# Enhanced Aerosol Delivery During High-Flow Nasal Cannula Therapy

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**BACKGROUND: Aerosolized drug delivery via high-flow nasal cannula (HFNC) decreases as gas flow is increased. To improve aerosol delivery, breath-enhanced jet nebulizer may increase aerosol output. This study tested that hypothesis and compared breath-enhanced jet nebulizer to vibrating mesh nebulizer technology. METHODS: First, in an isolated circuit, breath-enhanced jet nebulizer and vibrating mesh nebulizer aerosol outputs were measured during simulated HFNC by using infused saline solution at rates of 5–60 mL/h. Limits were defined when nebulizer filling was detected. The devices were then tested by using $^{99m}$Tc/saline solution to measure maximum rates of aerosol production. After the output experiments, drug delivery was measured in vitro by using a model that consisted of an HFNC circuit interfaced to a realistic 3-dimensional printed head. The $^{99m}$Tc/saline solution was infused at rates of 5 to 60 mL/h for the breath-enhanced jet nebulizer and 5 to 20 mL/h for the vibrating mesh nebulizer with HFNC gas flows of 10 to 60 L/min. Aerosol delivery to the trachea was measured by using a shielded ratemeter, which defined the rate of drug delivery (μg NaCl/min). RESULTS: With increasing gas flow, breath-enhanced jet nebulizer output increased to a maximum of 50 mL/h, the vibrating mesh nebulizer maximum was 12 mL/h. At HFNC gas flow of 60 L/min, breath-enhanced jet nebulizer delivered 3.16 to 316.8 μg NaCl/min, the vibrating mesh nebulizer delivered 23.5 to 61.7 μg NaCl/min. For infusion pump flows of 5 to 12 mL/h, the rate of drug delivery was independent of nebulizer type ($P = .19$) and dependent on infusion pump flow ($P < .001$) and gas flow ($P < .001$). CONCLUSIONS: Increasing gas flow increased breath-enhanced jet nebulizer output, which demonstrated the effects of breath enhancement. At 60 L/min, breath enhanced jet nebulizer delivered up to 5 times more aerosol compared with conventional vibrating mesh nebulizer technology. Breath-enhanced jet nebulizer delivered a wide range of dose rates at all high flows. In patients who are critically ill, breath-enhanced jet nebulizer technology may allow titration of bedside dosing based on clinical response by simple adjustment of the infusion rate.** *Key words: High flow nasal cannula; continuous infusion; aerosol; nebulizer.* [Respir Care 2023;68(9):1221–1228. © 2023 Daedalus Enterprises]

## Introduction

High-flow nasal cannula (HFNC) oxygen therapy is routinely used to treat patients with ARDS and other forms of respiratory failure.[1] Typical gas flow through the cannula ranges from 30 to 60 L/min. Anecdotally, particularly during the COVID pandemic, clinicians have delivered pulmonary vasodilator aerosols to the lung in attempting to improve ventilation/perfusion mismatch by supplying oxygen and the vasodilating drug simultaneously.[2] The potential benefits of this therapy include improved oxygenation, reduced dead space, improved ventilation/perfusion, and avoidance of intubation.[3] However, there may be limitations of the nebulizing technology to deliver particles through heated and humidified circuits, HFNC patient interface devices, and the nasal airways at the higher oxygen flows required for patients who are the sickest. In addition, there is uncertainty in control of dosing with changing high-flow conditions.[4] For clinical trials to answer questions with regard to treatment efficacy, the dose of the drug should be predictable and controllable.

For delivery of aerosols during HFNC, there are several in vitro and in vivo studies that reported drug delivery for different nebulizer technologies.[5-8] The results indicate that the higher the gas flow in the cannula, the lower the drug delivery. Losses in the tubing and nasal interface increase with increasing flow, and, for clinically relevant oxygen flows, conventional technology may not supply the patient with sufficient drug. In addition, the successful use of rapidly acting drugs often requires the precise adjustment of dose while clinical effects are monitored. Attempts to reduce tubing losses are inherently limited, and turbulence

in the nasal turbinate cannot be easily modified. Aerosols leaking around the catheter-nasal interface are unpredictable. Intuitively, once the tubing limits are known, drug delivery can be increased simply by increasing the rate of drug infusion. However, conventional nebulizers have limited volumetric output rates. One form of jet nebulizer, the breath-enhanced jet nebulizer, theoretically lends itself to high-flow therapy. Different from conventional nebulizers with fixed outputs, in the breath-enhanced jet nebulizer, the flow to the patient passes through the chimney of the nebulizer to enhance output. The magnitude of this effect is unknown during HFNC therapy.

We hypothesized that this mechanism, unique to breath-enhanced jet nebulizer, would increase aerosol output in proportion to increases in gas flow. The test protocol was designed to (1) define the maximum output of a prototype breath-enhanced jet nebulizer (i-AIRE, InspiRx, Inc., Somerset, New Jersey) receiving gas flows over the clinically relevant spectrum seen in the hospital (eg, 10–60 L/min), and (2) measure aerosol delivery in vitro to a human model by using a newly developed 3-dimensional printed replica of an intact human nasal airway system. The breath-enhanced jet nebulizer system was compared with a conventional vibrating mesh system (Aerogen Solo, Aerogen, Galway, Ireland), which operated under the same conditions.

**QUICK LOOK**

**Current knowledge**

High-flow nasal cannula oxygen therapy is being used for acute hypoxic respiratory failure in patients who are critically ill. Aerosol delivery via the cannula can be limited when higher oxygen flows are used.

**What this paper contributes to our knowledge**

A breath-enhanced jet nebulizer provided a wide range of aerosol delivery at the highest flows of oxygen, which allows clinical titration of drugs to the individual patient.

## Methods

We hypothesized that breath-enhanced nebulization would have a variable output affected by high flow. The limits of this function were unknown. A protocol was designed to quantify the limits of output under changing conditions. The principle of the drop-by-drop method of nebulization implies that, over time, no fluid should accumulate in the nebulizer. In this protocol, the maximum output of the breath-enhanced and mesh nebulizers was first defined by visual assessment. The protocol was designed to test the hypothesis that increasing high flow will increase nebulizer output. High-flow gas input was connected to the breath-enhanced jet nebulizer at the top of the nebulizer, so the interior of the nebulizer was affected by 2 flow sources, the high flow from the top at 50 psi gauge and the flow energizing the nebulizer from the bottom.[9]

The breath-enhanced jet nebulizer was operated at 5 L/min by using compressed air at 50 psi gauge; therefore, for a nominal gas flow of 60 L/min, the actual flow was 65 L/min. To equalize the high-flow gas rates, gas flow for the mesh nebulizer was adjusted by increasing the protocol flow by 5 L/min. The breath-enhanced jet nebulizer was interfaced to an infusion pump (Alaris Pump Module, Becton, Dickinson and Co., Franklin Lakes, New Jersey) via a side infusion port. The vibrating mesh nebulizer was connected to the high-flow circuit by using the T connector and to the infusion pump by the proprietary infusion port. The vibrating mesh nebulizer was energized by the Pro-X controller. At a given combination of gas flow and pump infusion rate, the nebulizers were observed for 20 min to define maximum infusion pump rates that generated a visual aerosol cloud without solution accumulating in the nebulizer. Based on these findings, the maximum infusion rates for each HFNC gas flow are outlined in Table 1.

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The State University of New York at Stony Brook holds patents in the fields of nebulizer development and inhaled drug delivery, which have been licensed to InspiRx. Dr Smaldone discloses a relationship with InspiRx. The other authors have disclosed no conflicts of interest.

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Table 1. Maximum Infusion Flows for Breath-Enhanced Jet Nebulizer and Vibrating Mesh Nebulizer at Nominal Gas Flows After 20 min of Observation

| Breath-Enhanced Jet Nebulizer | | Vibrating Mesh Nebulizer | |
|---|---|---|---|
| HFNC Flow, L/min | Maximum Infusion Flow, mL/h | HFNC Flow, L/min | Maximum Infusion Flow, mL/h |
| 60 | 60 | 60 | 20 |
| 50 | 50 | 50 | 20 |
| 40 | 50 | 40 | 20 |
| 30 | 50 | 30 | 20 |
| 20 | 40 | 20 | 20 |
| 10 | 30 | 10 | 20 |

HFNC = high-flow nasal cannula

With the data provided in Table 1, which outlines the limits of nebulizer function, the actual aerosol produced by the nebulizers was measured by using the setup described in Figure 1. This technique quantified output during high flow with only the humidifier as an added factor. The syringe pump used a 60-mL syringe filled with normal saline solution mixed with ~3 mCi of $^{99m}$Tc. The radioactivity of the prepared solutions was measured with a radioisotope calibrator (Atom Lab 100, Biodex, Inc., Shirley, New York), which defined the initial charge before starting each experiment. Before the start of each experiment, the nebulizer was dry, empty, and free of radioactivity. The time at which this initial charge was measured served as the baseline time for decay correction of the subsequent measurements obtained throughout the experiment. The test nebulizer (breath-enhanced jet nebulizer or vibrating mesh nebulizer) was attached to the dry side of a humidifier (MR-850, Fisher & Paykel Healthcare, Ltd., Panmure, Auckland, New Zealand) connected via a 6-inch hose to an output filter. The output filter consisted of 2 filters connected in series, a filter with removable media (Pari, Sternberg, Germany) and a high-efficiency particulate air filter (bacterial/viral filter, Westmed, Tucson, Arizona).

This combination was attached to the outlet of the humidifier. The output rate (counts/min) was measured for each infusion pump flow for 10- to-20-min intervals in real time by using a ratemeter (model 2200 Scalar Ratemeter, Ludlum Measurements, Sweetwater, Texas). The ratemeter counts/min were converted to an output rate defined as μg NaCl/min.[9] Based on the results listed in Table 1, at the clinical maximum gas flow of 60 L/min, saline solution mixed with $^{99m}$Tc was infused at 5, 12, 20, 30, 40, 50, and 60 mL/h for the breath-enhanced jet nebulizer, and at 5, 12, 20, and 30 mL/h for the vibrating mesh nebulizer. A single run was carried out at each infusion flow. For infusion pump flows of 5 mL/h, the pump was run for 20 min to allow the nebulizer to reach a steady state, otherwise all other infusion pump flows were run for 10 min. These data defined the maximum rates of aerosol generation in μg NaCl/min for each condition before being directed to a patient.

After demonstrating the range of nebulizer outputs for the breath-enhanced jet nebulizer and vibrating mesh nebulizer, at 60 L/min, the nebulizers were attached to a ventilated model designed to assess aerosol delivery in a system that mimics HFNC therapy. This model is detailed in an accompanying paper.[9] The experimental setup is outlined in Figure 2. The HFNC humidifier circuit was connected to an HFNC (Optiflow, Fisher & Paykel, Auckland, New Zealand) interfaced to a 3-dimensional printed anatomically correct model of an adult head, which provided all ventilation through the nose. Collection filters were placed after the 3-dimensional printed head and connected to a piston pump for tidal ventilation. Activity on these filters was defined as inhaled mass (IM). The shielded ratemeter was positioned at the level of the IM filters for real-time measurement of radiolabeled aerosol accumulating on the filter. Aerosol reaching the filter complex represented particles that traversed all tubing and upper airways.[9]

Tests were conducted using a single breathing pattern (tidal volume 750 mL, breathing frequency 30 breaths/min, and duty cycle 0.5), previously described as a distressed breathing pattern.[10] Two molded breath-enhanced jet nebulizer prototypes and 2 vibrating mesh nebulizers were used in rotation for all the experiments. The nebulizers were positioned in the circuit as described in Figure 1. A saline solution that contained 4 to 6 mCi of $^{99m}$Tc was drawn into a 60-mL syringe to achieve $^{99m}$Tc concentrations of 67 to 100 μCi/mL. Infusion rates over ranges, defined in Table 1, were tested for gas flows of 10, 20, 30, 40, 50, and 60 L/min. Testing each infusion/gas flow combination would take 2–3 h and provide several hundred data points. The complete range of experimental parameters were tested twice. The inhaled mass filter complex was changed every 80 to 100 min, and a new background count was obtained. After each experiment, the inhaled mass filter was measured by using the radioisotope calibrator to obtain the amount of radioactivity in μCi for a given count rate.

Filter data were used to calculate a conversion factor of ratemeter counts to μCi for each measurement. These data were converted to μg of salt (NaCl) based on the salt content of normal saline solution by using the formula:

$$\mu g \text{ of } NaCl_{\text{time interval}} = \text{measured } \mu Ci_{\text{time interval}} / [(\mu Ci_{\text{syringe charge}})/(mL_{\text{syringe charge}} \times 9{,}000\ \mu g/mL)],$$

which represents the amount of the drug being aerosolized and delivered during continuous nebulization. The μg of NaCl delivered to the output and inhaled mass filters was plotted as a function of time. The slope of each 10- or 20-min experimental condition represented the rate of drug delivery (μg NaCl/min). Examples for these tracings are included in the accompanying study by McPeck et al.[9]

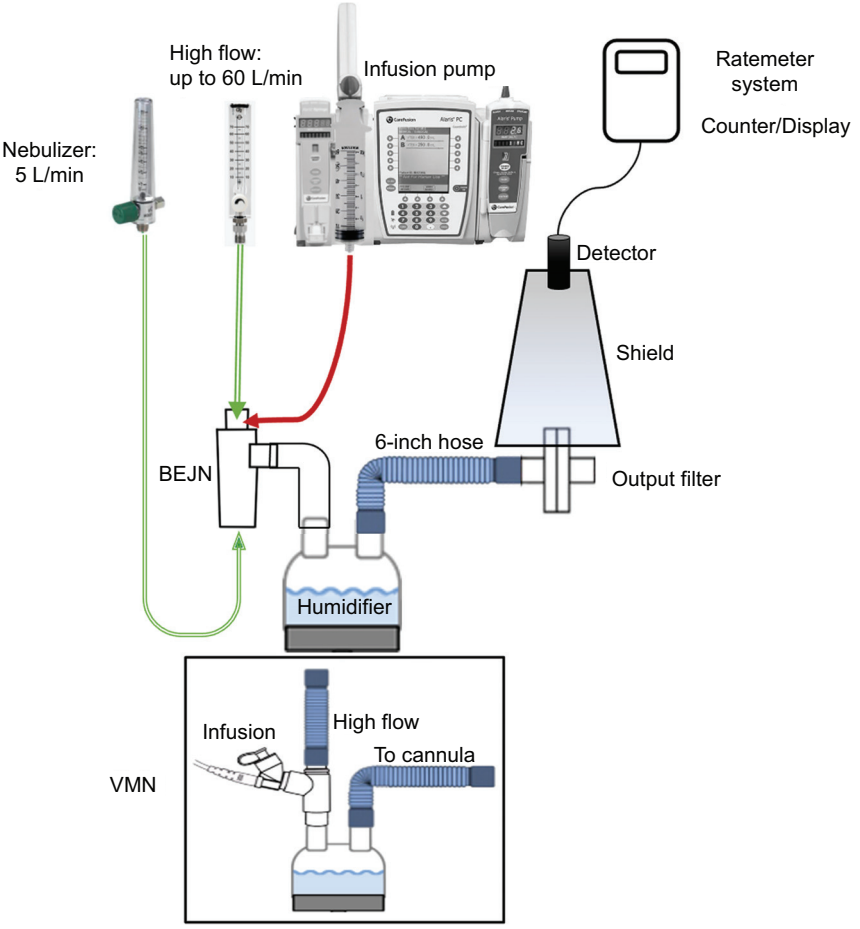


Fig. 1. Experimental setup for breath-enhanced jet nebulizer (BEJN), or vibrating mesh nebulizer (VMN), designed to measure maximum aerosol output during high flow. Medical air from a high-pressure cylinder operates the breath-enhanced jet nebulizer at a flow of 5.0 L/min at 50 psi gauge. High-flow air at 50 psi gauge was supplied at 60 L/min (breath-enhanced jet nebulizer) or 65 L/min (vibrating mesh nebulizer) via a 0 to 70 L/min back pressure compensated flow meter to the top of the breath-enhanced jet nebulizer or to the T connector of the vibrating mesh nebulizer. The nebulizers were located on the dry side of the humidifier. Saline solution mixed with $^{99m}$Tc was infused at different rates. Radioactive particles delivered to the output filter were measured by the shielded ratemeter.

The rate of drug delivery was analyzed by using multiple linear regression. Nebulizer technology, infusion pump flow, and HFNC flow were variables assessed. In a typical experiment, there were 5–10 data points for each condition used to define the slope that yields the output rate.[9] Data were reported as μg NaCl/min. To allow statistical comparison, a multiple regression analysis was performed for experiments in which both nebulizers had a measurable output. The reported analysis included 48 data points, which represented 48 slopes. For some infusion rates, statistical comparisons were not possible, for example, for the experiments in which the vibrating mesh nebulizer had no output. All slope calculations and statistical analysis were performed by using GraphPad Prism 9.0 for Mac OS (GraphPad Software, San Diego, California). The magnitude of the regression coefficients define how much of the variability in the rate of drug delivery is ascribed to each independent parameter.

The mass median aerodynamic diameter of aerosol exiting the HFNC was determined by using a Marple 8-stage cascade impactor (Thermo Fisher Scientific, Waltham, Massachusetts) operated at 2 L/min. Normal saline solution mixed with $^{99m}$Tc was infused at 12 mL/h for the vibrating mesh nebulizer and 20 mL/h for the breath-enhanced jet nebulizer at gas flows of 60 L/min and sampled for 30 min. These infusion rates were chosen because rates of drug delivery at these infusion rates were similar. The ratemeter was used to measure the counts on the stages of the cascade impactor. Each experimental setting was run 3 times to ensure reproducibility. Activity on the cascade stages was plotted against probability to determine the mass median aerodynamic diameter.[11]

## Results

Observational data for the first protocol are listed in Table 1. Analysis of these data illustrates effects of breath enhancement

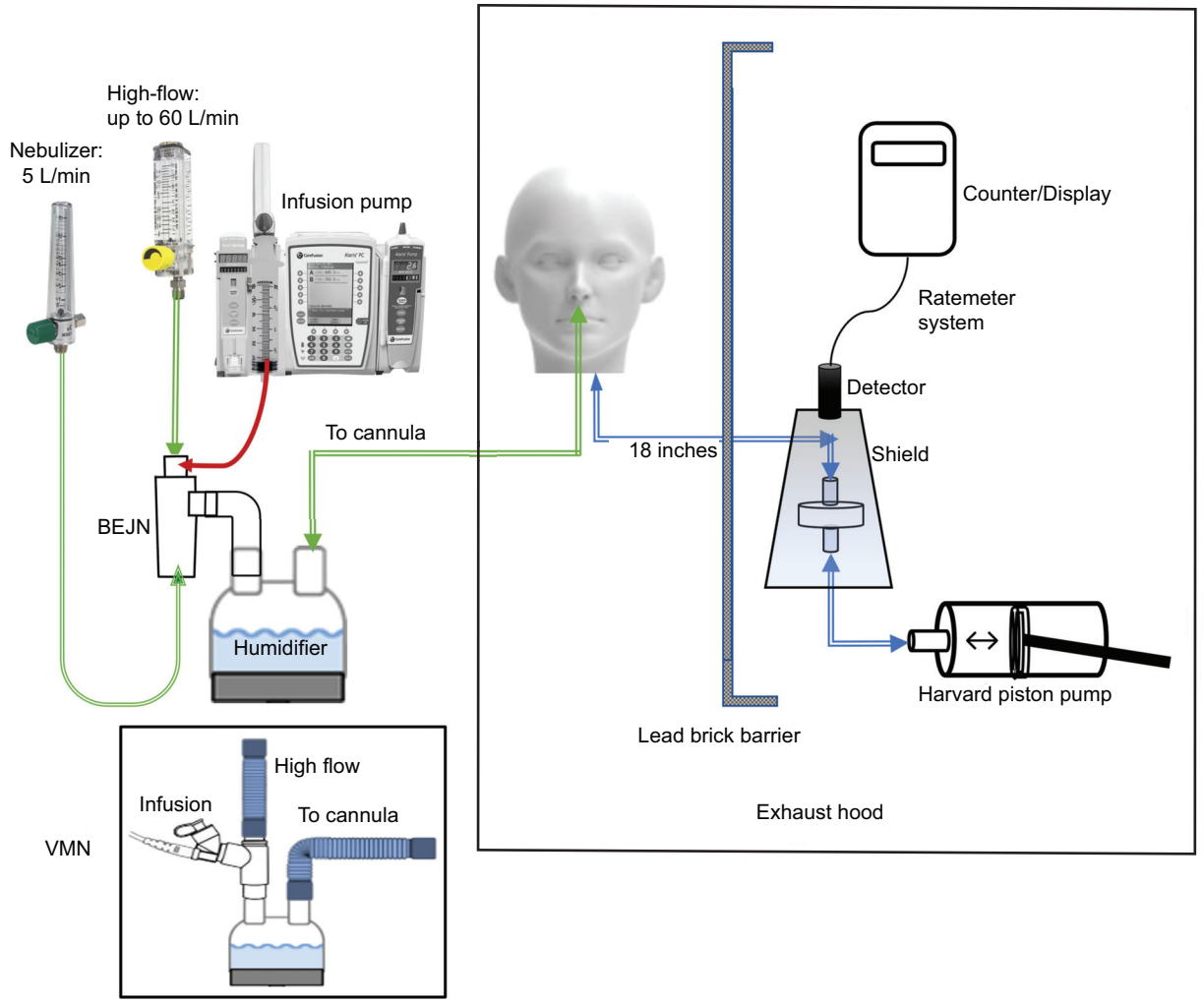


Fig. 2. Schematic diagram for experimental setup to measure aerosol delivery via high-flow nasal cannula (HFNC) to the 3-dimensional printed head model (From Reference 9).

and defines the limits of nebulizer output. For each gas flow, the infusion pump flow was increased until fluid was seen filling the nebulizer, which indicated maximum output for that condition. For the breath-enhanced jet nebulizer, increasing the gas flow resulted in nebulizer outputs between 30 and 60 mL/h, with filling seen at 60 mL/h. For the vibrating mesh nebulizer, changes in gas flow had no effect with the nebulizer beginning to fill at 20 mL/h for all gas flows.

The rate of aerosol delivery to the output filter/min with increasing infusion flow is quantified in Figure 3. All data were for a gas flow of 60 L/min. For the breath-enhanced jet nebulizer, aerosol output increased with each increment of infusion flow until, at 60 mL/h, the device started to fill. Therefore, its maximum output was an infusion rate of 50 mL/h. The measured output increased from 40.3 to 3,442 μg NaCl/min as infusion rates were increased. At the same gas flow, the vibrating mesh nebulizer aerosol output ranged from 396.1 to 1,060 μg NaCl/min and reached a maximum at an infusion rate of 12 mL/h. The vibrating mesh nebulizer began to fill at 20 mL/h. Infusion rates > 20

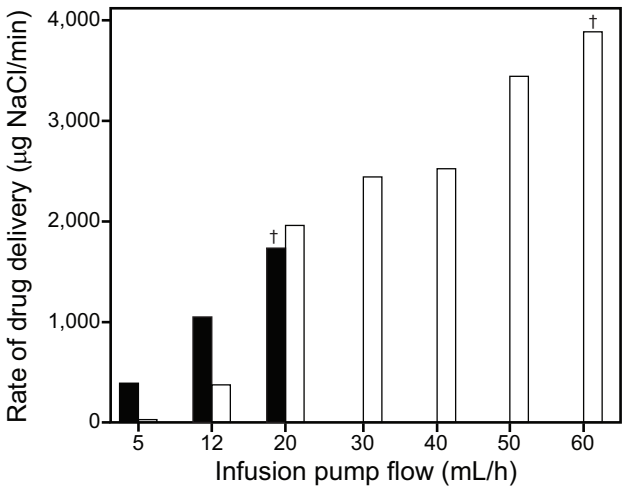


Fig. 3. The rate of drug delivery (μg NaCl/min) for vibrating mesh nebulizer (black) and breath-enhanced jet nebulizer (white) at a high-flow gas rate of 60 L/min and various infusion pump flows (mL/h). † Denotes an infusion pump flow in which the nebulizer filled with prolonged infusion (eg, 1 h).

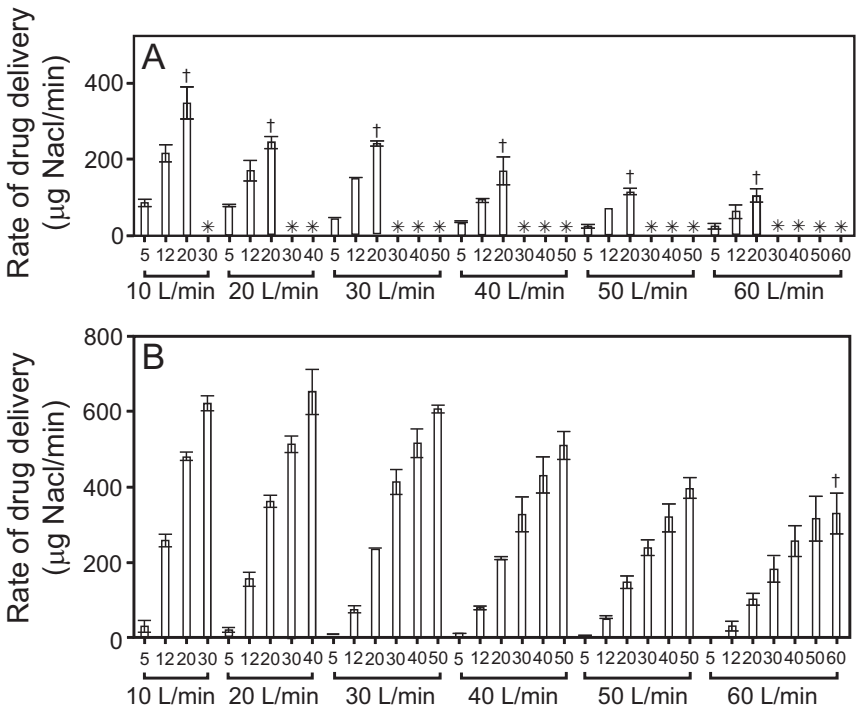


Fig. 4. The rate of drug delivery (μg NaCl/min) for vibrating mesh nebulizer (A) at infusion pump flows 5 mL/h to 20 mL/h and breath-enhanced jet nebulizer (B) at infusion pump flows 5 mL/h to 60 mL/h. † Denotes the nebulizer filling during prolonged continuous nebulization. Brackets denote high-flow nasal cannula (HFNC) gas flow in L/min. Asterisks denote conditions in which only the breath-enhanced jet nebulizer could function.

mL/h resulted in rapid filling of the vibrating mesh nebulizer, and aerosol outputs were not reported. Outputs marked with a cross in the figure denote infusion flows that resulted in filling. This protocol demonstrated the maximum potential for aerosol delivery at the highest practical gas flows before particles pass into the clinical delivery apparatus.

The results for the bench model described in Figure 2 are shown in Figure 4. These results measure the aerosol delivery rate to the trachea, the IM/min. Changes in the scale of the y axis (compared with Fig. 3) indicated that much of the aerosol measured in Figure 3 had been lost, with the output values shown in Figure 3, an order of magnitude greater than those in Figure 4. For each gas flow, IM/min increases with infusion flow, but the increase is limited for the vibrating mesh nebulizer, which reaches maximum output at 12 mL/h. Breath-enhanced jet nebulizer output rates seemed similar to the vibrating mesh nebulizer for infusion flows of 12 mL/h. Regression analysis for these infusion flows were compared statistically. This analysis indicated similar function between the devices because nebulizer technology was not statistically important as a variable (Table 2). Multiple linear regression analysis of the rate of drug delivery indicated that 79% of the data was accounted for by this analysis ($R^2 = 0.79$).

Drug delivery was independent of nebulizer type ($P = .19$) and dependent on infusion pump flow ($P < .001$) and gas flow ($P < .001$). For the rest of the conditions described in the figure, for example, infusion flows of 20–50 mL/h, only the breath-enhanced jet nebulizer produced aerosol with outputs that increased with increasing infusion flow up to 50 mL/h at all gas flows. In addition to the responsiveness of the nebulizers to infusion flow, the figure demonstrated that aerosol losses were greater at increasing gas flow. These losses are likely due to circuit losses and leaking at the nasal interface.[9] At the higher gas flows often needed for those who are critically ill, the range of output for vibrating mesh nebulizer was limited. For example, at 60 L/min, output rate ranged from 23.5 to 61.7 μg NaCl/min compared with the breath-enhanced jet nebulizer (3.16 to 316.8 μg NaCl/min).

For all gas flows, breath-enhanced jet nebulizer was able to deliver more drug, and, despite circuit losses, analysis of the data in Figure 4 shows that, at each gas flow, drug delivery could be adjusted over a wide range by changes in

Table 2. Multiple Linear Regression: Rate of Drug Delivery as a Function of Nebulizer Type, Infusion Pump Flow and Gas Flow

| Independent Variables | $\beta$ | Standard Error | 95% CI | $P$ | $R^2$ | $\Delta R^2$ * |
|---|---|---|---|---|---|---|
| Nebulizer type | 26.2 | ±19.6 | –13.3 to 65.6 | .19 | 0.04 | NA |
| Infusion pump flow | 12.5 | ±2.1 | 8.15 to 16.8 | <.001 | 0.45 | 0.45 |
| Gas flow | –2.3 | ±0.27 | –2.86 to –1.75 | <.001 | 0.79 | 0.34 |

*Represents the contribution to the total R value for each individual variable.
NA = not applicable

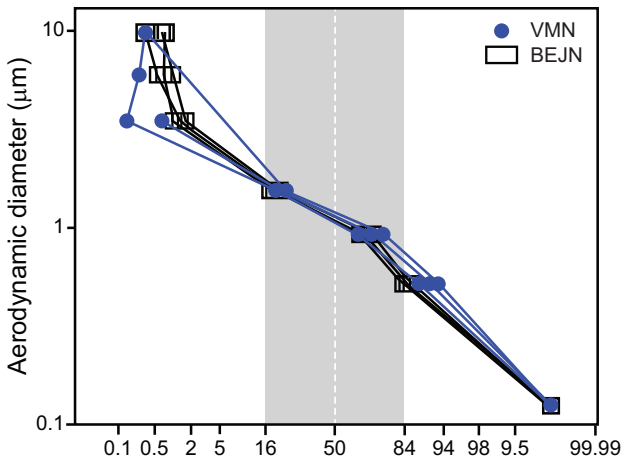


Fig. 5. Log aerodynamic diameter (μm) plotted against probability for aerosols from vibrating mesh nebulizer (VMN) and breath-enhanced jet nebulizer (BEJN) at gas flows of 60 L/min. The infusion rate was 12 mL/h for the vibrating mesh nebulizer and 20 mL/h for the breath-enhanced jet nebulizer. Mass median aerodynamic diameter at 50% probability ± 1 SD (shaded area).

infusion rate. Particle size distributions are illustrated in Figure 5. For the vibrating mesh nebulizer, mass median aerodynamic diameter of 1.14 ± 0.06 μm, with Geometric Standard Deviation (GSD) = 1.37 ± 0.07, and for the breath-enhanced jet nebulizer, mass median aerodynamic diameter of 1.10 ± 0.03 μm, with GSD = 1.41 ± 0.04.

## Discussion

This paper demonstrated that during high-flow therapy, breath-enhanced jet nebulizer can increase aerosol output beyond that of conventional nebulizers. When interfaced with an HFNC circuit, some of the observed circuit losses can be balanced by increases in aerosol output facilitated by breath-enhanced nebulization. Comparing Figures 3 and 4 demonstrates that, in general, 90% of the aerosol generated is lost in the clinical circuit but, as shown in Figure 4, breath-enhanced jet nebulizer provides greater range of aerosol delivery. The sensitivity of the breath-enhanced jet nebulizer to the infusion rate allows regulation of drug delivery over a wide range. Aerosol delivery can be adjusted over 2 orders of magnitude, flexibility that may allow titration of therapy based on clinical response. Both the vibrating mesh nebulizer and breath-enhanced jet nebulizer allow some titration of therapy at the lower infusion rates and lower gas flows. The breath-enhanced device can function over a wider range, with increases in drug delivery at the bedside between 5 and 50 mL/h without having to increase drug concentration in the syringe or intravenous bag.

This study establishes a unique application of breath-enhanced technology. As shown in Table 1 and Figure 3, the maximum output rates for the breath-enhanced jet nebulizer varied from 30 to 50 mL/h, depending on the high flow used. These values far exceed those reported in the general literature for typical nebulizers. In our experience, outputs usually approximate 10 mL/h and this value was measured for the breath-enhanced jet nebulizer during mechanical ventilation, which exposes the nebulizer to lower mean gas flows.[12] The same device exposed to constant high flow generates 5 times as much aerosol.

Most bench studies, including ours, test devices over relatively short periods of time, especially when compared with a clinical situation that can require hours of continuous nebulization. To be clinically useful, a device should not fill. For some conditions, a 20-min observation period will not detect slow device filling. Prolonged testing of vibrating mesh nebulizer and breath-enhanced jet nebulizer beyond 1 h indicated that both devices tend to fill at the limits indicated in Figure 3, which suggests that the practical infusion limit for vibrating mesh nebulizer is 12 mL/h. Therefore, for the vibrating mesh nebulizer to increase drug delivery, it would be necessary to increase the drug concentration. This approach was advocated by Li et al,[13] who mimicked a weight-based dosing regimen in which inhaled epoprostenol was delivered at different concentrations (7.5, 15 and 30 μg/mL) to a bench model designed to deliver 30 and 50 ng/kg/min for predicted body weights of 50,70, and 90 kg.

Their model used invasive ventilation with continuous nebulization of the vibrating mesh nebulizer, which delivered epoprostenol to an IM filter over 20-min treatment periods.[13] This weight-based dosing required higher infusion pump flows (12.0, 16.8, 21.6 mL/h).[13] A re-analysis of their data is detailed in Supplementary Figure 6 of the present paper (see the supplementary materials at http://www.rcjournal.com). The data of Li et al[13] support our observation that, for continuous nebulization, the maximum output of the vibrating mesh nebulizer is closer to that reported in the company's service instructions, of 12 mL/h. Clinicians should be aware that higher infusion rates may not yield proportionate increases in drug delivery. To ensure that a device can provide reliable continuous nebulization, it should be tested over periods that mimic actual clinical use, which could be hours. Vibrating mesh nebulizer infusion rates reported >12 mL/h have only been tested for 20 min.[14]

The regression analysis indicates that most of the variation in the data are due to infusion pump flow and gas flow (eg, $R^2 = 0.79$). Nebulizer technology is not important for the conditions in which the devices will run continuously without filling, as shown in Figure 4. These observations are predicted by the drop-by-drop method in which, in a steady state, all liquid infused into the nebulizer is nebulized. In addition to turbulent deposition in the delivery system, it is obvious from direct observation that large numbers of particles leak out around the nose as well as particles that are exhaled, even with nasal breathing. From mass balances performed in preliminary studies, we have reported nasal losses of ~25%.[9] Although the statistical analysis did not reveal significant

differences between the nebulizers, inspection of Figure 3 indicates that, at the lowest infusion rates, the vibrating mesh nebulizer output is greater than that of the breath-enhanced jet nebulizer. These differences are reduced in Figure 4. A likely explanation can be found in the mass balance data from McPeck et al, who reported that circuit losses are greater for vibrating mesh nebulizer technology.[9] When considering the limitations described above, at flows often used in those who are critically ill (30–60 L/min), the breath-enhanced jet nebulizer delivered 5 times more aerosol to the IM filter.

Our study has important limitations. First, this was a bench study performed at only one breathing pattern. The breath-enhanced jet nebulizer, pending 510 K submission, has not been tested in a clinical environment and may have unforeseen problems. Our model may not duplicate clinical reality. However, our results are consistent with those reported by other investigators when using similar models.[9]

It is our goal to improve patient care, and we think that these data are important in designing future clinical trials. Reported clinical treatment plans for the off-label use of inhaled vasodilators have adapted a weight-based algorithm for deciding on dosing.[13] From the few papers that summarize clinical response to continuous nebulization, it seems that the drugs fail to improve oxygenation ~50% of the time.[13] This suggests that weight-based dosing may be a limitation to adequate aerosol delivery to ensure patient improvement. It is unknown why treatment fails some patients. Do they get sufficient drug? Perhaps dosing should be increased until a desired physiologic outcome is attained or adverse effects are detected. To reach this point, the clinician should know that the device can deliver the drug. Breath-enhanced jet nebulizer offers an aerosol delivery device that can deliver the drug over a wide range at all clinically relevant oxygen high flows from very low doses to significant maxima. Only at the maximum point would the therapist have to change the solution to a higher concentration (eg, an infusion rate of 50 mL/h, for a gas flow of 60 L/min). This would allow careful control and titration of drug delivery for infusion flows of 5–50 mL/h.

## Conclusions

Breath-enhanced jet nebulizer produces increasing aerosol with increasing gas flow in a model of HFNC delivery. This study outlines conditions that may provide a therapeutic dose of vasodilators and other important drugs to the patient who requires high flows of oxygen.


## ACKNOWLEDGMENTS

Mr Michael McPeck RRT FAARC, passed away unexpectedly on August 11, 2022, as this paper was being prepared. He designed the model and the experimental apparatus. His personal contributions to interpretation of data were unique. This manuscript and the research behind it would not have been possible without his extensive knowledge and expertise. The authors thank Stony Brook University Hospital Respiratory Care Department.


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