nebulizer had a lower residual drug volume but more radioaerosol deposited in the face mask and upper airways and significantly greater deposition on the expiratory filter compared with the jet nebulizer during NIV. No significant differences were found regarding the radioaerosol deposited in the stomach, circuit, and inspiratory filter for either group. Inhaled deposition and radioaerosol mass balance obtained in each compartment from both groups are shown in Table 3. Figure 5 shows representative scintigraphic images of deposition in the different compartments of each nebulizer during NIV.

Discussion

This is the first in vivo study to quantify pulmonary deposition of radio-tagged aerosol expressed in counts and as a percentage of the nominal dose and to compare deposition efficiency achieved with a jet nebulizer (AirLife Misty Max) and a vibrating mesh nebulizer (NIVO) during NIV, with deposition expressed as a percentage on the radiation dose placed into the nebulizer. With the jet nebulizer, pulmonary deposition during NIV (1.45%) was lower than previously reported levels (8–12%) in spontaneously breathing subjects.[27,28] França et al[26] examined pulmonary radioaerosol particles in lungs by scintigraphy in 13 healthy subjects and compared a jet nebulizer during spontaneous breathing to nebulization during NIV. Substantially greater pulmonary aerosol deposition was observed in subjects using nebulization without NIV. The authors hypothesized that high inspiratory flows associated with bi-level ventilation produced a large deposition of particles in the upper airways.

The low pulmonary deposition with jet nebulizers during NIV is consistent with the 1–3% deposition via jet nebulizers reported in intubated subjects during conventional mechanical ventilation.[28,29] In one of the few scintigraphy studies comparing jet and mesh nebulizers, Dubus et al[19] reported the amount of radio-tagged aerosol deposited using vibrating mesh and jet nebulizers (AirLife Misty-Neb, Allegiance Healthcare Corporation, McGaw Park, Illinois) in a macaque model of neonatal mechanical ventilation. In this case, the authors reported up to a 20-fold increase in lung dose with the vibrating mesh nebulizer. They identified the difference in the residual volume at the end of nebulization (1.2 vs 0.1 mL for the jet and vibrating mesh nebulizers, respectively) and the difference in particle size and gas flow added to the circuit (jet nebulizer) as factors contributing to the large difference in delivery efficiency. In our study, the NIVO generated particles with a size of 3.4 μm, and the AirLife Misty Max generated particles with a size of 5 μm.

Before the advent of modern bi-level NIV, intermittent positive-pressure breathing was applied in the acute care setting to administer noninvasive ventilatory support and medical aerosol. Dolovich et al[30] compared lung deposition from a jet nebulizer with spontaneous breathing and the same nebulizer with intermittent positive-pressure breathing with an inspiratory pressure of 15 cm H_2O in 9 subjects with stable chronic bronchitis. The authors reported ~30% lower deposition of radioaerosol throughout the lungs with intermittent positive-pressure ventilation breathing compared with the nebulizer alone. This was attributed to the flow at the onset of inspiration, which strongly affects the deposition of aerosol particles in the oropharynx, trachea, and large airways. It was thought that this reduction in lung dose of bronchodilators using this modality of ventilation would reduce bronchodilator efficacy in relieving bronchial obstruction. In contrast, Maccari et al[31] recently reported similar lung counts after administration of a jet nebulizer with spontaneous breathing, CPAP at 10 cm H_2O, and BPAP at 15/5 cm H_2O. They reported counts (mean ± SD) in the right lung of 196 ± 167 with spontaneous breathing, 109 ± 40 with CPAP, and 112 ± 15 with BPAP, with a similar trend in the left lung of 225 ± 293, 93 ± 15, and 98 ± 14, respectively. Although the trend favors greater counts in the spontaneously breathing group than in the CPAP or BPAP group, the larger SD resulted in no significant difference among the 3 groups.

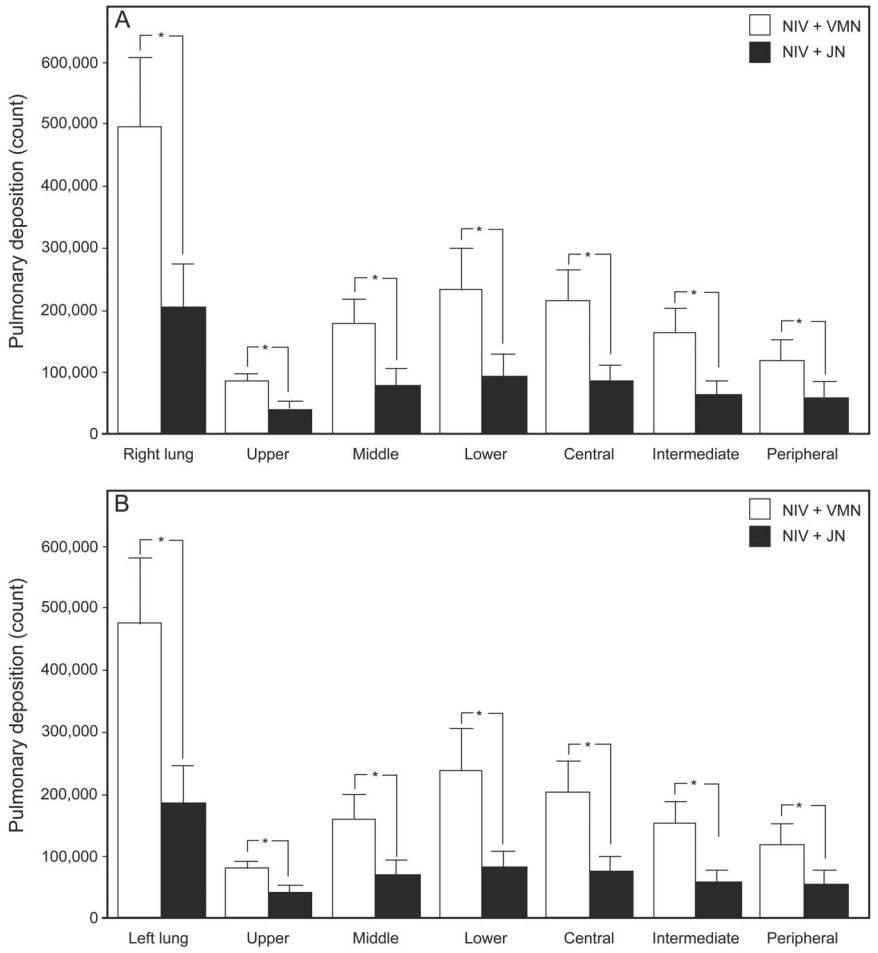

Fig. 4. Intergroup comparison of the radiation counts of radioaerosol deposited in the vertical (upper, middle, and lower thirds) and horizontal (central, intermediate, and peripheral) regions of the right (A) and left (B) lungs during noninvasive ventilation (NIV) with a vibrating mesh nebulizer (NIV + VMN) or a jet nebulizer (NIV + JN). Bars show mean pulmonary deposition ± SD. * $P = .005$ (Wilcoxon test).

Although in vivo reports of pulmonary deposition of radio-tagged aerosol via scintigraphy using jet and vibrating mesh nebulizers during NIV are limited, in vitro studies have provided valuable guidance. Our results demonstrated that the vibrating mesh nebulizer was more efficient than the jet nebulizer, with counts higher for both lungs in the NIV + vibrating mesh nebulizer group compared with the NIV + jet nebulizer group. These results are consistent with in vitro studies reporting a > 3-fold inhaled dose with the vibrating mesh versus jet nebulizer during NIV. The inhaled mass (calculated as the sum of deposition in the lungs, upper airway, and stomach) was 23.1% of the dose with the vibrating mesh nebulizer and 6.1% with the jet nebulizer, correlating to lung doses of 5.5% and 1.5%, respectively. Abdelrahim et al[10] used a breath simulator and measured inhaled dose on a filter, reporting inhaled doses of 24% with a jet nebulizer (Sidestream, Philips Respironics) and 51% with a vibrating mesh nebulizer (Aeroneb Pro, Aerogen, Mountain View, California) when placed between the fixed orifice and inspiratory filter. The authors cautioned that their method likely overestimated inhaled dose, as there was no mask or face surface collecting aerosol. Using a bi-level ventilator with single-limb circuit and an oropharyngeal mask attached to the face of an anatomic adult upper airway, AlQuaimi[32] collected drug on a filter distal to the trachea of a model of an adult upper airway attached to a passive test lung and reported inhaled masses of 13.2% with a jet nebulizer (AirLife Misty-Neb), 28.8% with a vibrating mesh nebulizer (Aeroneb Solo, Aerogen), and 23.5% with pressurized metered-dose inhaler and spacer (AeroVent, Monaghan Medical, Plattsburgh, New York).

Our results showed only 5.1% of the total radioaerosol mass balance remaining in the vibrating mesh nebulizer reservoir compared with 41.3% remaining in the jet nebulizer. Similarly, in the animal model reported by Dubus et al,[19] the vibrating mesh nebulizer tested presented a

Table 2. Radioaerosol Deposition Index According to Vertical and Horizontal Gradients for Each Pulmonary Region in Both Phases of the Study

Group	Vertical Gradient		Horizontal Gradient	
	Lung Region	P*	Lung Region	P†
Right lung				
NIV + jet nebulizer ($n = 10$)	U/M vs U/L	.38	C vs P + I/C	.005
	U/M vs M/L	.001		
	U/L vs M/L	.001		
NIV + vibrating mesh nebulizer ($n = 10$)	U/M vs U/L	.38	C vs P + I/C	.005
	U/M vs M/L	.006		
	U/L vs M/L	.001		
Left lung				
NIV + jet nebulizer ($n = 10$)	U/M vs U/L	.001	C vs P + I/C	.005
	U/M vs M/L	.006		
	U/L vs M/L	.001		
NIV + vibrating mesh nebulizer ($n = 10$)	U/M vs U/L	.001	C vs P + I/C	.005
	U/M vs M/L	.81		
	U/L vs M/L	.001		

Values are mean ± SD.
NIV = noninvasive ventilation
U = upper third
M = middle third
L = lower third
C = central third
I = intermediate third
P = peripheral third
* Friedman and Tukey tests, $P < .01$.
† Wilcoxon test, $P < .01$.

Table 3. Mass Aerosol Balance Presented in Pulmonary and Extrapulmonary Deposition in Each Study Group

Compartment	NIV + Vibrating Mesh Nebulizer ($n = 10$)	NIV + Jet Nebulizer ($n = 10$)	P*
Lungs, %	5.5 ± 0.9	1.5 ± 0.6	.005
Upper airways, %	16.2 ± 4.2	4.3 ± 2.0	.005
Stomach, %	1.4 ± 1.8	0.4 ± 0.7	.008
Inhaled, %	23.1 ± 5.8	6.1 ± 2.5	.005
Nebulizer, %	5.1 ± 1.5	41.3 ± 4.2	.005
Face mask	20.0 ± 3.5	9.9 ± 6.2	.005
Circuit, %	8.2 ± 9.9	12.5 ± 4.0	.10
Inspiratory filter, %	0.2 ± 0.2	0.1 ± 0.1	.31
Expiratory filter, %	43.0 ± 6.4	30.3 ± 12.8	.005

Values are mean ± SD.
* Wilcoxon test ($P < .01$).
NIV = noninvasive ventilation

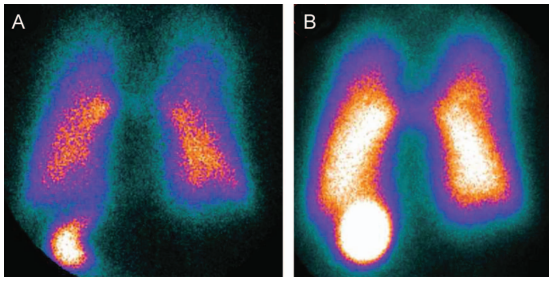

Fig. 5. Scintigraphic images obtained during nebulization with noninvasive ventilation using a jet nebulizer (A) and a vibrating mesh nebulizer (B).

lower residual volume compared with the jet nebulizer. In the in vitro study performed by McPeck,[33] residual drug volumes from 3.0-mL doses were 3.5% and 55.0% for vibrating mesh and jet nebulizers, respectively.

Pulmonary scintigraphy is an important tool to quantify aerosol drug deposition into the respiratory tract with a variety of aerosol-generating devices both on and off the ventilator.[7,19,26,28,29,34,35] Thus, this is a well-established approach, with published studies demonstrating that radiolabeling of solutions with technetium-99m does not alter particle size generated by nebulizers and inhalers.[27,36]

Many factors could alter radioaerosol distribution, including interface, respiratory pattern, humidification, aerosol apparatus, particle size, nebulizer position, circuit type, set parameters, and patient synchrony.[8-12] To minimize confounding variables, subjects were fitted with masks and adapted to pressure application with NIV, and parameters were adjusted to the same level as in our previous study involving healthy subjects.[26] Subjects were instructed to relax and let the machine do the work of breathing as much as possible.

The radioaerosol pulmonary index increased in all regions of interest using the vibrating mesh nebulizer compared with the jet nebulizer. Intragroup analysis of vertical differences demonstrated higher counts in the lower third than upper third in both lungs for each group. This might be explained by greater volumetric variation in the alveoli of the lung base than in those located in the lung apex during NIV. On the other hand, counts registered in the horizontal differences showed that intragroup radioaerosol deposition was more significant when comparing central and peripheral regions in both lungs for each group, demonstrating that substantial aerosol reached the central areas, which should be relevant during inhalation of anticholinergic bronchodilators, with a higher concentration of bronchodilator receptors in the central airways.[37-39]

According to Branconnier and Hess,[20] positioning inhalers between the leak port and mask is more effective in delivering a higher amount of aerosol into the lungs. This has been confirmed with both jet and vibrating mesh nebulizers by Abdelrahim et al.[10] The effect of nebulizer position during NIV was confirmed by White et al,[39] who reported 2-fold greater deposition with the NIVO placed between the circuit leak and patient airway compared with the Aeroneb Solo mesh nebulizer placed between the ventilator and humidifier and between the humidifier and leak port in a pediatric single-limb circuit. It should be noted that the NIVO and Solo use a similar mesh with a similar range of aerosol characteristics.

In our study, both types of nebulizers were positioned between the circuit leak and subject, although the jet nebulizer was placed in the circuit using a T-piece, and the vibrating mesh nebulizer was positioned directly in the elbow of the mask. This was the same placement as reported by McPeck.[33]

Some limitations should be considered when interpreting the results of this study. First, there are no validated protocols in the literature regarding the levels of inspiratory and expiratory pressures to apply during NIV, and we used only one set of parameters. Second, we tested the efficacy of nebulization coupled with NIV in healthy subjects, limiting the ability to demonstrate a differential response to inhaled medication. We did not correct for tissue absorption of radiation, which means we may be underestimating thoracic deposition by as much as 40%. Further studies should be performed in subjects with diseases such as asthma, COPD, bronchiectasis, and cystic fibrosis, in whom differences in clinical outcomes could be assessed.

Conclusions

In summary, this study showed that the NIVO delivered > 3-fold radiolabeled drug into the respiratory tract of healthy subjects compared with the AirLife Misty Max during NIV. As improved bronchodilator response has previously been shown with a jet nebulizer and NIV despite low lung doses, future studies will be required to demonstrate the clinical benefit of the higher deposition efficiency demonstrated with the vibrating mesh nebulizer.

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