Study of Humidified Air to Improve Mucociliary Clearance (MCC) in COPD:

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Hypothesis: The delivery of humidified air by nasal cannula will result in real-time improvement in mucociliary clearance.

Intervention: Delivery of humidified air using Fisher and Paykel myAirvo 2 and Optiflow nasal cannula for 4 hours at 30 L/min, reduced to 25 L/min if required for tolerance and 37 degrees C.

Population: n=12, female or male subjects 40 – 85 years of age with chronic bronchitis

Inclusion criteria:
(1) Male or Females 40 to 85 years old
(2) Diagnosis of chronic bronchitis
(3) Able to regularly produce sputum
(4) Clinically stable
(5) Current smoker or ex-smoker with a tobacco history of ≥10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year)
(6) History of moderate to very severe COPD with a post-bronchodilator FEV1/FVC<0.70 and a post-bronchodilator FEV1>20% and ≤70% of predicted normal value at enrollment. (5) CAT score ≥ 10, with questions 1 and 2 responses ≥ 5

Exclusion criteria:
(1) Pregnant or nursing or unwilling to perform pregnancy testing
(2) Unwilling or unable to refrain for SABA/LABA use ahead of the study
(3) Unable to lie recumbent for 90 min
(4) Clinically important pulmonary disease other than COPD (e.g. active lung infection, clinically significant bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hyper-eosinophilic syndrome) and/ or radiological findings suggestive of a respiratory disease other than COPD that is contributing to the subject's respiratory symptoms.
(5) Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and/or could:
• Affect the safety of the subject throughout the study
• Influence the findings of the study or their interpretation
• Impede the subject's ability to complete the entire duration of study
(6) Treatment with systemic corticosteroids and/or antibiotics, and/or hospitalization for a COPD exacerbation within 2 weeks prior to enrollment, based on last dose of steroids or last date of hospitalization whatever occurred later
(7) Acute upper or lower respiratory infection within 2 weeks prior to enrollment

(8) Supplemental oxygen use at greater than 3L/min

Study procedures:

MCC assessment

1) Subjects will perform 2 MCC assessment study days. One to measure baseline MCC and the other to measure MCC during treatment with the cannula. Study days will be separated by 4-7 days. The order of the days will be randomized. Subjects will refrain from SABA use for 6 hours and LABA/LAMA use for 24 hours prior to Visits 2 and 3.

2) Subjects will arrive in nuclear medicine. They will lie recumbent in the nuclear medicine camera while background images are collected. They will then perform a Cobalt-57 transmission scan which allows for visualization of the lung outlines. Both scans are utilized during image analysis.

3) Subjects will be seated for the inhalation of the radiolabeled particles. 4 mCi of Technetium 99m sulfur colloid (Tc-SC) in 2ml of saline will be added to a DeVilbiss 646 Nebulizer driven by a DeVilbiss 8650D compressor and attached to a Spira Dosimeter. Using standardized procedures developed the Cystic Fibrosis Foundation (1), we will deliver the aerosol for 5 approximately minutes using a specified breathing pattern (30 breaths/minute) using inhalation flowrates of ~0.5 L/s.

4) Subjects will then return to the camera and lie recumbent while serial two-minute gamma camera images are collected for 90 minutes. On the intervention day, the nasal cannula will be applied after 5 images are collected. On the baseline day there will be no intervention. Coughs will be manually logged by study personnel.

5) After 90 minutes the subjects will exit the camera and remain in the waiting areas around radiology. They will continue inhaling from the cannula on the intervention day. Subjects will perform a 10 minute follow up image at t=4 hours and 10 minutes after the start of the imaging sequence. The 10 minute image may be delayed for several minutes if the gamma camera is in use at the specified time Subjects would resume their normal medications.

6) We will plot normalized retention vs. time and compare the percentage of deposited material cleared at t=90 min and up to 6 hours on the intervention days. Areas above the curve 90 min clearance curve will also be compared. We will calculate the central deposition percentage of the Tc-SC aerosol to ensure that Tc-SC aerosol delivery was similar on both testing days.

7) Previous measurements from our group demonstrated a standard deviation of the intrasubject differences in MCC measurements (σ) = 7.7% (2). Assuming α=0.05, β=0.2, and n=12 matched pairs, we could detect a 6.8% (absolute) change in MCC rates via paired t-test. Average MCC rates in control subjects over 90 minutes have been reported to be 28.2% (1). MCC rate differences reported by Hasani et al were approximately 8% after 7 days of daily therapy (3).

8) We will replace subjects who do not complete both testing days until we have a total of 12 subjects with completed studies.

Spirometry Testing

Each subject will undergo baseline spirometry assessment to determine eligibility. All subjects will perform baseline pre and post bronchodilator spirometry at Visit1 . Subjects will be asked to hold their bronchodilator (albuterol) for 2 hours prior to the PFT test.

Subjects who meet the PFT criteria at Visit 1 will be required to be tested for COVID-19 prior to undergo the MCC measurements at Visits 2 and 3. The COVID testing will be done at the CTRC Montefiore Hospital by a trained nurse. The COVID testing is a safety measure requested by the PI to make sure staff present during the MCC measurements will not be placed at risk of contracting the virus during the study procedures. Subjects found ineligible per the PFT results, will be considered a screen fail and will not be tested.

Only patients with COVID testing negative will be invited to complete study visits 2 and 3.

Study Questionnaires

All subjects will complete the following self-administered questionnaires at Visit 1:

1) St. George's Respiratory Questionnaire (SGRQ)
2) COPD Assessment Test (CAT)
3) Modified Medical Research Council Dyspnea Scale (mMRC)
4) Exacerbation history

Schedule of Assessments

Visit schedule

	Visit 1	Visit 2	Visit 3
Baseline MCC*		X	
Treatment MCC*			X
Questionnaires	X		
Pre and Post Bronchodilator Spirometry	X		

* Baseline and Treatment MCC are randomized.

The Fisher and Paykel myAirvo2 heater/humidifier and Optiflow nasal cannula are commercially available devices that are used together to deliver heated humidified air or oxygen for breathing. The purpose of this study is to determine whether 4 hours of use of this device will improve mucus clearance in patients with chronic bronchitis. This may occur through hydration of airway secretions and possibly through splinting of the airways. Twelve subjects will be enrolled and perform two imaging days and a possible screening day. The primary outcome measure is mucociliary clearance as measured using a nuclear medicine imaging technique.

References

1. Bennett WD, Laube BL, Corcoran T, Zeman K, Sharpless G, Thomas K, Wu J, Mogayzel PJ, Jr., Pilewski J, Donaldson S. Multisite comparison of mucociliary and cough clearance measures using standardized methods. *Journal of aerosol medicine and pulmonary drug delivery* 2013; 26: 157-164.

2. Locke LW, Myerburg MM, Weiner DJ, Markovetz MR, Parker RS, Muthukrishnan A, Weber L, Czachowski MR, Lacy RT, Pilewski JM, Corcoran TE. Pseudomonas infection and mucociliary and absorptive clearance in the cystic fibrosis lung. *Eur Respir J* 2016; 47: 1392-1401.
3. Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. *Chron Respir Dis* 2008; 5: 81-86.