Cover Page for Protocol

Sponsor-Investigator:	Spyridon Fortis
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Co-Investigators:	Alejandro Comellas, MD Eric Hoffman, Ph.D
Title of Study:	The effect of heated, humidified high-flow air in COPD patients with chronic bronchitis
Study Center:	University of Iowa
Estimated number of subjects:	30 subjects (50% male, 50% female) will be recruited and enrolled in this study.
Study Period:	June 2019 until completion
Estimated date of first enrollment:	June 2019 will be the earliest day of enrollment.
Estimated date of last enrollment:	We estimate that all subjects will be enrolled by June 2021.

I. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by respiratory exacerbations which increase in frequency as the severity of the disease progresses. COPD exacerbations may lead to hospitalizations, which make up the largest proportion of the total direct health-care cost of the disease and are a significant burden for patients and family. Chronic bronchitis, defined as chronic cough with sputum production for at least 3 months a year for 2 consecutive years, is one of the clinical manifestations of COPD. Chronic bronchitis doubles the risk of COPD exacerbations and hospitalizations, and is associated with increased dyspnea, worse health-related quality of life, and poorer quality of sleep. Chronic bronchitis also results in increased air trapping and hyperinflation, which decreases exercise capacity. Unfortunately, other than traditional inhaled pharmacological agents, there are no treatment options for COPD patients with chronic bronchitis.

Heated, humidified high-flow air (HHHFA) devices improve airway clearance. HHHFA use for an average of 1.6 hours a day in COPD patients with chronic bronchitis improves health-related quality of life, lung function, and delays the first respiratory exacerbation. However, HHHFA for an average of 1.6 hours a day had no effect on COPD exacerbation frequency or hospitalization, dyspnea, or exercise capacity, likely due to short duration of the treatment. Conversely, the effect of HHHFA for longer time periods on chronic bronchitis patients has not been studied. Moreover, the effect of HHHFA on sleep quality has not been studied. A prior study in COPD patients showed that use of HHHFA for more than 7 hours during sleep can be achieved. The *overall objective* of this research is to examine the effect of HHHFA during sleep on COPD patients with chronic bronchitis. In this pilot study, we will examine the effect of HHHFA during sleep on clinically relevant short-term outcomes including: respiratory symptoms, quality of life and sleep, lung function and exercise capacity.

Hypothesis 1: HHHFA during sleep in COPD patients with chronic bronchitis improves respiratory symptoms, sleep quality, lung function, and exercise capacity.

Aim 1: To examine the effect of HHHFA during sleep on respiratory symptoms, sleep quality, lung function, and exercise capacity in COPD patients with chronic bronchitis.

The effect of HHHFA on air trapping and hyperinflation has not been studied. Air trapping and hyperinflation as well as other radiographic measurements associated with chronic bronchitis (e.g. airway wall thickness) can be measured using chest CT.

Hypothesis 2: HHHFA during sleep in COPD patients with chronic bronchitis improves air trapping and hyperinflation.

Aim 2: To examine the effect of HHHFA in COPD patients with chronic bronchitis during sleep on air trapping and hyperinflation through chest CT imaging.

Design: We will include COPD subjects with a post-bronchodilator FEV1%predicted below 70% and chronic bronchitis. We will include subjects with at least 2 exacerbations in the last year to identify patients with significant burden due to chronic bronchitis. We will exclude subjects with recent respiratory events or procedures as we want to capture the benefit of HHHFA on chronic, stable COPD participants. Subjects who meet eligibility criteria will be randomized to HHHFA(intervention arm) or usual care (usual care arm). At baseline we will perform measurements in all subjects that include dyspnea, cough, health-related quality of life, and sleep quality questionnaires, spirometry, a 6-minute walk test, and chest CT. The HHHFA device will be provided to participants at the baseline visit.

Subjects will use the device during sleep for 6 weeks and return for an end-of-study visit. At the follow-up visit (6 weeks), participants will repeat all baseline evaluations. At the follow-up visit, participants using the HHHFA will be asked whether they want to continue to participate in the sub-study. For participants that have consented to participate in the sub-study, they will use the HHHFA device for an additional 42 weeks. We will follow these participants who continue to use the HHHFA for 42 additional weeks (total 48 weeks) to assess for respiratory exacerbations.

We will compare changes in variables (e.g. FEV1 etc) over time in each treatment group. We will also compare changes in variables over time between groups. To evaluate the effect of treatment, we will use linear mixed effect models controlling for demographics and lung function.

II. Background

COPD is a leading cause of mortality in the U.S.[1] and worldwide[2] and is associated with high morbidity[3] and resource utilization[3], including costs due to clinic visits, chronic therapy, and frequent hospitalizations.[3, 4] COPD patients experience respiratory exacerbations defined as acute worsening of dyspnea, cough, and sputum production.[5]

Severe acute COPD exacerbations require hospitalization and have a 5-year mortality of 50-76%.[6-10] Fifty percent of patients admitted to the intensive care unit (ICU) with COPD exacerbations are re-hospitalized within 6 months of discharge.[9] COPD exacerbations also reduce patients' quality of life.[11] Moreover, direct health care expenditures for COPD in 2010 were $32.1 billion and projected to increase to $49 billion by 2020.[12] Hospitalizations due to COPD exacerbations alone are responsible for more than 70% of these direct health care costs.[4, 13] Preventing COPD exacerbations, in particular those requiring hospitalizations, would improve patients' quality of life and decrease health care costs of the disease. Therefore, preventing COPD exacerbations is of major importance.

Chronic bronchitis is associated with worse quality of life, exacerbations, and mortality

COPD is a heterogenous disease with various phenotypes.[14] Identifying those COPD phenotypes is critical to individualizing treatment for COPD and improving outcomes.[15] Chronic bronchitis, defined as chronic cough with sputum production for at least 3 months a year for 2 consecutive years, accelerates lung function decline, is associated with more dyspnea and worse health-related quality of life,[16] increases exacerbations and hospitalizations,[16-20] and may increase mortality.[21, 22] Prior studies have shown that COPD patients with chronic bronchitis experience twice as many exacerbations and hospitalizations than COPD patients without chronic bronchitis.[16, 19, 23] Chronic bronchitis is a risk factor for exacerbations independent of lung function impairment.[24] More than half of COPD patients with chronic bronchitis have more than 2 exacerbations every year.[18] Even in smokers with normal lung function, sputum production is associated with increased risk for respiratory exacerbations.[25]

In addition, chronic bronchitis is associated with poor quality of sleep and awakening during the night.[16, 26] Poor quality sleep is very common among COPD patients. Sputum production is the most prominent factor associated with poor sleep in COPD.[27] Thus, more effective treatment of COPD patients with chronic bronchitis would have a great impact on disease burden and likely reduce associated health care costs.

Chronic bronchitis is associated with air trapping and hyperinflation

Chronic bronchitis is associated with increased dynamic hyperinflation during exercise[28] likely due to airway secretions. COPD patients with chronic bronchitis have been shown to cover shorter distances in a 6-minute walk test compared to COPD patients without chronic bronchitis.[28] COPD patients with chronic bronchitis have larger function residual capacity (FRC) and total lung capacity (TLC), and greater airway wall thickness on chest CT than COPD patients without chronic bronchitis[16], again likely due to increased airway secretions. Airway mucus plugging is considered a characteristic of COPD.[29] Nevertheless, quantification of mucus plugging in COPD patients with chronic bronchitis using chest CT is understudied.

Current treatment of chronic bronchitis

Treatment of chronic bronchitis is not different than treatment of COPD in general. Apart from smoking cessation, inhaled pharmacological agents are the mainstay of treatment. Long-acting bronchodilators reduce respiratory exacerbations by 15-20%.[30] Adding inhaled corticosteroids have a similar effect on exacerbations.[31] In a selected group of COPD patients, oral pharmacological agents and non-pharmacological therapies are also associated with decrease in COPD exacerbations.[32] However, the effect of those medications in every daily life may be less.[33] Other than common inhaled pharmacological agents, treatment options specifically for chronic bronchitis are limited.[34] Randomized, placebo-controlled trials examining N-acetylcysteine, the most-known mucolytic, have shown disappointing results.[35, 36]

Heated humidified high flow oxygen/air in chronic obstructive pulmonary disease

Recently, novel nasal cannula systems have become available that can deliver a heated and humidified air/oxygen mixture with a flow rate up to 60 L/minute.[37] Although the main use of these devices is to provide oxygen supplementation in hypoxemic respiratory failure, high-flow nasal cannula devices can be used without oxygen supplementation, providing only heating and humidification in the inspiratory gases (heated humidified high flow air; HHHFA). It is known that proper humidification improves airway clearance[38] and may preserve mucosal integrity and function, facilitate gas exchange, reduce the metabolic cost of breathing, and improve airway host defense.[37] The warm and humidified gas also provides comfort and reduces costs of breathing.[37] The metabolic cost to warm and humidify the cold and dry gas provided by regular oxygen supplementation devices is not negligible. [37] Moreover, HHHFA can wash out the dead space, facilitating CO_2 removal[39] and has a positive end-expiratory pressure (PEEP) effect[40] and, as a result, the cost of breathing is reduced.

HHHFA may be more beneficial in patients with chronic bronchitis as it facilitates airway clearance, improves host defense, and decreases the metabolic cost of breathing,[37] particularly in those patients with recent hospitalizations who are at high risk for subsequent readmissions.[41]

Heated humidified high flow oxygen in patients with stable chronic obstructive pulmonary disease

In a randomized, prospective trial conducted in Denmark, 200 COPD outpatients with chronic hypoxemic respiratory failure were randomized to high-flow nasal cannula or usual care.[42] The average high-flow nasal cannula was 20 L/minute for an average of 6 hours per day. Exacerbation rates were lower in the high-flow nasal cannula group (3.12 per year) relative to the usual care group (4.95 per year; $p<0.001$). Although there was no difference in hospital admission rates between the two groups, increasing duration of high-flow nasal cannula was associated with reduction in COPD hospitalizations. One-year use of high-flow nasal cannula treatment was associated with a statistically significant reduction of hospitalizations, from 1.39 to 0.79 per year ($p<0.001$).

In a multicenter crossover trial, 32 stable COPD patients with hypoxemic and hypercapnic respiratory failure were randomized to receive either HHHFA with oxygen supplementation for 6 weeks followed by oxygen supplementation alone for another 6 weeks, or oxygen supplementation alone for 6 weeks followed by HHHFA plus oxygen supplementation for another 6 weeks.[43] HHHFA was used during the night at flow rates between 30 and 40 L/minute. The flow rate was allowed to be decreased down to 20L/minute for patient comfort. The average usage time was above 7 hours per night. Oxygen could be blended in the HHHFA device and was adjusted to maintain the peripheral oxygen saturation above 88%.

HHHFA improved health-related quality of life and reduced $PaCO_2$ by an average of 4.1 mmHg compared to oxygen supplementation alone.

HHHFA improves outcomes in chronic bronchitis

HHHFA improves airway clearance in patients with bronchiectasis and chronic sputum production.[38] In a prospective study in New Zealand, 108 patients with at least moderate COPD or non-cystic fibrosis bronchiectasis, who had ≥2 respiratory exacerbations in the last year and daily sputum production, were randomized to either HHHFA at 25 L/minute or standard care for 12 months.[44] Patients randomized to HHHFA were instructed to use the device for at least 2 hours per day. HHHFA increased FEV1 and FVC by 0.12 and 0.28L, respectively. HHHFA did not affect the rate of decline in 6-minute walk distances. In the HHHFA group, there was a 14.1 meter (4%) decline whereas in the control group, there was a 29 meter (8.6%) decline (p=0.485). The study showed that rate of decline of the 6-minute walk distance was inversely correlated with improvement of FVC. HHHFA increased the time to the first exacerbation from a median of 27 days to 52 days (p=0.0495). Patients using the HHHFA had 18.2 annual exacerbation days whereas patients in the standard of care group had 33.5 annual exacerbation days (p=0.045). However, exacerbation frequency was not different between the HHHFA (2.97 exacerbations per year) and regular treatment groups (3.63 exacerbations per year; p=0.067). Similarly, hospital admission rates in the HHHFA group (0.39 hospitalizations per year) did not differ from those in the regular treatment group (0.47 hospitalizations per year; p=0.439). The modest effect of HHHFA can be explained by the short duration of treatment. The authors acknowledged that the goal of treatment adherence was 2 hours a day but the average treatment was only 1.6 hours a day. The short duration of treatment is likely the reason that HHHFA did not improve 6-minute walk distances and inspiratory capacity.

Use of HHHFA for longer time periods can be achieved during sleep. In study by Nagata et al, patients were instructed to use HHHFA for at least 4 hours during sleep and patients used it an average above 7 hours a night.[43] Adherence was confirmed by device records. The effect of HHHFA for longer time periods during the night on COPD with chronic bronchitis is unknown. Moreover, the effect HHHFA on COPD patients' sleep is unknown. In this pilot study, we will focus on clinically relevant short-term outcomes that include symptoms, quality of life, quality of sleep, lung function and exercise capacity.

III. Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection and Good Clinical Practice training.

IV. IRB Oversight

Human Subjects Office / IRB
J. Andrew Bertolatus, MD
Hardin Library, Office 105
600 Newton Rd
Iowa City, IA 52242
FWA#: FWA00003007
Voice: 319-335-6564
Fax: 319-335-7310
Email: irb@uiowa.edu

V. Location of Study Procedures

University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242

VI. Main Hypothesis

HHHFA during sleep in COPD patients with chronic bronchitis improves respiratory symptoms, sleep quality, lung function, and exercise capacity.

VII. Main Screening Criteria

We will recruit COPD men and non-pregnant women of any ethnic background with the age above 18 years with the following characteristics: post-bronchodilator FEV1%predicted below 70%, chronic bronchitis defined as cough with daily sputum production, and at least 1 exacerbations in the last year.

VIII. Recruitment procedures

The study team will utilize email blasts and University of Iowa Noon News advertising to recruit subjects for this study. We will also advertise study at the Iowa City VAMC. Upon study beginning and ensuring the smooth operation of the protocol, we will apply to the VA for permission to recruit subjects from the Iowa City VAMC. To avoid any coercion all subjects are offered the opportunity to talk with their primary care provider or family prior to signing a consent form. Study participation has no influence on their medical care.

IX. Inclusion Criteria

- COPD diagnosis by health care provider
- Smoking with at least 10 pack-years
- Post-bronchodilator FEV1/FVC <0.7
- Post-bronchodilator FEV1%predicted <70%
- Chronic bronchitis, defined as chronic cough with daily sputum production
- ≥1 COPD exacerbations within the last year

X. Exclusion Criteria

- Obstructive sleep apnea or suspected obstructive sleep apnea that requires positive airway pressure treatment
- Patients that use oxygen supplementation continuously (patients that use oxygen supplementation only at exertion, as needed, or at night will NOT be excluded)
- Any planned procedure that makes ineligible according the PI clinical judgement
- Unable to perform a spirometry, 6-minute walk test or chest CT
- Recent diagnosis (<2 weeks prior to study entry) of pneumonia, respiratory infection, COPD exacerbation, or acute bronchitis requiring antibiotics and new/increased dose of systemic corticosteroids
- Thoracic surgery or another procedure in the last six months that may result in instability of pulmonary status
- Recent medical or surgical history of upper airway disease that may interfere with intervention (e.g., sinus surgery, significant nasal polyps)
- Recent chest illness (trauma, pneumothorax etc).
- Basal skull surgery in the last 6 months
- Open skin ulcer or rash where the nasal cannula will be worn
- Tracheostomy or laryngectomy
- Pregnancy

XI. Schedule of events

After obtaining informed consent, participants will perform a screening pre-bronchodilator and post-bronchodilator spirometry using the EasyOne Spirometer (Zurich, Switzerland) according to American Thoracic Society-European Respiratory Society standards. Participants who meet eligibility criteria will be randomized (2:1) to receive either HHHFA or usual care for 6 weeks. Randomization will be performed using sealed envelopes.

Baseline visit. After randomization, participants will have baseline measurements and training in the device. Participants will provide information regarding demographics, medical history, COPD history including prior exacerbations, hospitalizations, and pertinent medication use. Weight, height, and vitals will be recorded. Participants will complete Medical Research Council dyspnea scale (MRC),[45] St. George's Respiratory Questionnaire (SGRQ),[46-48] COPD Assessment Test (CAT),[49], Pittsburgh Sleep Quality Index (PSQI),[50], and Cough and Sputum Assessment Questionnaire (CASA-Q).[51] Subsequently, participants will perform a 6-minute walk test follow by an inspiratory and expiratory chest CT. Chest CT will be performed based on quantitative CT lung protocols.[52] TLC and residual volume (RV) will be measured at maximal inspiration and maximal expiration, respectively. We will quantify % emphysema and % gas trapping based on chest CT images. Quantified % emphysema will be defined as the percentage of voxels less than -950 Hounsfield units at TLC. Quantified % gas trapping will be measured at TLC as the percentage of voxels less than -856 Hounsfield units at RV. A parametric response map (PRM) will be constructed to reduce the misclassification of emphysema as gas trapping. Voxels with emphysema on TLC will be eliminated from the voxel count of gas-trapped areas after image matching of TLC and RV images. Airway geometry including Pi10, wall thickness, and visual mucus plugs will also be assessed.[52, 53] Lastly, subjects will receive training and the HHHFA with information materials and a study personnel contact number.

Phone Call at Week 1. Three to seven days after enrollment, a member of the research team will contact the participant to address any concerns or questions regarding the device (device training) and/or the study, and adverse events.

Follow-up visit (6-weeks). After 6 weeks, participants will return to the CRU with the HHHFA device and perform the same procedures in the same order as at the baseline visit including weight, height, vitals, spirometry, MRC questionnaire, CAT questionnaire, PSQI questionnaire, CASA-Q questionnaire, 6-min walk test, inspiratory and expiratory chest CT. Information regarding changes in medication usage including frequency of rescue inhaler, exacerbation and hospitalizations since the last visit will also be collected. Participants in the HHHFA arm will be asked whether they want to continue to participate in the sub-study that will have them use the HHHFA for an additional 42 weeks. Participants that are not interested in participating in the sub-study, will return the device at the 6 week follow-up visit. Participants interested in participating in the sub-study can ship the device to the research team following their completion of the sub-study that will end at 48-weeks.

Phone Call visit at 12-weeks Only participants in the HHHFA sub-study group will receive a phone call at 12 weeks. Assessment for respiratory exacerbations will be performed.

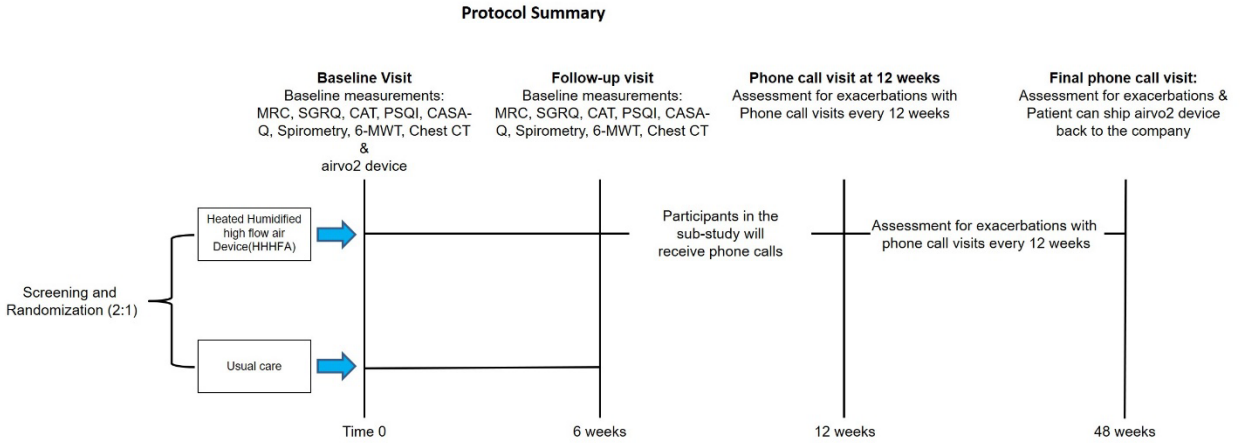
Phone Call visit at 24-weeks. Only participants in the HHHFA sub-study group will receive a phone call at 24 weeks. Assessment for respiratory exacerbations will be performed.

Phone Call visit at 36-weeks. Only participants in the HHHFA sub-study group will receive a phone call at 36 weeks. Assessment for respiratory exacerbations will be performed.

Phone Call visit at 48-weeks. Only participants in the HHHFA sub-study group will receive a phone call at 48weeks. Assessment for respiratory exacerbations will be performed. Patients will ship the HHHFA device back to the company.

Table 1. Schedule of events summary

Activity	**Visit 1**	**Phone Call visit (week 1)**	**Follow-up visit (6-weeks)**	**Phone Call visit (12-weeks)**	**Phone Call visit (24-weeks)**	**Phone Call visit (36-weeks)**	**Phone Call visit (48-weeks)**
Informed Consent	X						
Screening evaluation and enrollment	X						
Spirometry	X		X				
Demographics and medical history	X		X				
Respiratory condition-related medications only	X		X				
Modified physical exam	X		X				
SaO2 at rest	X		X				
Randomization	X						
HHHFA device training and support	X	X	X	X	X	X	X
MRC questionnaire	X		X				
SGRQ Questionnaire	X		X				
CAT score	X		X				
PSQI	X		X				
CASA-Q	X		X				
6-MWT	X		X				
Chest CT	X		X				
Respiratory exacerbation assessment	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
HHHFA Return device			X	X	X	X	X



XII. Study procedures

Vitals, Height and Weight

The subject will have vitals taken by a CRU nurse: Height, weight, blood pressure, SaO2 (saturation of oxygen in the blood), heart rate, temperature, and breathing rate. This will take approximately 20 minutes.

Six-min walk test

The test measures the distance a patient can walk on a flat, hard surface in six minutes.

Urine Pregnancy Test

Women of childbearing potential will have a urine pregnancy test as well. Before beginning the CT and MRI scans, the urine pregnancy test for females of childbearing potential will be checked. If the result is positive for pregnancy subject will be withdrawn.

Spirometry

The subject's FEV1, FVC and the FEV1/FVC ratio will be determined after three acceptable spirometry efforts are obtained. After prebronchodilator spirometric manoeuvres, two puffs of albuterol metered dose inhaler were administered using a spacer. Postbronchodilator manoeuvres were performed between 15 and 20 min.

CT Scans

The subject will be then taken to the Research CT Imaging Suite for their CT scan. A CT scan combines a series of X-ray images taken from different angles and uses computer processing to create cross-sectional images of the lungs. The CT scan will provide more detailed information than a standard x-ray. Once in the CT lab, the subject will be asked to remove any metallic items from their person (jewelry, piercings that can be removed easily, etc.). If the items to be removed involve clothing, the subject will be allowed to change in a

private restroom within the CT Suite and will be given a hospital scrub top to wear. We will explain the scanning procedures again to the subject and they will be reminded that they may ask questions at any time during the procedure(s). The subject will then be placed on the movable exam table of the CT scanner.

Three scans will be done in the CT scanner. One scout scan will be done to position the subject and then a total of two non-contrast CT scans will be done: Total Lung Capacity (TLC) and Residual Volume (RV).

The first scan that will be done is called a scout scan. This brief scan, which is similar to an x-ray, is simply used to help the technologists make sure that the subject is positioned correctly. The subject will then be told to take in as deep of a breath as they can and hold it while the scout scan is done.

Total Lung Capacity (TLC) the subject will be asked to take a deep breath and blow out completely two times, they will then be asked to take a deep breath and hold their breath while the CT scan is being done. This breath hold will last approximately 5-8 seconds.

Residual Volume (RV). For this scan, we will tell the subject to take in a deep breath and blow it out twice before instructing them to take another deep breath in and blowing all of their air out until we see they've reached 0-10% of their SVC and then we will tell them to hold their breath while an image is being taken at RV (5-10 seconds).

Subjects will be asked to bring their cigarettes or electronic cigarettes with them to the visit. They will be asked to smoke one of their cigarettes or vape with their electronic cigarette. They will then repeat the same CT scans.

The spiral volumetric scan protocols use dose modulation with 36 reference mAs, 120kV, pitch of 1, & rotation time of 0.5sec. The CTDIvol for one scan at 36mAs is 2.41mGy, with total DLP of 81.5mGycm for a 30cm scan.

Total effective dose equivalents (HE) for one spiral volumetric scan is estimated to be 160mrem

Total effective dose equivalents (HE) for TLC and RV spiral volumetric scan combined is estimates to be 320mrem

320mrem is ~8% of annual radiation limit for a medical worker.

Total mrem is 640 or ~16% of annual radiation limit for a medical worker.

Heated humidified high flow air (HHHFA)
Participants will be provided the HHHFA at baseline visit (time 0). At follow-up visit (6 weeks), participants using the HHHFA that are not interested in participating in the sub-study, they can return the device at the follow-up visit (6 weeks) . Participants that will participate the sub-study they can ship the device back to the research team at the end of the sub-study(48 weeks).

Participants will be instructed to use the HHHFA for at least 4 hours during their sleep but will be allowed to use it as long as they want during sleep.[43] HHHFA will be administered using myAIRVO 2 device (Fisher & Paykel Healthcare), which provided humidified high-flow gas via Optiflow nasal cannula interface (Fisher & Paykel Healthcare). The temperature will be set at 32-37˚C and flow will be set at 35L/minute but can be titrated down to 20L/minute for comfort based on a previous study.[44] Subjects use oxygen at night can blend the oxygen at the same flow through the device. Adherence of the device will be recorded using the device log.

XIII. Possible Risks of the Study

Spirometry: The subject may become short of breath or experience chest tightness while doing the pulmonary function tests.

CT scans: The subject will be exposed to radiation from the CT scans.

Heated humidified high flow air (HHHFA): According to a previous randomized control trials, that HHHFA applied during the night, six of 32 participants experienced adverse effects related to HHHFA.[43] Four participants experience night sweat, one had nasal discharge, one had insomnia, and one had a skin rash. Other adverse effects associated with the HHHFA device include but are not limited to the following: fire, burns, nosebleed, dry mouth and throat, headache, tripping over the equipment, electrical shock and injury, noise irritation, low oxygen due to improper use of device, skin irritation and injury/damage.

Possible Loss of Confidentiality: To reduce risk of a loss of confidentiality, precautions will be taken to ensure privacy. The PI and study team will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Research records generated in this study will be stored in file cabinets in a locked room and/or on a secure electronic database. The text message server stores the minimum amount of data possible-participant phone numbers and text message responses, no other participant information will be stored on that server. Only authorized study team at the sites will have access to the data. Imaging collected during the study will be identified by a subject number, IRB protocol number, and date of collection.

Abnormal findings:

- False positive scan, which is an abnormality that initially is of concern that is later found not to be a concern. Anxiety may result from false positive results.
- Detection of abnormalities that could lead to unnecessary testing or treatment.
- Failure to detect an abnormality that is present and possibly miss an opportunity for care.

XIV. Adverse Event Assessment

Adverse event information will be collected from all participants at every encounter throughout the study. The investigator and research team will inquire about adverse events until the end of the study at the 6-week follow up study. Medical records will be reviewed for adverse effects.

XV. Adverse Event Reporting

Adverse events will be evaluated by the investigatory for severity and relatedness. Severe adverse events defined as those that interfere participant's daily activity and/or require treatment will be reported to the manufacturer.

XVI. Data Management

The following people/agencies may have access to subject data/records:

- Study team
- Federal government regulatory agencies
- Auditing departments of the University of Iowa
- University of Iowa IRB
- The National Institute of Health

To protect confidentiality, we will assign each subject a study ID. All records will be in a locked cabinet in a locked office or password protected computer system. Data and records will be managed as follows:

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Whenever possible, subject identifying information will be blacked out on all paper or hard copy records and replaced with the subject's unique study identifier. Paper records will be stored in a locked file cabinet in the study team's locked office.
- Electronic records (computer files, electronic databases, etc.) – All electronic data bases will only be accessed by the study team and available only with a username and password assigned to study team by the PI.

XVII. Subject Safety

- To minimize risks all subjects are carefully pre-screened and screened trying to identify any factors that could contribute to increased risk.
- All testing is completed at University of Iowa Hospitals and Clinics by a very experienced and well-trained staff and monitored by the Principal Investigator.
- All confidential information is kept in locked offices and password protected computers only available to study team members.
- The participant has contact information and study team members available 24/7.
- A urine pregnancy test is done on all women of child bearing potential.

XVIII. Statistical Analysis Considerations

Primary outcomes: Sleep quality (PSQI)

Secondary outcomes: Dyspnea (MRC), health-related quality of life (SGRQ and CAT), cough (CASA-Q), lung function (Spirometry), and exercise capacity (6-min walk distance)Chest CT measurements.

Variables will be collected: medical history, comorbidities, MRC, SGRQ, CAT, PSQI, CASA-Q, spirometric variables, 6-min walk distance, Chest CT measurements.

Hypothesis 1: We expect that HHHFA will improve MRC, SGRQ, CAT, PSQI, CASA-Q scores in COPD patients with chronic bronchitis. It will also increase FEV1, and distanced covered in a 6-minute walk test.

Hypothesis 2: We anticipate that HHHFA will reduce air trapping and hyperinflation.

Decrease in air trapping and hyperinflation can explain the improvement in respiratory symptoms, lung function, and exercise capacity. The putative mechanism of that is that HHHFA improves airway clearance.

Statistical considerations and power calculation. Prior studies have shown that HHHFA improves dyspnea, quality of life, and lung function in patients with COPD and daily sputum production. HHHFA has not been shown to improve quality of sleep. A prior study has shown that the average of PSQI in COPD patients with FEV1%predicted above 50% is 9.3 ± 3.8(SD).[54] To achieve a power of 80% at a 2-sided 5% level of significance to detect a clinically significant improvement in PSQI (below 5), we need a sample size at least 27 subjects enrolling ratio of 2:1(HHHFA: usual care). To account for an increased rate of attrition, our goal will be a sample of 30.

Statistical analysis. We will compare variables (e.g. MRC score, FEV1) between baseline and 6-week visits and changes over time in each group. We will use Fisher's exact test for categorical variables and paired t-test or Wilcoxon signed-rank test for normal and non-normal continuous variables, respectively. We will also compare changes in those variables (e.g. change in FEV1 between baseline and 6-week visits) between groups. We will use Fisher's exact test for categorical variables and t-test or Wilcoxon rank sum test for normal and non-normal continuous variables, respectively. To evaluate the effect of treatment, we will use linear mixed-effect models controlling for demographics and lung function.

Statistical analysis will be performed using SAS, version 9.4 and R statistical software (http://www.r-project.org/).

XIX. References

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