Title: Capnography-Assisted Learned Monitored (CALM) Breathing Therapy for COPD

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Statistical Design and Power
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Study Design. The CALM Breathing pilot trial is a single-center, prospective randomized clinical trial. Participants with chronic obstructive pulmonary disease (COPD), dyspnea, and anxiety symptoms will be enrolled and randomized in a 1:1 fashion to the CALM Breathing intervention or to Wait List control. Approximately 40 participants will be randomized from NYU Langone Health (NYULH), Rusk Rehabilitation's outpatient pulmonary rehabilitation referral list. The racial diversity of patients at NYULH will improve generalizability of our findings. The research assistant and psychologist will screen potential participants for eligibility.

A. Study Objectives. The primary objectives of the study are to evaluate the feasibility and acceptability of CALM Breathing.

B. Randomization. Participants will be randomized to two groups in a 1:1 ratio, CALM Breathing of Wait List. The randomization schedule will be generated using a permuted block randomization method, with variable block sizes of 2 and 4 to maintain allocation balance over time. Randomization will be stratified by severity of COPD (GOLD stage I or 2, versus stage 3 or 4) and gender to control for these confounding variables.[1-3] Gender differences have been identified for interoceptive awareness and anxiety.[1] Dr. Oh will prepare the randomization schedule and upload it into the REDCap database.

C. Sample Size Justification. This is a pilot trial, and a formal sample size calculation is not appropriate. Part of the rationale of a pilot is to gather data to inform the design of a full trial; therefore, more robust estimates for non-compliance and loss to follow-up rates in patient groups will be generated by the end of the pilot study and this will inform power calculations for a potential full trial.[4]

D. Feasibility Aim 1. We will calculate % and means to determine whether the following success criteria are met: (1) 40 participants are recruited within 12 months (±3 months); (2) ≥75% participant retention at 4-week (±2 week) evaluation and 3-month follow-up; (3) CALM Breathing session attendance is ≥70%; (4) CALM Breathing homework exercise adherence is ≥70% for (5 days/week) using RR device data and exercise log; (5) A mean of 1 is achieved on CALM Breathing fidelity checklist items and mean of 4 on MITI-4 scale; and (6) PR intake assessment is scheduled for week 6 –10 for ≥75% of all participants. Cutoffs are based on our previous CATCH study and other studies.

E. Acceptability Aim 2. The acceptability of the CALM Breathing therapy will be evaluated based on mixed methods data collected from CALM Breathing attendance, drop-out, and satisfaction ratings, and from semi-structured interviews.[5,6] Acceptability of CALM Breathing will be determined by: (1) ≥70% CALM Breathing attendance; (2) CALM Breathing drop-out rate of ≤10–15%; and (3) mean of ≥2 "good" satisfaction rating for CALM Breathing treatment overall (item 8 of FACIT; (0–4 scale).[6] Single FACIT Treatment Satisfaction items (6 and 8) ask: (1) "Would you recommend this treatment to others with your illness?" (with 0–2 rating scale, 0 = "No", 1 = "Maybe", 2 = "Yes"); and (2) "How do you rate this treatment [CALM Breathing] overall?" (with 0–4 rating scale, 0 = "poor" and 4 = "excellent"). We will also ask, "How do you rate the CALM Breathing home exercises overall?" (and use the same FACIT 0–4 rating scale).

F. Qualitative Analyses Aim 2. Qualitative analyses of de-identified transcribed interviews will be conducted using an inductive approach, whereby, through an iterative process of analysis, acceptability themes emerge from the content of the participants' comments. With close supervision by Dr. Kwon, two raters (a research assistant and research fellow) will independently develop an initial set of core codes, informed by our prior qualitative research.[7] For each core code, raters will ultimately develop one or more "secondary codes" that represent either more specific or restricted aspects of the phenomenon, to contextualize it, or to suggest underlying personal meanings. A codebook defining the codes will be prepared and refined with emerging insights throughout the coding process. Coded transcripts will be analyzed with Dedoose software.[8] We will use the constant comparative analytic method.[9-11] Discrepancies in coding will be resolved through open discussion with the coding team.

G. Secondary Clinical Outcomes.

The patient reported outcomes (PROs) as described below take ~1-hour to administer in total.

a. Dyspnea:
   i. We will use the standardized Chronic Respiratory Disease Questionnaire (CRQ)[12,13] to measure dyspnea intensity with activities. The minimal clinically important difference (MCID) of the CRQ is 0.5 units.[14,15] We will also use the Dyspnea Management Questionnaire Computer Adaptive Test (DMQ-CAT)[16] to measure dyspnea anxiety.

ii. Borg dyspnea will be administered with standardized Six-Minute Walk Test (6MWT) at 0 weeks, after week 4 (post-CALM Breathing), and at 3-month follow-up.[17]

b. Anxiety Symptoms. We will use the following validated anxiety scales to measure change:
   i. Generalized Anxiety Disorder Scale, 7 items (GAD-7).[18] GAD-7 was shown to be sensitive to treatment changes in a large (N = 790) cognitive-behavioral therapy trial.[19]
   ii. Stress: We will measure stress with the 14-item Perceived Stress Scale related to feelings and thoughts. Response choices are from 0 (never) to 4 (very often).[20-22]

c. Exercise Tolerance: We will use the 6MWT to measure exercise tolerance (walk distance) in a 70-feet hallway according to ATS guidelines.[17] Each 6MWT takes ~15-min to administer. To control for a learning effect, the 6MWT will be administered twice at baseline, with at least a 30-minute rest between tests; the highest score will be recorded. The MID for the 6MWT is 26±2 meters for severe COPD.[23,24] The 6MWT distance is correlated moderately-highly with PA,[25] as high as 0.72-0.75 in COPD.[26,27] We will also include a VAS measure of dyspnea anxiety.

d. Physical activity (PA). We will use the norm-referenced Physical Activity Scale for the Elderly (PASE).[28,29] Items use a "past 7 days" time interval and refer to 12 types of activities. PASE scores correlated moderately with a wearable accelerometer (0.64, $p < 0.5$) for participants over age 70 years.[30] A PASE score of <111 predicted severe physical inactivity in COPD.[29]

e. Quality of life. We will use COPD-specific, well validated 8-item COPD Assessment Test (CAT) to measure symptoms and quality of life. The CAT correlates 0.80 with the St. George's Respiratory Questionnaire, a COPD-specific quality of life measure.[31,32] The MCID for the CAT is 1.3 – 2.0 points.[33-35] Generic quality of life will be measured with Patient-Reported Outcomes Measurement Information System (PROMIS-24).[36,37] The Short-form (SF) PROMIS-24 measures: physical function, fatigue, sleep disturbance, and ability to participate in social roles.[37] Higher scores indicate more of the concept being measured.[36] Raw scores will be transformed into item response theory (IRT) calibrations with a mean score of 50 and a SD ±10. The MID of PROMIS scales is half a standard deviation.[37]

f. $ETCO_2$ and RR: Using a breath-by-breath mode, mean resting $ETCO_2$ ("the concentration of CO_2 in exhaled gas at the end of exhalation")[38] and RR will be measured with capnography at rest at baseline, 4-weeks, and 3-month follow-up.[39] A normocapnic range is between 35mmHg and 45 mmHg.[40]

g. Lung Function: Spirometry will be used to measure lung function at 0 weeks (baseline), 4-weeks, and 3-month follow-up.[41] This assessment (plus $ETCO_2$ and RR testing) takes ~10-min.

H. Utilization Outcomes.

a. System Usability Scale: For measuring participant acceptability of using MightySat™ pulse oximeter with RR biofeedback and related Massimo app.[42]

b. CALM Breathing is a transitional care intervention. To begin to explore a potential impact of CALM Breathing on PR utilization and acceptability, we will measure the following participant engagement outcomes: uptake, treatment initiation, attrition rate, and patient activation (using the unidimensional 13-item Patient Activation Measure[43,44]).

Table 2. Pulmonary Rehabilitation Engagement Outcomes

Engagement Outcome	Description
Uptake	% of participants completing initial intake evaluation; drop-out rate at PR commencement.
Treatment Initiation Rate	% completing at least one ET session; drop-out rate after PR evaluation.
Attrition Rate	Drop-out % after commencing PR exercise training.

Proportion of ET Sessions Completed	Number of ET sessions completed in relation to total program number.
Patient Activation	Active engagement by participants in the care process as measured by the Patient Activation Measure.[43,44]

Note. ET = Exercise training; PR = Pulmonary rehabilitation.

I. Mediating (Process) Outcomes.

We will also test feasibility and acceptability of measuring the following mediator variables:

a. Objective Sleep: All participants will wear a triaxial Actigraph (GT3X-BT accelerometer; ActiGraph Corp, Pensacola, Florida) continuously on their non-dominant wrist for 24 hours, 7 consecutive days at pre-intervention (0 weeks), post-intervention (week 6 ±2), and at 3- month follow-up. The GT3X device features validated 3-axis accelerometer and includes integrated wear time, with a sampling rate of 30-100 Hz, recording the degree and intensity of motion every minute. Light sensors embedded in the device will facilitate identification of bedtimes and rise times. Sleep variables will include total sleep time, sleep onset latency (time it takes to fall asleep), awakenings, wake after sleep onset (WASO), sleep efficiency (total time asleep divided by total time in bed). Ten consecutive immobile minutes will be interpreted as sleep onset or end.[45] Participants will be encouraged to use the device event marker or a diary to record: (1) time attempted to fall asleep at night, (2) wake time in the morning to start the day, (3) the start and end time of naps, and (4) any time the Actigraph is removed and replaced. A sleep diary will be used in conjunction with the actigraph device to record such additional information as time reading or working in bed, exercise, use of sleeping pill, and time of an evening meal.

   The Actigraph has been well validated in COPD for objective assessment of both sleep duration and physical activity.[46,47] Bouts of any duration of activity will be included in the volume of PA.[48] A derived physical activity variable will be steps/day, since step counts are associated with adverse COPD clinical outcomes.[49-51] We will also have participants wear a Nonin WristOx$_2$® Model 3150 with USB for one night only at 0 weeks, post-intervention (week 6 ±2), and at 3- month follow-up to identify sleep hypoxia/intermittent hypoxia and to diagnose obstructive sleep apnea.[52] Participants will either bring devices back in person or mail devices back with a pre-stamped, pre-addressed envelope. Objective sleep measurement will enable improved study of endpoints and mechanisms of CALM Breathing efficacy and sleep as a potential mediator in a future efficacy trial.

b. Interoceptive Awareness: We will use the 37-item Multidimensional Assessment of Interoceptive Awareness (MAIA) scale, version 2.[53,54] It consists of eight factors or scales (noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting). Its 6-point scale ranges from 0 (‘never”) to 5 (“always”) relevant to general daily life.

c. Anxiety Sensitivity Index (ASI-16). Anxiety sensitivity or “fear of arousal-related physical sensations,”[55] a personality trait, is measured with the ASI-16, a well-validated 16-item scale. Its 5-point scale ranges from 0 (“very little”) to 4 (“very much”); it has a 0-64 total score range.[56] The ASI-16 consists of four subscales: fear of trembling and fainting, fear of cardiopulmonary and gastrointestinal sensations, fear of cognitive symptoms, and fear of symptoms in public.[56]

d. Dyspnea Self-Efficacy: We will use the Dyspnea Management Questionnaire (DMQ) Computer Adaptive Test (DMQ-CAT) to measure dyspnea self-efficacy.[16] Raw scores are transformed into IRT calibrations with a mean score of 50 and a SD ±10.

e. Nasal symptoms: The 20-Item Sino-Nasal Outcome Test (SNOT-20)[57] measures rhinosinusitis, a common comorbidity of COPD. Items use a 0 to 5 scale; higher scores are worse. It is valid and sensitive to change.

f. Depression: Patient Health Questionnaire (PHQ-9),[58,59] with 9 items, will be used to measure depression symptoms. It is derived from the PRIME-MD, a diagnostic instrument. Nine items use a 4-point response scale (0 = "not at all", 3 = "nearly every day"). An additional item asks participants to rate the impact of their depression symptoms on daily activities ("do work", "take care of things at home", or "get along with others"); this item has 4 response choices ranging from "not difficult at all" to "extremely difficult". PHQ-9 was shown to be responsive to treatment changes (N = 790).[19] Depression was found to mediate the relationship between change in dyspnea and change in dyspnea-anxiety in COPD.[60]

J. Analysis Plans. Statistical comparisons will be performed using two-sided significance tests and two-sided confidence intervals. We will begin all analyses with descriptive summary statistics and graphical displays of all variables, with attention to assessing balance in these characteristics by intervention group, and with assessment of the distribution of variables, relevant to the choice of statistical tests. All analyses will be conducted using the principle of "intention-to-treat" in which every participant is assumed to have received his/her assigned intervention, regardless of adherence. As indicated, rather than firm "go/no-go" feasibility and acceptability criteria, our criteria permit a range of acceptable results. Preliminary analyses will compare the demographics and scores of the CALM Breathing and Wait-List Control groups at baseline to identify any differences that may need to be controlled for in subsequent analyses. Assessment of secondary clinical outcomes will not involve hypothesis testing. We will explore within- and between-group effects for secondary clinical outcomes and PR uptake and treatment initiation outcomes. We will adjust for stable anti-anxiety and antidepressant medication use (SSRIs and SNRIs) in statistical analyses. We will conduct sub-group analyses based on gender and presence or absence of anxiety disorders to identify any differences in CALM Breathing session attendance and home breathing exercise adherence. We will use this information to determine whether refinement of the intervention is needed to improve tolerance and acceptability in preparation for a larger clinical trial.

K. Other Considerations

a. Missing data. We will make every effort to prevent and avoid missing data. Even with the most robust processes, however, some missing data is inevitable. We will assess the mechanism of missing data by comparing participants with and without missing values to detect any patterns in demographics or other characteristics associated with missing data. For continuous endpoints, we will consider multiple imputation before analysis; this robust approach imputes several values for each missing element to properly account for variability and provide correct inference.

b. Multiple comparisons. Because of the limited sample size in this pilot feasibility trial, and the descriptive/exploratory nature of the planned analyses, we have not proposed any formal corrections for multiple comparisons.

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