Supplemental files of "Identifying Dose Response to Trans-nasal Pulmonary Administration of Bronchodilator Aerosols via Nasal High-Flow Therapy in Adults with Stable Chronic Obstructive Pulmonary Disease and Asthma" (Li J, et al)

1. The procedures of bronchodilator delivery via MDI with VHC

Albuterol MDI (Ventolin, GSK, 100 μg/ puff) was shaken and primed per label. The primed MDI was inserted into a VHC, which had a large volume chamber with one way valve (OptiChamber Diamond, Philips, USA). Patients sat upright in a chair and were instructed to place the spacer mouthpiece into the mouth, between the teeth with lips sealed. Patients were instructed to exhale fully then take a slow deep breath through VHC as one actuation from the MDI was administered at beginning of inhalation, followed by a breath hold of 5 – 10 sec, and slowly exhale via the nose. The MDI was shaken and the process was repeated three more times at 60 s intervals to deliver four puffs (400 mcg). Forced vital capacity tests were performed before and after inhaling bronchodilator.

2. Albuterol sulfate solution preparation for delivery via NHF.

Albuterol (Ventolin, GSK, 5mg in 2.5mL with the concentration of 2.0mg/mL) was diluted with normal saline to 1.0, 0.5 and 0.25mg/mL. A total fill volume of 2.0 mL with each dose of 0.5, 1.0, 2.0 and 4.0mg was placed in nebulizer.

3. The forced vital capacity test

Tests were completed by a body plethysmograph (JAEGER-Vyaire, Germany), which was calibrated by a 3-L syringe daily, consistent with ATS/ERS standards. Before the test, patients were informed that bronchodilator treatment needed to be withheld, according to standard practice (immediate release theophylline needed to be withheld for 24 hours before the test, long acting β_2-agonist for 12 hours, short acting β_2-agonist for 6 hours and short acting anticholinergic for 8 hours). During test, the patients sat up straight on the chair and asked to take the deepest breath they could and then exhale into the sensor as hard as possible, for as long as possible, preferably at least 6 seconds. To ensure the quality of the test, all the tests were completed via the same calibrated spirometer by the same pulmonary function technologist. To meet the ATS/ERS acceptability and reproducibility criterion, a minimum of three acceptable FVC maneuvers were needed, with the difference between the two largest FVCs of less

than 150mL. FEV_1, forced vital capacity (FVC), forced expiratory flow (FEF) 75%, FEF 25–75, FEF 25 and peak expiratory flow (PEF) were recorded. Calculations: FEV_1 change from initial [FEV_1 % Δ init: (post FEV_1 – pre FEV_1)/pre FEV_1 × 100] and FEV_1 absolute change (FEV_1 abs Δ: post FEV_1 – pre FEV_1)

4. In vitro results of flow measurement

With F_IO_2 setting at 0.28, oxygen flow set at 5 L/min, total flow was 49.6 ± 0.1 L/min at the outlet of the venturi device without connecting the circuit, using a mass flowmeter (4040, TSI, Shoreview, MN). When the circuit was connected and flowmeter was placed at the end of circuit, flow decreased to 29.9 ± 0.08 L/min and continued to decrease after connecting to nasal cannula, flows were 20.3 ± 0.1, 16.7 ± 0.04 and 15.1 ± 0.05 L/min, respectively with large, medium and small size of nasal cannula.

5. In vitro experiment setup and results of aerosol deposition with the venturi entrainment device

5.1. Experiment setup

An adult manikin (Adult airway management trainer, Laerdal Stavanger, Norway) was used with collecting filter (Respirgard 303, CareFusion, San Diego, CA) placed between the "trachea" and the one chamber of the model lung (TTL, Michigan Instruments, Grand Rapids, MI), in which the other chamber was driven by a critical care ventilator (PB 840, Medtronic, Minneapolis, MN) to simulate inspiratory muscle, a quiet spontaneous breathing (Vt 500ml, RR 15bpm, Ti 1.3s, I:E 1: 2.1) was generated in the manikin via the rigid bar connecting~~ed~~ both chambers. A vibrating mesh nebulizer was placed at the inlet of heated humidifier and a large size of nasal cannula was placed at the manikin's nasal prongs.

With the use of the venturi entrainment device, albuterol with different dosing regimens were nebulized for each condition (n=3). Moreover, an additional test with albuterol (2.0mg in 2mL) was completed with Optiflow™ (Fisher & Paykel, Auckland, New Zealand) at 20 L/min. Drug was eluted from the filter and assayed with UV spectrophotometry (276 nm).

5.2. Results

With the given dose increased from 0.5, 1.0, 2.0 to 4.0mg, aerosol deposition significantly increased from 116.7 ± 3.3, 201.4 ± 9.5, 349.8 ± 18.1 to 662.9 ± 6.3 mcg (p = 0.016), respectively. Compared to

Optiflow™, aerosol deposition with Venturi entrainment device was similar [333.2 ± 14.9 vs 349.8 ± 18.1 mcg (16.7 ± 0.7% vs 17.5 ± 0.9%, p = 0.2].

6. Information about the two patients who withdrew from the study

One patient's FEV_1 increased from 1.03L to 1.14L after inhaling 0.5mg albuterol, but stopped inhaling at 1.0mg with FEV_1 1.21L; the other patient's FEV_1 increased from 2.79L to 2.95L after 0.5mg, but stopped inhaling at 1.0mg with FEV_1 3.16L.

7. Information about COPD patients in the study.

Of the 13 COPD patients, 1, 9 and 3 patients were classified as GOLD 1, 2 and 3, respectively, based on the global initiative for chronic obstructive lung disease (GOLD) classification.

Figure S1. Study flowchart

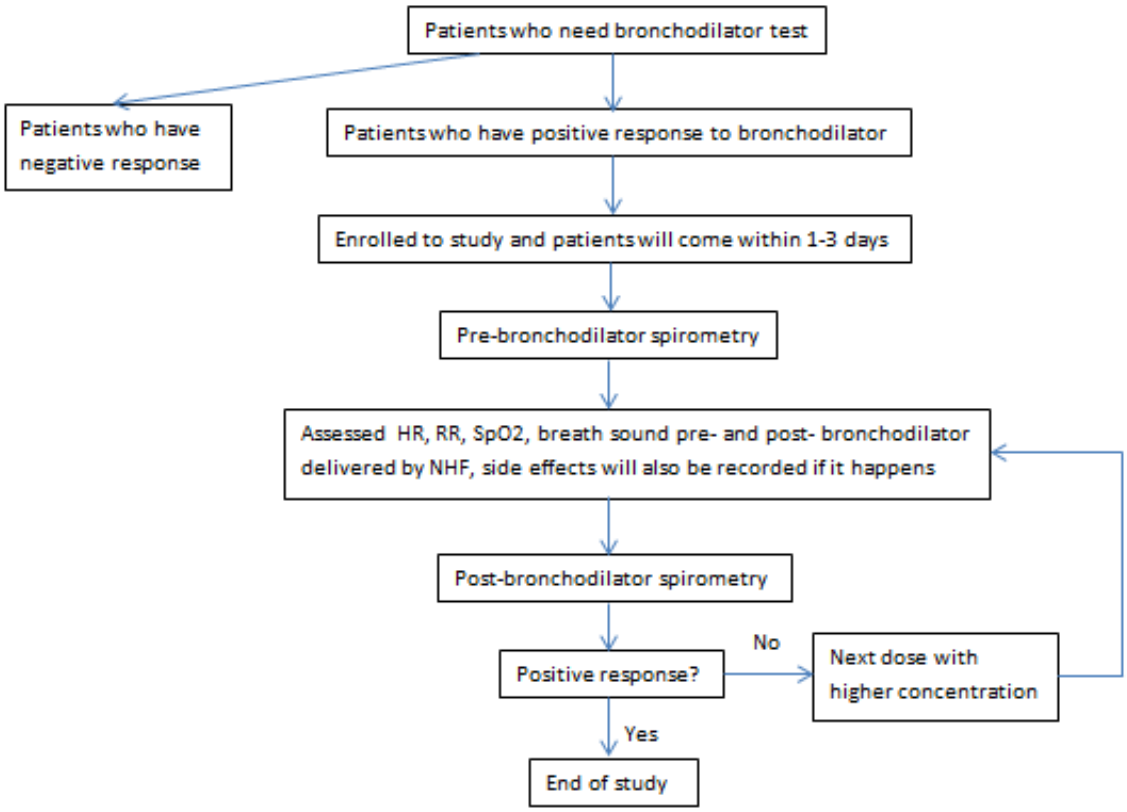

Figure S2. Experiment nasal high flow set up

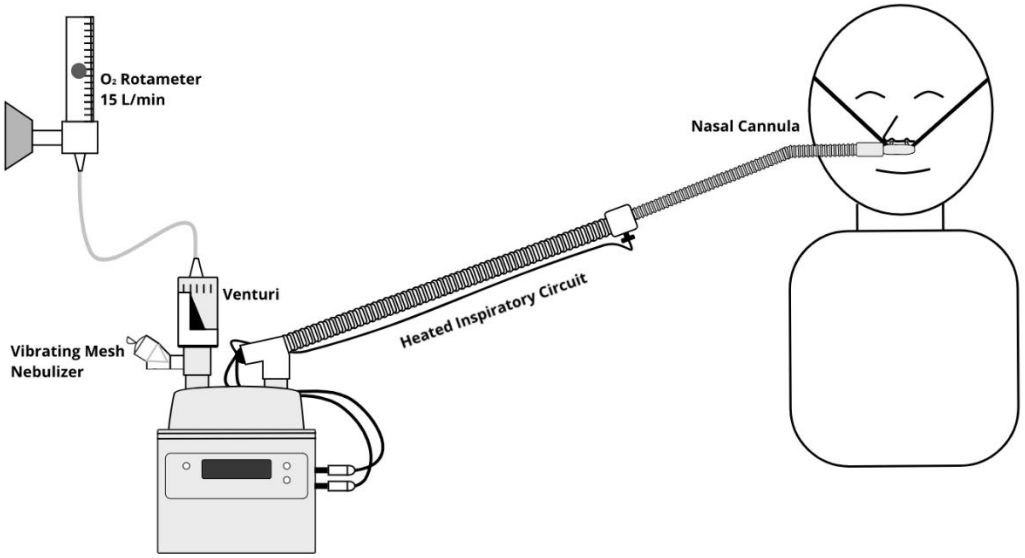

Table S1. FEV_1 pre and post at each accumulative dose of bronchodilator delivered via nasal high-flow for the 34 patients who inhaled accumulative doses of 0.5, 1.5 and 3.5mg

	Pre MDI+VHC	Post MDI+VHC	Pre NHF	0.5mg	1.5mg	3.5mg
FEV_1 (L)	1.93 ± .65	2.26 ± .70	1.96 ± .63	2.18 ± .65*	2.30 ± .68*	2.34 ± .69*
FEV_1 % predict	67.5 ± 16.7	79.2 ± 17.1	68.8 ± 16.8	76.4 ± 17.2	80.5 ± 17.0	82.0 ± 17.2

Compared with FEV_1 pre bronchodilator, FEV_1 at 0.5mg, 1.5mg and 3.5mg were significantly higher ($P<0.001$). Compared to FEV_1 at 1.5mg, FEV_1 at 3.5mg was significantly higher ($P<0.001$)

Table S2. FEV_1 pre and post at each accumulative dose of bronchodilator delivered via nasal high-flow for the 8 patients who inhaled accumulative doses of 0.5, 1.5, 3.5 and 7.5mg

	Pre MDI+VHC	Post MDI+VHC	Pre NHF	0.5mg	1.5mg	3.5mg	7.5mg
FEV_1 (L)	1.77 ± .53	2.05 ± .61	1.82 ± .55	1.96 ± .52*	2.05 ± .52*	2.12 ± .54*	2.12 ± .52*
FEV_1 % predict	63.1 ± 14.7	73.1 ± 16.5	65.2 ± 17.3	70.1± 15.0	73.3 ± 14.5	75.7 ± 13.9	76.1 ± 14.3

Compared with FEV_1 pre bronchodilator, FEV_1 at 0.5mg, 1.5mg and 3.5mg were significantly higher ($P<.05$). However, compared to FEV_1 at 1.5mg, FEV_1 at 3.5mg was not significantly different ($P=.073$)