Aerosol Delivery with Two Nebulizers Through High-Flow Nasal Cannula: A Randomized Cross-Over Single-Photon Emission Computed Tomography-Computed Tomography Study

Jonathan Dugernier, PT, MSc,1–3 Michel Hesse, PhD,4 Thibaud Jumetz, PT, Emilie Bialais, PT, MSc,1–3 Jean Roeseler, PT, PhD,2 Virginie Depoortere, NMT,4 Jean-Bernard Michotte, PT, PhD,5 Xavier Wittebole, MD,2 Stephan Ehrmann, MD, PhD,5–8 Pierre-François Laterre, MD,2 François Jamar, MD, PhD,4 and Gregory Reychler, PT, PhD1,3,9

Abstract

Background: High-flow nasal cannula use is developing in ICUs. The aim of this study was to compare aerosol efficiency by using two nebulizers through a high-flow nasal cannula: the most commonly used jet nebulizer (JN) and a more efficient vibrating-mesh nebulizer (VN).

Methods: Aerosol delivery of diethylenetriaminepentaacetic acid labeled with technetium-99m (4 mCi/4 mL) to the lungs by using a VN (Aerogen Solo®; Aerogen Ltd., Galway, Ireland) and a constant-output JN (Opti-Mist Plus Nebulizer®; Convatec, Bridgewater, NJ) through a high-flow nasal cannula (Optiflow®; Fisher & Paykel, New Zealand) was compared in six healthy subjects. Flow rate was set at 30 L/min through the heated humidified circuit. Pulmonary and extrapulmonary deposition was measured by single-photon emission computed tomography combined with a low-dose computed tomographic scan and by planar scintigraphy.

Results: Lung deposition was only 3.6 (2.1–4.4) and 1 (0.7–2)% of the nominal dose with the VN and the JN, respectively (p<0.05). The JN showed higher retained doses than the VN. However, both nebulizers were associated with substantial deposition in the single limb circuit, the humidification chamber, and the nasal cannula [58.2 (51.6–61.6)% of the nominal dose with the VN versus 19.2 (15.8–22.9)% of the nominal dose with the JN, p<0.05] and in the upper respiratory tract [17.6 (13.4–27.9)% of the nominal dose with the VN and 8.6 (6.0–11.0)% of the nominal dose with the JN, p<0.05], especially in the nasal cavity.

Conclusions: In the specific conditions of the study, pulmonary drug delivery through the high-flow nasal cannula is about 1%–4% of the initial amount of drugs placed in the nebulizer, despite the higher efficiency of the VN as compared with the JN.

Keywords: Aerosol delivery, High-flow nasal cannula, Single-photon emission computed tomography
Hypoxemic patients in acute respiratory failure require sufficient oxygen administration to ensure proper tissue oxygenation. Conventional interfaces are limited in providing enough oxygen once patients’ peak inspiratory flow exceeds the oxygen flow that can barely increase above 15 L/min in clinical practice. Administering an air-oxygen mixture through a high-flow nasal cannula (HFNC) at 30–60 L/min ensures a higher and an accurate inspired fraction of oxygen, better oxygenation and comfort than standard non-rebreathing masks in patients suffering from acute respiratory failure.

Adult patients with HFNC may benefit from combined aerosol therapy as the etiology of hypoxemia might justify the administration of inhaled bronchodilators, corticosteroids, or antibiotics, that is, the three main inhaled drugs prescribed by clinicians in ICU. Aerosolized drugs are delivered in children with HFNC, as illustrated by a recent case series on aerosolized β agonists for the treatment of respiratory distress in acute bronchiolitis. Different types of nebulizers exist. Conventional JNs are the most widely used nebulizers in hospitals because of their easy handling and lower cost. Vibrating-mesh nebulizers (VNs) and drug-targeting systems have emerged. The clinical efficacy of aerosol therapy depends on pulmonary deposition, which is, in part, related to the type of nebulizer. The characteristics of the HFNC therapy (i.e., the high flow rate, the heated humidification, and the nasal filter) may also alter aerosol delivery to the lungs. All new nebulizers or delivery methods require rigorous evaluation.

In vitro studies have investigated the optimal setup for aerosol administration through HFNC. Authors reported 0.2%–32% of aerosol delivered at the outlet of the adult nasal cannula of commercial systems depending on the nebulizer, the position on the HFNC circuit, and the flow rate running through the HFNC circuit. However, the pulmonary deposition of aerosol administered through HFNC has never been investigated in humans.

The amount of drugs reaching the lungs and the site of deposition (regional distribution, lung penetration) are key elements for the efficiency of aerosolized drugs. These can be assessed by radioisotopic imaging by using single-photon emission computed tomography (SPECT) that has been validated to analyze the regional pulmonary deposition of aerosolized particles.

The aim of this study was to compare in vivo the total and the regional pulmonary deposition of an aerosol generated with a VN and with a conventional constant-output JN through HFNC in healthy adult subjects.

Materials and Methods

Study design and subject selection

This randomized, single, blind cross-over study involved six healthy subjects. Inclusion criteria were as follows: male, nonsmoker, aged 18 or older, no evidence of respiratory disease, and lung function within normal range. Lung function was tested according to the American Thoracic Society guidelines by using a MicroLoop spirometer (CareFusion, San Diego, CA). The study was approved by the Ethics Committee of the hospital (Comité d’Éthique Hospitalo-Facultaire B403201422655—ClinicalTrials registration NCT02429817). Each subject gave written informed consent to participate in the study. The sequences of the two tested nebulizers were randomized by a computer-generated random number list.

Nebulization procedure

The two nebulizers compared in this study were a VN (Aerogen Solo; Aerogen Ltd., Galway, Ireland) and a constant-output JN (Opti-Mist Plus Nebulizer; ConvaTec, Bridgewater, NJ). Both nebulizers were placed upstream of the humidifier of an HFNC circuit (Optiflow™ RT202; Fisher & Paykel, Auckland, New Zealand) based on in vitro evidence. The flow rate through HFNC was adapted to obtain 30 L/min to reflect clinical practice in respiratory distress conditions while optimizing aerosol delivery to the lungs. The flow rate was set at 30 L/min with the VN. While an operating gas flow of 8 L/min was applied through the JN, the flow rate through HFNC was set at 22 L/min. The single-limb circuit was heated at 37°C, and the inspired oxygen fraction was 21%.

Nebulizers were filled with technetium-99m labeled diethylelenetriaminepentaacetic acid (99mTc-DTPA, 4 mCi in 4 mL). Aerosol particles were nebulized continuously through a medium-sized nasal cannula. Subjects were comfortably seated and breathed with the mouth closed during inhalation. Each subject tested both nebulizers, with a delay of 60 hours to allow for washout and complete radioactive decay. Radiation doses from the radioactive aerosols were calculated according to the International Commission on Radiological Protection (ICRP 53). Nebulizations were performed in the same room, at a similar temperature and humidity level. The room was equipped with an appropriate ventilation system, and subjects wore a coverall and overshoes to protect themselves from a potential contamination with the radioactivity that trickled from the nostril interface or particles emitted in the environment. The duration of nebulization was measured until there was no visual evidence of aerosol generation with the VN and sputtering point with the JN.

Inductance plethysmography (RespiTrace®, Ambulatory Monitoring, Ardsley, NY) was used to monitor the breathing pattern of the subjects with HFNC. Subjects were asked to breathe spontaneously and to reproduce a similar breathing pattern. This was verified by using the screen of the inductance plethysmography.

Deposition analysis

SPECT-CT and planar image acquisition and processing. Radionuclide imaging for aerosol deposition analysis involved SPECT with a low-resolution computed tomography (SPECT-CT) and planar images acquired on a dual-head gamma camera (Philips Brightview XCT, Philips, Milpitas, CA) (Supplementary Data; Supplementary Data are available online at www.liebertpub.com/jamp). SPECT images were reconstructed on a Philips Extended Brilliance Workspace (Philips Medical Systems, Best, The Netherlands) by using the Astonish iterative algorithm, which is based on Ordered Subsets Expectation Maximization, and includes attenuation, scatter, and resolution recovery corrections. SPECT-CT fusion, volumes and regions of interest (VOIs and ROIs) definition and counts quantification were carried out.
out by using a home-made plug-in to ImageJ software (Rasband WS, http://imagej.nih.gov/ij/, 1997–2014, Bethesda, MD) based on international recommendations. (19, 24) All data were analyzed in random order, and operators were blinded to the subject and method of nebulization involved. A detailed description of the lung deposition assessment method using SPECT-CT and planar imaging appeared in a previous publication. (25)

**SPECT-CT analysis**

Penetration of nebulized particles from the trachea to the lung periphery was assessed by using VOIs derived from the CT: the trachea and the main bronchi together, the right lung and the left lung. Both lung VOIs were divided into 10 concentric shells, starting from the hilum to the lung periphery (Fig. 1). Lung deposition was obtained by summing the total counts of 10 shells from each lung. Both lung depositions were compared through the right to left lung deposition ratio. A penetration index (PI) was calculated as the outer to inner lung region ratio [five outer (O) shells/five inner (I) shells] from the 99mTc-DTPA SPECT acquisition normalized to the O/I lung volume ratio from the CT-scan acquisition.

Counts were corrected for radioactive decay between inhalation and SPECT-CT and for clearance of the radiolabeled compounds during the whole SPECT-CT procedure as previously described. (19, 25) Aerosol deposition was expressed in counts and as percentage of the nominal dose (i.e., radioactivity placed in the nebulizer reservoir at the start of experiments) and as percentage of the emitted dose (i.e., radioactivity emitted at the exit of the nebulizer). The emitted dose was equal to the nominal dose minus the dose retained in the nebulizer reservoir.

**Planar analysis**

Planar images were used to quantify all sites of aerosol deposition from the nebulizer reservoir to the subject. ROIs were adapted on the geometric mean of anteroposterior–posteroanterior (AP-PA) planar images to quantify the retention in the nebulizer reservoir, the HFNC circuit (single-limb circuit, humidification chamber, and the nasal cannula), the upper respiratory tract, the trachea, the stomach, and the kidneys and the lung deposition. An ROI including the nasal cavity and the nasopharynx enabled an investigation of the deposition in this specific area. Quantifications were corrected

![FIG. 1. Shell decomposition of SPECT-CT coronal slice at the level of the right hilum of a healthy subject after inhalation of a radiolabeled aerosol administered by using a VN. Both lungs were divided into ten shells (colored lines through both lungs) that were distributed from the hilum to the lung periphery. The deposition of the radiolabeled particles of aerosol is depicted in color. Activity is seen in the kidneys (white arrows). SPECT-CT, single-photon emission computed tomography-computed tomography; VN, vibrating-mesh nebulizer.](image-url)
for decay, background, and attenuation as previously described.\(^{(24-25)}\)

The environmental loss (i.e., dose of radioactivity that trickled from the nostril interface or was lost in the ambient air (leakages or exhaled)) was calculated by using the nominal dose minus the dose retained in the nebulizer reservoir, the HFNC circuit, the upper respiratory tract, the trachea, the stomach, and the kidneys and deposited into the lungs. The extrapulmonary deposition was calculated as the sum of the dose retained in the HFNC circuit, deposited in the upper respiratory tract, the stomach, and the kidneys, and lost in the environment.

Pulmonary, extrapulmonary deposition and the retention in the nebulizer reservoir were expressed in counts and as percentage of the nominal dose. Pulmonary and extrapulmonary deposition was also expressed as percentage of the emitted dose.

**Statistical analysis**

Statistical analysis was performed by using SPSS software (version 23.0, IBM software). The sample size needed for detecting a 10% difference in deposition at the 5% significance level for a two-sided test with 90% power was determined on the basis of previous data \((n = 5)\). Data were expressed as median (25%–75% interquartile range). The signed-rank Wilcoxon test was used to compare both nebulizers and to compare the deposition in both lungs. A p-value lower than 0.05 was considered significant.

**Results**

The anthropometric and lung function parameters and the breathing pattern during inhalation are detailed in Tables 1 and 2. Subjects applied a similar breathing pattern with both nebulizers. Figure 2 illustrates a sample of inhalation waveform during HFNC. Nebulization duration was 16.5 (15–18) and 13.5 (12–17) minutes with the VN and the JN, respectively.

The total and regional pulmonary deposition from SPECT-CT analysis is shown in Tables 3 and 4. Aerosol delivery to the lungs was higher with the VN as compared with the JN (3.6 (2.1–4.4)% of the nominal dose with the VN and 1 (0.7–2)% of the nominal dose with the JN, \(p < 0.05\)). The emitted dose was also higher with the VN as compared with the JN (97.3 (96.1–97.9)% of the nominal dose with the VN and 56.6 (50.2–59.1)% of the nominal dose with the JN, \(p < 0.05\)). Expressed as a percentage of the emitted dose, lung doses were comparable with both nebulizers (\(p > 0.05\)).

**Table 1. Anthropometric and Lung Function Parameters of the Six Healthy Male Subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (25%–75% IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 (24–27)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 (174–181)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 (67–74)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22 (21–23)</td>
</tr>
<tr>
<td>FEV(_1), % of predicted</td>
<td>94 (92–96)</td>
</tr>
<tr>
<td>FVC, % of predicted</td>
<td>97 (95–99)</td>
</tr>
</tbody>
</table>

BMI, body mass index; FEV\(_1\), forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

**Table 2. Breathing Pattern of the Six Healthy Male Subjects with a High-Flow Nasal Cannula**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (25%–75% IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (mL)</td>
<td>774 (690–841)</td>
</tr>
<tr>
<td>Tidal volume (mL/kg)</td>
<td>10.8 (9.6–11.7)</td>
</tr>
<tr>
<td>Respiratory rate (cycle/min)</td>
<td>12 (8–13)</td>
</tr>
<tr>
<td>Inspiratory flow rate (L/min)(^a)</td>
<td>32 (24–37)</td>
</tr>
<tr>
<td>Inspiratory time (seconds)</td>
<td>1.4 (1.2–1.8)</td>
</tr>
<tr>
<td>Expiratory time (seconds)</td>
<td>3.6 (3.0–5.8)</td>
</tr>
<tr>
<td>Duty cycle (T(<em>{\text{imp}})/T(</em>{\text{TOT}}), %)</td>
<td>26 (20–34)</td>
</tr>
</tbody>
</table>

\(^a\)Calculated using the ratio of the tidal volume to the inspiratory time. IQR, interquartile range; T\(_{\text{imp}}\), inspiratory time; T\(_{\text{TOT}}\), breathing cycle time.

The right and the left lung volumes measured from the CT scan were 1.39 (1.31–1.48) and 1.26 (1.18–1.39) L \((p < 0.05)\). Similar dose and PI were measured in the right and in the left lung with both nebulizers \((p > 0.05)\).

The pulmonary and the extrapulmonary deposition and the lost particles fraction from planar analysis are shown in Tables 3 and 4. A majority of the aerosol was trapped in the ventilator circuit, the upper respiratory tract and lost in the environment with both nebulizers (Fig. 3). Extrapulmonary deposition was higher with the VN as compared with the JN (94.8 (94.0–96.1)% of the nominal dose with the VN and 53.8 (49.5–57.1)% of the nominal dose with the JN, \(p < 0.05\)).

However, higher doses were retained in the reservoir of the JN as compared with the VN. Particles lost in the HFNC circuit (single limb circuit, humidifier, and nasal cannula) were higher with the VN as compared with the JN (58.2 (51.6–61.6)% of the nominal dose with the VN and 19.2 (15.8–22.9)% of the nominal dose with the JN, \(p < 0.05\)).

The upper respiratory tract deposition was also higher with the VN (17.6 (13.4–27.9)% of the nominal dose with the VN and 8.6 (6.0–11.0)% of the nominal dose with the JN, \(p < 0.05\)). It was essentially related to the nasal cavity and the nasopharynx with both nebulizers, that is, 93% and 94% of the upper respiratory tract deposition with the VN and the JN, respectively. A similar environmental loss was calculated with both nebulizers (around 20% of the nominal dose).

The absorbed dose related to the radioactive aerosol is 4.1 μGy/MBq for the kidneys, 47.2 μGy/MBq for the bladder, and 17 μGy/MBq for the lungs, resulting in an effective dose of 7 μSv/MBq (inhaled fraction). No data are available for the upper airways, but as a surrogate, the absorbed dose to the stomach wall is 1.7 μGy/MBq. The effective dose to subjects, thus, greatly varied with the type of nebulizer as the fraction of the nominal dose lost in the nebulizer reservoir, the HFNC circuit, and the environment was much higher with the JN (90.6% with the JN and 79.5% with the VN). The mean effective dose was 212.4 μSv for the VN and 99.4 μSv for the JN. These doses were low in comparison with, for instance, a standard lung perfusion study (2.5 mSv).

**Discussion**

This first in vivo study on aerosol delivery through a high-flow nasal cannula reports poor pulmonary aerosol deposition in healthy male subjects, regardless of the type of nebulizer.
Lung doses delivered through HFNC (1.0%–3.6% of nominal dose) were very low, predicting a poor clinical efficacy of this combination with concentration-dependent drugs, for example, antibiotics. However, a relevant bronchodilation effect was measured in ventilated patients even at a 3% lung dose, which highlights the possibility to administer bronchodilators through HFNC. This first in vitro study may provide some guidance for clinicians attempting to deliver an effective target dose to the lungs of patients on HFNC.

With the same model of VN and similar conditions of administration, Réminiac et al. (17) found in vitro a respirable dose of 6.7%±0.1% of the nominal dose. The characteristics of the thermoplastic polymer head model and the controlled-breathing pattern may explain the higher respirable dose found in vitro (6.7% vs. 4% of the nominal dose measured in the present in vivo study). The absence of nasal mucosa and the cylindrical, cold, and dry pharynx model did not reflect the characteristics of the upper respiratory tract (complex anatomy with heated humidified turbulent flow). The deposition in such areas may have been limited, improving aerosol delivery to the filter placed downstream of the model. Moreover, the fixed sinusoidal inspiratory flow of 15 L/min and the duty cycle (T_{insp}/T_{TOT}) of 50% applied in vitro may have also increased the respirable dose in comparison to the breathing pattern spontaneously adopted by the subjects. Indeed, the higher and variable inspiratory flow of 32 L/min and the lower T_{insp}/T_{TOT} of 26% promoted aerosol retention in the HFNC circuit or the upper airways.

Overestimation of lung doses observed in vitro confirmed the necessity of further in vivo studies to adapt doses according to the clinical impact of inhaled drugs through HFNC. Low deposition in the lungs resulted from a high loss of particles in the HFNC circuit or in the upper airways.

![FIG. 2. Inhalation waveform of a healthy subject during a high-flow nasal cannula. The breathing pattern of the subject was a tidal volume of 770 mL, a respiratory rate of 13 cycles/min, and a duty cycle (T_{insp}/T_{TOT}) of 40%.

| Table 3. Imaging Outcome of Aerosol Deposition from Single-Photon Emission Computed Tomography-Computed Tomographic Scan and Planar Analysis Expressed as Percentage of Nominal Dose |
|---------------------------------|--------|--------|
| **VN**                         | **JN** |
| Both lungs (from SPECT-CT analysis) | 3.6 (2.1–4.4)* | 1.0 (0.7–2.0) |
| Both lungs (from planar analysis) | 2.0 (1.4–2.8)* | 0.7 (0.6–1.2) |
| Right lung                      | 1.7 (1.2–2.2)* | 0.5 (0.4–1.0) |
| Left lung                       | 1.8 (0.9–2.2)* | 0.4 (0.3–1.0) |
| Right/left lung ratio           | 1.04 (0.96–1.29) | 1.18 (1.00–1.77) |
| 3D penetration index            |        |
| Right lung                      | 1.02 (0.93–1.18) | 0.81 (0.77–0.95) |
| Left lung                       | 0.85 (0.75–1.16)* | 0.65 (0.49–0.84) |
| Tracheal area                   | Negligible (<0.1%) | Negligible (<0.1%) |
| Extrapulmonary deposition       | 94.8 (94.0–96.1)* | 53.8 (49.5–57.1) |
| Stomach and kidneys             | 0.2 (0.1–0.4)* | 0.07 (0.03–0.40) |
| Upper respiratory tract         | 17.6 (13.4–27.9)* | 8.6 (6.0–11.0) |
| Nasal cavity and nasopharynx    | 16.4 (12.4–26.0)* | 8.1 (5.5–10.2) |
| Trickling from the nostril interface, particle leaks, and exhaled particles | 20.5 (10.6–26.4) | 22.0 (17.9–37.2) |
| Single-limb circuit + nasal cannula (NC) | 48.0 (46.0–50.0)* | 17.2 (14.4–20.1) |
| Humidification chamber          | 7.5 (6.3–13.1)* | 2.3 (1.6–2.8) |
| Nebulizer retention              | 2.6 (2.1–3.8)* | 45.0 (42.4–50.0) |
| Pulmonary/extrapulm. deposition ratio | 0.021 (0.015–0.029) | 0.008 (0.006–0.012) |

Data expressed as median (25%–75% IQR) and as percentage of nominal dose (i.e., radioactivity placed in the nebulizer reservoir at the start of experiments).

*p<0.05 for comparison of both nebulizers.

HFNC, high-flow nasal cannula; JN, jet nebulizer; VN, vibrating-mesh nebulizer.
respiratory tract. This could be explained by the characteristics of the HFNC circuit (high flow, components, geometry, and heating humidification). The high flow promotes particle impaction in the upper respiratory tract (especially the nasal cavity and the nasopharynx) and in the HFNC circuit, presenting a heating wire, curves, a nasal cannula, and a humidification chamber.\(^ {14-17}\) It also increases the particle leakage at the nostril interface during inspiration (through a mismatch between the HFNC flow rate and the subject’s inspiratory flow)\(^ {17}\) and the washout of particles from the single-limb circuit during expiration.\(^ {29}\)

Although the spontaneous inspiratory flow rate (32 (24–37) L/min) adopted by the subjects matched with the flow imposed by the system, the long expiratory time (3.6 seconds) may have induced a substantial loss of particles that trickled from the nostril interface during expiration. A minimal flow rate of 30 L/min was applied according to clinical studies in acute respiratory failure patients (30–60 L/min).\(^ {5,20,21}\) Exceeding 30 L/min was applied according to clinical studies in acute respiratory failure patients (30–60 L/min).\(^ {5,20,21}\) Exceeding 30 L/min was applied according to clinical studies in acute respiratory failure patients (30–60 L/min).\(^ {5,20,21}\) Exceeding 30 L/min was applied according to clinical studies in acute respiratory failure patients (30–60 L/min).\(^ {5,20,21}\) Exceeding 30 L/min was applied according to clinical studies in acute respiratory failure patients (30–60 L/min).\(^ {5,20,21}\)

Another potential explanation of low lung delivery is the thermodynamic effect on aerosol particles (hygroscopic growth and evaporation) with heated-humidified gas that could have potentially assisted aerosol loss in the HFNC circuit.\(^ {15,31,32}\) Condensational growth methods were recently developed to reduce particle impaction within the HFNC circuit and the upper respiratory tract.\(^ {13}\) Submicron particles were generated in the HFNC circuit and grown sufficiently to be deposited in the lungs. In vitro studies reported a three- to fourfold decrease of aerosol retention in the circuit and a nose–mouth–throat model, with emitted particles with a mass median aerodynamic diameter (MMAD) of 900 nm in comparison to a conventional size aerosol of 4.5 μm MMAD.\(^ {32,33}\) These methods have to be tested in vivo.

The impact of the HFNC on aerosol delivery using a facemask or a mouthpiece has never been investigated. An alternative method to administer aerosol to an HFNC-dependent patient could be performed by using a nebulizer that is directly connected to a facemask or a mouthpiece. Many scintigraphic studies in healthy subjects (without HFNC) reported higher lung doses with other models of continuous VN (35% of the nominal dose)\(^ {34,35}\) or JN (up to 20% of the nominal dose) connected to a mouthpiece.\(^ {11,36}\) Using this common interface in patients with HFNC may be an alternative to the placement of the nebulizer within the circuit, but the impact of the nasal high flow imposed by the system on aerosol delivery through a mouthpiece should be investigated.

Lung deposition was higher by using the VN as compared with the JN. It was explained by its negligible retained volume (2.6% of activity) in comparison to the high retained volume observed with the JN reservoir (45% of activity—1.1 mL of collected volume as reported by the manufacturer). As a consequence, lung doses normalized by the emitted dose were similar for both devices. The superiority of the vibrating-mesh technology in emitting aerosol particles over the jet technology was previously reported.\(^ {37,38}\)

A homogeneous aerosol distribution between both lungs was found among subjects, although the SPECT-CT analysis confirmed the higher physiological right lung deposition illustrated in recent tomographic studies performed in healthy subjects.\(^ {25,39}\) A PI between 0.6 and 1 was obtained, indicating a predominantly central deposition of nebulized particles. Aerosol penetration depends on many factors, such as the particle size, the inspiratory flow, and the morphology and lung anatomy of the subject.\(^ {40}\) The particle size characterized by the MMAD measured at the outlet of the cannula with the same model of VN under similar conditions of administration (1.8 ± 1.9 μm) supports a better penetration through the airways than is found in vivo.\(^ {41}\) In this study, particles were delivered through the airways by using a continuous high flow of 30 L/min.

This high flow may have more likely promoted deposition by inertial impaction and turbulent mixing on proximal bronchi rather than being deposited in the lung parenchyma. Poor penetration was also reported by using other models of continuous VN and JN tested (PI between 0.5 and 1) in healthy subjects without HFNC\(^ {34,35,41}\) or during noninvasive ventilation through a single-limb circuit.\(^ {12}\) A penetration index above 1 was reported in tomoscintigraphic

### Table 4. Imaging Outcome of Aerosol Deposition from Single-Photon Emission Computed Tomography-Computed Tomographic Scan and Planar Analysis Expressed as Percentage of the Emitted Dose

<table>
<thead>
<tr>
<th></th>
<th>VN</th>
<th>JN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both lungs (from SPECT-CT analysis)</td>
<td>3.7 (2.2–4.7)</td>
<td>1.9 (0.9–2.3)</td>
</tr>
<tr>
<td>Both lungs (from planar analysis)</td>
<td>2.1 (1.5–2.9)</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>Right lung</td>
<td>1.8 (1.2–2.3)</td>
<td>1.1 (0.6–1.8)</td>
</tr>
<tr>
<td>Left lung</td>
<td>1.9 (0.9–2.3)</td>
<td>0.8 (0.6–1.7)</td>
</tr>
<tr>
<td>Tracheal area</td>
<td>Negligible (&lt;0.1%)</td>
<td>Negligible (&lt;0.1%)</td>
</tr>
<tr>
<td>Extrapulmonary fraction</td>
<td>97.9 (97.1–98.5)</td>
<td>98.5 (97.8–98.9)</td>
</tr>
<tr>
<td>Stomach and kidneys</td>
<td>0.2 (0.1–0.4)</td>
<td>0.1 (0.1–0.2)</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>18.4 (13.7–28.6)</td>
<td>17.4 (10.3–28.6)</td>
</tr>
<tr>
<td>Nasal cavity and nasopharynx</td>
<td>17.1 (12.7–26.7)</td>
<td>17.3 (10.3–28.6)</td>
</tr>
<tr>
<td>Trickling from the nostril interface, particle leaks, and exhaled particles</td>
<td>21.4 (10.8–26.9)</td>
<td>42.7 (34.6–65.5)</td>
</tr>
<tr>
<td>Single-limb circuit + nasal cannula (NC)</td>
<td>49.1 (47.3–51.7)</td>
<td>32.9 (25.2–38.8)</td>
</tr>
<tr>
<td>Humidification chamber</td>
<td>7.7 (6.5–13.5)</td>
<td>4.3 (2.8–5.8)</td>
</tr>
</tbody>
</table>

Data expressed as median (25%–75% IQR). *p<0.05 for comparison of both nebulizers.

HFNC, high-flow nasal cannula; JN, jet nebulizer; SPECT-CT, single-photon emission computed tomography-computed tomographic scan, VN, vibrating-mesh nebulizer.
studies performed in healthy subjects without HFNC by using drug targeting systems. A better penetration of aerosol particles was ensured through aerosol delivery only during the first part of the inspiration and guidance of the breathing pattern of the subjects (low inspiratory flow and deep inspiration). The VN emitted two times more drugs than the JN but delivered a low and similar amount of emitted particles to the lungs. A low inhaled dose (from 0.2% to 32% of the nominal dose) measured with commercial systems in previous in vitro studies suggests high particle loss in the HFNC circuit.

The VN emitted two times more drugs than the JN but delivered a low and similar amount of emitted particles to the lungs. A low inhaled dose (from 0.2% to 32% of the nominal dose) measured with commercial systems in previous in vitro studies suggests high particle loss in the HFNC circuit.
Most emitted particles were trapped in the HFNC circuit (56.8% with the VN and 37.2% with the JN) or deposited in the upper respiratory tract (18.4% with the VN and 17.4% with the JN). As mentioned earlier, the characteristics of the HFNC circuit probably explain particle impaction on internal walls of the HFNC circuit and also in the upper airways with both nebulizers. However, larger particle size emitted with the VN in the HFNC circuit as compared with the JN (i.e., the MMAD mentioned by the manufacturer was 3.4 and 1.8 μm for the VN and the JN at 8 L/min of driving flow rate, respectively) may have contributed to the higher aerosol loss in the HFNC circuit with the VN. Moreover, the 8 L/min, dry, cold driving flow added to the 22 L/min with the JN may have probably interfered with humidification and influenced temperature and condensation within the circuit.

However, particles that were susceptible to reach the airways were stopped at the nostril interface (two times more particles were impacted in the nostril interface with the JN in comparison to the VN). Hence, a similar amount of emitted drugs was deposited in the upper respiratory tract and the lungs with both nebulizers. Aerosol deposition in the nasal cavity and the nasopharynx was substantial with both nebulizers (around 93% of the upper respiratory tract deposition), as already suggested by using a thermoplastic polymer head model. This would probably explain the lower stomach deposition in comparison to spontaneously breathing subjects receiving an aerosol through a mouthpiece in which particles are more likely being swallowed from the oropharynx to the stomach. Systemic availability and air contamination with aerosolized drugs were not investigated. It should be noticed by using HFNC that kidneys could be particularly exposed, possibly due to the systemic absorption in the nasal cavity promoted by vasodilation induced by the nasal heated airflow (Fig. 2). Moreover, 21.4%–42.7% of emitted particles trickled from the nostril interface or were lost in ambient air because of particle impaction, leakage, or exhalation at the cannula due to the high flow and the prolonged expiratory time spontaneously adopted by the subjects. Some limitations have to be considered. First, this study was performed in healthy subjects to compare both nebulizers. Pulmonary deposition cannot be extrapolated to respiratory failure conditions (bronchospasm, secretions, and atelectasis). However, it offers a comparison of both nebulizers in similar conditions. Moreover, patients in respiratory distress often require a flow rate above 30 L/min due to a higher inspiratory peak flow, a higher inspired oxygen fraction and present open mouth breathing that alters aerosol delivery through HFNC. Therefore, lower lung doses may be expected in respiratory failure patients. Second, for methodological consideration, only men were enrolled and all subjects were in a sitting position. However, it was previously shown that regional deposition differs with the gender and the position (e.g., higher deposition in the upper zones of the lungs in the supine than in the sitting position). Third, this imaging study imposed to place a radiotracer in the nebulizer reservoir, but lung deposition may also differ with another drug considering its aerodynamic and physicochemical characteristics. Fourth, the positive airway pressure generated by the HFNC was not measured to investigate its effect on aerosol delivery. However, a positive airway pressure inferior to 2.7 cmH₂O (reported for 35 L/min) was not expected to impact lung deposition in healthy subjects.

In conclusion, aerosol delivery to the lungs through HFNC is only 1%–3% of the nominal dose in the specific conditions of the study, despite the higher efficiency of the VN as compared with the JN. Placing the nebulizer on the HFNC circuit at 30 L/min induces high aerosol loss in the circuit and the oropharynx. Delivering an aerosolized bronchodilator through HFNC may induce a significant clinical effect to be tested on patients, whereas the technique should be optimized further before we can expect a significant bactericidal effect with nebulized antibiotics. Further in vivo studies are needed to determine the proper technique to administrate an aerosol to an HFNC-dependent patient. Only in a subsequent step, the potential clinical effect associated to the aerosol-HFNC combination may be assessed.

Acknowledgments

The authors would like to acknowledge Aerogen Ltd. for the unrestricted research grant and Fisher & Paykel (New Zealand) for providing the single-limb adult breathing circuits. The authors acknowledge the editorial assistance provided by Mrs Carline Dugernier.

Author Disclosure Statement

J.D. received an unrestricted grant provided by Aerogen Ltd. to perform this study. S.E. received research support for his institution from Aerogen Ltd., Fisher & Paykel, Hamilton medical and consultancies/lecture fees: Aerogen Ltd., La diffusion technique française. Other authors have no conflicts to declare.

References


42. Galindo-Filho VC, Ramos ME, Rattes CS, Barbosa AK, Brandao DC, Brandao SC, Fink JB, and de Andrade AD: Radioaerosol pulmonary deposition using mesh and jet nebulizers during noninvasive ventilation in healthy subjects. Respir Care. 2015;60:1238–1246.


Received on January 6, 2017 in final form, March 1, 2017

Reviewed by: Kim Chan
P. Worth Longest

Address correspondence to: Jonathan Dugernier, PT, MSc
Soins Intensifs Cliniques Universitaires Saint-Luc
Avenue Hippocrate 10
1200 Brussels
Belgium

E-mail: jonathan.dugernier@uclouvain.be