Sustainability of Pulmonary Rehab Gains
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Introduction. Chronic obstructive pulmonary disease (COPD) is characterized by progressive airway obstruction and limited exercise tolerance.[1,2] A major determinant of limited exercise tolerance in COPD is the development of exercise-induced dynamic hyperinflation.[3] The severity of exercise-induced dynamic hyperinflation can be reduced using several strategies[4] including a novel breathing-retraining technique that we developed.[5] By combining this technique with exercise-training, patients with COPD can achieve greater improvements in symptoms, functional status, and quality of life than with exercise-training alone.[6-8]

A crucial aspect of any pulmonary rehabilitation program is the maintenance of the early benefits of rehabilitation over the long-term.[9,10] Unfortunately, in most patients those benefits significantly decrease six to twelve months after traditional rehabilitation programs have ended,[9,11,12] and nearly disappear thereafter.[13] The inability to maintain the benefits of traditional rehabilitation over time exposes patients to an increased risk of functional decline, exacerbations, hospitalizations, and worse quality of life.[9,12,14,15] The few patients in whom the benefits of traditional pulmonary rehabilitation persist over time are those who achieve high self-efficacy.[13]

Cognizant of these findings, we explored whether self-efficacy was affected by our breathing technique in 64 COPD patients undergoing rehabilitation.[5] In that study, self-efficacy (quantified in terms of mastery over breathing) was greater after exercise-training plus breathing-retraining than after exercise-training alone.[5] This observation raises the possibility that COPD patients undergoing rehabilitation programs where breathing-retraining is combined to traditional exercise-training may maintain the beneficial effects of rehabilitation for a longer time than patients undergoing traditional exercise alone. Accordingly, we propose to test the hypothesis that in COPD patients, improvements in exercise duration on a constant-load treadmill test will be greater after completing 12-weeks of breathing-retraining plus treadmill exercise followed by a 42-week adherence-intervention program (one year total) than after completing 12-weeks of treadmill exercise alone followed by a 42-week adherence-intervention program. The adherence-intervention will consist of weekly phone calls and monthly 'booster' visits to reinforce both exercise and, for the breathing-retraining group, breathing training. In addition, we propose to study potential mechanisms that can affect long-term sustainability of the gains achieved through pulmonary rehabilitation.

Hypothesis/Research Questions

Primary

H_1 In patients with COPD, improvements in exercise duration on a constant-load treadmill test will be greater after completing 12 weeks of breathing-retraining plus treadmill exercise-training followed by a 42-week adherence-intervention program (one year total) than after completing 12 weeks of treadmill exercise-training alone followed by a 42-week adherence-intervention program (one year total).

Secondary

H_2 One year after randomization, reductions in exercise-induced dynamic hyperinflation during a constant-load treadmill test will be greater in the breathing-retraining group than in the exercise-alone group.

H_3 One year after randomization, improvements in the 6-minute walk distance will be greater in the breathing-retraining group than in the exercise-alone group.

H_4 One year after randomization, improvements in perceived mastery over breathing will be greater in the breathing-retraining group than in the exercise-alone group.

General Overview of Design. The proposed study has been designed as a randomized, controlled clinical trial. After completing baseline testing, patients will be randomized to one of two groups: breathing-retraining plus exercise-training or exercise-training alone. We did not include a non-treatment group as it has been clearly demonstrated that patients randomized to a non-treatment group (no exercise-training) experience no significant improvements in exercise capacity.[12,16]

Sample Size Calculation. Sample size calculations for the current proposal are based on two considerations. First, in our previous investigation[6] we observed that the mean exercise endurance 6 weeks after the completion of training was 7.0 min greater with exercise plus breathing-retraining than with exercise alone. When the analysis was restricted to those patients who developed exercise-induced dynamic hyperinflation, the difference was 8.27 min. Second, due to greater gains in mastery over breathing with exercise plus breathing-retraining than with exercise alone,[47] we expect that the difference in exercise endurance between the two groups will widen over time – i.e., we expect that the breathing-retraining group will better maintain the benefits of rehabilitation than the exercise-alone group. Based on these considerations we conservatively estimate that the difference in exercise duration between the groups at 12 months will be 8.27 minutes with a pooled standard deviation of 13.7 min (effect size =.60).

This means that to achieve 85% power, 100 patients are needed (50 in each group) using two-sample t-test (α =.05).

According to the local IRB, enrollment is the equivalent to a patient signing an informed consent. In our three latest studies,[6,7,84] 30-46% of patients who signed the informed consent (i.e., enrollees) did not meet PFT criteria or did not qualify for other reasons. Accordingly, to have complete data on 100 patients while accounting for attrition due to disqualifying conditions, lack of exercise-induced dynamic hyperinflation, and short-term and long-term attrition, we plan to 'enroll' 250 patients (i.e., signed informed consent) and to 'randomize' 140 of them.

Recruitment. Patients with moderate-to-severe COPD, ≥ 40 years of age, will be recruited from the outpatient Pulmonary Medicine Service at the Hines VA (**Table 1**). No patient will be excluded based on gender or ethnicity. About 9 patients per month will be 'enrolled' with 5 of them being 'randomized'.

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• ≥ 40 yr of age	• Respiratory infection/exacerbation within the previous four weeks
• $FEV_1 \leq 70\%$	• Exercise limiting heart disease (+ stress test or other indicators of heart disease or complaints of angina during the stress test)
• $FEV_1/FVC < 70\%$	• Primary asthma
• $RV/TLC \geq 120\%$	• Congestive heart failure (New York Heart Association Class III or IV)
• mean $SpO_2 \geq 90\%$ at peak exercise (w/ or w/o O_2)	• Exercise-limiting peripheral arterial disease (stops exercise due to intermittent claudication)
• Inspiratory capacity decline of >0.15L from rest to peak exercise	• Stops exercise due to arthritic pain in the knee or hips (self-report)
	• Inability to walk on the treadmill
	• Pregnancy
	• Any unforeseen illness or disability that would preclude exercise testing or training
	• Participation in a formal exercise program within the previous 12 weeks

Screening and Baseline Testing. Proposed study participants will be screened for eligibility and written informed consent will be obtained. All testing and training will take place at Hines VAH's Physical Performance Research Laboratory. During screening, patients will be asked about their medical history and medication use. This will be followed by physical examination, pulmonary function testing and completion of quality of life/dyspnea questionnaires. Then, patients will undergo an incremental-load treadmill test. Thereafter, eligible patients will perform the baseline tests[7] that include two constant-load treadmill tests, functional assessment of the respiratory muscles and quadriceps, quadriceps ultrasonography, physical activity monitoring and 6-min walk test. After the baseline testing is completed and study criteria are met, patients will be randomized to breathing-retraining plus exercise-training or to exercise-training alone.

Randomization will be computer-generated with permuted blocks with random block sizes. This strategy is intended to preserve balance in the randomization of patients to maintain unpredictability of the treatment assignments. Group assignment will be managed by the Hines Cooperative Studies Program Coordinating Center (CSPCC). When a patient is ready for randomization, we will contact the CSPCC to receive the randomization designation. To maintain testing integrity, one Co-PI will supervise patient testing and will be blinded to group assignment. When data are reviewed, the data will be void of any identifiers.

Exercise Prescription (All patients). Ambulation is a critical element to achieve adequate quality of life and independence. Accordingly, the primary mode of training will consist of ambulation on a treadmill. An individualized treadmill exercise prescription (interval training)[34,36,89] will be prepared for each patient. This prescription will specify exercise intensity, duration of exercise intervals, duration of recovery intervals, and number of repetitions). During training, patients will progress through six levels of exercise intensity.[90] At *'Level 1'*, patients will exercise for a total of 25 min with 5 min of aerobic exercise at workloads equivalent to 60, 65, 70, 75 and 80% of VO_{2peak}. By the time patients progress to *'Level 6'*, they will complete a total of 50 min of aerobic exercise, with 35 min of training at 80 and 85% of $VO_{2peak.}$ Rest periods between exercise intervals will be based on individual recovery patterns.[7]

All training sessions will also include progressive upper and lower body resistance exercises.[7] Upper body resistance exercises will be carried out using rubber bands (TheraBand™), light hand weights and a Series II 8400 Schwinn Strength system.[7] Lower body resistance exercises will be carried out using a LifeFitness leg curl, leg extension and leg press.[45] Patients will complete upper body exercises that recruit accessory muscles of respiration[7] and lower body exercises that recruit muscles of ambulation. Upper and lower body resistance training will include 6-8 exercises (e.g., triceps extensions, lateral arm raises, leg press), it will be progressive (i.e., bands with greater resistance and heavier weights will be used as

patients' strength improves), and it will be completed in two sets of 12-15 repetitions per exercise.[7] Patients will be instructed to avoid breath-holding during resistance exercise training.

All patients will exercise 3 times weekly for approximately 25-50 min of aerobic training and approximately 15 min of resistance training. To enhance self-efficacy for exercise during activities of daily living and mirror "real-life" home exercise, two exercise sessions during the last two weeks of training will take place outside of the lab (i.e., in the hallways or outdoors). During these sessions, the patient and trainer will problem solve real-life issues such as using perceived severity of exertion and perceived severity of breathless to gauge exercise intensity outside of the lab and, for the breathing-retraining group, practice slow breathing without the computer feedback. During testing and training, supplemental oxygen will be administered as needed to maintain SpO_2 ≥90%.

Exercise-Training. For all patients, training sessions will include a warm-up period, an interval training period, and a cool down period.[7] Before, during and after training, heart rate, blood pressure, perceived severity of exertion and perceived severity of dyspnea (Borg ratio scale) will be recorded.[7] Patients will receive instructions on how to use the Borg scale.[7] The *Level* of exercise intensity will be based on protocol guidelines. Patients will complete at least two training sessions at each *Level* before progressing to the next *Level*.[7] This progression will be based on rating of dyspnea (consistent ratings < 3 [moderate dyspnea]) and/or reduction in the duration of rest periods between exercise intervals.

Breathing-Retraining. Breathing-retraining will be conducted with the same strategy we successfully used in our previous studies .[6-8] Patients will breathe through a pneumotachometer interfaced to a computer. Inhalation (T_I) and exhalation times (T_E) will be displayed on the computer's screen as moving horizontal bars. T_I and T_E goals will be shown as ''targets'' on the screen. These goals, and thus, respiratory frequency goals will be based on the breathing pattern recorded during the baseline incremental-load test.[6-8] During inhalation, the bar on the computer screen will move to the left of the screen; during exhalation, it will move to the right. Patients are given a score ("hit" or "miss") with each breath. If at any time during training the patient is not able to hit the exhalation and inhalation targets at least 85% of the time, the respiratory rate will be increased by 1 breath/min increments until the patient can consistently "hit" the targets. When the patient is again able to hit the targets at least 85% of the time, the breathing-retraining parameters will be returned to levels corresponding to the goals of respiratory pattern for the given level of exercise. To avoid a potential placebo effect (i.e., desensitization to exercise-induced dyspnea as a result of being distracted by the computer screen), patients in the exercise-only group will train while watching scenic venues on the computer screen.

Adherence-Intervention Program. Following the 12 weeks of supervised training, all patients will participate in the adherence-intervention program developed. This adherence intervention program consists of three elements: use of pedometer, weekly motivational phone interviews and monthly 'booster' structured rehabilitation session in the lab.

Pedometer. All patients will receive a pedometer with weekly step goals. The initial goal will be to walk 800 more steps than the number of steps walked during Week-12 of supervised training. Patients will be instructed to increase the number of weekly steps as recommended by Moy et al.[91]

Weekly Motivational Interviewing by Telephone. Motivational interviewing is a patient-centered, directive style intervention intended to enhance readiness for lifestyle change by helping patients explore and resolve ambivalence.[92] The weekly motivational interviews by telephone will be preferably carried out by the trainer who primarily worked with the patient. The purpose of these interviews is to strengthen the patients' motivation and commitment to the program. The trainer will ask patients how often they exercised during the previous week and for how long. Patients in the breathing-retraining plus exercise group will also be asked on their use of the breathing techniques taught in the lab. If patients are not adherent to the home program, the trainer will work with them to overcome or minimize real or perceived barriers to adherence. We expect that each phone call will last about 10 min.

Monthly Booster Training Sessions. These sessions are intended to review information previously taught to the patients, to re-evaluate each patients' home program and to provide reinforcement and encouragement. During the booster sessions, patients will undergo exercise-training at the same intensity as in the last lab session. (We recognize that there may be a need to adjust the intensity of exercise in some patients.) Upon completion of exercise, staff will discuss facilitators and barriers to physical activity outside the lab. For breathing-retraining patients, the booster session will include breathing-retraining set with the same specifications as the last session completed in the lab. In these patients, the session will include a discussion to reinforce the need to practice the breathing strategies taught in the lab during activities of daily living. Based on the findings of McAuley et al,[93] we reason that the proposed booster

sessions will have a powerful effect on self-efficacy as they will provide information on mastery and additional motivation to the patients.

Time Summary. The two groups of patients will complete the same testing procedures at the same time intervals. During training, all patients will exercise in the laboratory for about 1 hour thrice weekly.

Treadmill Test Protocols. All treadmill tests will be separated by at least 48 hours of rest.

Incremental-Load Treadmill Test. The purpose for this test is to determine the patient's VO_{2peak} and his/her breathing pattern during exercise. This information will be used to set the workload during the constant-load treadmill test and to set the breathing-retraining goals during exercise-training. At the start of the incremental-load test the treadmill will be set at 0% grade and at a speed of 1.8 mph. Every 30 seconds during testing, the incline will increase by 0.5%. Additionally, after minute 6 of the protocol, the treadmill's speed will increase by 0.2 mph every 3 min. With this protocol, energy demands step up by one metabolic equivalent (MET)[94] every 3 min.

Constant-Load Treadmill Test. The purpose of this test is to determine exercise duration, respiratory pattern, extent of exercise-induced dynamic hyperinflation, dyspnea and leg fatigue at randomization, after 12-weeks of training and 6 and 12 months after randomization. The speed and grade of the treadmill will be the same as the speed and grade recorded when patients reached 85% of their VO_{2peak} during the baseline incremental-load treadmill test.

Recordings During Incremental-Load and Constant-Load Tests. During all treadmill tests, cardiac activity (Leads II, V1, and V5; General Electric), SpO_2 (Nellcor Works), airflow (MedGraphics). VO_2 and VCO_2 (MedGraphics) will be monitored continuously. This setup allows us to record of minute ventilation, tidal volume, and respiration rate as well as breath-by-breath recordings of gas exchange.

As previously described,[6,7,84] VO_{2peak} will be the highest value of VO_2 recorded between the 60 sec before and 30 sec after the incremental-load treadmill exercise test ends, when patients have reached their 'peak effort'.

Inspiratory capacity will be measured just before each exercise test, every 2 min throughout the test, at peak exercise and at 2 and 4 min into recovery.[7] Similarly, blood pressure will be recorded every 2 min. Ratings of perceived dyspnea and exertion will be obtained using Borg's ratio scale[49,50] during the last 30 sec of each stage of exercise. For patients experiencing exercise desaturation (SpO_2 <90%), an oxygen reservoir system (100 L Douglas bag) will be used for continuous oxygen supplementation.[7]

Chronic Respiratory Disease Questionnaire (CRQ). This questionnaire is designed to determine how the lives of patients with chronic airflow limitation are affected by the illness and the perceived impact of symptoms and limitations on quality of life.[105] The 20 questions on the CRQ measure four dimensions: dyspnea, fatigue, emotional function, and the patient's feeling of control over the disease (mastery). Each question is scored during a structured interview. Test-retest reliability and validity of the CRQ have been established.[106] Patients will not be informed of their previous responses on the questionnaire when the CRQ is administered at follow-up. CRQ scores will be used as covariates in the final analysis if appropriate.

Short Form-36 Health Survey (SF-36): This is a general health-related quality of life instrument to quantify perceived physical function and mental health.[107,108] The SF-36 will be used to describe the sample and to have a comparator measure to published clinical pulmonary rehabilitation programs.[109]

Charlson Comorbidity Index. This validated[110] and widely utilized index[65,66] will be used to determine whether comorbidities influence study outcomes.

Depression and Anxiety. To control for the influence of ongoing depression and anxiety on adherence, the Center for Epidemiologic Studies Depression Scale (CES-D)[111] and the State-Trait Anxiety Inventory (STAI)[112-114] will be administered at baseline and at major data collection time-periods. CES-D and STAI scores will be used as covariates in the final analysis if appropriate.

Self-Efficacy. The Self-Efficacy for Walking[115] and the Self-Efficacy for Shortness of Breath questionnaires[116] will be used to measure self-efficacy at all time periods.[115,117] These are reliable and valid[116] instruments designed to assess a patient's confidence in keeping shortness of breath from interfering from walking or from doing what they want to do.

Exacerbations. Approximately 50% of patients with moderate-severe COPD are expected to experience an exacerbation over the course of 12 months.[15] Exacerbations negatively impact adherence to exercise programs and quality of life.[15] Exacerbations will be monitored weekly throughout the study. Acute exacerbations are defined by changes in sputum color, volume or consistency and are accompanied by an increase in dyspnea.[60] Acute exacerbations are classified as mild (the need for increased use of inhaled bronchodilators only), moderate (the need for systemic corticosteroids and/or antibiotics), or severe (the need for hospitalization).[60] Since moderate exacerbations usually resolve in approximately two weeks,[118]

patients who experience an exacerbation within two weeks of testing will have their testing deferred until the exacerbation has resolved.

Statistical Analysis. Descriptive statistics will be used to summarize baseline characteristics of participants. Comparison of the two groups (breathing-retraining plus exercise-training and exercise-training alone) will be undertaken for all baseline variables to determine whether any imbalances on purported prognostic factors exist. T-test for two independent samples will be used for comparison of the two groups at baseline, continuous data and changes in continuous outcomes from baseline to end of treatment. The continuity-corrected chi-square test will be used to compare categorical data in the two groups at baseline and end of treatment. When this test is not appropriate due to small category frequencies, Fisher's exact test will be used. To examine the potential for response bias, baseline measurements of patients who complete and do not complete follow-up visits will be compared. This procedure will be done for the overall study sample and for each randomized group.

Primary Hypotheses:

H_1: IN PATIENTS WITH COPD, IMPROVEMENTS IN EXERCISE DURATION ON A CONSTANT-LOAD TREADMILL TEST WILL BE GREATER AFTER 12 WEEKS OF BREATHING-RETRAINING PLUS TREADMILL EXERCISE-TRAINING FOLLOWED BY A 42-WEEK ADHERENCE-INTERVENTION PROGRAM (ONE YEAR TOTAL) THAN AFTER 12 WEEKS OF TREADMILL EXERCISE-TRAINING ALONE FOLLOWED BY A 42-WEEK ADHERENCE-INTERVENTION PROGRAM (ONE YEAR TOTAL).

The principal analysis of the primary outcome measure will compare changes in duration of exercise from baseline to end of follow-up in the constant-load treadmill test using the 2-sample t-test (two-tailed P =.05). The primary analysis will be based on intention-to-treat principles (i.e., all randomized patients will be included in the analysis). Multiple imputation will be used for study patients who are missing the 12-month measurement. This imputation model will be based on the baseline characteristics of the study participants. The primary analysis will be repeated, restricted to patients who complete the treatment protocol. Linear regression will be used to determine whether the observed treatment persists after adjustment for baseline covariates and measures of treatment adherence. Since several measurements will be taken on each patient, mixed-models analysis will be used to compare the changes on the constant-load treadmill test over time between the two groups. The missing data pattern will be explored to determine whether data have been informatively censored. If the data do not appear to be missing at random, an indicator variable (alone and as an interaction with slope) will be used in the model to separately estimate intercepts and slopes for the censored group and the group with complete data. At the patient level, random intercepts and slopes will be assumed. Several correlation structures will be evaluated to determine which best represents the observed correlation structure. We will also use multiple imputation to estimate the missing values in the mixed-model ANOVA as a sensitivity analysis. This will be accomplished in two ways. The first multiple imputation technique will account for the treatment group to which each study participant was randomized. We will then use a second multiple imputation model in which all missing values are imputed from a model that only includes data from the control group. This latter multiple imputation model will provide a lower bound (or conservative) estimate of the treatment differences.

***Secondary Hypotheses*:**

H_2: ONE YEAR AFTER RANDOMIZATION, REDUCTIONS IN EXERCISE-INDUCED DYNAMIC HYPERINFLATION WILL BE GREATER IN THE BREATHING-RETRAINING GROUP THAN IN THE EXERCISE-ALONE GROUP.

Statistical analysis for H_2 will parallel that of H_1.

H_3: ONE YEAR AFTER RANDOMIZATION, IMPROVEMENTS IN THE 6-MINUTE WALK DISTANCE WILL BE GREATER IN THE BREATHING-RETRAINING GROUP THAN IN THE EXERCISE-ALONE GROUP.

Statistical analysis for H_3 will parallel that of H_1.

H_4: ONE YEAR AFTER RANDOMIZATION, IMPROVEMENTS IN PERCEIVED MASTERY OVER BREATHING WILL BE GREATER IN THE BREATHING-RETRAINING GROUP THAN IN THE EXERCISE-ALONE GROUP.

Statistical analysis for H_4 will parallel that of H_1.

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