

Performance of Large Spacer Versus Nebulizer T-Piece in Single-Limb Noninvasive Ventilation

Hadeer S Harb, Ahmed A Elberry PhD, Hoda Rabea PhD, Maha Fathy PhD, and Mohamed EA Abdelrahim PhD

BACKGROUND: Predosing patients with COPD with salbutamol by using a pressurized metered-dose-inhaler (pMDI) as a bronchodilator was hypothesized to improve the distribution of the subsequent nebulized dose. This study determined the effect of a pMDI preliminary bronchodilator dose on the aerosol delivered by a mesh nebulizer during single-limb noninvasive ventilation. **METHODS:** Twelve subjects with COPD who received noninvasive ventilation were enrolled in a randomized, open-label, urinary pharmacokinetic study. A bi-level ventilator with a dry single-limb circuit and the fixed expiratory port was set in the spontaneous mode, with initial inspiratory and expiratory pressures of 20 and 5 cm H₂O respectively, a 1:3 inspiratory-expiratory ratio, and 15 breaths/min. Salbutamol was administered via a mesh nebulizer with a large spacer or T-piece placed between the fixed-orifice expiratory valve and the oronasal mask. In vivo dosing methods were randomized for days 1, 3, and 5 of the study. On each day, a 1-mL respirable solution that contained 5,000 µg salbutamol was nebulized by using a mesh nebulizer with 3 setting: (1) T-piece, (2) large spacer, and (3) large spacer plus pMDI. Only with the large spacer plus pMDI setting, 2 pMDI doses, which contained 100 µg salbutamol each, were actuated before nebulization. Urine samples were collected at 0.5 h (as an index of pulmonary bioavailability) and pooled up to 24 h after dosing (as an index of systemic absorption). On day 2, ex vivo studies were performed for the 3 setting with salbutamol collected onto filters placed before the mask. The drug was eluted from the filters and analyzed to determine the inhaled dose. **RESULTS:** A large spacer plus pMDI showed a trend to deliver a higher fraction (percentage of nominal dose) of both ex vivo filters and 0.5-h urinary salbutamol. The 0.5-h urinary salbutamol excreted with a large spacer plus pMDI (1.99%) was larger than with the T-piece (1.73%) and large spacer (1.78%). This trend did not extend to the 24-h levels, in which bioavailability with the large spacer plus pMDI (49.9%) was lower than with the T-piece (52.8%) and with the large spacer (54.3%). However, no differences were significant. **CONCLUSIONS:** The T-piece and large spacer were equally efficient for salbutamol delivery from the mesh nebulizer in patients with COPD and on single-limb noninvasive ventilation. Adding a preliminary bronchodilator dose by pMDI prenebulization showed a trend toward greater pulmonary bioavailability of nebulized salbutamol and may be worth considering to maximize delivery of salbutamol to patients who are severely ill. *Key words:* pMDI; salbutamol; NIV; COPD; lung; bioavailability nebulizer. [Respir Care 2018;63(11):1360–1369. © 2018 Daedalus Enterprises]

Introduction

Medical aerosols are commonly administered to patients with COPD during exacerbations that require ven-

tilator support. Patients with COPD often have irregular aerosol distribution in the lungs due to inflammation

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Controllers and vibrating mesh nebulizers were supplied by Aerogen. Combihaler spacers were supplied by Laboratoire ProtecSom.

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and bronchoconstriction,¹⁻³ although aerosol deposition is higher in patients with COPD than those without.⁴ We hypothesized that initial administration of 2 puffs of a fast-acting β_2 agonist bronchodilator from a pressurized metered-dose-inhaler (pMDI) may provide an initial airway response that would improve the distribution of subsequently administered nebulized drug. This would be evidenced by a greater proportion of the dose absorbed from the lung and assayed in the urine. In addition, adapters commonly used to administer medical aerosols to patients who require mechanical ventilation impact delivery efficiency based by their design and placement.

Placing relatively large-volume spacers in the inspiratory limb of a conventional ventilator circuit proximal to the patient has improved the inhaled dose with continuous aerosol generators, such as jet, ultrasonic, and vibrating mesh nebulizers. The large-volume reservoir acts to collect aerosol between inspirations, which makes as much as 35% more aerosol available distal to the endotracheal tube.⁵ Similarly, Boukhettala et al⁶ demonstrated that add-on devices could improve aerosol delivery from vibrating mesh nebulizers and hypothesized that larger spacers could conserve more aerosol during the expiration phase.⁷

CombiHaler (Laboratoire ProtecSom, Valognes, France) is a large-volume (210 mL) spacer chamber designed to administer aerosols through the ventilator circuit with both pMDIs and vibrating mesh nebulizers (Aerogen Solo, Aerogen, Galway, Ireland). Aerosol emitted by the vibrating mesh nebulizer into the large spacer has a distance of 70 mm between the aerosol-generating mesh and the interior wall of the spacer.⁶ In contrast, the standard T-piece has an internal volume of 35 mL and distance from the mesh to the opposing internal wall of 35 mm. The internal volume of the spacer acts as a reservoir that collects aerosol between breaths, that makes more available with the next breath; the greater the distance from the aerosol-generating mesh to an opposing wall, the lower the proportion of aerosol particles that impact en route to the ventilator circuit.

During invasive mechanical ventilation with a 2-limb circuit, the large spacer has been shown to deliver a larger inhaled dose than the T-piece for aerosol delivery from vibrating mesh nebulizers.^{6,8,9} However, those findings may not be relevant to use in a single-limb circuit

QUICK LOOK

Current knowledge

The CombiHaler (large spacer) is a large-volume spacer designed to connect both pressurized metered-dose inhalers and vibrating mesh nebulizers into conventional and noninvasive ventilation circuits. Adapters used to administer aerosol therapy during mechanical ventilation impact delivery based on design and placement in the circuit. Optimum device placement is different with invasive and non-invasive ventilation.

What this paper contributes to our knowledge

A vibrating mesh nebulizer standard T-piece and large spacer were equally efficient for salbutamol delivery from a vibrating mesh nebulizer in subjects with COPD on single-limb NIV. Adding a preliminary bronchodilator dose prenebulization could improve the inhaled salbutamol fraction delivered to the lungs in the first 30 min by enhancing peripheral penetration of the aerosol. However, the effect was not observed at 24 h, and differences were not statistically significant.

with a noninvasive ventilator, in which higher continuous gas flow passes through a fixed orifice resistor. In addition, the patient interface (mask vs endotracheal tube) and placement of the aerosol generator differ with noninvasive ventilation (NIV) compared with conventional invasive ventilation.¹⁰⁻¹³

In a previous *in vitro* study, we reported that the standard T-piece and large spacer were equally efficient for salbutamol delivery by a vibrating mesh nebulizer in a single-limb NIV under nonhumidified conditions.¹⁴ *In vitro* methods that study the aerodynamic characteristics and fate of aerosol by using a lung simulator model are thought to offer some degree of guidance to clinical delivery and response. However, inhaled doses determined *in vitro* do not accurately account for the variability of breath parameters *in vivo*, and the lung dose *in vivo* is lower than filters because lungs exhale more aerosol than do collecting filters.¹⁵ *In vitro* studies often use respiratory parameters that may not reflect variations encountered in patients. *Ex vitro* methods collect aerosol on filters placed between the ventilator circuit and the subject during NIV, which better represents actual breathing parameters of each subject.

We hypothesize that predosing with pMDI would increase inhaled drug delivered *ex vivo* and the proportion of drug recovered *in vivo*. This supports the case to establish *ex vitro*–*in vivo* correlation.¹⁶⁻²³ This *in vivo* study with an *ex vivo* component compared aerosol delivery by a vibrating mesh nebulizer by using standard T-piece and

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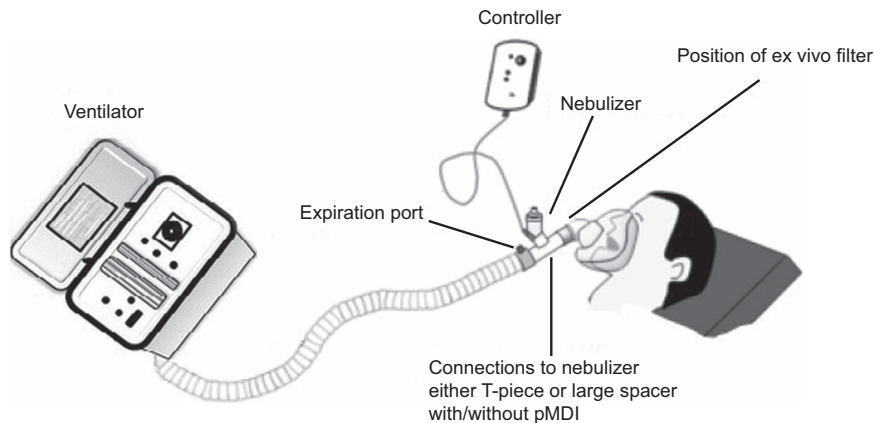


Fig. 1. Schematic design of in vivo and ex vivo single-limb noninvasive ventilation setup.

by using large-spacer adapter, and determined the possible effect of preliminary bronchodilator dose with a pMDI on the delivered nebulizer dose when using a single-limb circuit NIV in subjects with COPD.

Methods

Study Design

The in vivo study was an experimental, randomized, open-label study with a crossover design.

Inclusion and Exclusion of Subjects

The study included 12 subjects (6 women) with a previous diagnosis of COPD who had been admitted in the chest department at Beni-Suef University Hospital and Hospital of Chest with an exacerbation that required NIV as prescribed by their attending physician. Local hospital research ethics committee approval (FM-BSU REC FWA: FWA00015574) was obtained. Subjects with an exacerbation of COPD and with normal renal function who required NIV support for respiratory acidosis prescribed to receive nebulized salbutamol were included. Inclusion approval was taken under the care of a consulting chest physician. Patients were ineligible to participate if they had taken part in a research study during the previous 6 months, had a known hypersensitivity to salbutamol, systolic blood pressure of <100 mm Hg, or severe renal impairment defined as creatinine clearance or estimated glomerular filtration rate of <20 mL/min.

Study Protocol

This study was conducted in accordance with the amended Declaration of Helsinki. Written informed consent was obtained from all the subjects. A washout period

of 12–24 h allowed the body to excrete salbutamol delivered before the study. During the course of the study, prescribed salbutamol treatments were substituted with 25 $\mu\text{g/mL}$ ipratropium bromide aerosol (Boehringer Ingelheim, Ingelheim am Rhein, Germany). The subjects participated in the study for 6 days, in which they received 3 salbutamol study doses. The choice of inhaled salbutamol dosage was in accordance with previous literature.^{16,18,24–36} As recommended previously in studies that used single-limb NIV,^{10,30} the nebulizers were placed proximal to the subject and distal to the fixed expiratory valve, as shown in Figure 1.

The subjects were randomized to receive the salbutamol dosing iterations in a crossover design on days 1, 3, and 5. A washout period of 48 h was provided between each salbutamol dosing.³⁷ The subjects received nebulized doses of 1 mL of salbutamol respirable solution that contained a nominal dose of 5,000 $\mu\text{g/mL}$ salbutamol (Pharco Pharmaceuticals, Alexandria, Egypt) by using an Aerogen Solo vibrating mesh nebulizer (Aerogen) powered by the Aerogen Pro-X Controller with a standard T-piece and CombiHaler (large spacer) positioned in the single-limb NIV circuit between the fixed valve and the subject (Fig. 2). A 1-mL respirable solution that contained 5,000 μg salbutamol was nebulized by using a mesh nebulizer with 3 connection methods: (1) T-piece, (2) large spacer, (3) large spacer plus pMDI. Only with the large spacer plus pMDI group, 2 pMDI doses, which contained 100 μg salbutamol each (Ventoline, GlaxoSmithKline, Brentford, United Kingdom) synchronized with the beginning of subject inspiration, with 30 s between actuations, as a preliminary bronchodilator dose, followed by nebulization via a vibrating mesh nebulizer.

A bi-level ventilator (B&D Electromedical, Stratford-Upon-Avon, United Kingdom) with a dry single-limb

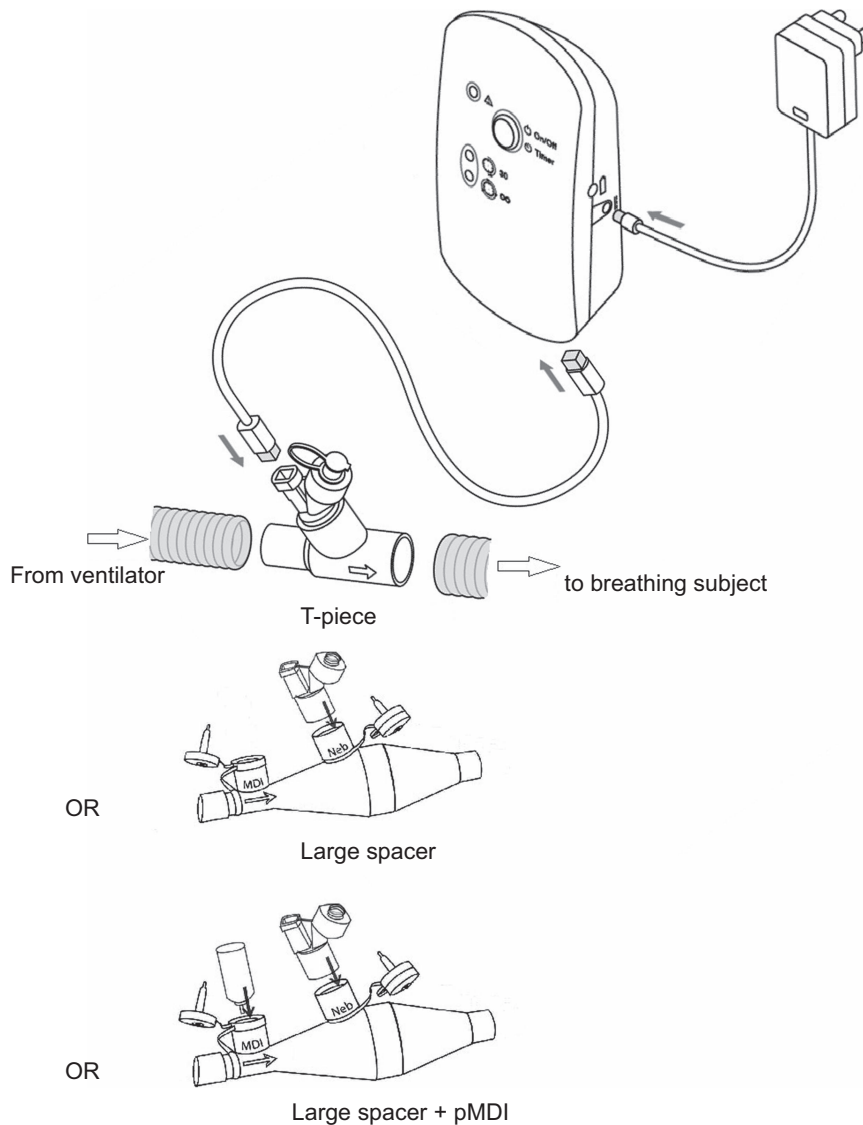


Fig. 2. Assembly of aerosol delivery system and its connections; all 3 connections incorporated the vibrating mesh nebulizer.

circuit and fixed orifice expiratory port was set in the spontaneous mode with initial inspiratory and expiratory pressures of 20 and 5 cm H₂O, respectively 1:3 inspiratory-expiratory ratio, 15 breaths/min, when using a well-fitted patient mask (Respironics AF531 oronasal mask, Philips Respironics, Murrysville, Pennsylvania). The subjects received pressure support ventilation with a PEEP of 5 cm H₂O. The subjects' spontaneous tidal volumes were monitored, and a clinician titrated the inspiratory pressure support to reach the targeted tidal volume of 500 mL. The inspiratory pressures in pressure support ventilation ranged between 15 and 20 cm H₂O. A vibrating mesh nebulizer with a T-piece and large spacer was placed in the ventilator circuit proximal to subjects' oronasal mask.

The subjects voided their urine 15 min before each study dose and then were asked to provide a urine sample 30 min after the start of the nebulization (USAL0.5) as an index of salbutamol delivery to the lungs.³⁷ The subjects collected all their urine into a container over the next 24 h (USAL24) as an index of systemic absorption of salbutamol after inhalation.³⁷ The urine sample volumes were measured, and aliquots were retained for salbutamol content solid-phase extraction with an Oasis MCX 60 mg, 10 mL XL cartridge (Waters Corporation, Milford, Massachusetts) with the application of a low vacuum (<3 bars) through a VAC-ELUT 10 manifold (Varian, Palo Alto, California) extraction station.³⁶ The salbutamol amount in each extract was determined by using high-performance liquid chromatography, described in the High-Performance Liquid Chromatography Analysis.

Ex Vivo Protocol

On day 2 of the study, a collecting filter (Filta Guard breathing filter, Intersurgical, Wokingham, United Kingdom) was placed between the nebulizer and the adapter, and the subject's mask (AF531 oronasal mask, Philips Respironics) so that the subjects would not inhale the drug, as shown in Figure 1. The same study dose and/or adapters were administered to each subject, with filters changed with each administration. Salbutamol entrained on the filter was desorbed by sonication with 25 mL, 30% acetonitrile before rinsing, to be analyzed by using the high-performance liquid chromatography method with ultraviolet detection, described in High-Performance Liquid Chromatography Analysis.

Solid-Phase Extraction

Urine samples 30 min postdose were prepared by acidification with 2 mL 0.5 N HCL for each 10 mL of urine, whereas urine samples 24 h postdose used acid hydrolysis of salbutamol ester conjugate by adding 2 mL 0.1 N HCL for each 10 mL urine. The sample was mixed well by shaking, then vortexed, covered with aluminum foil, boiled in a water bath at 100°C for 5 min, and then cooled and filtered.^{38,39}

Solid-phase extraction protocol steps included conditioning the cartridge with 6 mL methanol, then equilibrated with 6 mL water before loading with 10 mL of the prepared urine sample, followed by several washes to remove any possible urine from the extract. The washes included 10 mL 5% methanol in 0.1 N HCL, 10 mL methanol and 6 mL 2.5% triethanolamine in methanol and finally elution by 10 mL 5% ammonium hydroxide in methanol.³⁶

High-Performance Liquid Chromatography Analysis

Urine Samples. The high-performance liquid chromatography system was composed of an ODS 5 μ m (4.6 \times 250 mm, ZORBAX Eclipse, Agilent, Santa Clara, California) C18 high-performance liquid chromatography column with a 4 \times 3 mm (Agilent) C18 (ODS) guard column. The mobile phase, which contains acetonitrile-water (90:10 v/v), was pumped through the columns at a flow of 1 mL/min maintained at 25°C and photodiode array detection was set at 220 nm. The lower limit of detection and lower limit of quantification for salbutamol were 0.36 and 1.00 μ g/mL, respectively. Calibration solutions ranged from 8 to 70 μ g/mL (wt/v) was used in the construction of a calibration curve to interpret sample concentrations.

Aqueous Samples of Ex Vivo Filters. The system was composed of an ODS 5 μ m (4.6 \times 250 mm, ZORBAX Eclipse) C-18 high-performance liquid chromatography

column. The mobile phase, which contained (90:10, v/v) acetonitrile-water, was pumped through the columns at a flow of 1 mL/min maintained at 25°C and photodiode array detection was set at 225 nm. The lower limit of detection was 0.35 μ g/mL, and the lower limit of quantification was 2.55 μ g/mL. Calibration solutions, which range from 10 to 100 μ g/mL (wt/v), were used in the construction of a calibration curve to interpret samples concentrations.

Statistical Analysis of Data

All data are expressed as mean \pm SD. Two-way analysis of variance with the application of least significant difference correction was used to compare both the urinary excretion of salbutamol and salbutamol on ex vivo filters postinhalation through the 3 different nebulizer connections by using SPSS V17.0 (SPSS, Chicago, Illinois), with $P < .05$ considered significant.

Results

Twelve subjects with COPD (6 women) were screened, had consented, and had completed the protocol, with mean \pm SD age, weight, and height of 63.3 \pm 8.5 y, 85.42 \pm 10.17 kg, and 165.92 \pm 6.33 cm, respectively. The mean \pm SD amount (μ g) and proportion of nominal dose (%) found in USAL0.5 and USAL24, and ex vivo salbutamol from filters for the T-piece, the large spacer, and the large spacer plus pMDI are shown in Table 1 and Figures 3–5, respectively.

USAL0.5

The amount of salbutamol with the large spacer plus pMDI showed a trend toward 16% and 18% higher than the T-piece and the large spacer, respectively, but no differences were significant with the P values of comparison between the T-piece versus the large spacer; the T-piece versus the large spacer plus the pMDI, and the large spacer versus the large spacer plus the pMDI were $P = .87$, $P = .35$, and $P = .43$, respectively.

USAL24

Large spacer and large spacer plus pMDI were nearly equal, as shown in Table 1 and Figure 4. The P values between the T-piece versus the large spacer; the T-piece versus the large spacer plus pMDI and large spacer versus large spacer plus pMDI was $P = .85$, $P = .89$, and $P = .96$, respectively (Fig. 4).

Table 1. The Nominal Dose of Salbutamol on Ex Vivo Filters and at USAL0.5 and USAL24 After Inhalation of Salbutamol Respirable Solution Via Vibrating Mesh Nebulizer Through the 3 Different Connections

Dose	T-Piece	Large Spacer	Large Spacer + pMDI
USAL0.5, mean \pm SD			
μg	86.56 \pm 33.04	88.86 \pm 25.32	103.43 \pm 38.60
%	1.73 \pm 0.66	1.78 \pm 0.51	1.99 \pm 0.74
USAL24, mean \pm SD			
μg	599.84 \pm 99.06	610.27 \pm 159.88	631.69 \pm 133.39
%	12.00 \pm 1.98	12.21 \pm 3.20	12.15 \pm 2.57
SALF (ex-vivo inhaled dose), mean \pm SD			
μg	1106.15 \pm 302.17	1155.66 \pm 311.84	1265.22 \pm 296.43
%	22.12 \pm 6.04	23.11 \pm 6.24	24.33 \pm 5.70
USAL24 as a percentage of SALF, %	54.3	52.8	49.9

N = 12.

pMDI = pressurized metered-dose inhaler

USAL0.5 = urinary salbutamol at 0.5 h after administration

USAL24 = urinary salbutamol over 24 h after administration

SALF = Salbutamol collected on filter

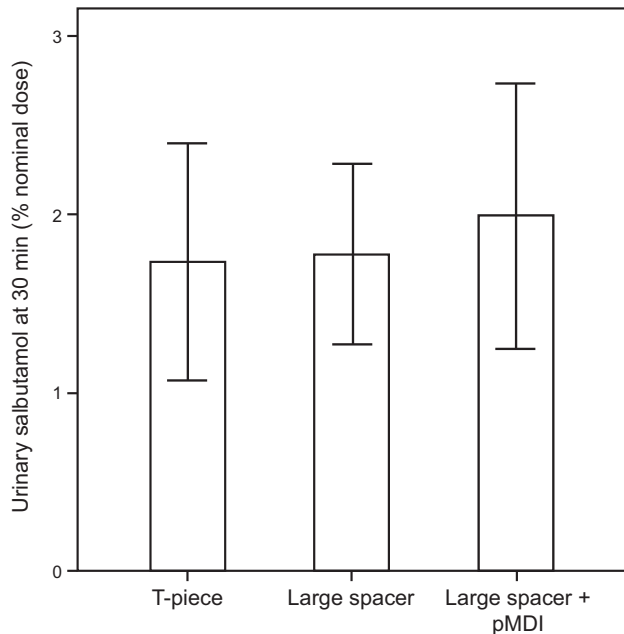


Fig. 3. The mean \pm SD urinary excretion of salbutamol 30 min after inhalation via vibrating mesh nebulizer through the 3 different connections expressed as the percentage of the nominal dose (*N* = 12). The *P* values of the comparison between the T-piece vs the large spacer; the T-piece vs the large spacer plus the pressurized metered-dose-inhaler (pMDI), and the large spacer vs the large spacer plus pMDI were *P* = .87, *P* = .35, and *P* = .43, respectively.

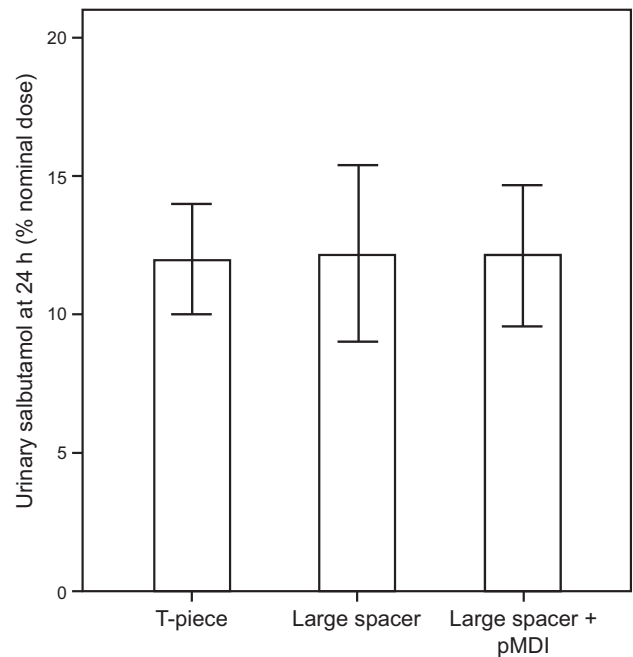


Fig. 4. The mean \pm SD urinary excretion of salbutamol 24 h after inhalation via the vibrating mesh nebulizer through the 3 different connections expressed as percentages of the nominal dose (*N* = 12). The *P* values of comparison between the T-piece vs the large spacer, the T-piece vs the large spacer plus pressurized metered-dose-inhaler (pMDI), and the large spacer vs the large spacer plus pMDI were *P* = .85, *P* = .90, and *P* = .96, respectively.

Ex Vivo

The inhaled dose was similar with the T-piece and the large spacer with an incremental increase associated with the 2 puffs by using a pMDI, but the differences were not

significant. The *P* values of comparison between the T-piece versus the large spacer, the T-piece versus the large spacer plus the pMDI, and the large spacer versus the large spacer plus the pMDI were *P* = .70, *P* = .39, and *P* = .63, respectively.

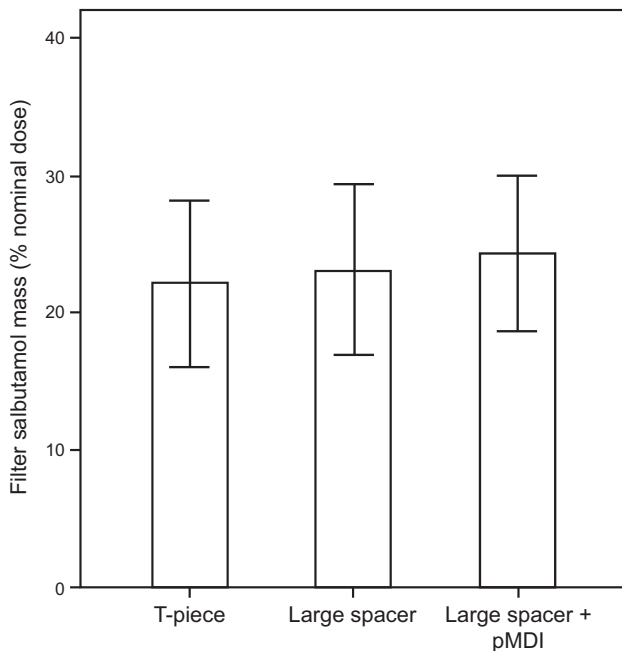


Fig. 5. The mean \pm SD amount of salbutamol recovered from the ex vivo filter after nebulization via the vibrating mesh nebulizer through the 3 different connections expressed as percentages of the nominal dose ($N = 12$). The P values of comparison between the T-piece vs the large spacer, the T-piece vs the large spacer plus pressurized metered-dose-inhaler (pMDI) and the large spacer vs the large spacer plus the pMDI were $P = .70$, $P = .39$, and $P = .63$, respectively.

Discussion

This study was the first to compare ex vivo inhaled dose to in vivo urinary drug levels after medical aerosol delivery from a nebulizer and a pMDI during NIV with a single-limb circuit. These findings were consistent with previous in vitro work to assess the performance of a vibrating mesh nebulizer in single-limb NIV.¹⁴ Our ex vivo findings were consistent with in vitro testing with both vibrating mesh nebulizer with the T-piece and the pMDI during NIV in a study by Al-Quaimi et al.⁴⁰

Similarly Galindo-Filho et al⁴ administered radiolabeled aerosol via a vibrating mesh nebulizer to 10 healthy subjects during NIV with inspiratory and expiratory pressures 12/5 cm H₂O by using an oronasal face mask. They reported an inhaled dose of 23.1% and a lung dose of 6.5% in healthy normal subjects. They subsequently reported similar study findings in subjects with stable COPD with an inhaled dose of 19.9% and lung dose of 8.8%.⁴ This confirmed the range of the inhaled dose in vivo and hypothesis that lung dose is higher in subjects with COPD versus normal subjects and the presence of greater airway obstruction with COPD. These regions of obstruction in the airways would be a likely target for benefit from prenebulization bronchodilation with pMDI.

The urine analysis method developed by Hindle and Chrystyn,³⁷ reflects the relative bioavailability of salbutamol to the lungs after inhalation by assessing urinary salbutamol excretion based on its absorption lag time. The amount of urinary salbutamol 30 min after inhalation represents an index of salbutamol delivery to the lungs. The amount of salbutamol excreted in urine within 24 h after inhalation represents an index of systemic absorption of salbutamol.^{37,41} Our findings were consistent with previously reported urine levels of salbutamol in a study of aerosol delivery in subjects on mechanical ventilation with salbutamol 5,000 μ g via the vibrating mesh nebulizer with a T-piece in the inspiratory limb of a conventional 2-limb circuit. Moustafa et al³⁶ reported salbutamol levels in the urine at 0.5 h of 1.8 (1.1) %, with 10.5 (4.0) % at 24 h. Our findings of inhaled dose percentage of 1.73% at 0.5 h and 12% at 24 h with a vibrating mesh nebulizer with a T-piece are similar, despite the difference in the type of ventilator and circuit used. They reported that pMDI administered with a large-volume adapter had a USAL0.5% at 2.5 (1.3) % with USAL24% of 8.0 (3.4) %. The pMDI had a higher USAL0.5% than the vibrating mesh nebulizer, but the USAL24% was lower.

The ex vivo filter data as a percentage of the nominal dose showed a trend that the large spacer was marginally higher than the T-piece (1%), and the addition of the 2 puffs from the pMDI with a large spacer was an additional 1.2% higher. This confirmed that a portion of the 2 puffs from the pMDI had an additive effect on the inhaled dose. We found that 2 puffs from the pMDI was reflected in the urine at 0.5 h after administration, with a trend to levels that seemed higher with the large spacer plus pMDI than the incremental increase shown ex vivo, which suggested that total bioavailability showed a trend toward higher with the prenebulizer administration of the pMDI. However, at 24 h, the difference in the drug amount was lower than with the nebulizer alone, and the percentage of the nominal dose showed a trend toward lower with the pMDI. This suggested that the addition of prenebulization administration of the pMDI may have a short-term effect but did not increase total bioavailability of salbutamol at 24 h. This was seen in the USAL24 amount because a proportion of the ex vivo inhaled dose was higher with the T-piece (54.3%) than with the large spacer (52.8%) and the large spacer and the pMDI (49.9%).

Adding a preliminary bronchodilator dose prenebulization resulted in a trend to higher USAL0.5% than delivering the nebulizer bronchodilator dose alone. This trend could lend some support to our hypothesis. However, the short-term benefit of the pMDI did effect, not extend to the USAL24%. This could be of benefit to decrease systemic adverse effects and at the same time increase pulmonary bioavailability.

Our protocol included an arm with the additional 2 puffs from a pMDI administered in addition to the 5,000 μg nebulizer dose. The magnitude of an additional dose, from the 200 μg dose from the pMDI (4% increases) was deemed not to pose an additional risk when administered to patients with COPD who were critically ill. A positive correlation was previously reported by scintigraphic studies between FEV_1 and the depth of aerosol penetration into the lungs of patients with different obstructive lung diseases.^{42,43} Pavia et al⁴⁴ demonstrated that, for subjects with COPD, the depth of aerosol deposition is directly related to FEV_1 . So, when FEV_1 was increased through prenebulization, 2 pMDI puffs before dose administration, deeper penetration of subsequently administered medical aerosol particles was achieved as reported by Labiris and Dolovich.¹ This could be the reason for our relatively higher USAL0.5 with the large spacer plus the pMDI.

Previous in vitro comparisons during conventional mechanical ventilation reported a 35% higher inhaled dose with a large spacer compared with the T-piece.⁵ In contrast, we found a <5% difference between the 2 adapters during single-limb NIV. With the single-limb circuit, placement of the chamber between the fixed orifice and patient airway requires patients to exhale through the spacer, purging much of the aerosol collecting in the reservoir. Reduced aerosol delivered with the T-piece associated with the shorter distance between the aerosol-generating mesh and the opposing interior wall of the adapter, which is half the distance of the large spacer. This is consistent with our observation of condensed aerosol droplets forming within the T-piece during administration. The relatively higher USAL0.5% of the large spacer plus pMDI in addition to the comparable USAL24% compared with the large spacer showed that the 2 pMDI salbutamol puffs showed a trend toward increasing pulmonary bioavailability (USAL0.5%) of the subsequent nebulized medication but not the systemic absorption (USAL24%). This small improvement might be of no importance in a patient who has stable mild or moderate obstructive lung disease, in which most of the delivered nebulized medication, if needed, reaches the plateau of action.⁴⁵ However, in patients who are critically ill, exacerbated, and on ventilation, any increase in lung delivery may be of importance. The addition of 2 pMDI puffs added only 30–60 s to the treatment time, and the cost of adding the short-acting bronchodilator pMDI to the nebulizer was minimal because all of the enrolled subjects had been prescribed a pMDI with a short-acting bronchodilator before initiation of NIV.

Limitations of the Study

During mechanical ventilation at our institution, it is not customary to interrupt ventilatory support to measure forced expiratory maneuvers, consequently, spirometry pre- and

postbronchodilator administration was not measured. No significance difference was found between the T-piece and the large spacer in USAL0.5%, USAL24, and salbutamol entrained on the filter. This was consistent with previous in vitro data that reported no significance difference between fine particle dose ($\leq 5 \mu\text{m}$ and $\leq 3 \mu\text{m}$) of the vibrating mesh nebulizer with both the T-piece and the large spacer.¹⁴ The coefficient of variation for urinary salbutamol was reported to be relatively high, as seen in our results.⁴⁶ This and the expected 35% intra- and interpatient variability contributed to the lack of statistical significance in our small patient population. However, these data can now be used to appropriately size future studies. The small mean increase in salbutamol delivery to the lungs with the large spacer and the pMDI was hypothesized to be due to enhanced depth of aerosol penetration into the lungs. However, the use of prebronchodilation before nebulization of other drugs targeted to more peripheral airways may have a more pronounced benefit. Our findings of greater bioavailability at 0.5 h with administration of pMDI bronchodilator prenebulization merit further evaluation of the effects on lung function of additional pMDI doses.

Conclusions

Salbutamol delivery from a vibrating mesh nebulizer in subjects with COPD who were on single-limb NIV was equally efficient with a T-piece and a large spacer. Administration of a bronchodilator with a pMDI before nebulization showed a trend toward increasing bioavailability at 0.5 h, which suggested that a preliminary bronchodilator dose prenebulization could improve the inhaled salbutamol fraction delivered.

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