Improving exercise capacity in chronic obstructive pulmonary disease patients through uphill walking

September 14, 2023

NCT04026529

A. BACKGROUND AND SIGNIFICANCE

A.1 COPD is an important Veteran health issue. COPD is currently the third leading cause of death in the United States and worldwide.[5] The prevalence of COPD in the United States Veteran population, ranging from 33%-43%, is approximately five-fold higher than among the general population of the United States.[1, 2, 4] A two-fold increase in risk of developing COPD was found in those working in the armed forces.[6] Active smoking continues to be a significant risk factor for COPD in the Veteran population.[7] Further, the prevalence of chronic lung disease (i.e., COPD, asthma, and interstitial lung disease) has steadily increased from 2003 to 2011 in VA care[8] inferring that pulmonary disease will continue to be a major health concern for the VA.

A.2 Exercise performance is limited in COPD and largely attributed to dyspnea (breathlessness) and dynamic hyperinflation (air trapping).[9, 10] For a large number of patients, exercise is limited by reaching a maximal amount of additional air that can be drawn into the lungs (inspiratory reserve volume). Dynamic hyperinflation in the presence of expiratory airflow limitation is a characteristic of COPD. Increasing respiratory rate causes insufficient time for subsequent emptying. As a consequence, air becomes progressively retained in the lung (dynamic hyperinflation), and this is the primary cause of symptomatic breathlessness in COPD.[11] Skeletal muscle strength also limits exercise in COPD, and this is often the outcome of severe detraining (i.e., use it or lose it) that develops in COPD patients.[12]

Exercise performance is the result of the interaction between intensity (power output) and exercise duration. Exercise intensity is characteristically limited by inspiratory capacity, which, in turn, can be compromised by dynamic hyperinflation and ensuing dyspnea. Our study is based on the observation that respiratory rate will increase if gait speed increases, since breathing and walking coupling is less likely to vary at a simple ratio (1 stride:1 breath) in patients with COPD. The key hypothesis we will test is that exercise on a slope will permit higher intensity exercise without increasing respiratory rate. This is important, as intensity is a major driver of training benefit.

A.3 Coupling of walking and breathing presents a novel approach to increase exercise performance. Extensive research demonstrates the presence of entrainment of movement and respiration in humans.[13-16] It is well established that locomotor and respiratory rhythms strongly influence each other.[17-19] There have been several pathways proposed that may mediate this coupling.[17, 20-22] Importantly, when rhythms are optimally coupled, energy expenditure is economized.[23, 24] Our work demonstrates that patients with COPD display an unvarying coupling pattern with very low ratios at a self-selected walking speed (e.g., 1 stride:1 breath; Figure 2).[3] Further, we show that energy expenditure is increased during walking in patients with COPD and is associated with abnormal coupling of breathing and walking as compared to healthy controls.[25] Thus, in COPD patients, faster treadmill speeds drive increased stepping cadence and increased respiratory rates with earlier onset of dynamic hyperinflation and dyspnea, ultimately contributing to shorter exercise duration.

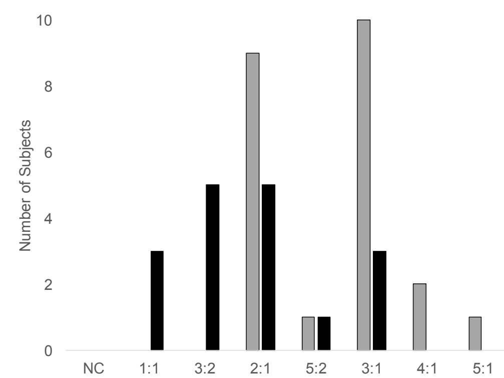

Figure 2. The most frequently used coupling frequency ratios (strides:breath) from 17 patients with COPD (black) and 23 control subjects (gray) while walking at a self-selected walking speed.[3] More patients with COPD use less complex ratios such as 1:1 and 3:2. Patients with COPD do not use higher ratios such as 4:1 and 5:1. These results are consistent under various walking speeds. NOTE: NC=no coupling

A.4 Walking uphill offers a unique approach to optimizing walking and breathing coupling. Walking uphill presents different mechanical and metabolic demands from level ground walking. Uphill walking introduces a new obstacle as compared to level walking because the body must expend more energy to fight the increased amount of work needed to move the body's mass against gravity.[26] Energy requirements, amount of work, and muscle activation increase with steeper uphill slopes. At slopes greater than 0.2%, the energy cost of walking becomes proportional to the slope.[27] During uphill walking, self-selected speed decreases with increasing slope.[28] This could be due to metabolic constraints and/or mechanical constraints that are altered during uphill walking.[28-30]

Our preliminary work, as well as published literature, supports the overall hypothesis that having patients with COPD walk a slight slope at a slower walking speed may lower respiratory rate, mediated by optimized walking and breathing coupling, and result in a delayed onset of dynamic hyperinflation and dyspnea as compared to level treadmill walking that relies on increased speed to increase workload.

B. PRELIMINARY STUDIES AND CURRENT STATUS OF THE FIELD

B.1 Preliminary work

In addition to our published work[3, 25, 31] demonstrating abnormal coupling ratios and their association with energy expenditure in patients with COPD, we have conducted a preliminary study investigating the effects of uphill walking on coupling ratios.

Walking on a slope alters coupling in older adults. The goal of this study was to investigate the effect of walking on a slope on energy expenditure and breathing and walking coupling in healthy young and healthy older adults. Ten healthy young adults (Mean(SD): 22.5(1.1) years) and 10 healthy older adults (67.9(3.9) years) were asked to walk at their preferred walking speed on a treadmill that was either level (0% slope) or sloped (10% slope). Energy expenditure, rating of perceived exertion, as well as breathing and walking coupling ratios were quantified. Older adults walked at a slower speed uphill as compared to young adults. Uphill walking increased energy expenditure ($p<0.001$) and rating of perceived exertion ($p<0.001$) above level walking. Breathing and walking coupling ratios became more variable in older adults during uphill walking as compared to level walking (Figure 3).

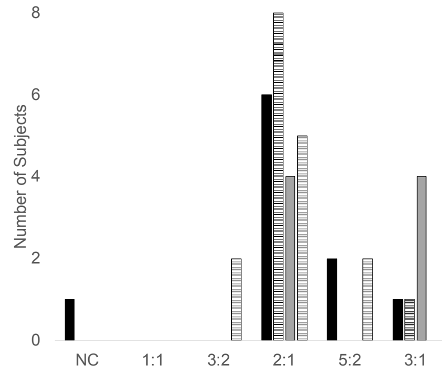

Figure 3. The most frequently used coupling frequency ratios (strides:breath) from 10 young (black) and 10 older adults (gray) while walking level (solid) and uphill (stripe). Older adults used more ratios (increased variability) when walking uphill as opposed to level walking. NOTE: NC=no coupling

B.2 Current status of the field

A dearth of information exists on the effect of slope walking in patients with COPD. Previous focus, although limited, has been on downhill walking.[32-34] Decline walking requires controlled, eccentric contractions of the lower-extremity musculature, considered a more stressful walking condition compared to level walking.[35] Eccentric muscle contractions lead to increased muscle damage, muscle soreness, and fatigue.[36, 37] Recent research demonstrates improvements in exercise capacity after a downhill walking program; however, muscle soreness between training sessions was not measured and reported.[32, 33] In addition, it has been shown that during decline walking, healthy young persons must tightly control their angular momentum as to maintain stability and this may be difficult for pathological populations, increasing their risk of falls.[38] Our approach focuses on uphill walking at slight slopes. This approach increases exercise intensity through increased mechanical demand to move the body against gravity; however, this is done through concentric muscle contractions. For the most detrained individuals, this approach limits immediate effects of muscle damage, soreness, and fatigue, leading to increased confidence and efficacy in exercise performance.

Other strategies have been explored to permit tolerable exercise at higher intensity in COPD. Interval exercise, for example, has been shown to increase exercise duration,[39, 40] but has yet to show a superior training effect.[41, 42] Bronchodilators, helium-oxygen, and oxygen supplementation have been shown to reduce dynamic hyperinflation.[43-47] Our approach could be combined with any combination of these other interventions and offers a separate means to permit improved exercise performance in COPD.

Current pulmonary rehabilitation programs vary but generally include exercise, most commonly on a treadmill, behavioral change, and educational and nutritional counseling components.[48, 49] Rehabilitation improves exercise capacity primarily through muscle training; however, not all individuals benefit from rehabilitation.[48, 50-52] Rehabilitation (or exercise training) has a positive impact on strength, exercise tolerance (measured in a laboratory setting), dyspnea, self-efficacy, and health-related quality of life; rehabilitation, however, does not improve lung function.[48, 49, 53-56] Further, the activity levels of COPD patients are not consistently improved following conventional rehabilitation.[50, 57-59] **Improving the effectiveness of pulmonary rehabilitation will improve the outcomes for participants. In addition, many of those referred to rehabilitation are unable to continue and do not report benefit. Improving one's ability to participate in rehabilitation will increase the percentage of COPD patients for whom rehabilitation will be beneficial**.

C. RESEARCH DESIGN AND METHODS

C.1 Overall Design

This study will utilize a cross-sectional design to determine if walking on a slope 1) results in less dynamic hyperinflation, 2), improves dyspnea, and 3) leads to more complex coupling as compared to walking faster. The study will be completed over four visits. A total of 25 patients (aged 45-80 years) with moderate to severe COPD will be enrolled in the study. Hereinafter the patients will be referred to as subjects. During visit 1, subjects with moderate to severe COPD, recruited and consented from the Omaha VAMC pulmonary and general medicine clinics, will undergo a maximal cardiopulmonary exercise test under medical supervision. Only those that are cleared for participation by a physician will be enrolled into the study. Subjects, stratified by disease severity[60] upon enrollment (Table 1), will complete experimental conditions. The second visit a cardiopulmonary exercise test will be used to determine a set speed and slope that equates to 70%-80% of peak work rate using VO_2 (volume of oxygen consumed). Specifically, the time course of work rate will be calculated from the cardiopulmonary exercise test. The speed and slope that corresponds to where 70%-80% of peak work rate was identified will be used. After sufficient rest, an additional constant work rate test will be given using increases in speed with a level treadmill to determine the speed that elicits a VO_2 comparable to the previous walking test. In addition, subjects will be asked to a series of questionnaires to characterize their disease state. During the third and fourth visits, airflow, respiratory rate, oximetry, dynamic hyperinflation, and walking cadence will be recorded during the trials at the speed/no slope or speed/slope determined in the previous visit. Speed or slope conditions will be randomized across visits. At the end of each trial, dyspnea rating will be recorded.

Table 1. Stratification strategy [60]

Category	Criteria
Mild	$FEV_1 \geq 80\%$ predicted
Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Severe	$30\% \leq FEV_1 < 50\%$ predicted
Very Severe	$FEV_1 < 30\%$ predicted

C.2 Subjects, Sample Size, and Inclusion Criteria

C.2.a Sample size justification: For this proposal, we are requesting funding to recruit and enroll a pilot population of 25 subjects. Subjects will be recruited and screened until all 25 subjects are enrolled. Stratified sampling will be conducted as subjects are enrolled. Subjects will be stratified by disease severity (Table 1). According to Omaha VAMC patient numbers, more than 45,000 visits are documented in the pulmonary clinics and other general health clinics with over 2,000 pulmonary function tests yearly. We anticipate recruiting 3-4 subjects/month during months 3-18. We anticipate meeting our enrollment goal of 1-2 enrolled/month.

C.2.b Inclusion and exclusion criteria: Veterans from all sex/gender, race, and ethnicity will be recruited. All subjects will undergo post-bronchodilator spirometry and be clinically stable. All subjects must have documented FEV_1/FVC ratio of <0.7, and between 30% to 80% $FEV_1\%$ predicted (Table 1).[60] If subjects have non-qualifying spirometry, they will not be screened further. Subjects with qualifying spirometry will be screened further (Figure 4). Potential subjects must have a BMI of less than 35 kg/m^2 and must be free from co-morbidities that may affect walking patterns (e.g., peripheral arterial disease, diabetes, low back pain). Subjects must also be free from other co-morbidities that may have confounding effects such as neurological or musculoskeletal disease. Those that meet the initial eligibility criteria will undergo a cardiopulmonary exercise test. Those that are cleared for participation by a physician will be enrolled in the study following informed consent. Based on the exercise test and the pulmonary function test, subjects will need to meet the following criteria for enrollment: have moderate to severe COPD and have no other pulmonary or cardiac issues that will pose a safety hazard when participating in the laboratory treadmill trials.

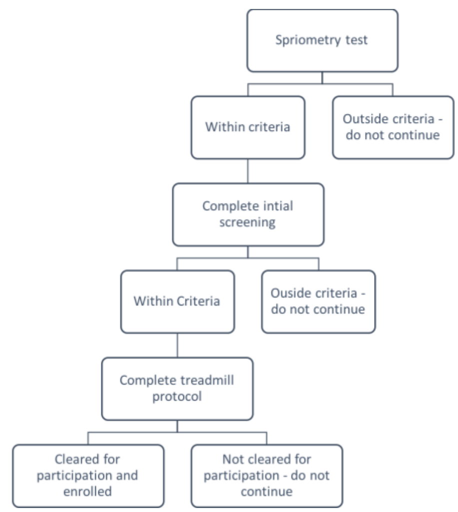

Figure 4. Flow chart of enrollment process.

C.2.c Recruitment of subjects: The PI conducts a Pulmonary Clinic at the Omaha VAMC every Wednesday. During clinic, a member of her research team, will be present. When a subject that fits the preliminary inclusion criteria, the PI will refer the patient to speak with the research team before leaving. The research team will also be allowed to recruit subjects through Veteran communications such as newsletters and, by accessing potential subject names through VINCI, with generic letters informing them of the study.

C.3 Protocol – Common for all aims

C.3.a Screening and eligibility (VISIT 1): All potential subjects will be consented and begin screening at the Omaha VAMC. Screening includes a comprehensive medical history and spirometry test. Potential subjects that meet the initial screening criteria will undergo a cardiopulmonary exercise test administered at the Omaha VAMC. The Porszasz treadmill protocol[61] will be used. This treadmill protocol provides a linear increase in work rate and is appropriate for testing those with a low exercise tolerance. Medical professionals will oversee this test with all safety precautions in place (e.g., 12-lead ECG, crash cart). Potential subjects that are cleared to participate by a physician will be enrolled.

C.3.b VISIT 2: Once eligibility is determined, subjects will come to the Biomechanics Research Building at the University of Nebraska at Omaha (VA-leased space). They will complete a series of questionnaires that will be used as covariates in the analysis. Health-related quality of life and activity-related dyspnea will be assessed through the Chronic Respiratory Disease Questionnaire[62, 63] and SF-36.[64] To assess severity of dyspnea, they will be asked to complete the modified British Medical Research Council Questionnaire. To assess the impact COPD has on their everyday life, subjects will be asked to complete the COPD Assessment Tool.[65] To determine work rate, the time course of work rate (done against gravity) from the Porszasz treadmill protocol will be calculated. The speed and slope that corresponds to 70%-80% peak work rate will be used.

Subjects will be outfitted with a face mask that covers their nose and mouth attached to a portable metabolic cart (K5, Cosmed USA, Inc., Chicago, IL). We previously have used this method to measure energy expenditure in COPD patients without reported adverse events. Resting heart rate, respiratory rates, and tidal volume will be recorded as well through this device. Subjects will stand quietly for five minutes while energy expenditure is collected through the metabolic unit. Subjects will have a transcutaneous oximeter attached to their abductor pollicis brevis (The Moxy Monitor System, Moxy, Minneapolis, MN). Subjects will walk at the speed and slope that corresponds to 70%-80% peak work rate. Subjects will maintain this level of exercise for one minute. If fatigued, they will be instructed to stop. (As exercise time at 80% VO_2 max is generally six minutes, we anticipate most subjects will complete the test without difficulty.) After sufficient rest and the return of heart rate and respiratory rate to resting levels for at least 10 minutes, subjects will complete an additional constant work rate test. They will walk at increasing speeds until the same VO_2 from the previous walking test is achieved. This speed will be recorded, and the subject will be asked to continue to exercise at this rate for one minute.

C.3.c VISIT 3: Within seven days, subjects will return for their first experimental visit. Subjects will be prepared for data collection by wearing a form-fitting suit (i.e., wrestling singlet) and obtaining height and body weight. Retro-reflective markers will be placed bilaterally on anatomical locations of the feet, legs, and hips (Figure 5), in addition to 89 markers on the thorax and abdomen.[66-69] Subjects will be outfitted with the portable metabolic cart and oximeter as in the previous visit. One of two treadmill trials will be performed: 1) at the speed and 2) at the slope +speed determined in the previous visit. Trial order will be randomized among subjects and across visits 3 & 4. For each trial, subjects will be asked to walk on a treadmill for up to 6 minutes. Speed or slope will be increased every 30 seconds and they will be asked to walk for one minute at that speed or slope. Once they reach the speed or slope that was determined to be 70%-80% of peak work rate, they will walk for an additional one minute. This procedure will allow for multiple data points for interpolation. Immediately at the end of the trial, dyspnea will be assessed by Borg scale.[70] Dynamic hyperinflation will be assessed through motion capture of the thorax and abdomen (optoplethysmography).[66-69]

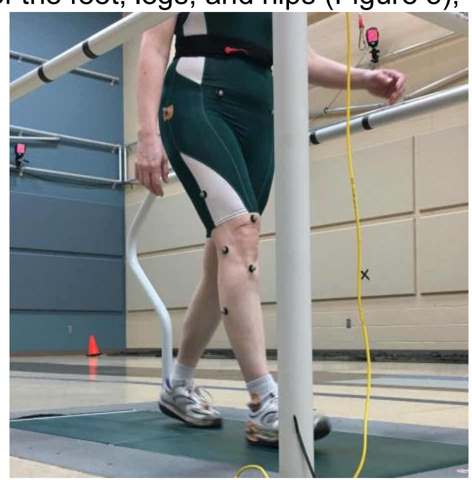

Figure 5. Subject wearing form-fitting suit while walking on a level treadmill.

C.3.d VISIT 4: Within seven days, subjects will return for their last experimental visit. Methods will be similar to C.3.c. Subjects will complete the treadmill trial that was not completed in Visit 3, either the speed or the slope trial. The treadmill trial will be administered in the same manner between both visits.

C.4 Instrumentation and Data Processing Measures (Table 2):

C.4.a Questionnaires to be used as covariates

Chronic Respiratory Disease Questionnaire:[62, 63] A 20-item questionnaire in which items are scored from 1 (most severe) to 7 (no impairment). There are four subscale areas tested: dyspnea, fatigue, emotion, and mastery. In the dyspnea section, the subject is asked to recall the five most important activities that caused dyspnea over the past two weeks. Items within each subsection can range from 1 to 7 or most severe to no impairment. A total score, as well as individual subscale scores, can be calculated.

SF-36:[64] A generic assessment of health-related quality of life from the subject's perspective. The SF-36 contains eight domains: physical functioning, role-physical, general health perceptions, vitality, social functioning, role-emotional, mental health, and health transition. Two composite scores result: physical health composite score and mental health composite score. Scores >50 indicate better physical or mental health than the mean and <50 indicate worse health. [22]

Modified British Medical Research Council Questionnaire:[71-73] A five-level rating scale based on the patient's perception of dyspnea in daily activities. Patients rate their level of perception of dyspnea on 5 grades, from 0 to 4. A grade of 0 reflects, "I only get breathless with strenuous exercise"; whereas a grade of 4 reflects "I am too breathless to leave the house" or "I am breathless when dressing."

COPD Assessment Tool (CAT):[65] A patient-completed instrument that complements existing approaches to assessing COPD. It is a simple and reliable measure of health status in COPD to quantifying the impact of

COPD on the patient's health. It is comprised of 8 questions and scores range from 1-40. A score 5 is typical of a normal, healthy individual. A score <10 is considered low impact; 10-20 is considered medium impact; >20 is considered high impact; and >30 is considered very high impact on everyday life.

Table 2. Measures to be collected during the course of the study.

General Descriptive Measures	Measurement Domain	Visit
Demographics	Description of subject population	1
FEV_1/FVC	Determination of presence of COPD	1
Medical history	Determination of co-morbidities	1
Potential Covariates		
Chronic Respiratory Disease Questionnaire	Health-related quality of life and activity-related dyspnea	2
mMRC	Dyspnea severity	2
CAT	Impact of COPD on everyday life	2
SF-36	Health-related quality of life	2
Variables Collected		
Respiratory rate	Exercise performance	3,4
VO_2	Oxygen uptake	3,4
Oxygenation	Dead space	3,4
Opto-plethysmography	Dynamic hyperinflation	3,4
Rate of perceived dyspnea	Dyspnea	3,4
Breathing rhythm	Coupling ratios	3,4
Walking rhythm	Coupling ratios	3,4

NOTE: mMRC=modified British Medical Research Council Questionnaire; CAT=COPD Assessment Tool

C.4.b Aim 1: Identify differences in dynamic hyperinflation and dyspnea during speed v. slope walking.

Dynamic hyperinflation: Dynamic hyperinflation will be assessed through opto-plethysmography, an established method of computing lung volumes, including dynamic hyperinflation.[66-69, 74-84] Opto-plethysmography uses three-dimensional motion capture information to determine lung volumes. The 3-D coordinates of the 89 markers on the abdomen and thorax will be used to create a representation of the surface of the trunk (Motion Analysis Corp., Santa Rosa, CA; 120Hz). The volume of the trunk enclosed by the surface will be obtained through a custom computer code (MathWorks, Inc., Natick, MA). Dynamic hyperinflation will be considered to be present when end-expiratory chest wall volume increased in relation to resting values.[75, 84]

Perceived dyspnea:[70] Breathlessness will be measured based on a 0 to 10-point Borg scale at the end of the treadmill trials.

C.4.c Aim 2: Compare differences in respiratory rate, oxygen uptake, and lung dead space from speed to slope walking.

Respiratory rate: Respiratory rate will be analyzed using motion capture markers on the chest. With custom computer code, the markers will be identified to model a sphere. The volume of the sphere will be recorded over time. As the volume increases and decreases, respiratory flow will be identified, and respiratory rate can be calculated.

Oxygen uptake: Heart rate and pulmonary gas exchange analysis will be recorded on a breath-by-breath basis (TrueOne2400; ParvoMedics, Sandy, Utah). This will provide an accurate measure of pulmonary gas exchange, including oxygen uptake, i.e. VO_2, in real-time. Steady-state VO_2 while walking will be averaged and normalized to standing metabolic rate. Heart rate is recorded via an interface with a Polar heart rate monitor and is synchronized to pulmonary gas exchange.

Dead space: Tidal volume and expired carbon dioxide will be measured using the same equipment as oxygen uptake above. Partial pressure of arterial carbon dioxide will be measured using a transcutaneous sensor (The Moxy Monitor System, Moxy, Minneapolis, MN). Dead space is equal to tidal volume multiplied by the partial pressure of arterial carbon dioxide ($PaCO_2$) minus partial pressure of expired carbon dioxide ($PeCO_2$) divided by $PaCO_2$.

C.4.d Aim 3: Determine the complexity of walking and breathing coupling ratios between speed v. slope walking.

Coupling: The laboratory is equipped with a 17-camera, digital motion capture system (Motion Analysis Corp., Santa Rosa, CA; 120Hz) to allow for collection of three-dimensional marker positions in real time. The marker position data will be analyzed using custom MATLAB code (MathWorks, Inc., Natick, MA) available in the laboratory. Data will be plotted to detect spikes and outliers. Spikes and data points greater than three standard deviations from the mean will be removed. A cubic spline will be used to interpolate the removed data points. All marker data are then normalized to the unit vector for comparison.

Coupling is often quantified as frequency coupling.[85, 86] Frequency coupling refers to how many heel strikes occur within a single cycle of respiration (one inhalation to the next); it is usually counted in integer or half-integer ratios, measured using discrete relative phase. Discrete relative phase values between 0º-360º have a 1:1 relationship, 360º-720º have a 2:1 relationship, 720º-1080º have a 3:1 relationship, and so on. Half-integer couplings (expressed as 3:2, 5:2, 7:2, etc.) exist when the frequency alternates between two integers. The range of ratios and the percentage of time each ratio is utilized will be recorded.

C.5 Statistical Analysis

For sample size justification, please see section C.2.a. Demographic characteristics will be compared between groups using independent t-tests for continuous variables and Chi-square tests for categorical variables. For all aims, data transformations, non-parametric tests, or generalized linear mixed models will be performed as appropriate.

Aim 1: A statistically significant decrease in dynamic hyperinflation and/or dyspnea during slope walking compared to speed walking will support our hypothesis. To determine the effectiveness of speed versus slope on dynamic hyperinflation and dyspnea in patients with COPD, linear mixed-effects models will be conducted. The model will include dynamic hyperinflation and dyspnea as the outcome variable and walking conditions as the independent variable, as well as possible confounders. Missing data will be explored in terms of the missing data mechanism, multiple imputations, or other missing data strategies will be considered depending on the extent of missing data.

Aim 2: A statistically significant decrease in respiratory rate and dead space with an increase in oxygen uptake during slope walking will support our hypothesis. Similar to Aim 1, linear mixed-effects models will be used to identify differences between the two walking conditions. Confounding variables and missing data will be dealt with in the same manner as Aim 1.

Aim 3: An increase in complexity of coupling during slope walking compared to speed walking will support our hypothesis. Similar to Aim 1, linear mixed-effects models will be used to identify differences in preferred ratios between the two walking conditions. Confounding variables and missing data will be dealt with in the same manner.

C.6 Anticipated Results and Alternative Strategies

We anticipate that dynamic hyperinflation and dyspnea will be reduced in patients with COPD due to slower walking and slower respiratory rates during sloped walking as compared to level speed walking. It is expected that this will be influenced by the complexity in breathing and walking coupling ratios.

Although the preliminary data indicate that change does occur in breathing and walking coupling in healthy controls, the pathophysiology of COPD may prevent a similar change in breathing and walking coupling while walking on a slope. In this case, data regarding changes in dynamic hyperinflation and dyspnea will still prove to be beneficial. These data will provide clinically meaningful data with regards to alternative approaches to pulmonary rehabilitation. Meaningful changes in these measures will provide fundamental data that may be used to guide pulmonary rehabilitation approaches in the future.

There is the possibility that the patients with COPD that have less severe disease and are healthier could perform better than those with greater disease severity. Therefore, only those with moderate to severe disease will be included (Table 1). We have addressed this by stratifying subjects as they are enrolled in the study. It is possible that age may influence the results as well; however, we anticipate disease severity to be a larger confounding variable than age. There is no research, at this time, to support the notion that age will influence one's ability to couple walking and breathing rhythms.

C.7 Timeline

The study will be divided into specific goals that will be targeted and achieved (Table 3). Every three months, intermediate objectives will be assessed, and decisions will be made regarding the course and direction of the continuing research effort.

Table 3. Timeline

	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Hire and train personnel	■							
Subject recruitment		■	■	■	■	■		
Data collection for all aims		■	■	■	■	■	■	
Data processing and analysis			■	■	■	■	■	■
Manuscript preparation							■	■
Grant preparation and submission						■	■	■

C.8 Future Directions

In summary, our research proposal uses a novel theoretical approach and a shift in clinical research through a new method. By exploring an innovative approach to improving exercise performance in COPD, it may be possible to increase exercise training intensity and duration and thus, improve the benefits of training during rehabilitation. **Results from this study, including the demonstration of physiologic and symptomatic benefits from the proposed method of slope walking, will set the stage for a rigorous, well-powered, full Merit award outcome study evaluating the effectiveness of a slope-based training regimen as part of rehabilitation.** This future Merit award clinical trial needs to demonstrate that physical activity and lung function, outcomes most associated with morbidity and mortality, improve after a sloped-based pulmonary rehabilitation approach.