

BMJ Open Effects of flow rate on transnasal pulmonary aerosol delivery of bronchodilators via high-flow nasal cannula for patients with COPD and asthma: protocol for a randomised controlled trial

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ABSTRACT

Introduction Both in vitro and in vivo radiolabelled studies on nebulisation via high-flow nasal cannula showed that inhaled dose decreases as the administered gas flow increases. In our previous in vitro study, we investigated the effects of the ratio of gas flow to subject's peak inspiratory flow (GF:IF) on the aerosol deposition, which increased as the GF:IF decreased, with an optimal GF:IF between 0.1 and 0.5 producing a stable 'lung' deposition in both quiet and distressed breathing. Thus, we aim to validate our in vitro findings in subjects with reversible airflow limitations by assessing their response to inhaled bronchodilator.

Methods and analysis This is a single-centre, randomised controlled trial. Subjects with chronic obstructive pulmonary disease or asthma with positive response to 400µg albuterol via metered dose inhaler and valved holding chamber will be enrolled and consented. After a washout period (1–3 days), subjects will be randomly assigned to inhale albuterol with one of three gas flows: 50 L/min, GF:IF=1.0 and GF:IF=0.5. In each arm, subjects will inhale 2 mL saline, followed by escalating doubling doses (0.5, 1, 2 and 4 mg) of albuterol in a fill volume of 2 mL, delivered by a vibrating mesh nebuliser via heated nasal cannula set up at 37°C. An interval of 30 min between each dose of albuterol, with spirometry measured at baseline and after each inhalation. Titration will be terminated if forced expiratory volume in 1 s improvement is <5%, or adverse event is observed.

Ethics and dissemination This trial has been approved by the Ethic Committee of People's Liberation Army General Hospital, Beijing, China (no. S2018-200-01). The results will be disseminated through peer-reviewed journals, national and international conferences.

Trial registration number NCT03739359; Pre-results.

INTRODUCTION

High-flow nasal cannula (HFNC) delivers medical gas at a flow exceeding patient inspiratory flow demand.¹ For hypoxaemic patients, it has been shown to improve oxygenation

Strengths and limitations of this study

- This is the first study to investigate the dose-response relationship in different flows: 50 L/min, match patient's own inspiratory flow and equal to 50% of patient's inspiratory flow.
- This is the first randomised controlled trial to compare the effects of bronchodilator delivered at three different flows via nasal cannula.
- This is the first study to measure the inspiratory flow demand of patients with chronic obstructive pulmonary disease and asthma and apply the gas flow based on individual flow demand to deliver bronchodilator.
- The patients enrolled are documented responders to bronchodilators due to the practical issues, and most of them are expected to be stable asthmatics who usually do not need high-flow nasal cannula, which might limit the direct transfer application of the results derived from this study to the patients who really need high-flow nasal cannula.
- This study tested only bronchodilators through nasal cannula at different flows, which might not be generalisable to other aerosolised medications such as corticosteroids, antibiotics, etc.

and help avoid intubation,² and for patients with chronic obstructive pulmonary disease (COPD), HFNC has been demonstrated to reduce work of breathing, improve ventilation and alleviate hypercapnia.^{3,4}

In clinical practice, many medications are preferred to be aerosolised to the lower airway or alveoli to have direct effects on the target organ. HFNC has recently become a feasible, effective and comfortable route to deliver aerosolised medication,^{5–10} and two recently published studies reported that regular dose of bronchodilator via HFNC at 30–35 L/min could generate similar bronchodilation

effects as jet nebuliser in stable COPD patients.^{6 7} Clinical observations found paediatric patients were more comfortable and less anxious while inhaling bronchodilator via HFNC.^{9 10}

Multiple *in vitro* studies have reported a range of influential factors associated with the delivery efficacy using HFNC system, such as delivery gas type, density and flow rate, nebuliser type and placement, breathing pattern, size of nasal cannula and type of humidification system,^{11–16} of which the administered gas flow rate is believed to play a critical role.^{14–16} Inhaled dose is found to increase when the administered gas flow rate decreases in quiet breathing.^{14 15} With the extreme low flow setting (5 L/min) for adults via 'HFNC' system with vibrating mesh nebuliser, the delivery efficiency was found to be comparable as standard jet nebuliser in pharmacokinetic studies.^{8 17} Our previous bench study further explored the effects of the ratio of nasal cannula gas flow to patient inspiratory flow (GF:IF), which was found to be the primary predictor of inhaled dose, while the ratio of 0.1–0.5 produced higher and more consistent inhaled dose than that of ratio at 1.0 or above in quiet breathing.¹⁶ Therefore, to validate our *in vitro* findings, we propose a randomised controlled trial to compare the bronchodilation effects of inhaled albuterol in three groups receiving different flow rates: (1) 50 L/min, which is a common HFNC flow setting in adult subjects; (2) gas flow is set to match subject inspiratory flow (GF:IF=1.0), which meets the minimal requirement of gas flow by HFNC definition that the gas flow at least equals subject inspiratory flow demand¹ and (3) gas flow is set at 50% of subject inspiratory flow (GF:IF=0.5). The hypothesis is that inhaled dose will be greater in subjects receiving GF:IF=0.5 than the two higher flow arms. Subject bronchodilation effect, represented by improvement in forced expiratory volume in 1 s (FEV₁), is directly related to the inhaled dose of bronchodilator up to full or plateau bronchodilator response. Escalating doses of bronchodilator will be administered to each subject. As the bronchodilator (albuterol) has a steep response curve, we hypothesise that at the low dose of albuterol, response rate in the group of GF:IF=0.5 will be higher than that in the groups of GF:IF=1.0 and gas flow at 50 L/min. We will also compare the effective dose that subjects meet the response criteria, and we hypothesise that a lower effective dose of bronchodilator might be required in the group of GF:IF=0.5 than the dose required in the group using higher gas flows.

METHODS

This is a randomised controlled trial, registered with ClinicalTrials.gov (NCT03739359). The report of the protocol followed the Standard Protocol Items: Recommendations for Interventional Trials guideline.¹⁸

Study population

Stable subjects will be recruited from outpatients with COPD or asthma who demonstrate positive response

during bronchodilator response testing in the pulmonary function test lab, People's Liberation Army General Hospital, Beijing, China.

Inclusion criteria

Adult stable subjects with COPD or asthma with positive bronchodilator responses to four actuations (400 µg) of albuterol (Ventolin, GSK, Brentford, UK) via metered dose inhaler (MDI) with valved holding chamber (VHC) (OptiChamber Diamond, Philips, Andover, Massachusetts, USA) will be eligible for enrollment. A positive bronchodilator response is defined in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines as follows: an increase in FEV₁ of ≥12% and absolute change ≥200 mL from baseline.¹⁹ COPD and asthma are diagnosed based on the standards recommended by the relevant guidelines.

Exclusion criteria

Subjects will be excluded if any of the following criteria are met: age ≥90 years; pregnancy; pulmonary exacerbation within 2 weeks before enrollment; reluctant to participate; inability to complete the follow-up spirometry after each bronchodilator inhalation; resting heart rate >100 bpm; resting systolic blood pressure >160 mm Hg or diastolic blood pressure >110 mm Hg.

Study procedures

For study diagram see [figure 1](#).

Recruiting and consent process

Subjects who are eligible for the study will be approached by the study investigator (Y.C). The study purpose and procedure, as well as risks and benefits will be explained thoroughly to the individual subject in a quiet room. Consent forms will be given to subjects and they will have up to 3 days to consider if they are willing to participate in the study. Consent will be signed after they return and witnessed by the study investigator. Randomisation group will be assigned after consent is signed. Subjects will be informed that bronchodilator treatment needs to be withheld prior to testing, according to standard practice (immediate release theophylline needs to be withheld for 24 hours before the test, long-acting β₂-agonist for 12 hours, short-acting β₂-agonist for 6 hours and short-acting anticholinergic for 8 hours).¹⁹

Randomisation and masking

A computer-based randomisation sequence will be generated before study commencement by an independent statistician. Randomisation will be assigned by permuted block methods using Fisher and Yates tables of random permutations.

Subjects will return to the pulmonary function test lab for randomisation within 1–3 days of initial screening to inhale saline and an escalating dose of albuterol administered by vibrating mesh nebuliser (VMN, Aerogen Solo, Aerogen Ltd., Galway, Ireland) via nasal cannula. Subjects will be randomly assigned to three groups of nasal

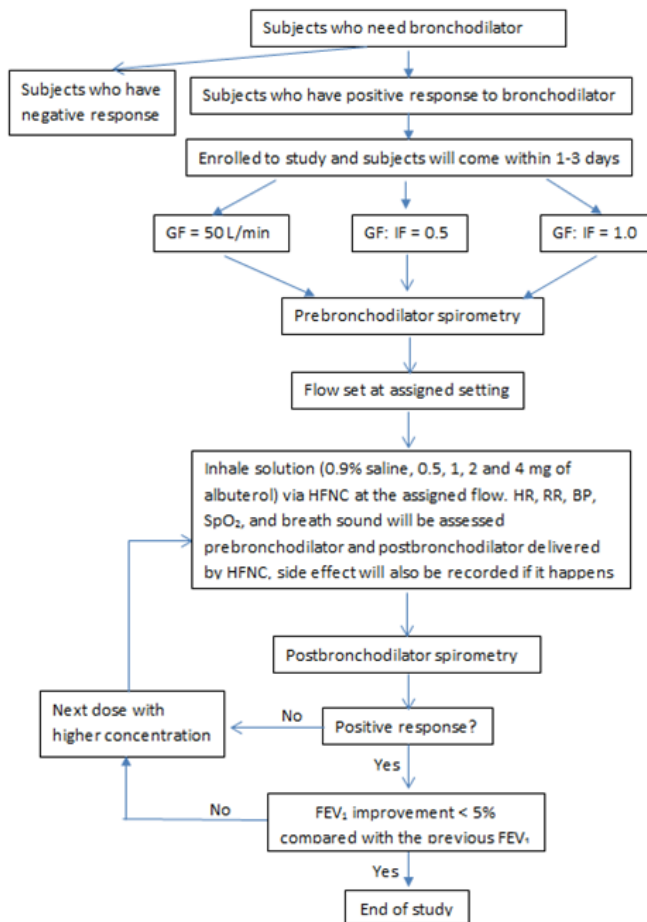


Figure 1 Study flow chart. GF, gas flow; IF, inspiratory flow; HFNC, high-flow nasal cannula; FEV₁, forced expiratory volume in 1 s; HR, heart rate; RR, respiratory rate; BP, blood pressure; SpO₂, peripheral capillary oxygen saturation.

cannula gas flow to inhale albuterol: 50L/min, GF:IF=1.0 and GF:IF=0.5.

Randomisation will also be stratified by disease (asthma and COPD). A block size of six subjects will be constructed to reduce predictability and the probability of serious mid-block inequality in the planned interim analyses. Two series of sequentially numbered, sealed, opaque envelopes containing the treatment assignment will be opened when eligibility criteria are met. This can ensure the number of subjects with asthma and COPD are equal in the three groups. Nebulisation will be offered in a separate room, and both subjects and the pulmonary function test technician will be blinded to the group. Only the investigator who opens the opaque envelope and sets up the gas flow for the subject knows the group assignment, she will also collect the data.

Bronchodilator delivery via HFNC

A calibrated back pressure compensated air flowmeter will be attached via T-piece adapter with VMN at the inlet (dry side) of a heated humidifier (MR 850, Fisher & Paykel, Auckland, New Zealand). A single limb heated wire circuit will be attached to an adult HFNC (Optiflow, Fisher & Paykel, Auckland, New Zealand), with prong size



Figure 2 Device set up.

chosen according to the diameters of subjects' nostrils. Assigned gas flow will be set and confirmed by a mass flowmeter (4040, TSI, Shoreview, Minnesota, USA), and the heater will be turned on (for approximately 15 min) to achieve 37°C prior to connecting to subjects (figure 2).

Subjects will be seated in an upright position and instructed to perform relaxed tidal breathing via nose with mouth closed. Subjects' vital signs will be continuously monitored including heart rate, cardiac rhythm, respiratory rate and blood pressure. Administration of 2mL of albuterol will take 6–8 min. Spirometry will be performed at baseline, and after each nebulisation. HFNC will be removed from the subjects and the subjects will be required to sit quietly for 10–12 min before performing spirometry test.

Prescreening bronchodilator delivery via MDI with VHC

Albuterol MDI (Ventolin, 100µg/puff) will be shaken and primed per label before use, and the primed MDI will be inserted into a VHC. Subjects will sit upright and be instructed to place the spacer mouthpiece into the mouth with sealed lips after a maximal exhalation. A slow and deep inhalation through VHC will be initiated immediately after one actuation of albuterol from the MDI is administered, followed by a breath hold of 5–10s and a slow exhalation via nose. This whole process will be repeated three more times at a 60s interval to achieve a total of four puffs.

Spirometry test

During screening and after randomisation, pulmonary spirometry will be measured at baseline, and after inhaling aerosol (saline and each dose of bronchodilator) via HFNC. To ensure the quality, all the tests will be completed using the same calibrated spirometer operated by the same pulmonary function technician.

Determining peak inspiratory flow during quiet breathing

Spirometry during tidal breathing will be firstly performed to determine subject's peak inspiratory flow. Subjects will be required to rest for at least 10 min and then be coached to breathe normally via mouthpiece with nose clipped for at least 3 min or when the tidal breathing is

stabilised, followed by a 1 min recording. Mean values of the resting peak inspiratory flows for 1 min will be used as individual's peak inspiratory flow.

Forced vital capacity test

A body plethysmograph (JAEGER-Vyaire, Mettawa, Illinois, USA) with daily calibration by a 3L syringe will be used to measure the FEV₁ and forced vital capacity (FVC) according to the ATS/ERS standardised practices.¹⁸ Briefly, subjects will be seated uprightly and guided to complete the following three distinct phases: (1) maximal inspiration; (2) a 'blast' of exhalation and (3) continued complete exhalation until the volume-time curve shows no change in volume (<0.025L) for ≥1s and the subject has tried to exhale for ≥6s. To meet the ATS/ERS acceptability and reproducibility criterion,¹⁹ a minimum of three acceptable FVC manoeuvres will be needed to ensure the difference between the two largest FVCs is <150 mL.

Drug preparation

The stock concentration of 2.0 mg/mL albuterol (Ventolin, 5 mg in 2.5 mL) diluted with normal saline to 1.0, 0.5 and 0.25 mg/mL. A total fill volume of 2.0 mL with each dose of 0.5, 1.0, 2.0 and 4.0 mg will be placed in nebuliser.

Termination criteria

Dose escalation will be terminated if any of the criteria is met: (1) adverse events are observed or reported including tachycardia, tremor, irregular heart rhythm, blood pressure increase >20% and headache; or (2) when improvement in FEV₁ is <5% greater than a previous dose in which bronchodilator response is identified.

Any subject who experiences adverse events will be rested and monitored in general unit, until the subject's recovery.

Outcomes

The primary outcome is to compare the response rate in three flow groups at each accumulative dose. The secondary outcome is to identify the cumulative dose of albuterol required across groups to produce positive bronchodilation response.

The bronchodilator response is determined by meeting any of the following criteria: (1) ATS/ERS criteria of positive response¹⁹; (2) absolute value of FEV₁ postbronchodilator via HFNC ≥ prescreening FEV₁ postbronchodilator. ATS/ERS criteria of FEV₁ increment is not the only criteria to decide if subject responds to bronchodilator, the reason is subjects' baseline FEV₁ may vary on daily basis,²⁰ FEV₁ increment might be less if baseline FEV₁ is high. As long as FEV₁ returns to prescreening FEV₁ postbronchodilator, the response is still deemed as positive. The response rate is calculated by the percentage of subjects who meet the criteria in each group.

Sample size calculation

This study is a superiority study. Since all the recruited subjects are responders to 400 µg of bronchodilator via

MDI+VHC and the inhaled dose of MDI+VHC is reported to be approximately 20% of emitted dose (80 µg).²¹ From our in vitro study, inhaled dose of bronchodilator via nasal cannula at GF:IF=0.5 was found to be approximately 20% of dose,¹⁶ compared with 3.5% with gas flow rate at 50 L/min.^{14 15} We hypothesise that a 20% inhaled dose of 0.5 mg in the group of GF:IF=0.5 would be 100 µg, which is >80 µg administered with MDI+VHC. In contrast, at 50 L/min with 3.5% lung dose an accumulative inhaled dose of 2.5 mg would provide an inhaled dose of 87.5 µg. We hypothesise that almost all subjects in the GF:IF=0.5 group would respond to albuterol at the accumulative inhaled dose of 1.5 mg. To calculate the sample size, with confidence level (α) of 95%, power ($1-\beta$) of 80% and margin (Δ) of 0.2, we assumed 80% of GF:IF=0.5 group will respond to cumulative dose of 1.5 mg albuterol, compared with 40% 50 L/min group. The number of subjects in each group will be 25 and the total number of subjects will be 75.

Data collection

Independent investigators will be allocated to record relevant data including demographic information (age, gender, height, weight, race, smoking history, diagnosis), baseline lung function via tidal breathing (tidal volume and peak inspiratory flow) and forced spirometry parameters (FEV₁, FVC, PEF, FEF₇₅, FEF₇₅₋₂₅ and FEF₂₅) before and after each dosage of bronchodilator inhalation.

Statistical analysis

For continuous variables, normality of distribution will be tested by the Kolmogorov-Smirnov test, and they will be presented as mean±SD or mean and IQR. The differences of forced spirometry parameters including FEV₁, FVC, PEF, FEF₇₅, FEF₇₅₋₂₅ and FEF₂₅ among the three flow groups will be tested by one-way analysis of covariance, whereas repeated measures analysis of variance will be used to compare the differences of the FEV₁ improvement among different doses of bronchodilator within the same group. Categorical variables will be expressed as percentage and analysed by X² test. A two-sided p value of <0.05 will be considered to be statistically significant for all tests. Data analysis will be conducted with SPSS software (SPSS V.23.0, Chicago, Illinois, USA).

The data for subjects who withdraw from the study (such as unwilling to continue the next dose) will be removed from data analysis, but will be reported in the supplement files.

Patient and public involvement

Patients and/or public were not involved in the study design.

DISCUSSION

Transnasal aerosol delivery via HFNC has become a popular route in the recent years, as for its benefits of patient's comfort, convenience for drug delivery and the

continuum of HFNC. However, the aerosol deposition is impacted by many factors, in which flow rate especially the ratio of GF:IF plays a key role.¹⁶ In the retrospective report of using inhaled epoprostenol via HFNC to improve hypoxaemia,⁵ patients whose oxygenation was improved had HFNC flow rate decreased, while flow rate was raised in the deteriorated patients. It might be explained that decreased flow rate improved inhaled dose of epoprostenol, which resulted in better oxygenation. It could also be vice versa that gas flow rate was reduced because of improved oxygenation. However, the sequence of adjusting flow rate and patient's response was not reported, it is difficult to identify the effects of flow rate adjustment on the drug delivery.²² Thus, to our knowledge, this is the first study to assess the influence of administered gas flow rate in relation to patient inspiratory flow on the clinical effects of transnasal aerosol delivery.

The dose escalation method used in this study will also help explore the effective dose in the three HFNC flow settings, which have clinical implications: (1) 50 L/min, the general HFNC flow setting in adult patients, especially those who require high flow to improve oxygenation/ventilation and also need aerosolised medication, such as inhaled epoprostenol to treat refractory hypoxaemia⁵ or inhaled bronchodilator to treat bronchospasm,¹⁰ decreasing flow with sacrifice of oxygenation/ventilation to serve aerosol delivery might not be realistic, but higher dose might be needed in order to elicit the effects, thus exploring the effective dose or starting dose is highly demanded; (2) GF:IF=1, the minimal flow setting per HFNC definition.¹ Because the requirement to measure patient inspiratory flow, our study becomes the first study to measure patient inspiratory flow before using HFNC, the breathing pattern for stable patients with chronic pulmonary disease will be studied, this result will also benefit for the HFNC flow setting for those stable patients with domiciliary use of HFNC, which has been reported to improve patients' mucociliary clearance²³ and life quality score,²⁴ with reduction in COPD exacerbation rates and hospital admissions.²⁵ The results of effective bronchodilator dose can guide the dose for these patients who need to inhale bronchodilator when they are at home and 3) GF:IF=0.5, at this flow ratio, the benefits of high flow rate might be compromised, which means the FiO₂ is not as accurate and consistent as it is supposed to be, due to the air entrainment. The effects of washing out dead space and positive airway pressure will also be sacrificed as well. Thus, the mode at this ratio should be described as low flow nasal cannula (LFNC). However, LFNC might serve those patients who just need a feasible and comfortable route to inhale aerosolised medication, such as inhaled epoprostenol for an extended periods of time to treat pulmonary hypertension,⁵ or patients who can tolerate temporary reduction on flow setting during HFNC in order to increase the inhaled dose, such as intermittent use of bronchodilator for patients with COPD or asthma,^{6–10} because the regular

dose and volume (1–2 mL) of bronchodilator costs <10 min to complete nebulisation, reducing flow in such short term is unlikely to influence the long-term clinical benefits of HFNC. Therefore, our study would ultimately help to guide the clinical practitioners to choose appropriate gas flow according to the individual situations.

Reminiac *et al* reported that HFNC alone had limited bronchodilation effects,⁷ thus the first step in our study is inhaling saline via HFNC to assess its effects in our population. However, we anticipate this effect will be observed but minimal, due to two facts in our design: firstly, our patients will only use HFNC for inhaling aerosol, which means the time of using HFNC is only 6–8 min per dose, much shorter than 30 min in the study by Reminiac *et al*; secondly, there is 10–12 min interval between disconnection from HFNC and spirometry test, the bronchodilation effects caused by HFNC may attenuate in the interval.

The major limitation of this study is that we only evaluate the stable patients with known response to bronchodilator, thus the effective dose from our finding might not directly apply for the hospitalised patients with exacerbation or distressed breathing, among whom HFNC is more frequently used. However, as the first attempt, this study will still investigate the effective transnasal pulmonary dosing of albuterol in stable patients at different gas flows, which might provide an appropriate starting nebulisation dose for asthma and COPD in acute exacerbation receiving HFNC.

ETHICS AND DISSEMINATION

Recruitment and consent

Prospective, written consent will be obtained from all the participants.

Data collection, storage and access

Data will be sourced from forced expiratory capacity test results, electronic medical records and monitors. Data will be de-identified and entered into a secure, web-based electronic database.

Only the investigators will have access to the final dataset.

Dissemination strategy

The results of the study will be presented in national and international conferences, and published via a peer-reviewed journal.

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Contributors JLi conceived and designed the study, drafted and revised the manuscript. JLu participated in the study design and revised the manuscript. YC is the study principal investigator, recruited the subjects, supervised the study and revised the manuscript. LX supervised the study and revised the manuscript. JF designed the study and revised the manuscript.

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Competing interests Dr JBF is Chief Science Officer for Aerogen Pharma Corp and discloses relationships with Dance Biopharm.

Patient consent for publication Obtained.

Ethics approval This study was approved by the Ethic Committee of People's Liberation Army General Hospital, Beijing, China (no. S2018-200-01, current approved protocol V.2, 12 March 2019).

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