Inhaled Bronchodilator Delivery via High-Flow Nasal Cannula for COPD and Asthma Patients: A Randomized Controlled Trial to Compare the Bronchodilation Effects of Gas Flow Rates

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Abstract

Background

Aerosol delivery via high-flow nasal cannula (HFNC) has attracted increasing clinician interest. In vitro studies report that the ratio of HFNC gas flow to patient inspiratory flow (GF:IF) is a key factor in the efficiency of trans-nasal aerosol delivery. This randomized controlled trial was aimed to validate this finding, and to explore the effective dose of inhaled bronchodilator to be given to patients via HFNC.

Methods

Patients with a history of COPD or asthma and documented positive response to inhaled bronchodilators in an outpatient pulmonary function laboratory were recruited. Subjects were randomized to receive inhalation at gas flow ratio/settings of : GF:IF=0.5, GF:IF=1.0, or GF=50L/min. Patients were assigned to inhale saline (control) followed by salbutamol via HFNC with an escalating dose sequence (0.5mg, 1.0mg, 2.0mg and 4.0mg). Spirometry was performed at baseline and after each inhalation.

Results

Seventy-five subjects (49 asthma and 26 COPD) demonstrating bronchodilator response (ATS/ERS) were enrolled. Using the criteria of post-bronchodilator FEV₁ returning to screening post-bronchodilator FEV₁ with salbutamol, a higher percentage of subjects receiving GF:IF=0.5 met criteria at cumulative dose of 1.5mg, than those receiving GF:IF=1.0, and GF=50L/min (64% vs 29% vs 27%, respectively, p=0.011). Similarly at 3.5mg (88% vs 54% vs 46%, respectively, p=0.005). The effective dose at GF:IF=0.5 was 1.5mg while for GF=50 L/min it was 3.5mg.

Conclusion

Dose response to salbutamol via HFNC was greater when administered with gas flow set at 50% of patient inspiratory flow, than with higher gas flow rates.

Trial registration: www.clinicaltrials.gov: NCT03739359. Registered 13 November 2018, https://clinicaltrials.gov/ct2/show/NCT03739359?term=03739359&draw=2&rank=1

Introduction

High-flow nasal cannula (HFNC) has gained increasing interest from clinicians due to evidence of improving oxygenation and avoiding intubation for patients with hypoxemic respiratory failure,¹,² (including patients with COVID-19),³ and reducing reintubation rate for patients with high-risk factors of extubation failure compared to conventional oxygen therapy.⁴,⁵ This is attributed to gas flow that meets or exceeds patient's inspiratory flow, resulting in a constant fraction of inspired oxygen (FİO₂) and some
amount of positive airway pressure. Moreover, the high gas flow washing out the dead space, work of breathing may decrease and carbon dioxide clearance may increase, thus the utilization of HFNC has been expanded to patients with hypercapnic respiratory failure, including the use for acute exacerbation of chronic obstructive pulmonary disease (COPD), for facilitating weaning from invasive ventilation, and for improving life quality with domiciliary long-term use.

More recently HFNC has been utilized as a vehicle to administer inhaled medication to the lower airways. Due to the comfort of the nasal cannula interface with heated humidity, HFNC seems to be better tolerated by small children who are sensitive to gas temperature and noise and resist the use of masks, as well as patients who need to inhale aerosolized medication for extended periods of time, such as inhaled bronchodilators for severe asthmatics or inhaled prostacyclin for patients with pulmonary hypertension and/or refractory hypoxemia. In the COVID-19 pandemic, this delivery route has become more popular, as patients can wear surgical mask over the nasal cannula to reduce the dispersion of fugitive aerosol particles into the surrounding environment, resulting in lower opportunities of virus transmission.

Compared to more traditional aerosol delivery with nebulizer via mouthpiece or face mask, trans-nasal aerosol delivery via HFNC at flow settings of 30–35 L/min (for adult patients) has been reported to achieve similar efficacy in both in vitro and in vivo studies. We reported an in vitro study in which the ratio of HFNC gas flow to patient inspiratory flow (GF:IF) was found to play a key role in the trans-nasal aerosol delivery that the inhaled dose distal to the trachea increased as the ratio decreased, with efficiency peaking at HFNC gas flow settings around 50% of patient inspiratory flow (GF:IF = 0.5). In vitro, the inhaled dose with GF:IF = 0.5 was observed to be 2–4 times higher than that with gas flow set at equal to or higher than the patient inspiratory flow. This finding raises the questions of how nominal doses loaded in the nebulizer might be adjusted to elicit patient response to aerosol bronchodilators administered with different gas flow settings.

To confirm our hypothesis that GF:IF ratio impacts the dose of inhaled bronchodilator required to elicit a clinically relevant response, we conducted a randomized controlled trial to investigate the effects of delivered and inspired flows on bronchodilator delivery via HFNC for patients with COPD or asthma, and to explore the minimal dose that is required to generate effective response at those flow settings.

### Methods

This study was approved by the ethic committees of People's Liberation Army General Hospital, Beijing, China (approval No.S2018-200-02) and Rush University, Chicago, IL (approval No.19041201-IRB01). It was registered with ClinicalTrials.gov (NCT03739359). The study protocol was also published.
Stable patients with COPD or asthma with positive results in the standard bronchodilator test per ATS/ERS standards were recruited at an outpatient pulmonary function test (PFT) laboratory in People's Liberation Army General Hospital. Positive response for the bronchodilator test was defined as a forced expiratory volume at the first second (FEV₁) increased by ≥ 12% with absolute change of ≥ 200 mL from baseline, after inhaling 400mcg salbutamol (Ventolin, GSK, UK) from a metered dose inhaler (MDI) with a valved holding chamber (VHC, OptiChamber Diamond, Philips, USA).

Subjects were excluded if meeting any of the following criteria: 1) age ≥ 90 years; 2) pregnancy; 3) pulmonary exacerbation within two weeks before enrollment; 4) lack of informed consent; 5) inability to complete the follow-up spirometry after each bronchodilator inhalation; 6) resting heart rate > 100 bpm; 7) resting systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg.

Study procedures

Following qualifying screening spirometry, after a minimum of 24 hour wash out period, subjects returned to PFT laboratory to participate in the study. After consent form was signed, subjects were randomized to three HFNC gas flow rates (50L/min, GF:IF = 1.0, and GF:IF = 0.5) to inhale saline followed by doubling doses of salbutamol. The randomization was stratified by disease (COPD or asthma) with a block size of 6 to ensure the number of subjects with COPD and asthma in the three groups was comparable. Two series of sequentially numbered, sealed, opaque envelopes containing the treatment assignment were prepared. When eligibility criteria were met, the investigator opened the envelope and set the assigned gas flow for subject. PFT technician who performed spirometry tests was blinded for the randomization.

Peak inspiratory flow was measured during quiet breathing prior to forced vital capacity test during baseline spirometry, then subjects were instructed to inhale saline (2 mL) followed by salbutamol at an escalating doubling dose sequence (0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg diluted in a constant 2 mL volume) via a vibrating mesh nebulizer (VMN, Aerogen Solo, Aerogen Ltd., Ireland), which was placed at the inlet of the humidifier chamber (MR850, Fisher & Paykel Healthcare, Auckland, New Zealand) of the HFNC circuit (Fisher & Paykel Healthcare). The assigned gas flow settings were confirmed by a mass flowmeter (TSI 4040, Shoreview, MN). HFNC was removed after nebulization was completed. After 10–12 min rest, subjects repeated the forced vital capacity test. Inhalation was terminated if adverse events including tachycardia, tremor, irregular heart rhythm, blood pressure increase > 20% or headache were observed or reported.

Outcomes

The primary outcome was the response rate in each of the three gas flows with each cumulative dose. Positive response was determined by meeting any of the following criteria: 1) ATS/ERS criteria of positive response, defined as FEV₁ increased by ≥ 12% with absolute change of ≥ 200 mL from baseline; 2) absolute value of FEV₁ post-bronchodilator via HFNC ≥ prescreening FEV₁ post-bronchodilator via MDI + VHC. The secondary outcome was the cumulative dose of salbutamol required with each delivered flow to produce a positive bronchodilation response.
Sample size calculation

This study was a superiority study. With confidence level \((1 - \alpha)\) of 95%, power \((1-\beta)\) of 80% and Margin \((\Delta)\) of 0.2, we assumed 80% of subjects in the group of GF:IF = 0.5 would respond to salbutamol at the cumulative dose of 1.5 mg, compared to 40% in the group of 50 L/min, the number of each group was calculated to be 25 subjects while the total number of subjects was 75 to account for potential patients lost to follow up.\(^2\)

Data collection

Demographic information (age, gender, height, weight, race, smoking history, diagnosis), baseline parameters during tidal breathing (tidal volume and peak inspiratory flow), and forced vital capacity results (FEV\(_1\), FVC, PEF, FEF\(_{75}\), FEF\(_{75-25}\) and FEF\(_{25}\)) before and after inhaling saline and salbutamol at each dose were recorded.

Statistical analysis

Kolmogorov-Smirnov test was performed to evaluate the normality of distribution for continuous variables, which were presented as mean ± standard derivation (SD) or median and interquartile rage (IQR) based on the results. One-way analysis of covariance (ANCOVA) was conducted to determine the difference among the three flow groups in post-inhalation measures and the increments including FEV\(_1\), FVC, PEF, FEF\(_{75}\), FEF\(_{75-25}\) and FEF\(_{25}\) after controlling for baseline variables, whereas ANOVA was used to compare the baseline variables among three groups and repeated measures ANOVA analysis was used to compare the differences of the FEV\(_1\) improvement among different doses of bronchodilator within subjects receiving the same flow. Categorical variables were expressed as percentage and analyzed by Chi-square test. A two-sided \(P\)-value of < 0.05 was considered statistically significant for all tests. Data analysis was performed with SPSS software (SPSS 23.0; Chicago, IL).

Results

From February 7th, 2019 to November 12th, 2019, 1098 patients demonstrating positive response to bronchodilators in the PFT lab were screened, and 75 subjects were recruited with 25, 24 and 26 subjects assigned to receive flows of GF:IF = 0.5, GF:IF = 1.0 and GF = 50 L/min, respectively. 49 subjects had asthma while 26 had COPD. Forty-eight (64%) subjects were male and 33 (44%) had smoking history. No significant differences of age, gender, height, weight, pulmonary disease (asthma or COPD), smoking history, tidal volume and inspiratory flow were observed among three groups (Table 1). Nebulization duration ranged from 6 to 8 min to administrate 2-mL volume. No adverse events were reported in the three groups.
Table 1
Demographic information of patients in the three groups

|                             | GF: IF = 0.5 (n = 25) | GF: IF = 1.0 (n = 24) | GF = 50 L/min (n = 26) | p    |
|-----------------------------|------------------------|-----------------------|------------------------|------|
| Age, years                  | 51.2 ± 13.4            | 51.9 ± 16.6           | 51.1 ± 14.0            | 0.978|
| Male, %                     | 16 (64%)               | 14 (58%)              | 18 (69%)               | 0.725|
| Asthma, %                   | 16 (64%)               | 16 (67%)              | 17 (65%)               | 0.981|
| COPD, %                     | 9 (36%)                | 8 (33%)               | 9 (35%)                |      |
| Height, cm                  | 164.3 ± 6.8            | 166.2 ± 7.4           | 164.4 ± 7.7            | 0.587|
| Weight, Kg                  | 71.7 ± 11.3            | 72.2 ± 12.8           | 68.7 ± 11.0            | 0.510|
| BMI, Kg/m²                  | 26.5 ± 3.5             | 26.0 ± 3.3            | 25.4 ± 3.6             | 0.523|
| Vt, mL                      | 766.4 ± 146.0          | 740.0 ± 190.3         | 800.2 ± 215.7          | 0.519|
| Patient inspiratory flow, L/min | 37.4 ± 7.8           | 34.5 ± 6.9            | 38.2 ± 6.0             | 0.137|
| HFNC flow settings, L/min   | 18.7 ± 3.9             | 34.5 ± 6.9            | 50                     | < 0.001|
| Smoker, %                   | 11 (44%)               | 11 (46%)              | 11 (42%)               | 0.969|

GF, gas flow; IF, patient inspiratory flow; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Vt, tidal volume; HFNC, high-flow nasal cannula.

**Bronchodilation responses after inhaling salbutamol via HFNC**

All recruited subjects completed testing with results shown in Table 2. Using the ATS/ERS criteria for positive bronchodilation response,22 44% of subjects receiving GF:IF = 0.5 met the criteria after inhaling the initial salbutamol dose of 0.5 mg compared to 25% and 27% for GF:IF = 1.0 and GF = 50 L/min, respectively. However, after 1.5 mg dose, 64% of patients responded with GF:IF = 0.5, a proportion similar to those receiving GF:IF = 1.0 and GF = 50 L/min (58% and 42%, respectively). In contrast, applying the criteria that post-bronchodilator FEV₁ via HFNC returned to the screening level post-bronchodilator, higher percentage of subjects receiving GF:IF = 0.5 than those receiving GF:IF = 1.0 and GF = 50 L/min met the criteria at the cumulative doses of 1.5 mg (64% vs 29% vs 27%, p = 0.011) and 3.5 mg (88% vs 54% vs 46%, respectively, p = 0.005). A higher percentage of subjects receiving GF:IF = 0.5 met both criteria than the two other flows at the cumulative dose of 1.5 mg.
Table 2
Bronchodilation responses after inhaling salbutamol via HFNC among three groups

|                | GF: IF = 0.5 (n = 25) | GF: IF = 1.0 (n = 24) | GF = 50 L/min (n = 26) | p    |
|----------------|------------------------|------------------------|-------------------------|------|
| Met ATS/ERS positive criteria, % | Saline 1 0 1 NA | 0.5 mg 11 (44%) 6 (25%) 7 (27%) .286 | 1.5 mg 16 (64%) 14 (58%) 11 (42%) .271 | 3.5 mg 17 (68%) 18 (75%) 18 (69%) .848 |
| Post- salbutamol FEV$_1$ via HFNC returns to post-salbutamol FEV$_1$ via MDI + VHC, % | Saline 1 0 0 | 0.5 mg 4 (16%) 3 (13%) 4 (15%) .934 | 1.5 mg 16 (64%) 7 (29%) 7 (27%) .011 | 3.5 mg 22 (88%) 11 (46%) 14 (54%) .005 |
| Met either of the two criteria | 0.5 mg 13 (52%) 8 (33%) 10 (39%) .388 | 1.5 mg 19 (76%) 17 (71%) 14 (54%) .213 | 3.5 mg 23 (92%) 20 (83%) 21 (81%) .497 |
| Met both criteria | 0.5 mg 2 1 1 NA | 1.5 mg 13 (52%) 4 (17%) 4 (15%) .013 | 3.5 mg 16 (64%) 9 (38%) 11 (42%) .366 |

GF, gas flow; IF, patient inspiratory flow; HFNC, high-flow nasal cannula; FEV$_1$, forced expiratory volume at the first second; MDI, metered dose inhaler; VHC, valved holding chamber; ATS/ERS positive criteria: FEV$_1$ increased by 12% and absolute volume increased $\geq$ 200 mL; ATS, American thoracic society; ERS, European respiratory society.

**FEV$_1$ changes after inhaling salbutamol via MDI + VHC and via HFNC at different doses**
Screening baseline FEV$_1$ in the subjects receiving GF:IF = 0.5 trended lower than subjects receiving GF:IF = 1.0 and GF = 50 L/min while on study day, they had slightly higher baseline FEV$_1$ pre-HFNC (1.72 ± 0.84 vs 1.65 ± 0.79 L), while the other subjects had slightly lower screening baseline FEV$_1$ pre-HFNC than their screening baseline FEV$_1$ (Table 3).
Table 3
The changes of FEV$_1$ after inhaling salbutamol via MDI with VHC and after inhaling saline and salbutamol at different doses via HFNC.

|                              | GF: IF = 0.5 (n = 25) | GF: IF = 1.0 (n = 24) | GF = 50 L/min (n = 26) | p       |
|------------------------------|------------------------|------------------------|-------------------------|---------|
| FEV$_1$ (ml) with salbutamol via MDI + VHC |                         |                        |                         |         |
| Pre                          | 1.65 ± 0.79            | 1.98 ± 0.80            | 1.91 ± 0.80             | 0.321$^a$|
| Pre FEV$_1$ in predicted (%) | 56.5 ± 23.8            | 66.2 ± 18.1            | 64.0 ± 18.9             | 0.221$^a$|
| Post                         | 2.03 ± 0.83            | 2.34 ± 0.86            | 2.30 ± 0.87             | 0.577$^a$|
| Increase (ml)                | 375 ± 125              | 365 ± 110              | 389 ± 135               | 0.577$^a$|
| Increase (%)                 | 27.3 ± 13.2            | 20.7 ± 9.3             | 23.5 ± 12.2             | 0.429$^a$|
| FEV$_1$ (ml) with salbutamol via HFNC |                         |                        |                         |         |
| Pre                          | 1.72 ± 0.84            | 1.91 ± 0.79            | 1.87 ± 0.80             | 0.691$^a$|
| Pre FEV$_1$ in predicted (%) | 58.5 ± 24.7            | 64.0 ± 19.0            | 63.2 ± 19.7             | 0.613$^a$|
| Saline                       | 1.74 ± 0.87            | 1.90 ± 0.77            | 1.83 ± 0.81             | 0.060$^b$|
| 0.5 mg                       | 1.95 ± 0.86            | 2.10 ± 0.80            | 2.02 ± 0.81             | 0.194$^b$|
| 1.5 mg                       | 2.05 ± 0.86            | 2.20 ± 0.81            | 2.16 ± 0.84             | 0.804$^b$|
| 3.5 mg                       | 2.09 ± 0.87            | 2.28 ± 0.80            | 2.26 ± 0.84             | 0.968$^b$|
| 7.5mg$^c$                    | 2.20 ± 0.93            | 2.21 ± 0.95            | 2.35 ± 0.89             | 0.567$^b$|
| FEV$_1$ increase (ml) with salbutamol via HFNC | Saline                |                         |                         | 0.060$^b$|
| Saline                       | 23 ± 87                | -5 ± 65                | -47 ± 139               |         |

GF, gas flow; IF, patient inspiratory flow; HFNC, high-flow nasal cannula; FEV$_1$, forced expiratory volume at the first second; MDI, metered dose inhaler; VHC, valved holding chamber

$^a$ comparison was conducted using ANOVA test; $^b$ comparison was conducted using ANCOVA test; $^c$ data available in 21, 21 and 23 patients in the three groups, respectively.
|                | GF: IF = 0.5 (n = 25) | GF: IF = 1.0 (n = 24) | GF = 50 L/min (n = 26) | p     |
|----------------|-----------------------|-----------------------|------------------------|-------|
| 0.5 mg         | 228 ± 146             | 197 ± 148             | 152 ± 147              | 0.194 |
| 1.5 mg         | 321 ± 161             | 298 ± 191             | 284 ± 240              | 0.804 |
| 3.5 mg         | 373 ± 171             | 375 ± 215             | 387 ± 264              | 0.968 |
| FEV<sub>1</sub> increase (%) with salbutamol via HFNC | Saline 0.7 ± 7.5 | 0 ± 5.0 | -3.0 ± 8.5 | 0.140 |
|                | 0.5 mg 16.5 ± 14.0 | 12.1 ± 9.4 | 9.1 ± 9.4 | 0.087 |
|                | 1.5 mg 23.7 ± 17.0 | 17.7 ± 11.7 | 16.8 ± 14.4 | 0.283 |
|                | 3.5 mg 27.1 ± 18.2 | 23.2 ± 14.8 | 23.3 ± 16.0 | 0.831 |

GF, gas flow; IF, patient inspiratory flow; HFNC, high-flow nasal cannula; FEV<sub>1</sub>, forced expiratory volume at the first second; MDI, metered dose inhaler; VHC, valved holding chamber

<sup>a</sup> comparison was conducted using ANOVA test; <sup>b</sup> comparison was conducted using ANCOVA test; <sup>c</sup> data available in 21, 21 and 23 patients in the three groups, respectively.

The screening post-bronchodilator FEV<sub>1</sub> was assumed to be the optimal FEV<sub>1</sub> that subjects could achieve. However, one subject had a higher baseline FEV<sub>1</sub> on study day than their screening post-bronchodilator FEV<sub>1</sub>. The difference between the optimal FEV<sub>1</sub> and post-bronchodilator FEV<sub>1</sub> at each dose in subjects receiving GF:IF = 0.5 was smaller than those receiving GF:IF = 1.0 and GF = 50 L/min at the cumulative dose of 0.5 mg (-98 ± 107 vs -241 ± 215 vs -272 ± 277 mL, p = 0.020) and 1.5 mg (2 ± 94 vs -140 ± 198 vs -140 ± 192 mL, p = 0.008) (Fig. 1). Subjects receiving GF:IF = 0.5 had smaller FEV<sub>1</sub> difference than GF = 50 L/min after inhaling salbutamol of 0.5 mg (p = 0.023) and 1.5 mg (p = 0.018) while no significant differences were found between GF:IF = 1.0 and GF = 50 L/min. The ratio of FEV<sub>1</sub> improvement to screening value was higher than salbutamol via HFNC at 0.5 mg in each group, however this difference became nonsignificant at the cumulative dose of 1.5 mg with GF:IF = 0.5 and 1.0, and with dose of 3.5 mg with GF = 50 L/min (Fig. 2a).

**Other spirometry results of inhaling salbutamol at different doses**
After inhaling salbutamol via HFNC at 0.5 mg, subjects’ PEF, FEF$_{25}$, and FEF$_{25-75}$ significantly increased in all three groups, compared to inhaling saline (Fig. 3). However, these variables did not change significantly with cumulative dose of 1.5 mg with GF:IF = 0.5, in contrast to improvement with both GF:IF = 1.0 and GF = 50L/min.

**Bronchodilation responses between asthma and COPD subjects at the three HFNC flows**

For subjects with asthma, the number of subjects who met the ATS/ERS criteria for positive responses at the cumulative doses of 0.5 mg, 1.5 mg and 3.5 mg were similar. However, more subjects receiving GF:IF = 0.5 had their post-HFNC FEV$_1$ return to the screen post-salbutamol FEV$_1$ than the other subjects at cumulative doses of 1.5 mg and 3.5 mg (e-table 1). The screening FEV$_1$ improvement was higher than FEV$_1$ improvement with HFNC at 0.5 mg for all three flows, while the difference became nonsignificant at 1.5 mg (Fig. 2b).

For subjects with COPD, 44% receiving GF:IF = 0.5 met the ATS/ERS positive response criteria after inhaling 0.5 mg of salbutamol via HFNC, in contrast to no subjects receiving the other flows. Moreover, FEV$_1$ improvement at 0.5 mg was higher with GF:IF = 0.5 than the other flows (e-table 2). Compared to screening FEV$_1$ improvement, post-bronchodilator FEV$_1$ improvement was similar at 1.5 mg only with flow of GF:IF = 0.5, the differences became insignificant at 3.5 mg with flows of GF:IF = 1.0 and GF = 50 L/min (Fig. 2c).

**Discussion**

This is the first randomized controlled trial to compare the effects of delivered gas and patient inspiratory flow rates on response to bronchodilator delivery via HFNC. We found that subjects receiving GF:IF = 0.5 responded to lower cumulative doses than GF:IF = 1.0 and GF = 50. The effective dose to generate responses similar to screening was 1.5 mg with GF:IF = 0.5 versus 3.5 mg in the group of GF = 50 L/min. These findings are consistent with our previous in vitro reports that aerosol delivery efficiency increased as GF:IF decreased to 0.5.

In a previous prospective study, of 42 stable COPD or asthma patients with similar screening criteria, 69% met ATS/ERS positive response criteria after inhaling cumulative salbutamol dose of 1.5 mg via HFNC with flow set at 15–20 L/min. This is consistent with the 64% response at 1.5 mg in subjects receiving GF:IF = 0.5 representing mean HFNC flow of 18.7 ± 3.9 L/min. As baseline FEV$_1$ prior to nebulization via HFNC was higher than screening baseline for subjects receiving GF:IF = 0.5. In contrast, baseline FEV$_1$ pre-HFNC was lower than screening baseline in the other two groups, which required less improvement during nebulization via HFNC to meet the ATS/ERS positive response criteria than for subjects receiving GF:IF = 0.5. This was identified as a potential cause of bias. Consequently, we applied a second criterion identifying subjects who had FEV$_1$ return to their screening optimal level.
Using this criteria, the effective dose was 1.5 mg with GF:IF = 0.5, and 3.5 mg in the other flows, consistent with our previous study.\textsuperscript{23} Interestingly, the effective dose was different for asthma and COPD subjects among three groups. For subjects with asthma, the effective dose was 1.5 mg for all three flows. As we only compared dose of 0.5 mg and 1.5 mg, future studies may benefit for finer gradation of cumulative doses between 0.5 and 1.5 mg for asthma subjects. In contrast, the effective dose for COPD subjects was 1.5 mg with GF:IF = 0.5, and 3.5 mg for both GF:IF = 1.0 and GF = 50L/min. This difference might be explained by the lower nominal dose needed to elicit effective beta-agonist response for asthma subjects than COPD subjects. Fishwick and colleagues found 50mcg salbutamol via Turbuhaler was able to achieve similar bronchodilation effects as 400mcg in asthma subjects (2.79 vs 2.84 L),\textsuperscript{24} while COPD patients’ FEV\textsubscript{1} increased as the dose of salbutamol increased from 100 to 800mcg.\textsuperscript{25} In our study, COPD subjects receiving GF:IF = 0.5 required lower cumulative dose to return FEV\textsubscript{1} to screening levels can be explained in part by the higher trans-nasal delivery efficiency of aerosol at the lower flow.\textsuperscript{20}

Overall, these findings suggest that salbutamol dose of 1.5 mg to 3.5 mg provided effective doses depending on HFNC flow applied. Depending on jurisdiction, standard salbutamol doses vary from 2.5 mg to 5.0 mg. A label dose of 5.0 mg should be sufficient for all stable patients receiving HFNC in the range of flows studied. As we only compared dose of 1.5 mg and 3.5 mg, it is unclear whether a unit dose of 2.5 mg would be sufficient as an effective dose at the higher flows studied. Future studies are needed to investigate if 2.5 mg is effective to elicit bronchodilation response at HFNC gas flow higher or equal to patient inspiratory flow, particularly for COPD subjects.

This is the first study to assess the inspiratory flow for adult subjects with stable asthma and COPD before administration of HFNC. These subjects were not in acute distress or exacerbation phase in which HFNC might be more commonly utilized. Our findings of average subject inspiratory flow of 35 L/min provides general guidance that 35–40 L/min should be the minimal flow via HFNC to avoid air entrainment in adults. Inspiratory flow would be higher for patients during acute exacerbation, thus higher flow settings might be reasonable. When aerosol therapy is administered, titrating flow to 15–20 L/min for stable subjects and 25–30 L/min for subjects with distressed breathing could increase the delivery efficiency.\textsuperscript{10} Notably, reducing flow to optimize aerosol delivery might cause desaturation and increase work of breathing, for subjects who rely on high gas flow and high oxygen concentration. For these patients, administration of small volumes of solution may reduce dosing time to shorten the periods of flow reduction.\textsuperscript{10,26} If reduced flow is not tolerated, or long term continuous inhalation is needed, higher nominal dose might be necessary.

**Limitations**

Similar to our prior study,\textsuperscript{23} the requirement to perform repeated forced expiratory maneuvers limited us to subjects with stable asthma and COPD. As utilization of HFNC has been expanded to stable COPD subjects,\textsuperscript{9} this population may more directly benefit from our results. The primary indication of HFNC is still acute patients, whose breathing patterns might be different from stable subjects. Therefore, future
studies are needed to compare outcomes, particularly long-term outcomes, such as need for respiratory support or length of hospital stay, with the utilization of different gas flows to deliver inhaled medication for acute patients. Secondly, we only evaluated bronchodilator delivery, future studies are needed to investigate other inhaled medication, such as inhaled antibiotics or steroids, etc.

**Conclusion**

Dose response to inhaled salbutamol via HFNC was greater when administered with gas flow set at 50% of patient inspiratory flow, than with gas flow equal to subject’s inspiratory flow or at 50L/min. At cumulative doses of 1.5 mg and 3.5 mg, more subjects receiving HFNC flow at 50% of subject inspiratory flow achieved comparable improvements in FEV₁ as their screening response to inhaled salbutamol than with the higher flows.

**Declarations**

**Ethics approval and consent to participate** This study was approved by ethic committees in People's Liberation Army General Hospital, Beijing, China (approval No. S2018-200-02) and Rush University, Chicago, IL (approval No. 19041201-IRB01)

**Consent for publication** Not required.

**Availability of data and materials** Data are available upon reasonable request. Proposals should be directed to the corresponding author.

**Competing interests** Dr. Li declares to receive research funding from Fisher & Paykel Healthcare Ltd and Rice Foundation and lecture honorarium from AARC and Fisher & Paykel Healthcare Ltd outside the submitted work. Dr. Fink is Chief Science Officer for Aerogen Pharma Corp. Dr. Ehrmann reports consultancies from Aerogen Ltd, research support from Aerogen Ltd, Fisher & Paykel healthcare, Hamilton medical, travel reimbursements from Aerogen Ltd and Fisher & Paykel. The companies had no role in the study design, data collection, analysis, preparation of the manuscript, or the decision to publish the findings. Other authors have no conflicts to disclose.

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**Author’s contributions** JL conceived and designed the study, analyzed the data, drafted and revised the manuscript. YC was the study principal investigator, recruited the subjects, supervised the study and revised the manuscript. SE interpreted the result and revised the manuscript. JW implemented the study and revised the manuscript. LX supervised the study, interpreted the result and revised the manuscript. JBF designed the study, interpreted the result and revised the manuscript. JL, YC and LX were the
guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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Figures

Figure 1

The difference of optimal FEV1 and FEV1 after inhaling saline and salbutamol via HFNC at different nominal doses in three groups. FEV1 post-MDI+VHC was deemed the optimal FEV1 for individual patients. Using the difference between the optimal FEV1 and each FEV1 after inhaling saline and salbutamol via HFNC at different nominal doses to compare among three groups (ANOVA test), no significant difference was found after inhaling saline. While at the cumulative doses of 0.5mg and 1.5mg, the difference of FEV1 in the group of GF:IF=0.5 was smaller than the other two groups, this difference became nonsignificant at the cumulative doses of 3.5mg and 7.5mg. FEV1, forced expiratory volume in one second; HFNC, high-flow nasal cannula; MDI, metered dose inhaler; VHC, valved holding chamber; GF, gas flow; IF, inspiratory flow.
Figure 2

The difference of optimal FEV1 and FEV1 after inhaling saline and salbutamol via HFNC at different nominal doses in three groups. FEV1 post-MDI+VHC was deemed the optimal FEV1 for individual patients. Using the difference between the optimal FEV1 and each FEV1 after inhaling saline and salbutamol via HFNC at different nominal doses to compare among three groups (ANOVA test), no significant difference was found after inhaling saline. While at the cumulative doses of 0.5mg and 1.5mg, the difference of FEV1 in the group of GF:IF=0.5 was smaller than the other two groups, this difference became nonsignificant at the cumulative doses of 3.5mg and 7.5mg. FEV1, forced expiratory volume in one second; HFNC, high-flow nasal cannula; MDI, metered dose inhaler; VHC, valved holding chamber; GF, gas flow; IF, inspiratory flow.

Figure 3
The results of PEF, FEF25, FEF25-75 and FEF75 after inhaling saline and salbutamol via HFNC at different nominal doses in three groups. In the group of GF:IF=0.5, all the spirometry results were higher after inhaling salbutamol at 0.5mg, compared to that with saline inhalation. However, in the groups of GF:IF=1.0 and GF=50 L/min, PEF, FEF25, FEF25-75 continued increasing after inhaling salbutamol via HFNC at the cumulative doses of 0.5mg, 1.5mg and 3.5mg. HFNC, high-flow nasal cannula; GF, gas flow; IF, inspiratory flow; PEF, peak expiratory flow; FEF25, forced expiratory flow at 25% of forced vital capacity; FEF25-75, forced expiratory flow at 25% to 75% of forced vital capacity; FEF75, forced expiratory flow at 75% of forced vital capacity.

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