Evaluation of aerosol drug delivery with concurrent low- and high-flow nasal oxygen

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Shareable abstract (@ERSpublications)
Concurrent low- and high-flow nasal oxygen cannula used with a mouthpiece and aerosol holding chamber is a safe and effective means of aerosol drug delivery in a spontaneously breathing simulated adult patient model https://bit.ly/3zmV2W1

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Abstract

Question addressed by study Administration of aerosol to patients receiving high-flow nasal oxygen (HFNO) ranges from concurrent aerosol delivery by mouthpiece to aerosol *via* cannula alone. This study examines the conditions to provide optimal aerosol delivery with low- or high-flow nasal oxygen with concurrent mouthpiece or through nasal cannula alone, and the impact on fugitive aerosols.

Materials and methods A vibrating mesh nebuliser delivered salbutamol *via* mouthpiece, aerosol holding chamber and nasal cannula to an adult head model simulating relaxed breathing. The mean±SD inhaled dose (%) was assayed from a filter distal to the trachea. Optical particle sizers were used to measure fugitive aerosol concentrations during aerosol delivery.

Results Concurrent low-flow nasal oxygen (LFNO) and aerosol delivery with a mouthpiece and aerosol holding chamber increased the inhaled dose (%) available, 31.44±1.33% when supplemented with 2 L·min^{-1} of nasal oxygen. Concurrent HFNO above 30 L·min^{-1} resulted in a lower inhaled dose (%) compared to aerosol delivered through HFNO alone. The addition of concurrent LFNO or HFNO resulted in no increase in aerosol levels in the test room.

Answer to question posed Concurrent LFNO with a mouthpiece and aerosol holding chamber is an effective and safe means of aerosol delivery.

Introduction

Supplemental oxygen is a common clinical intervention and often a first line therapy for patients in respiratory distress. Low flow nasal oxygen (LFNO), typically 1–10 L·min^{-1}, provides 24 to 50% inhaled oxygen [1]. High-flow nasal oxygen (HFNO) delivers heated humidified oxygen at flows that meet or exceed patients' inspiratory gas flows up to 60 L·min^{-1} [2, 3]. HFNO can reduce nasopharyngeal resistance, and generate positive pressure in the pharynx, increase alveolar recruitment and reduce arterial carbon dioxide tension (P_{aCO_2}) [4–7].

Transnasal pulmonary aerosol drug delivery *via* HFNO has become an increasingly popular treatment option due to its ease of use and patient tolerability, particularly for extended dosing periods or those that require continuous nebulisation [8]. Critical care physicians vary on the administration of aerosol to patients on HFNO, with 33% interrupting HFNO to administer aerosol, 40% delivered aerosol concurrently with HFNO, most placing nebuliser with face mask over the cannula, and 24% placed the nebuliser within the HFNO circuit [9]. Previous studies have shown that mouthpiece-mediated delivery results in higher levels of aerosol drug delivery compared to either a face mask [10] or nasal cannula [11, 12]. Previous reports suggest that use of an aerosol mask placed over HFNO greatly reduced aerosol delivery compared

to nebuliser with mask alone; however interruption of HFNO can seriously compromise patient oxygenation [13, 14].

There are limited studies of aerosol drug delivery *via* a mouthpiece during both concurrent nasal oxygen delivery (low or high flow) at clinically relevant flow rates. Bennett *et al.* measured aerosol drug delivery with a vibrating mesh nebuliser *via* an aerosol chamber and both a mouthpiece and face mask with concurrent HFNO at 50 $L \cdot min^{-1}$, and supplemental oxygen flow rates through the aerosol chamber of 0, 2 and 6 $L \cdot min^{-1}$ [14]. The authors reported a higher deposition with the mouthpiece than mask at 2 $L \cdot min^{-1}$.

An unintended consequence of aerosol therapy is distribution of fugitive aerosols, whether generated by an infected patient or the aerosol device, presenting serious health implications for caregivers, other patients and bystanders [15, 16]. Previous studies have reported healthcare workers experiencing airway irritation and skin rashes after treating patients with aerosolised pentamidine, liposomal cisplatin, S&R isomers of albuterol and ribavirin [17–19].

In a study examining the potential secondary inhalation of fugitive medical aerosols from different aerosol delivery interfaces, McGrath *et al*. found that caregivers could potentially inhale up to 8.5% of the nominal drug during HFNO and that the use of jet nebulisers in conjunction with unfiltered mouthpieces and valved face masks generated significant levels of fugitive aerosols [20, 21]. However, little is known about the potential release of fugitive medical aerosols during LFNO, or during mouthpiece-mediated aerosol delivery with concurrent high- or low-flow oxygen.

The hypothesis under investigation is that concurrent aerosol administration with low- and high-flow oxygen could result in greater aerosol delivery than aerosol administration *via* cannula. Furthermore, as oxygen gas flow rates increase, there is an increase in fugitive aerosols released into the environment.

Materials and methods

Aerosol delivery

A vibrating mesh nebuliser (VMN) (Aerogen Solo; Aerogen Ltd., Galway, Ireland) was used with an emitted droplet size of 4.02±0.01 µm and aerosol output rate of 0.45±0.00 $mL \cdot min^{-1}$, as determined by laser diffraction (Spraytec; Malvern Instruments, Malvern, UK) [22].

Experimental set up

Both gas and aerosol *via* HFNO and LFNO were delivered through a nasal cannula placed in the nares of an anatomically correct 3D printed adult head model, detailed by Gallagher *et al*. 2021 [11]. Concurrent aerosol was administered *via* a mouthpiece with a valved aerosol holding chamber (Aerogen Ultra; Aerogen Ltd.) and VMN. The chamber was attached to supplemental gas flow at rates of 0, 2 and 6 $L \cdot min^{-1}$ per manufacturer's instructions for use. The head model was connected distal to the trachea *via* a capture filter (RespirGard-II 303EU; Vyaire, Mettawa, USA) to a breathing simulator (ASL5000; IngMar Medical, Pittsburgh, USA). A simulated normal adult breathing pattern was used (tidal volume 500 mL, respiratory rate 15 breaths$\cdot min^{-1}$ and I:E ratio 1:1) [23]. 2000 µg salbutamol (Ventolin 2.5 mg/2.5 mL; GlaxoSmithKline Ltd., Dublin, Ireland) was nebulised (figure 1). The mass of drug captured on the filter, placed distal to the trachea of the head model, was quantified using ultraviolet spectrophotometry at a wavelength of 276 nm and interpolation using a standard curve of salbutamol concentrations ranging from 100 to 3.125 $\mu g \cdot mL^{-1}$.

HFNO circuit

The Airvo2 high-flow humidification system was used in combination with an adult nasal cannula (OPT +944; F&P, Auckland, New Zealand) and an adult breathing circuit (900PT552; F&P) to deliver gas flow rates of 10, 30, 50 and 60 $L \cdot min^{-1}$. For aerosol administration, the VMN was placed with the adapter on the wet side of the humidifier.

LFNO circuit

An adult breathing circuit (RT380, F&P, NZ) in combination with adult nasal cannula (Hudson RCI Comfort Flo; Teleflex Medical, Wayne, PA, USA) was tested at gas flow rates of 2, 3.5, 5, 7.5 and 10 $L \cdot min^{-1}$. The nebuliser was placed on the dry side of the humidifier set to 34°C.

Fugitive aerosol characterisation

Two optical particle sizers (OPS) (OPS 3300; TSI Inc., Shoreview, MN, USA) were used to characterise the fugitive aerosol levels, in the range 0.3–10 µm in diameter, and were positioned 0.8 m and 2.2 m from

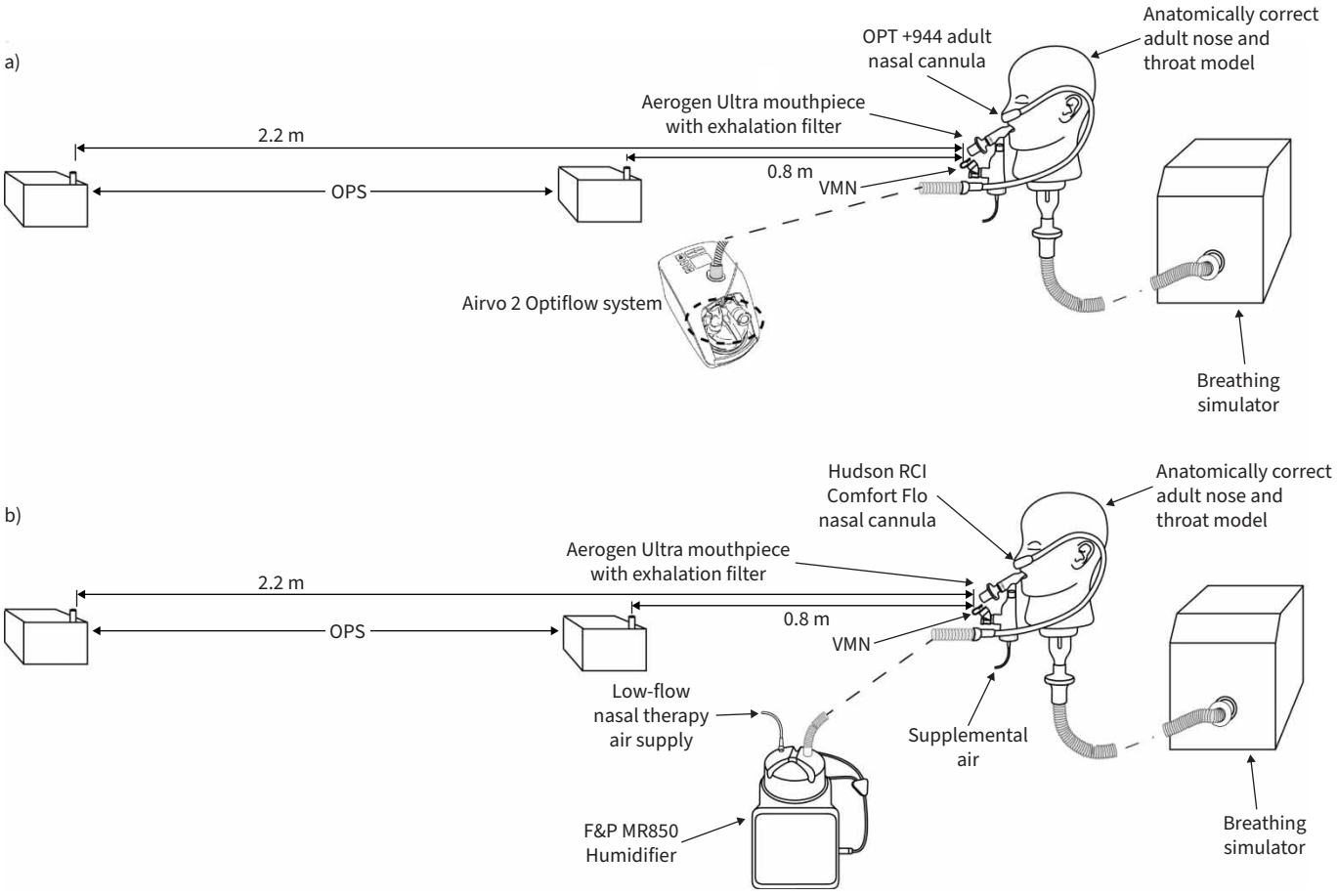

FIGURE 1 Schematic illustration of the experimental test facilities that were used to measure aerosol delivery (%) and fugitive medical aerosol emissions from aerosol therapy delivery using a mouthpiece and holding chamber with concurrent a) high-flow nasal oxygen and b) low-flow nasal oxygen. VMN: vibrating mesh nebuliser; OPS: optical particle sizer.

the exhalation port of the mouthpiece [24, 25]. These measurement positions were chosen as they are clinically relevant and have been used in multiple studies of this nature [21]. Tests were 20 min in duration, at a sampling rate of 10-s intervals. Each test began with a 5-min period where ambient conditions within the test room were established pre-nebulisation. The remaining 15 min were sufficient for dose nebulisation and period of decay post nebulisation.

Testing was performed at the lowest and highest supplemental air flow rates used in the aerosol delivery part of the study (table 1) to represent the maximum and minimum levels of fugitive aerosol in the test room (6.85×3.42×2.50 m, with a volume of 58.57 m^3). Ventilation was powered off for all testing. A single operator was positioned behind the breathing simulator so as not to affect the distribution of the fugitive aerosols. The air change rate was determined using the tracer CO_2 gas decay method [26].

TABLE 1 Fugitive aerosol characterisation test details

	Supplemental air flow rate in aerosol chamber			
	0 L·min^{-1}		6 L·min^{-1}	
LFNO circuit	2	10	2	10
HFNO circuit	10	60	10	60

LFNO: low-flow nasal oxygen; HFNO: high-flow nasal oxygen.

An indoor air quality probe (Direct Sense II multi-sensor probe; GrayWolf Sensing Solutions, Shelton, CT, USA) was used to measure the CO_2 levels. The air exchange rate was calculated to be ~1.92 h^{-1}.

Statistical analysis

Results are expressed as a percentage of the salbutamol dose (mean±SD) placed in the VMN medication cup and recovered from the capture filter. One-way ANOVAs were completed to assess the statistical significance ($p \leqslant 0.05$) in the inhaled dose delivered across the aerosol delivery methods. All aerosol performance testing was completed five times independently (n=5). For the fugitive emissions study, the results are expressed as the mean±SD of aerosol concentrations (in $\mu g \cdot m^{-3}$) measured over the 20-min test duration. All fugitive emissions testing was completed in triplicate.

Results

Low-flow nasal oxygen

The percentages of inhaled dose delivered distal to the trachea (mean±SD) during LFNO are presented in figure 2a (and supplementary table S1). Irrespective of flow rate, aerosol therapy delivered using the mouthpiece and aerosol holding chamber concurrent to LFNO delivered two to four times more aerosol ($p<0.001$ at all flow rates considered). As gas flow rates increased, the levels of delivered aerosol decreased. Concurrent mouthpiece-delivered aerosol in conjunction with the aerosol holding chamber and 2 $L \cdot min^{-1}$ of supplemental air resulted in the greatest inhaled dose of aerosol, with a maximum of 31.44±1.33%.

High-flow nasal oxygen

The percentages of inhaled dose delivered distal to the trachea (mean±SD) during HFNO are presented in figure 2b (and supplementary table 2). The method used to administer aerosol therapy has a statistically significant impact on the inhaled dose of aerosol (%) available to the simulated patient ($p \leqslant 0.05$). Similar to LFNO, as the gas flow rate increased, the aerosol available at the level of the trachea decreased. However, HFNO and concurrent aerosol therapy delivered with the mouthpiece and holding chamber did not outperform aerosol delivery with the nebuliser within the circuit at higher flows. Across all the different gas flow rates and aerosol delivery options considered in this part of the study, the mouthpiece delivered aerosol in conjunction with the aerosol holding chamber and 0 $L \cdot min^{-1}$ of supplemental air delivered the lowest levels of aerosol across all concurrent high flow rates: 4.27±0.90 and 0.47±0.04% respectively. The greatest quantities of aerosol were delivered using this delivery option with 6 $L \cdot min^{-1}$ of supplemental air, resulting in 24.29±0.39% delivered with 10 $L \cdot min^{-1}$ of concurrent nasal oxygen (Note: 10 $L \cdot min^{-1}$ is not high flow by clinical definition).

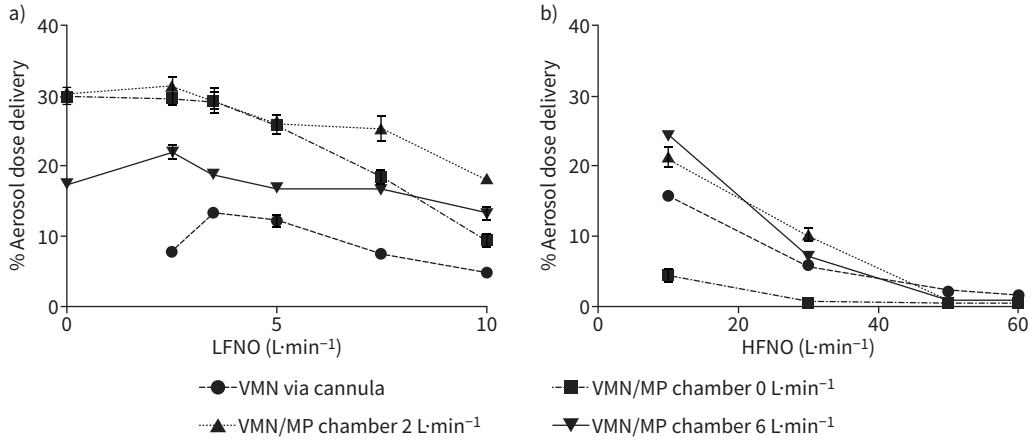

FIGURE 2 a) Aerosol drug delivery from a vibrating mesh nebuliser (VMN) at dry side of humidifier via cannula, and with aerosol holding chamber at 0, 2 and 6 $L \cdot min^{-1}$ during low-flow nasal oxygen (LFNO) at 0, 2, 3.5, 5, 7.5 and 10 $L \cdot min^{-1}$; and b) inhaled aerosol delivery efficiency (mean±SD %) at trachea from VMN at adapter and aerosol holding chamber at 0, 2 and 6 $L \cdot min^{-1}$ in model of spontaneously breathing adult patient with high-flow nasal oxygen (HFNO) gas flow of 10, 30, 50 and 60 $L \cdot min^{-1}$. MP: mouthpiece.

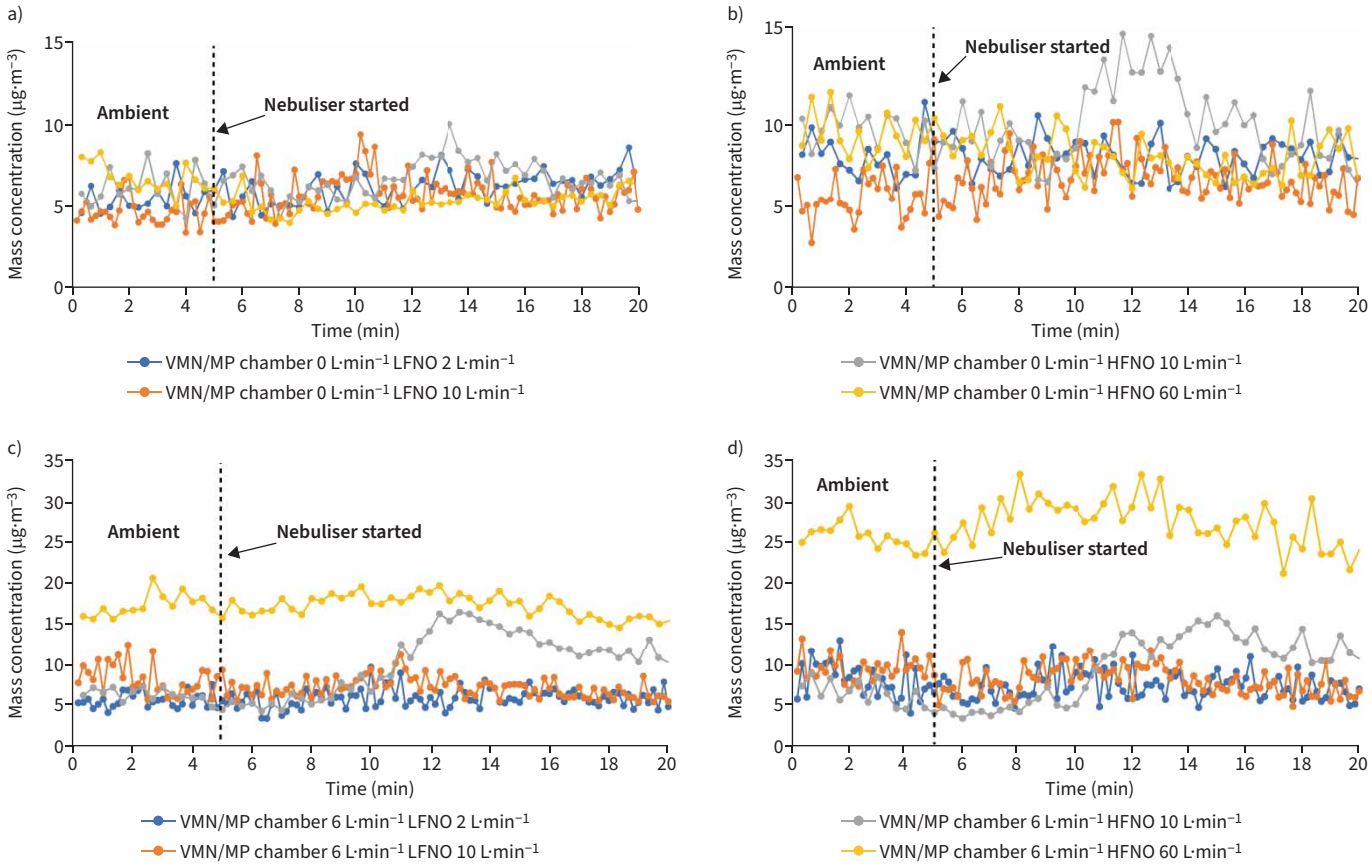

FIGURE 3 Mean aerosol concentrations against time measured at a) 0.8 m and b) 2.20 m with 0 L·min^{-1} supplemental air flow through the aerosol holding chamber and c) 0.8 m and d) 2.20 m with 6 L·min^{-1} supplemental air flow through the aerosol holding chamber. VMN: vibrating mesh nebuliser; MP: mouthpiece; LFNO: low-flow nasal oxygen; HFNO: high-flow nasal oxygen.

Fugitive aerosol levels

Prior to nebulisation, ambient aerosol concentration levels within the test room were 8.83±5.50 µg·m^{-3}. Figure 3a–d show the mean aerosol concentration levels measured over the course of the entire 20-min test duration for the different flow conditions. The plots compare the fugitive medical aerosol concentrations at two clinically relevant distances, 0.8 m (figure 3a and c) and 2.20 m (figure 3b and d), from the end of the filtered mouthpiece and with 0 L·min^{-1} (figure 3a and b) and 6 L·min^{-1} (figure 3c and d) supplemental air flow through the aerosol holding chamber. Peak emissions occurred when the aerosol delivery was supplemented with 10 L·min^{-1} HFNO and at 2.20 m from the end of the mouthpiece, 5.75±2.32 µg·m^{-3} and 18.16±5.50 µg·m^{-3} above ambient at 0 and 6 L·min^{-1} air flow through the aerosol holding chamber. There was no recorded increase in aerosol concentration when aerosol delivery was supplemented with LFNO.

Inhalation exposure

The relative quantity of the original drug that could potentially be inhaled by a caregiver and a bystander or patient in an adjacent bed was calculated. The supplemental air flow and circuit flow conditions that generated the highest levels of fugitive emissions was selected. The highest levels of emissions were measured when 6 L·min^{-1} of supplemental air was used with the aerosol holding chamber supplemented with 10 L·min^{-1} of flow through the HFNO circuit. The 5-min baseline mean ambient aerosol concentration was subtracted from the time-series data to focus solely on the fugitive medical aerosol emissions. The following assumptions were made: short-term exposure to the fugitive medical aerosols, light activity levels for the caregiver and a sedentary activity level for the bystander. Both the caregiver and bystander were in the 41–51 years age range. As such, the inhalation rates were determined to be: 1.3×10^{-2} m^3·min^{-1} and 4.8×10^{-3} m^3·min^{-1} [27]. Using these assumptions, in the worst-case scenario a caregiver would be exposed to 1.61×10^{-3} mg (0.116%) of the original dose, while a bystander or patient in an adjacent bed would be exposed to 6.69×10^{-4} mg (0.067%) of the original dose.

Discussion

This is the first study comparing aerosol delivery *via* LFNO and HFNO to concurrent aerosol therapy delivered with a mouthpiece and aerosol holding chamber, quantifying the effects of these aerosol therapy techniques on the release of fugitive medical aerosols. We found that a combination of LFNO with concurrent aerosol therapy delivered with a mouthpiece and holding chamber is more effective than administration *via* standard LFNO in delivering aerosol. However, aerosol *via* HFNO alone is more effective than a concurrent therapy at higher flows. The addition of supplemental oxygen in the mouthpiece/chamber resulted in marginal increases in fugitive aerosol levels above ambient.

Numerous studies have examined the delivery of aerosol through a nasal cannula during low and high flows. Our findings are in agreement with these studies [28–31], in that aerosol delivery *via* a nasal cannula decreases as gas flow rate increases, from 7.72±0.23% to 4.72±0.37% as the flow rate increased from 2 to 10 $L \cdot min^{-1}$ during LFNO and 15.72±0.02% to 1.37±0.18% as the flow rate increased from 10 to 60 $L \cdot min^{-1}$ during HFNO.

To the best of the authors knowledge there are no studies which have examined this concurrent approach of mouthpiece and valved holding chamber delivery with LFNO. A greater inhaled dose (%) was measured when the aerosol chamber was supplemented ($p \leqslant 0.05$). As the supplemental flow rate through the aerosol holding chamber increased, the inhaled dose (%) available increased. However, above a supplemental gas flow rate of 2 $L \cdot min^{-1}$, the inhaled dose (%) available decreased. This finding was consistent across all concurrent LFNO rates examined in this study. This reduction in aerosol delivery with higher supplemental flow may be due to the flushing of aerosol through the 103 mL holding chamber at 6 $L \cdot min^{-1}$ (100 $mL \cdot s^{-1}$) and out the exhalation valve, reducing the aerosol collected between inspirations.

MacDonnacha *et al.* conducted an exploratory investigation into this concurrent aerosol delivery approach [32]. Similar to the data presented in the present work, the authors found that high gas flow rates through the nasal cannula resulted in almost no aerosol delivery when used in combination with the mouthpiece and aerosol chamber, 0.53±0.56% to 1.27±0.63% at a maximum flow rate of 45 $L \cdot min^{-1}$ compared to 0.47±0.04% to 0.77±0.22% at 60 L min^{-1} in the present work. Furthermore, in both studies, increases in supplemental gas flow from 0 to 2 L min^{-1} through the aerosol chamber resulted in greater quantities of aerosol delivered, which was also observed in the LFNO part of this study.

There are several factors that influence the release and dispersion of fugitive aerosols including, but not limited to, delivery interface, patient type, room layout and dimensions, and ventilation [33, 34]. While this study did show an increase in the aerosol concentration levels above ambient, the increases were limited: 5.75±2.32 $\mu g \cdot m^{-3}$ and 18.16±5.50 $\mu g \cdot m^{-3}$ above ambient levels. At the time of this study, there were no data identified in the literature that measured fugitive aerosol levels from mouthpiece-mediated aerosol delivery with concurrent HFNO or LFNO. As such, no direct comparison can be made with data collected in this study.

However, there are a limited number of studies that have directly measured the fugitive aerosol concentration levels during HFNO. McGrath *et al.* measured the peak fugitive aerosol concentration above ambient during HFNO of between 10 and 60 $L \cdot min^{-1}$ [20]. Similar to the present study, the authors found that fugitive aerosol levels peaked at the lower delivery rate of 10 L min^{-1}, 0.636±0.067 $mg \cdot m^{-3}$ compared to 0.090±0.004 $mg \cdot m^{-3}$ at 60 $L \cdot min^{-1}$. These peaks at the lower flow rate correspond with a higher inhaled dose.

According to the findings of this study, a caregiver (0.8 m away) would be potentially exposed to 1.61×10^{-3} mg (0.116%) of the original nebulised dose, while a bystander or patient in the next bed (2.2 m away) would potentially be exposed to 6.69×10^{-4} mg (0.067%) of the original dose. Frank *et al.* derived occupation exposure limits for albuterol, ipratropium and budesonide, three commonly prescribed therapeutics used in the treatment of respiratory illnesses [19]. The levels were: 2 $\mu g \cdot day^{-1}$ (albuterol), 30 $\mu g \cdot day^{-1}$ (ipratropium) and 11 $\mu g \cdot day^{-1}$ (budesonide) respectively. These levels are low considering a patient can be prescribed up to 10 $mg \cdot day^{-1}$ albuterol, 1 $mg \cdot day^{-1}$ ipratropium and 2 $mg \cdot day^{-1}$ budesonide. The data from this study show that the combination of mouthpiece mediated aerosol delivery with concurrent HFNO or LFNO would present the lowest risk of secondary exposure of caregivers.

There are a number of limitations to this study. First, its *in vitro* nature constitutes one of its main limitations. Collection of aerosol on a filter distal to the trachea represents the aerosol entering the lungs but does not allow for the small proportion of exhaled aerosol observed *in vivo*, consequently overestimating lung delivery *in vivo*, but serving as an accepted method to compare the effects of different

conditions. It has been found that representative head model choice can significantly affect aerosol delivery [11]; thus, future studies are required to investigate how this combinational approach to aerosol therapy would affect aerosol deposition *in vivo* with, for example, scintigraphy studies. Supplemental oxygen is often used to deliver therapeutics to patients with exacerbations of COPD or asthma. As such the breathing patterns may be different from that examined in the present study, particularly the I:E ratio. The room airflow was switched off during the experiments to determine the greatest dispersion of fugitive aerosols without the interference of external airflow. Work is needed to assess the potential risks with room air exchange rates more representative of the clinical setting.

Conclusions

This study examined the potential effect on aerosol delivery from a mouthpiece and aerosol holding chamber when concurrently administered with LFNO and HFNO. During simulated healthy adult breathing, concurrent aerosol *via* mouthpiece and aerosol holding chamber with LFNO increases aerosol delivery, with the greatest benefit at $2\ L{\cdot}min^{-1}$. The addition of concurrent aerosol with HFNO above $30\ L{\cdot}min^{-1}$ resulted in a lower inhaled dose (%) compared to aerosol therapy administered through high-flow nasal cannula alone. The addition of concurrent LFNO or HFNO with aerosol resulted in a minor increase in aerosol levels presenting a low inhalation exposure risk to caregivers.

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References

1 Singh V, Khatana S, Gupta P, *et al.* Supplemental oxygen therapy: important considerations in oral and maxillofacial surgery. *Natl J Maxillofac Surg* 2011; 2: 10–14.
2 Golshahi L, Worth Longest P, Azimi M, *et al.* Intermittent aerosol delivery to the lungs during high-flow nasal cannula therapy. *Respir Care* 2014; 59: 1476–1486.
3 Rochwerg B, Einav S, Chaudhuri D, *et al.* The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med* 2020; 46: 2226–2237.
4 Réminiac F, Vecellio L, Heuzé-Vourc'h N, *et al.* Aerosol therapy in adults receiving high flow nasal cannula oxygen therapy. *J Aerosol Med Pulm Drug Deliv* 2016; 29: 134–141.
5 Hess DR. Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. *Respir Care* 2015; 60: 880–891.
6 Li J, Chen Y, Ehrmann S, *et al.* Bronchodilator delivery via high-flow nasal cannula: a randomized controlled trial to compare the effects of gas flows. *Pharmaceutics* 2021; 13: 1655.
7 Zhang J, Lin L, Pan K, *et al.* High-flow nasal cannula therapy for adult patients. *J Int Med Res* 2016; 44: 1200–1211.
8 Bennett G, Joyce M, Sweeney L, *et al.* In vitro study of the effect of breathing pattern on aerosol delivery during high-flow nasal therapy. *Pulm Ther Springer Healthcare* 2019; 5: 43–54.
9 Li J, Tu M, Yang L, *et al.* Worldwide clinical practice of high-flow nasal cannula and concomitant aerosol therapy in the adult ICU setting. *Respir Care* 2021; 66: 1416–1424.
10 Ari A, DeAndre A, Sheard M, *et al.* Performance comparisons of jet and mesh nebulizers using different interfaces in simulated spontaneously breathing adults and children. *J Aerosol Med Pulm Drug Deliv* 2015; 28: 281–289.
11 Gallagher L, Joyce M, Murphy B, *et al.* The impact of head model choice on the in vitro evaluation of aerosol drug delivery. *Pharmaceutics* 2022; 14: 24.
12 Fernández Fernández E, Joyce M, O'Sullivan A, *et al.* Evaluation of aerosol therapy during the escalation of care in a model of adult cystic fibrosis. *Antibiotics* 2021; 10: 472.
13 Réminiac F, Vecellio L, Loughlin RM, *et al.* Nasal high flow nebulization in infants and toddlers: an in vitro and in vivo scintigraphic study. *Pediatr Pulmonol* 2017; 52: 337–344.
14 Bennett G, Joyce M, Fernández EF, *et al.* Comparison of aerosol delivery across combinations of drug delivery interfaces with and without concurrent high-flow nasal therapy. *Intensive Care Med Exp* 2019; 7: 20.
15 Mirabelli MC, Zock JP, Plana E, *et al.* Occupational risk factors for asthma among nurses and related healthcare professionals in an international study. *Occup Environ Med* 2007; 64: 474–479.
16 White GE, Mazurek JM, Moorman JE. Asthma in health care workers: 2008 and 2010 behavioral risk factor surveillance system asthma call back survey. *J Occup Env Med* 2013; 55: 1463–1468.
17 Beach JR, Campbell M, Andrews DJ. Exposure of health care workers to pentamidine isethionate. *Occup Med* 1999; 49: 243–245.

18 Tsai RJ, Boiano JM, Steege AL, *et al.* Precautionary practices of respiratory therapists and other health-care practitioners who administer aerosolized medications. *Respir Care* 2015; 60: 1410–1417.

19 Frank E, Ishau S, Maier A, *et al.* An occupational exposure limit (OEL) approach to protect home healthcare workers exposed to common nebulized drugs. *Regul Toxicol Pharmacol* 2019; 106: 251–261.

20 McGrath JA, O'Toole C, Bennett G, *et al.* Investigation of fugitive aerosols released into the environment during high-flow therapy. *Pharmaceutics* 2019; 11: 254.

21 McGrath JA, O'Sullivan A, Bennett G, *et al.* Investigation of the quantity of exhaled aerosols released into the environment during nebulisation. *Pharmaceutics* 2019; 11: 75.

22 Hibbitts A, O'Mahony AM, Forde E, *et al.* Early-stage development of novel cyclodextrin-siRNA nanocomplexes allows for successful postnebulization transfection of bronchial epithelial cells. *J Aerosol Med Pulm Drug Deliv* 2014; 27: 466–477.

23 ISO. ISO 27427:2013: Anaesthetic and respiratory equipment — Nebulizing systems and components. Available at: https://www.iso.org/standard/59482.html Date last accessed: 9 May 2022.

24 Joyce M, McGrath JA, Mac Giolla Eain M, *et al.* Nebuliser type influences both patient-derived bioaerosol emissions and ventilation parameters during mechanical ventilation. *Pharmaceutics* 2021; 13: 199.

25 Mac Giolla Eain M, Cahill R, MacLoughlin R, *et al.* Aerosol release, distribution, and prevention during aerosol therapy: a simulated model for infection control. *Drug Deliv* 2022; 29: 10–17.

26 Sherman M. Simplified modeling for infiltration and radon entry. Thermal Performance of the Exterior Envelopes of Buildings Conference, Clearwater Beach, Florida, USA; 1992.

27 US Environmental Protection Agency. Exposure Factors Handbook: 2011 Edition. Washington, DC, US Environmental Protection Agency, 2011.

28 Li J, Gong L, Fink JB. The ratio of nasal cannula gas flow to patient inspiratory flow on trans-nasal pulmonary aerosol delivery for adults: an in vitro study. *Pharmaceutics* 2019; 11: 225.

29 Perry SA, Kesser KC, Geller DE, *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: e250–e256.

30 Dailey PA, Harwood R, Walsh K, *et al.* Aerosol delivery trough adult high flow nasal cannula with heliox and oxygen. *Respir Care* 2017; 69: 1186–1192.

31 Bhashyam AR, Wolf MT, Marcinkowski AL, *et al.* Aerosol delivery through nasal cannulas: an in vitro study. *J Aerosol Med Pulm Drug Deliv* 2008; 21: 181–188.

32 MacDonnacha I, Bennett G, Murphy S, *et al.* Assessment of the feasibility of mouthpiece-mediated aerosol delivery during high flow nasal therapy. *Drug Deliv to Lungs* 2017; 20: Suppl. 2, 94.

33 Long CM, Suh HH, Catalano PJ, *et al.* Using time- and size-resolved particulate data to quantify indoor penetration and deposition behavior. *Environ Sci Technol* 2001; 35: 2089–2099.

34 Ciuzas D, Prasauskas T, Krugly E, *et al.* Characterisation of indoor aerosol temporal variations for the real-time management of indoor air quality. *Atmos Environ* 2015; 118: 107–117.