Mitigating Fugitive Aerosols During Aerosol Delivery via High-Flow Nasal Cannula Devices

Jie Li, Amnah A Alolaiwat, Lauren J Harnois, James B Fink, and Rajiv Dhand

BACKGROUND: Aerosol delivery via high-flow nasal cannula (HFNC) has attracted clinical interest in recent years. However, both HFNC and nebulization are categorized as aerosol-generating procedures (AGPs). In vitro studies raised concerns that AGPs had high transmission risk. Very few in vivo studies examined fugitive aerosols with nebulization via HFNC, and effective methods to mitigate aerosol dispersion are unknown. METHODS: Two HFNC devices (Airvo 2 and Vapotherm) with or without a vibrating mesh nebulizer were compared; HFNC alone, surgical mask over HFNC interface, and HFNC with face tent scavenger were used in a random order for 9 healthy volunteers. Fugitive aerosol concentrations at sizes of 0.3–10.0 μm were continuously measured by particle sizers placed at 1 and 3 ft from participants. On a different day, 6 of the 9 participants received 6 additional nebulizer treatments via vibrating mesh nebulizer or small-volume nebulizer (SVN) with a face mask or a mouthpiece with/without an expiratory filter. In vitro simulation was employed to quantify inhaled dose of albuterol with vibrating mesh nebulizer via Airvo 2 and Vapotherm. RESULTS: Compared to baseline, neither HFNC device generated higher aerosol concentrations. Compared to HFNC alone, vibrating mesh nebulizer via Airvo 2 generated higher 0.3–1.0 μm particles (all $P < .05$), but vibrating mesh nebulizer via Vapotherm did not. Concentrations of 1.0–3.0 μm particles with vibrating mesh nebulizer via Airvo 2 were similar with vibrating mesh nebulizer and a mouthpiece/face mask but less than SVN with a mouthpiece/face mask (all $P < .05$). Placing a surgical mask over HFNC during nebulization reduced 0.5–1.0 μm particles (all $P < .05$) to levels similar to the use of a nebulizer with mouthpiece and expiratory filter. In vitro the inhaled dose of albuterol with vibrating mesh nebulizer via Airvo 2 was $\geq$ 6 times higher than vibrating mesh nebulizer via Vapotherm. CONCLUSIONS: During aerosol delivery via HFNC, Airvo 2 generated higher inhaled dose and consequently higher fugitive aerosols than Vapotherm. Simple measures, such as placing a surgical mask over nasal cannula during nebulization via HFNC, could effectively reduce fugitive aerosol concentrations. *Key words: high-flow nasal cannula; nebulization; aerosol generating procedure; COVID-19; mitigation.*
[Respir Care 2022;67(4):404–414. © 2022 Daedalus Enterprises]

Introduction

High-flow nasal cannula (HFNC) devices deliver warmed and humidified oxygen at flows that exceed the subject's inspiratory flow with F_{IO_2} up to 1.0.[1] Use of HFNC reduces the need for intubation among hypoxemic patients.[2-4] In-line placement of a nebulizer with HFNC has been employed to deliver aerosolized medications,[5] such as inhaled epoprostenol for patients with pulmonary hypertension or refractory hypoxemia[6,7] or inhaled albuterol for patients with asthma[8] or chronic obstructive pulmonary diseases.[9,10] HFNC has been shown to be advantageous for nebulized therapy compared to conventional aerosol delivery methods including nebulizers with face mask/mouthpiece, pressurized metered-dose inhalers (pMDIs), or dry powder inhalers.[11] The nasal interface is more tolerable than a face mask or mouthpiece because it does not interfere with talking, eating, and drinking. This is particularly important for patients who require long-term inhalation of aerosolized medication, such as continuous albuterol administration for patients with asthma[8] or inhaled epoprostenol for patients with pulmonary hypertension and/or refractory hypoxemia.[6,7]

Both HFNC and nebulizer therapy are categorized as aerosol-generating procedures (AGPs).[12-14] In particular, nebulization was found to increase aerosol concentration in the subject's vicinity,[15] and exhaled air dispersion distance with nebulization was higher than that with a simple oxygen mask or noninvasive ventilation.[16] When transnasal

aerosol delivery was implemented in vitro, fugitive aerosols could still be detected at 2.2 m from the manikin, and it was estimated that a person standing at 0.8 m and 2.2 m from the manikin would be exposed to 8.5% and 3.2% of the medication, respectively.[17] Concerns about the risks of aerosol transmission limited the utilization of AGPs, including HFNC and nebulization, increasing use of alternative modalities of treatment, such as ventilators or pMDIs, leading to reported shortage of these resources during the COVID-19 pandemic.[18] However, there is lack of in vivo evidence that fugitive aerosol generation during transnasal aerosol delivery could transmit infection.

Methods to minimize the risk of bioaerosol transmission in order to protect health care workers and further prevent spread of SARS-CoV-2 virus are the subject of ongoing discussion.[19] Placing a surgical mask over HFNC was found to significantly reduce aerosol particle concentrations at a distance of 1 ft and 3 ft from subjects[20]; however, its effects during transnasal aerosol delivery are unknown. In addition, a face tent scavenger that continuously suctions patient's exhaled aerosol particles has recently been introduced with little information on its ability to reduce fugitive aerosols.

Therefore, we aimed to seek the most effective modality to reduce the fugitive aerosol concentrations during transnasal aerosol delivery. Accordingly, we investigated the concentrations of fugitive aerosols generated by 2 commonly used HFNC devices (Airvo 2 and Vapotherm) with and without the in-line placement of a nebulizer. We also explored the ability of a surgical mask or a face tent scavenger to mitigate fugitive aerosols generated during transnasal aerosol delivery with HFNC.

Dr Li and Mss Alolaiwat and Harnois are affiliated with Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, Illinois. Dr Fink is affiliated with Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, Illinois; and Aerogen Pharma Corp, San Mateo, California. Dr Dhand is affiliated with Department of Medicine, University of Tennessee Graduate School of Medicine, Knoxville, Tennessee.

Dr Li discloses relationships with Fisher & Paykel Healthcare, Aerogen, The Rice Foundation, the American Associate for Respiratory Care, and Heyer. Dr Li also serves as Section Editor for RESPIRATORY CARE. Dr Fink is Chief Science Officer for Aerogen Pharma Corp. Dr Dhand discloses relationships with GSK Pharmaceuticals, Boehringer Ingelheim, Mylan, Teva, and AstraZeneca Pharmaceuticals. The other authors have disclosed no conflicts of interest.

This study was supported by an unrestricted research funding from Aerogen. Vapotherm supplied the face tent scavengers. The companies had no role in the study design, data collection, analysis, preparation of the manuscript, or the decision to publish the findings.

Correspondence: Jie Li PhD RRT RRT-ACCS RRT-NPS FAARC, 600 S Paulina St, Suite 765, Chicago, IL. E-mail: Jie_Li@rush.edu.

DOI: 10.4187/respcare.09589

QUICK LOOK

Current knowledge

Aerosol delivery via high-flow nasal cannula (HFNC) has attracted clinical interest in recent years. Both HFNC and nebulizer therapy have been considered as aerosol-generating procedure during COVID-19 pandemic. However, evidence is lacking about the fugitive aerosol concentrations generated during transnasal aerosol delivery and effective methods to reduce emission of these fugitive aerosols.

What this paper contributes to our knowledge

HFNC devices alone did not generate higher fugitive aerosol concentrations than baseline. Transnasal aerosol delivery via Airvo 2 produced higher fugitive aerosol concentrations than transnasal delivery via Vapotherm, which can be explained by the low inhaled dose of aerosol delivered in the in vitro studies. Simple measures such as utilizing a surgical mask on top of nasal prongs during transnasal aerosol delivery reduced fugitive aerosol particle concentrations.

Methods

This study has both an in vivo and an in vitro component. The in vivo study was conducted to evaluate fugitive aerosol concentrations when HFNC devices (Airvo 2 vs Vapotherm) were employed alone or with in-line placement of a vibrating mesh nebulizer. In vitro study was implemented to assess the inhaled dose of aerosol delivered via the two HFNC devices.

In Vivo Study

A prospective randomized crossover trial was registered at clinicaltrials.gov (NCT04681599) with approval of the ethics committee at Rush University (approval No. 20121804-IRB01). Healthy adults age 18–65 y were included in the study. Exclusion criteria included subjects with chronic lung disease; upper-airway anatomical abnormalities; uncontrolled diabetes; hypertension; untreated thyroid disease; pregnancy; and positive COVID-19 test or any COVID-19–related symptoms (including sore throat, cough, body aches or shortness of breath for unknown reasons, loss of taste or smell, and fever $\geq 100^{\circ}$F) within 21 d.

After reading study recruitment advertisement that was posted in respiratory care department at Rush University Medical Center, 9 healthy subjects volunteered to participate in the study and were consented. The study was implemented in an ICU room that is $3.65 \times 3.65 \times 2.8$ m^3 with air exchange frequency of 6 times/h. Two aerosol particle

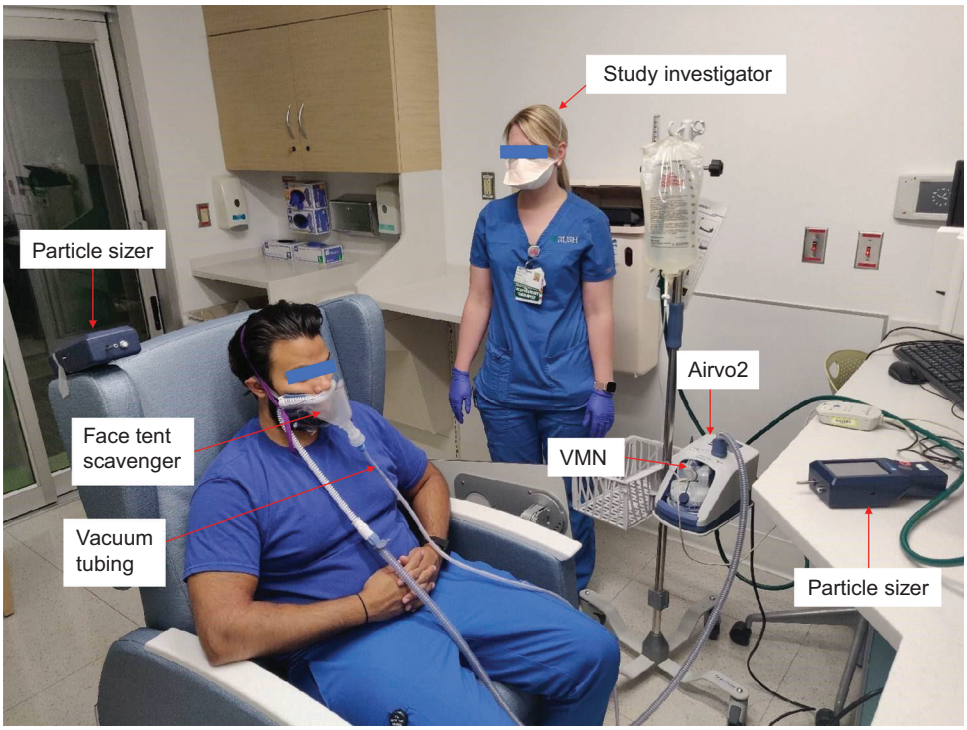

Fig. 1. In vivo study setup. The study participant sat in a chair to receive the nebulization via a vibrating mesh nebulizer placed in the humidifier of Airvo 2; a face tent scavenger connected with a vacuum pressure of −100 mm Hg was placed surrounding their face. Two particle sizers were placed at 1 and 3 ft from the participant to continuously measure fugitive aerosol concentrations at 0.3–10.0 μm. The study investigator wore a N95 mask and stayed with the participant throughout the study. VMN = vibrating mesh nebulizer.

sizers (Model 3889, Kanomax, Andover, New Jersey) were placed at 1 and 3 ft from subjects who were sitting on a chair to continuously measure the fugitive aerosol concentrations at sizes of 0.3–10.0 μm (Fig. 1). Throughout the study session, the door of the room was closed and talking, eating, or moving around were discouraged. The investigator wore an N95 mask and remained in the room with the participant. Participants wore N95 masks during baseline and 15-min intervals between experiments to minimize aerosol generation.

Fugitive aerosol concentrations were compared between Airvo 2 (Fisher & Paykel Healthcare, Auckland, New Zealand) and Vapotherm (Vapotherm, Exeter, New Hampshire). HFNC device alone, a surgical mask over HFNC interface, and HFNC with a face tent scavenger were tested in a random order (Fig. 2). The scavenger was connected to a vacuum pressure of −100 mm Hg. The HFNC flow was set at the highest level that the participant could tolerate, with the temperature set at 37°C. The size of nasal prongs was chosen based on nostril size. During transnasal aerosol delivery, a vibrating mesh nebulizer (Aerogen Solo, Aerogen, Galway, Ireland) was placed at the humidifier, and 3 mL of saline was used for each nebulization, which lasted 8–10 min, plus 15-min interval; thus, each test took approximately 25 min. On a different day, 6 of the 9 participants returned to receive 6 additional nebulizer treatments; a small-volume nebulizer (SVN) (AirLife 002446, CareFusion, San Diego, California) and a vibrating mesh nebulizer were used with a mouthpiece, a mouthpiece with an expiratory filter, and an aerosol face mask in a random order (Fig. 2). Per manufacturer's instructions, 8 L/min compressed air was used to drive the SVN, while 2 L/min air was connected to the vibrating mesh nebulizer chamber. 3 mL saline was used for both nebulizers.

The mean aerosol concentration for each particle size was measured from the beginning to the end of each test. Since 6 additional tests were completed on different days, due to the variance of baseline aerosol concentrations in the room, the fugitive aerosol concentrations generated by each device were calculated in proportion to baseline aerosol concentrations on the same day. In addition, participants self-evaluated comfort on the device and interface after use, utilizing a 5-point Likert scale scoring from 1 (very uncomfortable) to 5 (very comfortable).

In Vitro Study Evaluating Transnasal Aerosol Delivery via Airvo 2 Versus Vapotherm

An in vitro study was conducted to evaluate the effectiveness of aerosol delivery via Airvo 2 and Vapotherm. A

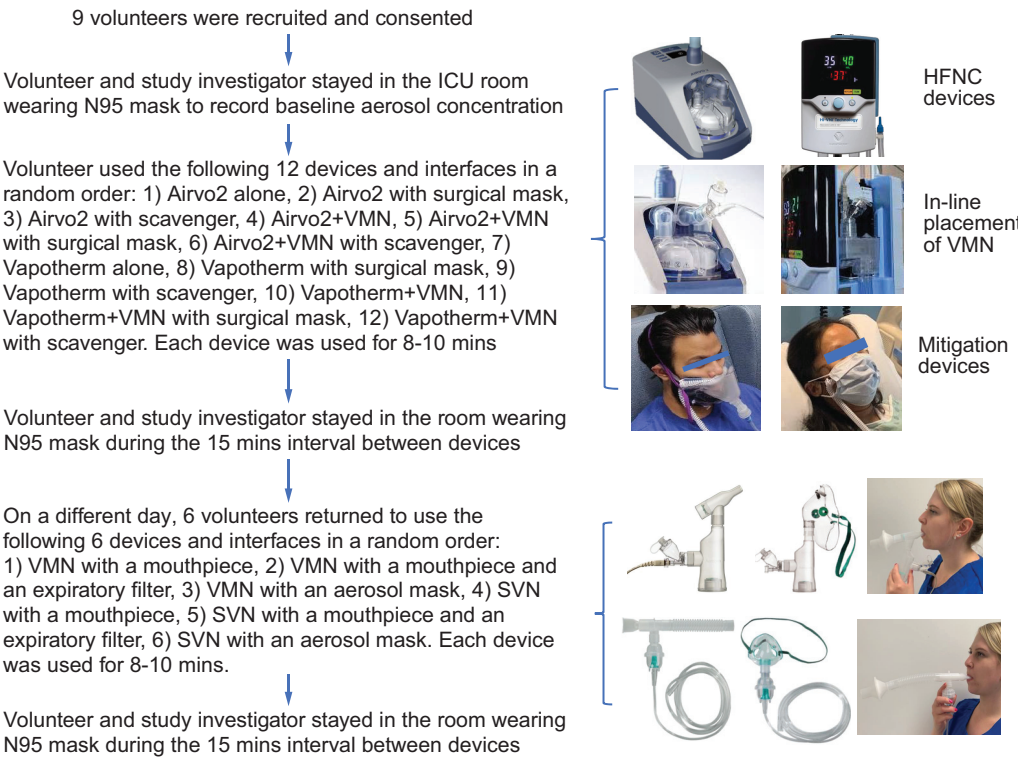

Fig. 2. Flow chart. SVN = small-volume nebulizer; VMN= vibrating mesh nebulizer; HFNC= high-flow nasal cannula; ICU= intensive care unit.

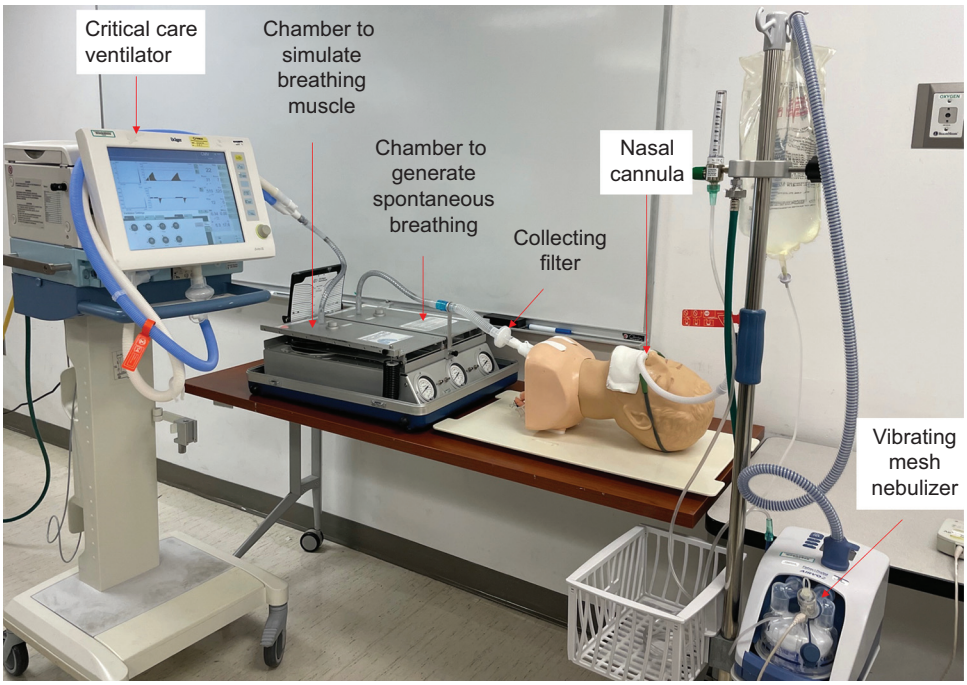

Fig. 3. In vitro study setup.

simulated adult manikin (Laerdal Airway Management Trainer, Stavanger, Norway) with appropriate upper-airway anatomy was utilized (Fig. 3) with a collecting filter (Respirgard 303, CareFusion) attached between the distal end of the manikin's trachea and one chamber of a 2-chamber model lung (TTL, Michigan Instruments, Grand

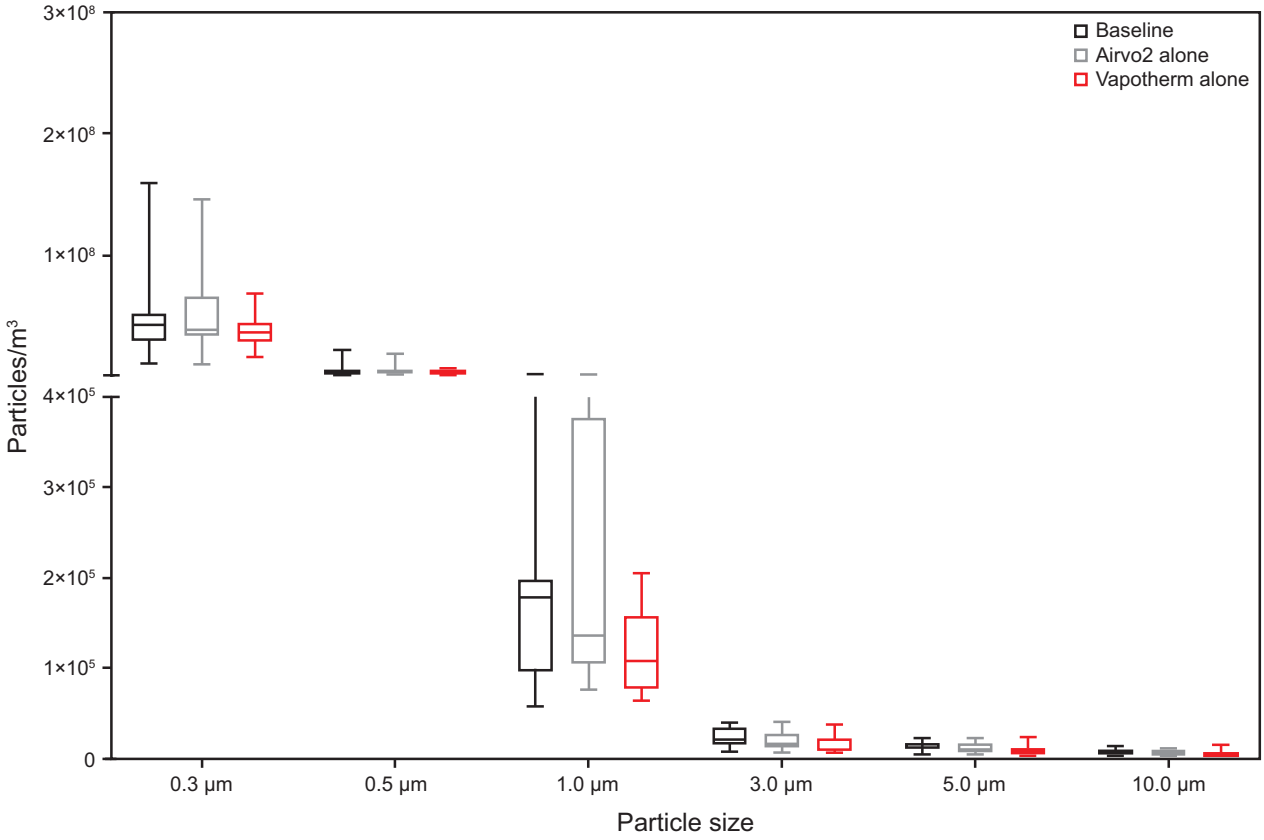

Fig. 4. Fugitive aerosol concentrations with Airvo 2 versus Vapotherm. The x axis presents different sizes of aerosol particles; the y axis presents the concentrations of aerosol particles (µ/m³). Compared to baseline, HFNC did not generate higher fugitive aerosol concentrations for both Airvo 2 and Vapotherm. No significant differences of fugitive aerosol concentrations between the 2 device at 1 ft from participants.

Rapids, Michigan). The 2 chambers could be moved together; displacement of one chamber that was connected to a critical care ventilator (Dräger XL, Dräger, Lübeck, Germany) caused the other chamber to rise and generate negative pressure, thereby simulating spontaneous breathing. A large-size adult nasal cannula was placed on the manikin's nares and connected to an adult HFNC circuit.

For each HFNC device, different flows tested were 20, 40, and 60 L/min for Airvo 2 and 20 and 40 L/min for Vapotherm (unable to operate at 60 L/min). Albuterol (2.5 mg in 3 mL) was placed in the vibrating mesh nebulizer for each run. After nebulization, the collecting filter was removed and eluted with 10 mL solution (0.1 M HCl mixed with 20% ethanol) and analyzed with spectrophotometry at 276 nm. The inhaled dose was calculated by determining the amount of albuterol captured on the collecting filter as a percentage of the nominal dose (2.5 mg).

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (interquartile range [IQR]) based on the distribution of variables, which was analyzed by Kolmogorov-Smirnov test. Paired *t* test or Wilcoxon test was used to compare the differences of fugitive aerosol particle concentrations or inhaled doses between 2 interfaces, depending on the normality of the data distribution. Subject comfort was compared by Wilcoxon test. $P < .05$ was statistically significant. Data analysis was conducted with SPSS software (IBM SPSS 26.0 for Windows; IBM, Armonk, New York).

Results

In Vivo Comparisons of Fugitive Aerosol Concentrations Between Nebulization via Airvo 2 Versus Vapotherm With Different Interfaces

Nine subjects (8 females) were enrolled in the study, age 27 (26–31) y with height of 167.5 ± 5.3 cm. Airvo 2 and Vapotherm were employed with highest tolerable flows at 50 (42.5–50.0) L/min and 30 (22.5–30.0) L/min, respectively.

There was no significant difference in fugitive aerosol concentrations generated at all particle sizes between Airvo 2 and Vapotherm (Figure 4), except lower fugitive aerosol

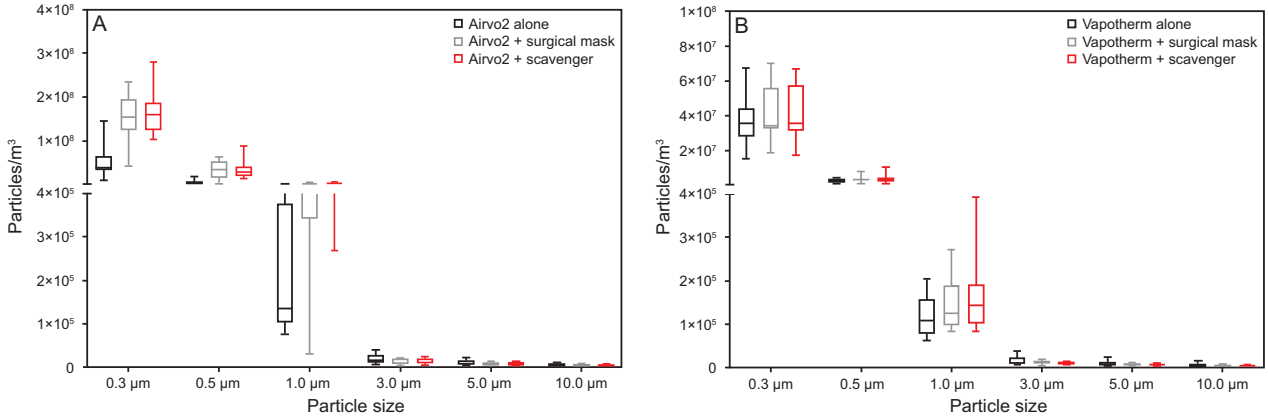

Fig. 5. Fugitive aerosol concentrations with mitigation devices for HFNC. Compared to the HFNC alone, wearing a surgical mask over the nasal cannula or wearing a face tent scavenger did not reduce fugitive aerosol concentrations for Airvo 2 (A) or Vapotherm (B) at all particle sizes. HFNC= high-flow nasal cannula.

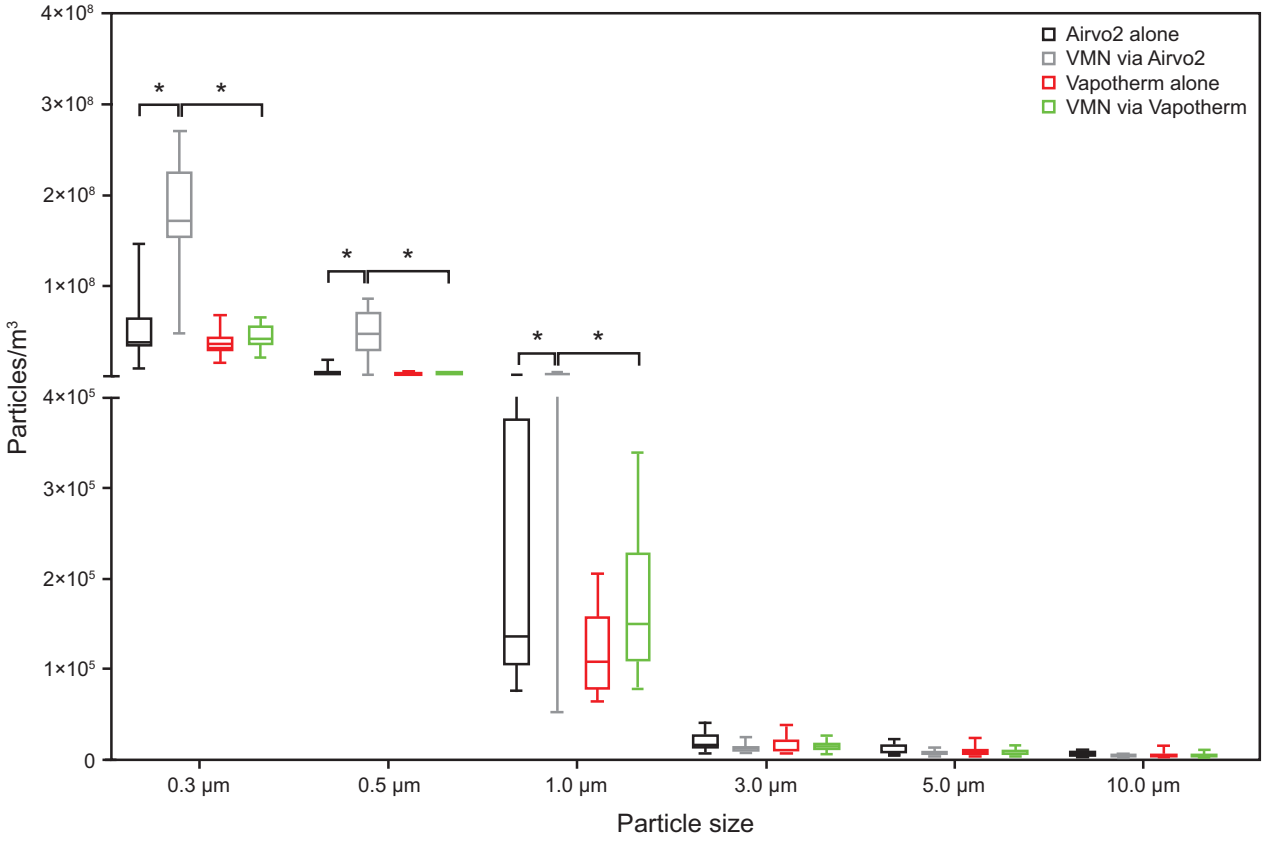

Fig. 6. Fugitive aerosol concentrations of HFNC with versus without vibrating mesh nebulizer. The x axis presents different sizes of aerosol particles, and the y axis presents the concentrations of aerosol particles (/m^3). Compared to HFNC alone, in-line placement of vibrating mesh nebulizer via Airvo 2 generated higher fugitive aerosol concentrations at particle sizes of 0.3–1.0 µm (all $P < .05$) but Vapotherm did not. Fugitive aerosol concentrations were higher with vibrating mesh nebulizer via Airvo 2 than vibrating mesh nebulizer via Vapotherm with particle sizes of 0.3–1.0 µm. HFNC = high-flow nasal cannula. * $P < .05$.

concentrations were noted with Vapotherm than Airvo 2 at particle sizes of 1.0–3.0 µm (all $P < .05$) with the particle sizer placed at a distance of 3ft from the subject (data not shown). At all other settings, there was no difference in the fugitive aerosol concentrations with the particle sizer placed at 1ft vs 3ft from the subject (data not shown). To

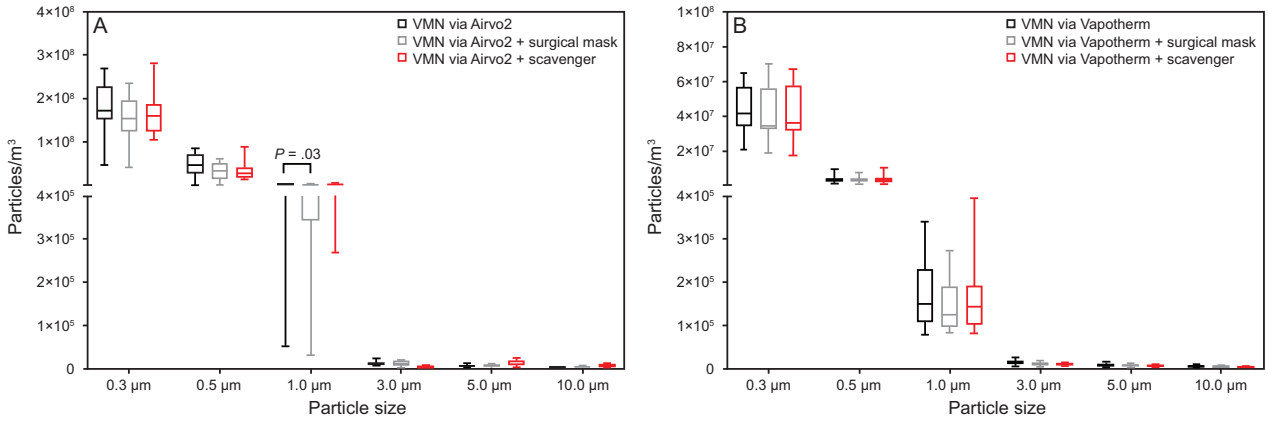

Fig. 7. Fugitive aerosol concentrations of aerosol delivery via HFNC with different interfaces. X axis presents different sizes of aerosol particles; y axis presents the concentrations of aerosol particles (/m^3). When vibrating mesh nebulizer was placed in-line with Airvo 2, wearing a surgical mask over nasal cannula significantly reduced fugitive aerosol concentrations at particle sizes 1.0 µm ($P = .03$) (A), whereas no differences in aerosol concentrations were observed with use of a face tent scavenger. When vibrating mesh nebulizer was placed in-line with Vapotherm, no significant differences of fugitive aerosol concentrations were found among different interfaces (B). VMN = vibrating mesh nebulizer.

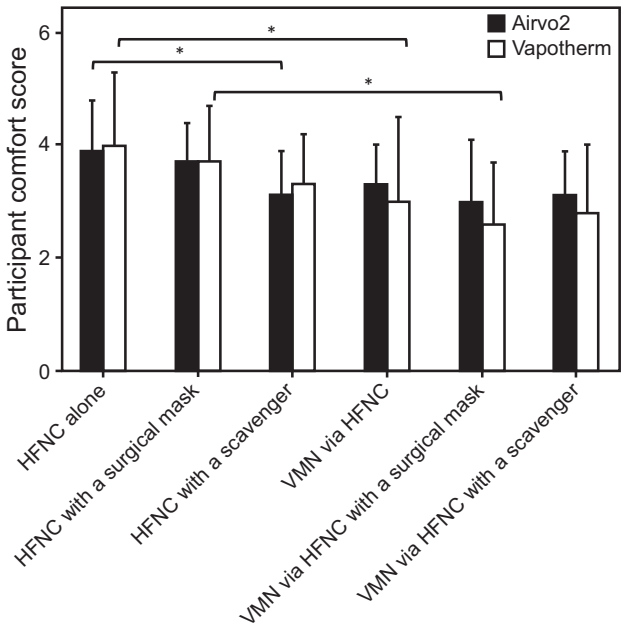

Fig. 8. Participant comfort score with different devices and interfaces. Participants reported similar levels of comfort with Airvo 2 and Vapotherm with or without the use of a surgical mask or a scavenger, except use of Airvo 2 with a scavenger had a lower comfort score than Airvo 2 alone. When vibrating mesh nebulizer was placed in-line with HFNC, the comfort scores were lower than HFNC alone, especially for Vapotherm. With the use of a surgical mask over the nasal cannula, participants reported lower comfort scores for Vapotherm and vibrating mesh nebulizer than Vapotherm alone. HFNC = high-flow nasal cannula. VMN = vibrating mesh nebulizer. * $P < .05$.

simplify the report, the rest of the results only report the particle concentrations at 1 ft from participants. Compared to baseline, aerosol concentrations were no different with use of either HFNC device and were not influenced by placing a surgical mask over the nasal cannula or use of a face tent scavenger (Figure 5A and 5B). When vibrating mesh nebulizer was placed in-line with Airvo 2, fugitive aerosol concentrations were higher than Airvo 2 alone at particle sizes of 0.3–1.0 µm (all $P < .05$) (Figure 6). In contrast, no significant differences were found for Vapotherm with versus without vibrating mesh nebulizer incorporation. Compared to vibrating mesh nebulizer via Vapotherm, use of vibrating mesh nebulizer via Airvo 2 generated higher 0.3–1.0 µm particles (all $P < .05$) (Figure 6). During transnasal aerosol delivery with Airvo 2, aerosol concentrations at particle size of 1.0 µm were significantly reduced when a surgical mask was placed over nasal cannula ($P = .03$) (Figure 7A). On the other hand, use of a face tent scavenger did not influence particle concentrations of any size. No significant differences in aerosol concentrations were found with versus without the use of a surgical mask or a face tent scavenger when vibrating mesh nebulizer was placed in-line with Vapotherm (Figure 7B).

Participants reported similar levels of comfort with Airvo 2 and Vapotherm with or without the use of a surgical mask or a scavenger, except use of Airvo 2 with a scavenger had a lower comfort score than Airvo 2 alone (3.0 [2.5–4.0] vs 4.0 [3.0–5.0]; $P = .038$) (Fig. 8).With vibrating mesh nebulizer placed in-line with HFNC, comfort scores were lower than HFNC alone for both Airvo 2 (3.0 [3.0–4.0] vs 4.0 [3.0–5.0]; $P = .059$) and Vapotherm (3.0 [1.5–4.5] vs 4.0 [3.5–5.0]; $P = .38$), largely attributed to condensation from the nasal cannula. With surgical mask over the nasal cannula, participants reported lower comfort scores for Vapotherm with vibrating mesh nebulizer than Vapotherm alone (3.0 [1.5–3.5] vs 4.0 [3.5–5.0]; $P = .03$) (Fig. 8).

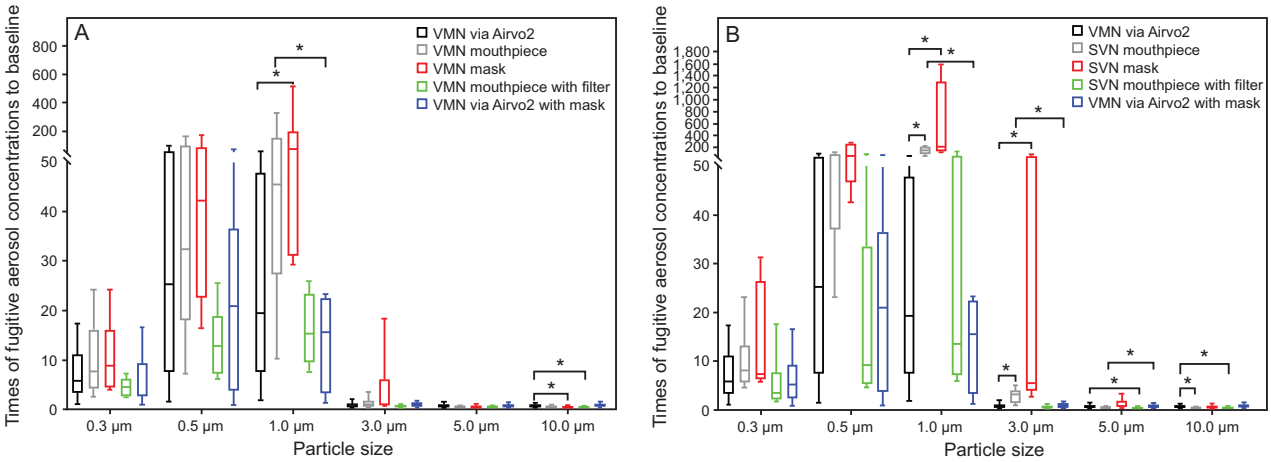

Fig. 9. Fugitive aerosol concentrations of transnasal aerosol delivery versus a nebulizer with a mouthpiece or a face mask. The x axis presents different sizes of aerosol particles, and the y axis presents the times of fugitive aerosol particle concentrations to baseline. Fugitive aerosols generated during the in-line placement of vibrating mesh nebulizer via Airvo 2 were similar to vibrating mesh nebulizer with a mouthpiece or a face mask (A) but lower than SVN with a mouthpiece or a face mask at particles of 1.0–3.0 μm (all $P < .05$) (B). Wearing a surgical mask over nasal cannula during transnasal aerosol delivery reduced the fugitive aerosol concentrations to the level of the use of an expiratory filter with a mouthpiece for vibrating mesh nebulizer (A) and SVN (B). SVN = small-volume nebulizer. VMN = vibrating mesh nebulizer. * $P < .05$.

In Vivo Comparisons of Fugitive Aerosol Concentrations Between Transnasal Aerosol Delivery and Nebulizer With a Mouthpiece or a Face Mask

When comparing transnasal aerosol delivery to conventional nebulizers with mouthpiece/face mask, in-line placement of vibrating mesh nebulizer with Airvo 2 generated lower fugitive aerosol concentrations than vibrating mesh nebulizer with a face mask for 1.0 μm particles ($P = .046$), but the results were similar to those with a vibrating mesh nebulizer and mouthpiece (Figure 9A). Vibrating mesh nebulizer via Airvo 2 generated lower fugitive aerosol concentrations than SVN with a mouthpiece or a face mask at particles of 1.0–3.0 μm (all $P < .05$) (Figure 9B). Placing an expiratory filter with mouthpiece reduced fugitive aerosol concentrations for both vibrating mesh nebulizer and SVN, which were lower than vibrating mesh nebulizer with Airvo 2 for 5.0–10.0 μm particles (all $P < .05$) but similar to the results when wearing a surgical mask over the nasal cannula.

In Vitro Study Evaluating the Inhaled Dose Delivered by Airvo 2 Compared to Vapotherm

The inhaled dose of albuterol was an order of magnitude higher when delivered via Airvo 2 than Vapotherm with HFNC flow of 20 L/min (12.9 ± 0.9 vs 1.3 ± 0.1%, $P = .050$) and > 6 times higher at 40 L/min (5.0 ± 0.2 vs 0.8 ± 0.1%, $P = .050$) (Table 1). The inhaled dose of albuterol was higher at lower HFNC flows for both Airvo2 ($P = .030$) and Vapotherm ($P = .02$).

Table 1. Inhaled Dose of Vibrating Mesh Nebulizer via Vapotherm and Airvo 2 at Different Flow Settings

Flow, L/min	Inhaled Dose (%)		*P*
	Vapotherm	Airvo 2	
20	1.3 ± 0.1	12.9 ± 0.9	.050
40	0.8 ± 0.1	5.0 ± 0.2	.050
60	NA	3.4 ± 0.1	NA

NA = not available (Vapotherm does not operate at 60 L/min).

Discussion

In this study, we found that (1) neither HFNC device when used alone generated higher aerosol concentrations compared to baseline values; (2) fugitive aerosol concentrations were higher when a vibrating mesh nebulizer was placed in-line with Airvo 2; in contrast, no differences in fugitive aerosol concentrations were observed when vibrating mesh nebulizer was used with Vapotherm; (3) during transnasal aerosol delivery via Airvo 2, fugitive aerosol concentrations were similar to vibrating mesh nebulizer with a mouthpiece but lower than vibrating mesh nebulizer and face mask or SVN with mouthpiece/face mask; and (4) placing a surgical mask over nasal cannula reduced fugitive aerosol concentrations, but a similar effect was not seen with use of a face tent scavenger. In the in vitro study, we found a several-fold higher inhaled dose with vibrating mesh nebulizer via Airvo 2 than vibrating mesh nebulizer via Vapotherm, regardless of HFNC flows.

Use of an HFNC alone did not generate higher fugitive aerosol concentrations with either Airvo 2 or Vapotherm. This observation agreed with previous studies that assessed fugitive aerosol concentrations among healthy volunteers during HFNC therapy.[21,22] Similar to the study conducted by Takazono and coworkers,[23] we did not find significant reduction in fugitive aerosol concentrations by wearing a surgical mask over nasal cannula during quiet breathing. In subjects with COVID-19, we previously reported that fugitive aerosol concentrations were reduced after wearing a surgical mask over HFNC.[20] This difference is probably due to the more frequent respiratory AGPs in subjects with COVID-19, such as talking, forced expirations, or coughing, which generate higher fugitive aerosol concentrations compared to healthy volunteers.[23-25]

Placing vibrating mesh nebulizer in-line with Airvo 2 generated higher fugitive aerosol concentrations than vibrating mesh nebulizer via Vapotherm. This might be explained by the results of our in vitro study that found 6–10 times higher inhaled dose with vibrating mesh nebulizer via Airvo 2 than vibrating mesh nebulizer via Vapotherm. Similarly, Perry and colleagues reported little to no inhaled dose delivered with Vapotherm when vibrating mesh nebulizer was placed proximal to the nasal cannula.[26] The lower inhaled dose as well as fugitive aerosol concentrations with Vapotherm might be explained by the design and structure of the Vapotherm device, which generates high velocity gas through a distinctive coaxial design that runs humidified gas between inner and outer lumens of the circuit tubing. The high velocity gas, small size of the humidifier chamber, and circuit lumens trap aerosol in the circuit rather than emitting it through the nasal cannula. Thus, the Vapotherm design does not appear to be ideal for transnasal aerosol delivery.

In our previous study that assessed fugitive aerosol concentrations during nebulization with different interfaces, we found that the face tent scavenger significantly reduced fugitive aerosol concentrations when a face mask was utilized with both SVN and vibrating mesh nebulizer.[27] However, when vibrating mesh nebulizer was placed in-line with Airvo 2 in the current study, we did not find differences of fugitive aerosol concentrations with and without the use of a face tent scavenger, whereas placing a surgical mask over the nasal cannula significantly mitigated fugitive aerosols. This difference might be explained by the anatomic structures of both interfaces and their method of sealing. The surgical mask firmly covers the nose and mouth area and can filter the aerosols leaked from the nasal cannula, whereas the face tent scavenger is manufactured with an open top that may allow aerosol particles to escape, even with the application of negative pressure to continuously suction the exhaled gas. The discrepancy in the effectiveness of the scavenger to reduce fugitive aerosol concentrations between nebulizer with a face mask and nebulizer with HFNC could be explained by the longer distance from the scavenger to the nasal cannula than to the nebulizer face mask.

Our results provide valuable clinical implications for administering aerosol via HFNC in an effective and safe manner. With the exception of our experience with Vapotherm, aerosol delivery via HFNC is an effective and safe route for aerosol delivery, with a lower risk of transmitting infection than a nebulizer with a face mask or a mouthpiece. Aerosol delivery via HFNC is less likely to be contaminated since the nebulizer is placed at the humidifier that is further away from the subject.[28] In addition, we found that fugitive aerosol concentrations with vibrating mesh nebulizer via Airvo 2 were lower than vibrating mesh nebulizer or SVN with a face mask and SVN with a mouthpiece.

Wearing a surgical mask can further reduce the fugitive aerosol concentrations during transnasal aerosol delivery, with levels that are similar to those with use of mouthpiece and exhalation filter. Wearing a surgical mask has additional practical advantages, especially for use with a patient who is coughing. Patients may cough at any time during nebulization, sometimes provoked by aerosolized medication, and it is not realistic to ask them to cough through the mouthpiece or to remove the mouthpiece and wear a surgical mask while coughing. Thus, using HFNC to deliver aerosolized medication and putting a surgical mask over the nasal cannula could be a practical method for aerosol delivery in critically ill patients with respiratory contagious diseases. Of course, clinicians should maintain a distance of 6 ft from patients and wear appropriate personal protective equipment when providing aerosol therapy. Lastly, the number of people inside the patient's room should be minimized during aerosol therapy.

There are some limitations to our study. First, this study was conducted among healthy subjects that have different breathing patterns than the patients who suffer from respiratory diseases. Patients have more tendency to generate productive cough during trans-nasal aerosol delivery that can substantially impact the findings. Thus, further clinical studies on subjects with varying respiratory patterns are warranted to validate our findings. Second, all the experiments were performed and corresponding measurements were recorded in one ICU room at one hospital. Measurements may differ in other hospital rooms depending on the room conditions, such as air exchange frequency and room volume.[25] Third, the fugitive aerosol concentrations were found to be slightly different with flow settings at 30–60 L/min during HFNC therapy,[21,24] and in our in vitro study we found that aerosol delivery decreased with higher HFNC flows.[29] Whereas we only investigated the maximum tolerable flow settings in this study, the effects of various HFNC flows on the fugitive aerosol concentrations during transnasal aerosol delivery need further investigation. Fourth,

we placed the particle counter at 1 ft behind and to the side of the participant, to conveniently stabilize the particle counter; the aerosol concentrations especially the large particles might vary at different position; future studies with more particle counter placements are needed. Lastly, our study used aerosol particle concentrations to indirectly evaluate the bioaerosol transmission risk, and we did not investigate the virus load nor its infectivity.[30]

Conclusions

HFNC alone did not generate higher fugitive aerosol concentrations than baseline for either Airvo 2 or Vapotherm. Compared to HFNC alone, in-line placement of vibrating mesh nebulizer via Airvo 2 produced higher fugitive aerosol concentrations but vibrating mesh nebulizer via Vapotherm did not, consistent with 6–10 times greater inhaled dose with Airvo 2 versus Vapotherm measured in vitro. The fugitive aerosol concentrations with vibrating mesh nebulizer via Airvo 2 were similar to vibrating mesh nebulizer with a mouthpiece but lower than vibrating mesh nebulizer or SVN with a face mask and SVN with a mouthpiece. Placing a surgical mask over nasal cannula during aerosol delivery via HFNC could effectively reduce fugitive aerosol concentrations.

ACKNOWLEDGMENTS

We thank all the volunteers for generously sharing their time to participate in this lengthy study.

REFERENCES

1. Li J, Scott JB, Fink JB, Reed B, Roca O, Dhand R, et al. Optimizing high-flow nasal cannula flow settings in adult hypoxemic patients based on peak inspiratory flow during tidal breathing. Ann Intensive Care 2021;11(1):164.
2. Baldomero AK, Melzer AC, Greer N, Majeski BN, MacDonald R, Linskens EJ, Wilt TJ. Effectiveness and harms of high-flow nasal oxygen for acute respiratory failure: an evidence report for a clinical guideline from the American College of Physicians. Ann Intern Med 2021;174(7):952-966.
3. Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannula for respiratory support in adult intensive care patients. Cochrane Database Syst Rev 2021;3(3):CD010172.
4. Li J, Jing GQ, Scott JB. Year in review 2019: High-flow nasal cannula (HFNC) oxygen therapy for adult patients. Respir Care 2020;65 (4):545-557.
5. Li J, Tu M, Yang L, Jing G, Fink JB, Burtin C, et al. Worldwide clinical practice of high-flow nasal cannula and concomitant aerosol therapy in critical care practice. Respir Care 2021;66(9):1416-1424.
6. Li J, Harnois LJ, Markos B, Roberts KM, Al Homoud S, Liu J, et al. Epoprostenol delivered via high-flow nasal cannula for ICU subjects with severe hypoxemia comorbid with pulmonary hypertension or right heart dysfunction. Pharmaceutics 2019;11(6):281.
7. Li J, Gurnani PK, Roberts KM, Fink JB, Vines D. The clinical impact of flow titration on epoprostenol delivery via high-flow nasal cannula for ICU patients with pulmonary hypertension or right ventricular dysfunction: a retrospective cohort comparison study. JCM 2020;9(2):464.
8. Baudin F, Buisson A, Vanel B, Massenavette B, Pouyau R, Javouhey E. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. Ann Intensive Care 2017;7(1):55.
9. Beuvon C, Coudroy R, Bardin J, Marjanovic N, Rault C, Bironneau V, et al. β agonist delivery by high-flow nasal cannula during COPD exacerbation: A prospective physiological study. Respir Care 2021;67 (1):9-15; Oct 26: respcare. 09242.
10. Li J, Chen Y, Ehrmann S, Wu J, Xie L, Fink JB. Bronchodilator delivery via high-flow nasal cannula: A randomized controlled trial to compare the effects of gas flows. Pharmaceutics 2021;13(10):1655.
11. Li J, Fink JB, MacLoughlin R, Dhand R. A narrative review on transnasal pulmonary aerosol delivery. Crit Care 2020;24(1):506.
12. Judson SD, Munster VJ. Nosocomial transmission of emerging viruses via aerosol-generating medical procedures. Viruses 2019;11 (10):940.
13. Jackson T, Deibert D, Wyatt G, Durand-Moreau Q, Adisesh A, Khunti K, et al. Classification of aerosol-generating procedures: a rapid systematic review. BMJ Open Resp Res 2020;7(1):e000730.
14. Chan VW, Ng HH, Rahman L, Tang A, Tang KP, Mok A, et al. Transmission of severe acute respiratory syndrome coronavirus 1 and severe acute respiratory syndrome coronavirus 2 during aerosol-generating procedures in critical care: A systematic review and meta-analysis of observational studies. Crit Care Med 2021;49(7): 1159-1168.
15. O'Neil CA, Li J, Leavey A, Wang Y, Hink M, Wallace M, et al; Centers for Disease Control and Prevention Epicenters Program. Characterization of aerosols generated during patient care activities. Clin Infect Dis 2017;65(8):1335-1341.
16. Hui DS, Chow BK, Chu LCY, Ng SS, Hall SD, Gin T, et al. Exhaled air and aerosolized droplet dispersion during application of a jet nebulizer. Chest 2009;135(3):648-654.
17. McGrath JA, O'Toole C, Bennett G, Joyce M, Byrne MA, MacLoughlin R. Investigation of fugitive aerosols released into the environment during high-flow therapy. Pharmaceutics 2019;11(6): 254.
18. Sethi S, Barjaktarevic IZ, Tashkin DP. The use of nebulized pharmacotherapies during the COVID-19 pandemic. Ther Adv Respir Dis 2020;14:1753466620954366.
19. Fink JB, Ehrmann S, Li J, Dailey P, McKiernan P, Darquenne C, et al. Reducing aerosol-related risk of transmission in the era of COVID-19: An interim guidance endorsed by the International Society of Aerosols in Medicine. J Aerosol Med Pulm Drug Deliv 2020;33(6):300-304.
20. Li J, Fink JB, Elshafei AA, Stewart LM, Barbian HJ, Mirza SH, et al. Placing a mask on COVID-19 patients during high-flow nasal cannula therapy reduces aerosol particle dispersion. ERJ Open Res 2021;7 (1):00519-2020.
21. Gaeckle NT, Lee J, Park Y, Kreykes G, Evans MD, Hogan Jr CJ. Aerosol generation from the respiratory tract with various modes of oxygen delivery. Am J Respir Crit Care Med 2020;202(8):1115-1124.
22. Bem RA, van Mourik N, Klein-Blommert R, Spijkerman IJ, Kooij S, Bonn D, et al. Risk of aerosol formation during high-flow nasal cannula treatment in critically ill subjects. Respir Care 2021;66(6):891-896.
23. Takazono T, Yamamoto K, Okamoto R, Morimoto S, Izumikawa K, Mukae H. Effects of surgical masks on droplet dispersion under various oxygen delivery modalities. Crit Care 2021;25(1):89.

24. Wilson NM, Marks GB, Eckhardt A, Clarke A, Young F, Garden FL, et al. The effect of respiratory activity, noninvasive respiratory support, and face masks on aerosol generation and its relevance to COVID-19. Anaesthesia 2021;76(11):1465-1474.
25. Dhand R, Li J. Coughs and sneezes: their role in transmission of respiratory viral infections, including SARS-CoV-2. Am J Respir Crit Care Med 2020;202(5):651-659.
26. Perry SA, Kesser KC, Geller DE, Selhorst DM, Rendle JK, Hetrzog JH, et al. Influences of cannula size and flow rate on aerosol drug delivery through the Vapotherm humidified high-flow nasal cannula system. Pediatr Crit Care Med 2013;14(5):e250-6.
27. Harnois L, Alolaiwat A, Jing G, Fink JB, Dhand R, Li J. Efficacy of various mitigation devices in reducing fugitive emissions from nebulizers. Respir Care 2022 [epub ahead of print].
28. Li J, Scott JB. Exploring and creating new evidence in a pandemic plays a crucial role in guiding clinical practice. Respir Care 2021;66 (6):1039-1040.
29. Li J, Gong L, Fink JB. The ratio of nasal cannula gas flow to patient inspiratory flow on transnasal pulmonary aerosol delivery for adults: an in vitro study. Pharmaceutics 2019;11(5):225.
30. Li J, Ehrmann S. High-flow aerosol-dispersing versus aerosol-generating procedures. Am J Respir Crit Care Med 2020;202(8):1069-1071.