CLINICAL RESEARCH PROJECT Protocol #14-CC-0027

Date: July 12, 2021
To: General Medicine IRB1

Protocol Title:

The NIH Exercise Therapy for Advanced Lung Disease Trials: Response and Adaptation to Aerobic Exercise in Patients with Interstitial Lung Disease

Principal Investigator:

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Estimated Duration of Study: 36-60 Months
Estimated Completion Date of Study: December 2021

Subjects of study:	**Number**	**Sex**	**Age range**
	60	M&F	21-80 years

60 subjects with Interstitial Lung Disease without Pulmonary Hypertension. Enrollment will remain open until 30 subjects in the Aerobic Exercise Training (AET) group and 30 subjects in the Control (CON) have completed the study.

Project involves ionizing radiation? No

Offsite project? Yes

Multi-Institutional project? Yes, NIH (medical and research testing, and exercise and educational training), Inova Fairfax Hospital (exercise and educational training),

DSMB involvement? No

Tech Transfer: CRADA, MTA No

Identifying Words: Exercise, Interstitial Lung Disease, Pulmonary Rehabilitation

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Précis

We propose a randomized controlled trial (RCT) to determine the safety and efficacy of aerobic exercise for patients who have interstitial lung disease (ILD) uncomplicated by pulmonary hypertension. Aerobic exercise training (AET) based rehabilitation has become a standard of care for patients with pulmonary diseases such as COPD. In an uncontrolled study, we have observed more efficient cardiorespiratory function, increased physical work capacity, and improved health related quality of life (HRQoL), following AET, in patients who have ILD without pulmonary hypertension. We have also observed in a RCT, similar findings in patients who have pulmonary hypertension complicated by ILD of various etiologies. Serious adverse events resulting from AET were not observed in these studies. Our work to date has established plausibility for the efficacy of AET and its safety for patients with ILD. A RCT is now needed to determine the efficacy of AET as a medically prescribed and supervised intervention in patients who have ILD. Our research team is uniquely qualified to undertake this research and is one of the few teams possessing the experience and background necessary for contributing to this novel, understudied, yet critical field of rehabilitation research.

Subjects will be over the age of 21 years and living within a reasonable travel distance from the greater Washington D.C. area. All tests will be conducted at the NIH Clinical Center and subjects will receive AET or a control regimen of patient education at either Inova Fairfax Hospital or the NIH Clinical Center. The staffs at both sites are well experienced in providing exercise therapy for patients with ILD.

There will be two primary treatment conditions. Patients with ILD will be randomized to either an intervention consisting of AET plus patient education (AET+) or a control condition that includes patient education only (CON). AET will consist of a 10-week regimen of supervised treadmill walking three times a week. The duration of the exercise sessions will progress from 30 minutes to 45 minutes per session over the 10 weeks as tolerated. The intensity of the exercise will be between 70 and 80% of the patient's heart rate reserve. Those randomized to control will not engage in AET. There will, however, be a secondary study: a crossover design in which subjects in the CON group will subsequently complete the AET regimen.

The primary outcome measure for our trial will be 6-minute walk test distance (6MWD). Secondary outcome variables will include treadmill cardiorespiratory exercise test (tCPET) results with, pulmonary gas exchange, central circulatory function, and muscle oxygenation. A number of questionnaires will also be completed including: St. George's Respiratory Questionnaire, Fatigue Severity Scale, SF-36v2 Health Survey, Human Activity Profile, Profile of Mood States, and King's Brief Interstitial Lung Disease Health Status Questionnaire. All of this data will be obtained before and after the AET+ and CON regimens and in both of the secondary studies.

AET is generally safe, inexpensive, and can easily be made available and accessible to almost everyone. It requires no approval by regulatory agencies and is thus available as a medically prescribed and supervised intervention almost immediately following confirmation of its safety and efficacy. Six-minute walk distance is associated with improved HRQoL in patients with ILD and in specific subsets. Effective use of AET as a rehabilitative intervention could have a high degree of impact on personal and public health outcomes in this advanced lung disease subset.

Background

Interstitial lung disease (ILD) is the result of over 200 etiological pathways arising from several different insults to the lung parenchyma: inhaled substances, drug side effects, connective tissue disease, infection, and malignancy.[1] The disease can also be of idiopathic origin. If prolonged, the resulting inflammation causes permanent and progressive fibrotic reorganization of the parenchyma and small airways, which reduces the distensibility of the lung and impedes O_2 and CO_2 exchange.

In addition to diminished longevity, patients with ILD experience low physical work capacity (PWC).[2] The distance walked on a 6-minute walk test (6MWT) is the most frequently used measure of PWC in patients with chronic lung diseases including both chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH). 6MWT distance is almost always reduced in patients who have ILD due to significant exertional dyspnea or increased fatigability. Du Bois and associates[3] reported that in the subset of patients who have idiopathic pulmonary fibrosis (IPF), a 26-meter reduction in 6MWT distance over a 24 week period predicted decreased survival at 1-year and a 24-week decline of 50-meters or more predicted a 4-fold increase in the risk of death at 1-year.

Aerobic exercise training (AET) is well known to improve cardiorespiratory fitness and physical work capacity in the general population,[4] including those who have illnesses that severely limit cardiorespiratory function.[5] Benefits, including decreased mortality,[6,7] have been documented in conditions such as coronary heart disease,[8,9] cerebrovascular disease,[10] peripheral vascular disease,[11] COPD,[12] diabetes mellitus,[13] and kidney disease.[14] There is also some evidence that AET may be beneficial for patients who have autoimmune, collagen vascular diseases[15-17] in which ILD is often a secondary co-morbidity. However, despite its potential benefits, there are only a few small studies conducted, which examine the influence of AET in patients who have ILD.

Four retrospective and three prospective studies have suggested that outpatient AET may increase 6MWT distance,[18-22] reduce exertional dyspnea,[19,21-24] and improve overall HRQoL[19-21,23,24] in patients with ILD. Two[20,21] of the three prospective studies were small, randomized trials but only 118 subjects were included in the interventional and control arms of all three of these studies combined. Similar findings were observed in a retrospective study of patients with ILD admitted for specialized inpatient AET rehabilitation[25] and in a prospective study of outpatient AET in subjects referred for lung transplantation.[26]

In our ongoing study of patients with PAH,[5] patients were randomized to either a group receiving AET plus education (AET+) or education only (CON). We observed improved 6MWT distance and HRQoL following a 10-week, medically supervised, outpatient AET rehabilitation program. Significant improvements were not observed in the CON group over baseline. Many of these patients had PAH secondary to ILD. We therefore initiated a parallel study in patients who have ILD without PAH. This study serves as preliminary work for the proposed RCT.

In this on-going preliminary study, we are using a prospective cohort design in which cardiorespiratory function, physical performance, and HRQoL comparisons are made for data obtained before and after 10 weeks of AET compared to base line. Subjects are free of ischemic heart disease; cor pulmonale; dilated, hypertrophic or non-idiopathic cardiomyopathy, and had normal ejection fraction and pulmonary capillary wedge pressure. None of the subjects have hepatic or renal failure; metastatic cancer with a life expectancy less than 6 months; history of disabling stroke; any severe psychiatric condition; active tobacco or substance use; uncontrolled

diabetes mellitus; any form of mitochondrial disease; pregnancy; or antiretroviral therapy. Additionally, subjects' medical regimens are required to be stable for at least three months prior to participation in the study. Subjects in the study are sedentary and have not participated in a routine aerobic exercise or pulmonary rehabilitation program that includes aerobic exercise for at least six months prior to their enrollment. All subjects receive a physical examination by a Rehabilitation Medicine Department physician prior to enrollment to verify the medical appropriateness of their participation, meeting the inclusion criteria, and the absence of exclusion criteria. The study is being carried out in the RMD and at Inova Fairfax Hospital Pulmonary Rehabilitation Center. . NIH Institutional Review Board will be the relying IRB for both sites. (NIH: 08-CC-0133; Inova: 08.129;) will be obtained before any recruitment of subjects or other study activity occurs.

At enrollment, blood samples are obtained and subjects undergo baseline research testing, which includes tCPET, 6MWT, muscle oxygenation tests, measurement of cardiac output and questionnaires to assess their perception of fatigue, daily physical activity, and general HRQoL. Subjects then participate in 10-weeks of AET with face to face supervision for each session in an outpatient pulmonary rehabilitation center. Following AET, all of the research tests and questionnaires completed at baseline are repeated, and post-AET values of the outcome variables are compared and assessed for significant differences.

Cardiorespiratory function is measured by pulmonary gas analysis during tCPET to volitional exhaustion at baseline and after AET. Subjects whose arterial hemoglobin desaturates rapidly during tCPET are tested under a hyperoxic condition in which FIO_2 is maintained at 40%. The principal pulmonary gas exchange measures include oxygen consumption (VO_2) at volitional exhaustion, peak respiratory exchange ratio (RER), end tidal partial pressure of CO_2 and O_2 ($PETCO_2$ and $PETO_2$), expired minute ventilation (Ve), tidal volume (Vt) and breathing frequency (f). We also use iterative methods of evaluating cardiorespiratory function including identification of the time taken to attain the anaerobic threshold (AT-time), time duration of tCPET to volitional exhaustion (tCPET-time), and determination of the time required to achieve one half of the peak VO_2 (VO_2-halftime). Heart rate is determined from continuous electrocardiography. Cardiac output (Qt) and stroke volume (Vs) are measured by bioimpedance cardiography. Measures of muscle oxygen extraction capacity include peak arteriovenous O_2 difference (a-vO_2peak) and hemoglobin saturation indices obtained by continuous wave near infrared spectroscopy.

Measures of PWC are peak work rate (WR) and 6MWT distance. Peak WR is calculated from treadmill speed and percent grade at peak exercise tCPET, and body weight. The 6MWT is performed on an 80-meter circular track according to the guidelines of the American Thoracic Society.[27]

Several questionnaires are used to examine patient reported health-related quality of life, including the SF-36 Version 2 (SF-36v2), Profile of Mood State (POMS), Fatigue Severity Scale (FSS) and Human Activity Profile (HAP). The SF-36v2 and POMS are multidimensional instruments that provide measures of fatigue severity and physical functioning in the overall context of health related quality of life. Specifically, fatigue severity is determined from the Vitality domain of the SF-36v2 and the Fatigue-Inertia scale from POMS, while physical activity is evaluated using the Physical Functioning domain of the SF-36v2 and the Vigor-Activity scales of POMS. One-dimensional instruments, including the FSS and HAP, are also used to capture patient-reported fatigue severity and physical activity.

All subjects participate in an AET program comprised of treadmill walking for 30-45 minutes per session, 3 sessions per week, for 10 weeks. A minimum of 24 out of the 30 possible AET sessions is required to maintain participation in the protocol. Treadmill speed and grade are continuously adjusted to keep subjects' heart rates as close as possible to a target zone corresponding to 70-80% of subjects' heart rate reserves, determined from tCPET. The target zone is determined using the method of Karvonen[28] in which the resting heart rate is subtracted from the peak heart rate and multiplied by 0.70 and 0.80. Each of these fractions is then added to the resting heart rate to establish the target heart rate training zone. At the beginning of each AET session, subjects participate in a 5-10 minute warm-up period where treadmill speed and inclination is gradually increased until subjects reach their target heart rate zone. The session timer begins once the target heart rate zone is reached.

Subjects unable to reach or sustain their training zones due to exertional dyspnea or lower extremity fatigue are allowed to exercise at symptom-limited intensities as needed. However, these subjects are instructed to increase their walking intensity to the prescribed heart rate training zone as soon as they were able. In the event that subjects are unable to sustain exercise, even at a modified intensity, brief rest breaks are permitted as needed. However, the duration of the rest breaks is not allowed to exceed one half of the duration of the preceding exercise bout. Upon returning from a rest break, the session timer does not resume until the subjects have once again attained their respective target heart rate zones. All subjects requiring supplemental oxygen during training are given an adequate flow rate to keep subjects' $SpO_2 \geq 85\%$.

Preliminary Results

Thirteen patients with ILD (Table 1) were studied. Participants had a variety of underlying causes of their ILD, but all were either New York Heart Association Functional Classification (NYHA)/WHO Functional Class II or III and 38% required supplemental O_2. Overall attendance of the exercise sessions averaged 90% (Table 2). Five subjects spent less than 70% of the targeted 30-45 minutes in their training heart rate zone, while 8 subjects spent 70% or more of the time in the zone (Table 2). No serious adverse events were reported during the aerobic exercise training intervention. No significant changes in subjects' body weight (81.5 ± 16.4 vs. 81.1 ± 17.1 kg, $p = 0.200$) or gastrocnemius skin fold (23 ± 11 vs. 21 ± 11 mm, $p = 0.239$) were observed during the study period.

Table 1. Baseline Characteristics of Study Patients

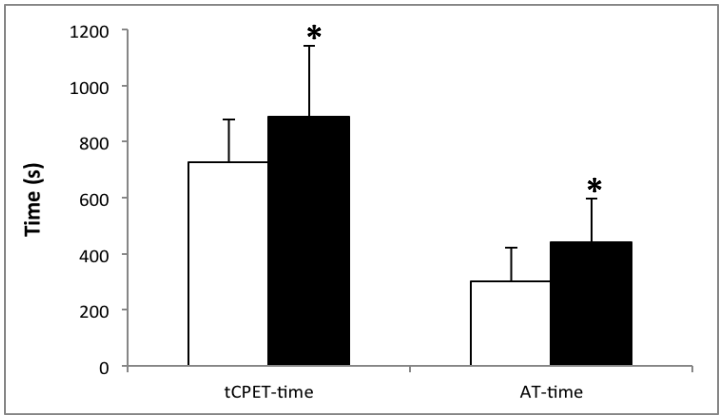
Characteristics	All Patients (n=13)
Age, mean (SD), years	57.0 (9.1)
Female, n (%)	9 (69)
Race/ethnicity, No. (%)	
White	11 (85)
African American	2 (15)
BMI, mean (SD), kg/m^2	28.6 (4.8)
Supplemental O_2 Use, No. (%)	5 (38)
Diagnosis	

Nonspecific interstitial pneumonitis	6 (46)
Idiopathic pulmonary fibrosis	3 (23)
Systemic sclerosis	2 (15)
Desquamative interstitial pneumonia	1 (8)
Sjögren's syndrome	1 (8)
NYHA/WHO Functional Classification, No. (%)	
Class II	6 (46)
Class III	7 (54)
Pulmonary Function Test, mean (SD)	
Forced Vital Capacity (FVC), % predicted	52.9 (18.0)
Forced Exhaled Volume in 1-s (FEV1), % predicted	57.0 (20.3)
Ratio FEV1/FVC, % predicted	83.4 (3.6)

Table 2. Aerobic Exercise Training Summary of Subjects Completing a Minimum of 24 Sessions

Subject	Total Sessions	Total Exercise Time (min)	Time in Training Zone (% of total exercise time)	Average HR (% HRR)	Supplemental Oxygen Use (L/min)
1	25	943	97	72	-
2	30	1159	97	71	6
3	27	1065	44	68	6
4	26	1020	73	70	6-15
5	25	976	85	72	-
6	25	975	96	71	3-6
7	28	1074	68	70	10-15
8	25	975	44	68	2-4
9	27	1027	11	67	6-15
10	27	1065	89	71	-
11	29	1036	82	70	-
12	28	1095	92	72	3-5
13	26	1042	38	69	2-12
Mean	27	1035	70	70	7
SD	1.6	59.0	27.7	1.7	1.5

The overall cardiorespiratory response during tCPET was improved as evidenced by significant increases in AT-time and tCPET-time (Figure 1) after aerobic exercise training. Physical work capacity increased significantly with a 12% increase (~ 52 meters) in 6MWD and 32% increase (39 watts) in peak work rate observed after training (Figure 1). Moreover, in the trained condition, work rate was higher at any given level of VO_2 (Figure 2), than in the untrained condition, underscoring an increase in work efficiency.



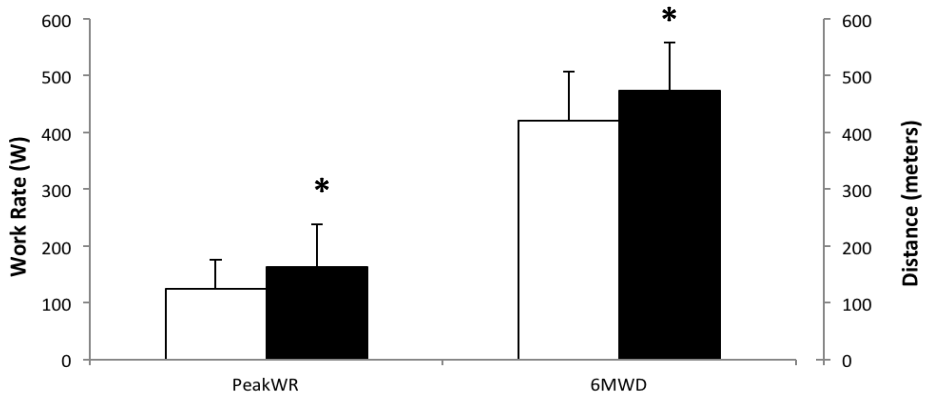


Figure 1 Test duration (tCPET), time to anaerobic threshold (AT-time), peak work rate (WR) and 6-minute walk test distance (6MWD) in the untrained (white bars) and trained (black bars) patients with ILD. tCPET was 163 ± 130 seconds ($p = 0.001$) and AT-time was 145 ± 15 seconds ($p < 0.001$) longer in the trained than in the untrained state. Peak work rate was 43 ± 37 watts ($p = 0.002$) higher and 6MWD was 52 ± 48 meters ($p = 0.001$) farther in the trained versus the untrained state. Error bars equal one standard deviation unit.

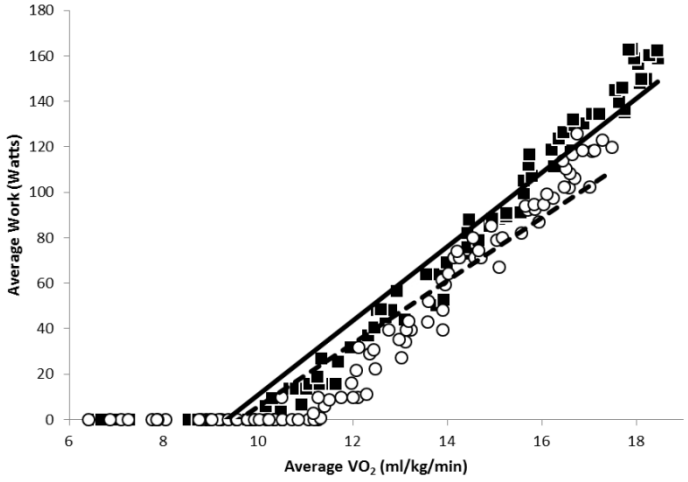


Figure 2 Work rate-VO_2 slope in the untrained (white circles) and trained (black squares) conditions. Regression equation was y=13.838x-132.54; R2 = 08813 for the untrained condition (dotted line) and y=16.274x-151.86; R2=09343 for the trained (solid line) condition. Slope was significantly higher (p=0.002) in the trained (14.89±4.94 than in the untrained (11.86±4.87) condition.

A statistically significant increase in peak VO_2 was observed after training, but the increase was deemed to be too small to be clinically relevant.[22,23,43-46] Resting HR and Qt were significantly reduced in the trained condition, however no other differences in resting cardiorespiratory function were observed (Table 3). While values for peak Qt, stroke volume, and heart rate were similar; a-vO_2 was 16% higher in the trained condition which was statistically significant. Additionally, the change in amplitudes for [deoxy-Hb/Mb] and [diff-Hb/Mb] were increased without a significant increase in [tot-Hb/Mb] amplitude after training (Figure 3); these findings suggested the improvement in muscle oxygenation was accomplished by an increase in cellular O_2 extraction capacity rather than by increased O_2 to the muscle cells.

Table 3. Cardiorespiratory Measures

Outcome Measures	Pre-training	Post-training	Difference	P value
Resting Values				
VO_2, ml/kg/min	5.4 (2.4)	5.2 (2.3)	- 0.2	0.384
VCO_2, ml/kg/min	4.3 (1.3)	4.0 (1.6)	- 0.3	0.234
f, breaths/min	31 (8.4)	31 (9.5)	0	0.463
Ve, l/min	15.3 (4.0)	14.7 (5.2)	- 0.6	0.323
Vt, ml/min	2.1 (0.6)	2.3 (0.8)	+ 0.2	0.172
RER	0.88 (0.21)	0.80 (0.23)	- 0.08	0.463
a-vO_2, vol%	6.1 (2.7)	6.6 (2.8)	+ 0.5	0.091
$PETO_2$, mmHg	154.8 (61.7)	149.4 (54.6)	- 5.4	0.197
$PETCO_2$, mmHg	38.0 (5.7)	38.9 (6.7)	+ 0.9	0.125
HR, beats/min	103 (13.1)	95 (11.3)	- 8	0.024
Vs, ml	72.0 (13.8)	67.9 (16.0)	- 4.1	0.136
Qt, l/min	7.3 (1.7)	6.4 (1.6)	- 0.9	0.027
HCT, %	40.5 (2.8)	40.7 (3.0)	+ 0.2	0.308
Peak Values				
VO_2, ml/kg/min	17.4 (5.5)	18.2 (5.0)	+ 0.8	0.048
VCO_2, ml/kg/min	19.5 (4.7)	19.8 (4.7)	+ 0.3	0.293
f, breaths/min	53 (11.0)	52 (9.3)	- 1	0.359
Ve, l/min	55.1 (15.13)	54.0 (16.1)	- 1.1	0.192
Vt, ml/min	1029 (361.2)	1055 (419.4)	+ 26	0.242
RER	1.17 (0.23)	1.11 (0.17)	- 0.06	0.037
a-vO_2 difference, %	9.2 (2.2)	10.7 (2.9)	+ 1.5	0.049[a]
$PETO_2$, mmHg	160 (58.4)	158 6.1)	- 2	0.08[a]
$PETCO_2$, mmHg	41 (9.6)	43 (9.7)	+ 2	0.055
HR, beats/min	148 (18.0)	144 (14.2)	- 4	0.086
Vs, ml	105 (20.1)	99 (21.8)	- 6	0.179
Qt, l/min	15.7 (3.8)	14.5 (4.0)	- 1.2	0.177

Abbreviations: tCPET, treadmill cardiopulmonary exercise test; VO_2, minute oxygen consumption; VCO_2, minute carbon dioxide expiration; *f*, breathing frequency; Ve, minute ventilation; Vt, tidal volume; RER, respiratory exchange ratio; a-vO_2, arteriovenous oxygen difference; $PETO_2$, end-tidal partial pressure of oxygen; $PETCO_2$, end-tidal partial pressure of carbon dioxide; HR, heart rate; Vs, stroke volume; Qt, cardiac output; HCT, hematocrit.

a Wilcoxon Signed Ranks Test

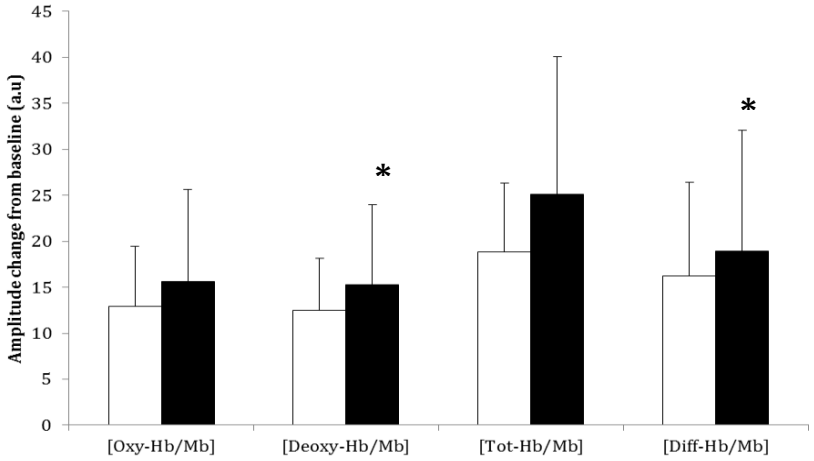


Figure 3 Muscle oxygenation capacity in the untrained and trained conditions. Bars represent concentration changes for oxygenated ([oxy-Hb/Mb]), deoxygenated ([deoxy-Hb/Mb]), total ([Tot-Hb/Mb]) and difference (diff-Hb/Mb) in hemoglobin/myoglobin. White bars represent the untrained condition and black bars represent the trained condition. [deoxy-Hb/Mb] ($p = 0.037$) and [diff-Hb/Mb] ($p = 0.027$) were significantly greater in the trained versus the untrained state. Error bars represent one standard deviation unit.

Significant improvements were seen in 5 out of 8 subsections on the SF-36v2, specifically in the vitality and physical functioning domain, as well as the overall physical and mental component scores (Figure 4). Specific improvements in the fatigue-inertia and vigor-activity domains of the Profile of Mood States, Fatigue Severity Scale scores, and the Average Activity Scale of the Human Activity Profile were also noted (Figure 4).

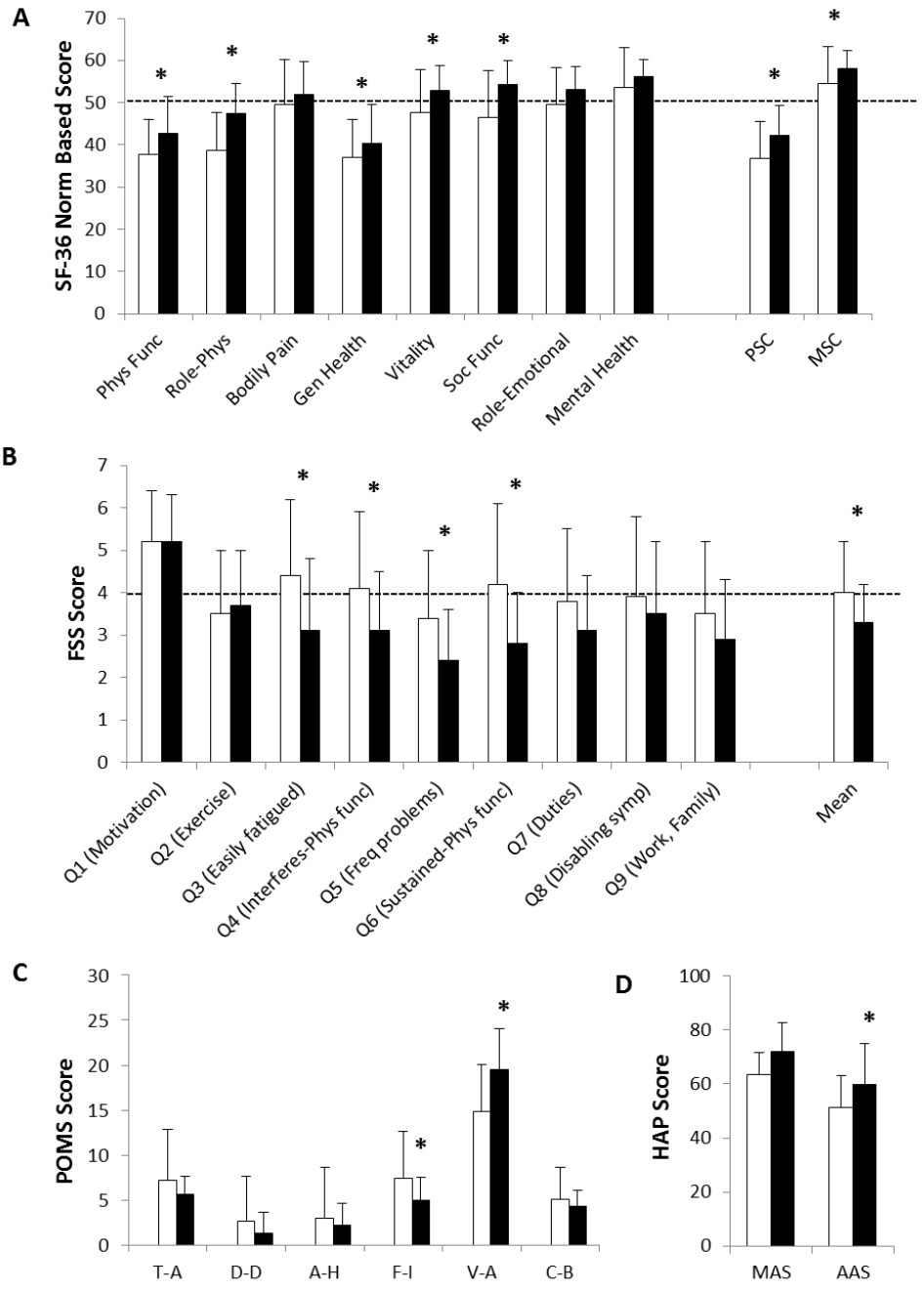


Figure 4 Item and composite scores for the SF-36v2 (A), Fatigue severity Scale (FSS; B), Profile of Mood States (POMS; C) and Health Activity Profile (HAP; D). The horizontal line in A and B represents the normative values. White bars represent values for the untrained condition and black bars represent values for the trained conditions. Improvements in the trained versus untrained state were observed in overall physical and mental health (SF36v2), fatigue severity (FSS), mood states associated with fatigue-inertia and vigor-activity (POMS) and Maximum (MAS) and Average (AAS) Activity Scales of the HAP. Bars represent 1 standard deviation unit.
*Indicates a significant difference between untrained and trained conditions ($p \leq 0.05$).

Informational Gaps

Outcomes of our preliminary study suggest the value of aerobic training for increasing cardiorespiratory capacity, diminishing fatigue severity, and improving the capacity for performing physical activities in patients with ILD. Increased cardiorespiratory function appears to mediate improvements in PWC, fatigue severity, and physical activity. However the cardiorespiratory adaptation results are somewhat atypical. In many conditions, peak VO_2 is 15-20% higher after training.[29] This occurs as a result of increases in both central circulatory O_2 delivery and peripheral O_2 extraction.[4] In our study of patients with ILD, peak VO_2 increased only by 4.6% after AET despite a 16.3% increase in peak a-vO_2. An increase in peak Qt was not observed. Resting right ventricular function was within normal ranges, Qt increased during exercise, and patients did not become symptomatic of congestive heart failure. Therefore the mechanisms limiting the improvement in peak VO_2 were likely impaired pulmonary gas exchange and restricted lung function, which are hallmarks of the ILD clinical course.

The mechanistic link to improvement provides relatively strong evidence for a substantial benefit of AET. However, some of the measurements, such as those made at volitional exhaustion, 6MWT distance and questionnaire responses could have been to some degree influenced by motivational factors and familiarity with the testing procedures. Therefore, a RCT is needed before the mechanistic and clinical effects of AET can be determined with confidence. We are proposing a small, phase 2 RCT to establish the safety and efficacy of AET in patients with ILD.

Research Objectives:

The objectives of the work proposed are, in patients who have ILD, to:

1. Determine the safety and tolerability of exercise training in patients with ILD to determine appropriate pulmonary rehabilitation exercise guidelines.
2. Examine responses and adaptations to exercise at quantifiable target intensities that correspond to energy expenditure requirements.
3. Understand changes in the symptom limited exercise test results, using training-specific testing modalities.
4. Examine the effects of exercise training on physical activity functioning.
5. Determine the relationships between patient's ability to achieve and maintain an aerobic steady state and to sustain physical activity.
6. Determine the effect of aerobic exercise training on psychosocial and behavioral functioning and other HRQOL components.
7. Based on the progression in training volume, delineate the time course of improvement in work capacity across an aerobic exercise training program.
8. Explore the relationships among measures of aerobic metabolic function and potential mechanistic factors that may limit oxidative metabolism.
9. Examine the relationships among indices of aerobic metabolic function and the mechanisms by which aerobic exercise training improves oxidative metabolism.

To accomplish these objectives, we will perform a RCT comparing a 10-week, interventional regimen of AET plus patient education (AET+) to a control condition of patient education only (CON) that does not include AET. A secondary study will also be conducted using a single "crossover" design in which the patients randomized to the control arm of the main study will receive AET after they are finished the 10-week education only regimen.

Our Specific Aims are:

1. "Determination of the Influence of AET+ on PWC in Patients with ILD".
   Specific Hypothesis: AET+ will improve measures of PWC, including our main outcome variable 6MWT distance, and peak WR, as well as performance and perceived fatigability over controls.
   "Sub-study On Crossover:" After completing the education-only regimen and subsequently completing the AET regimen, improvements similar to AET+ will be observed in 6MWT distance, peak WR, and fatigability.

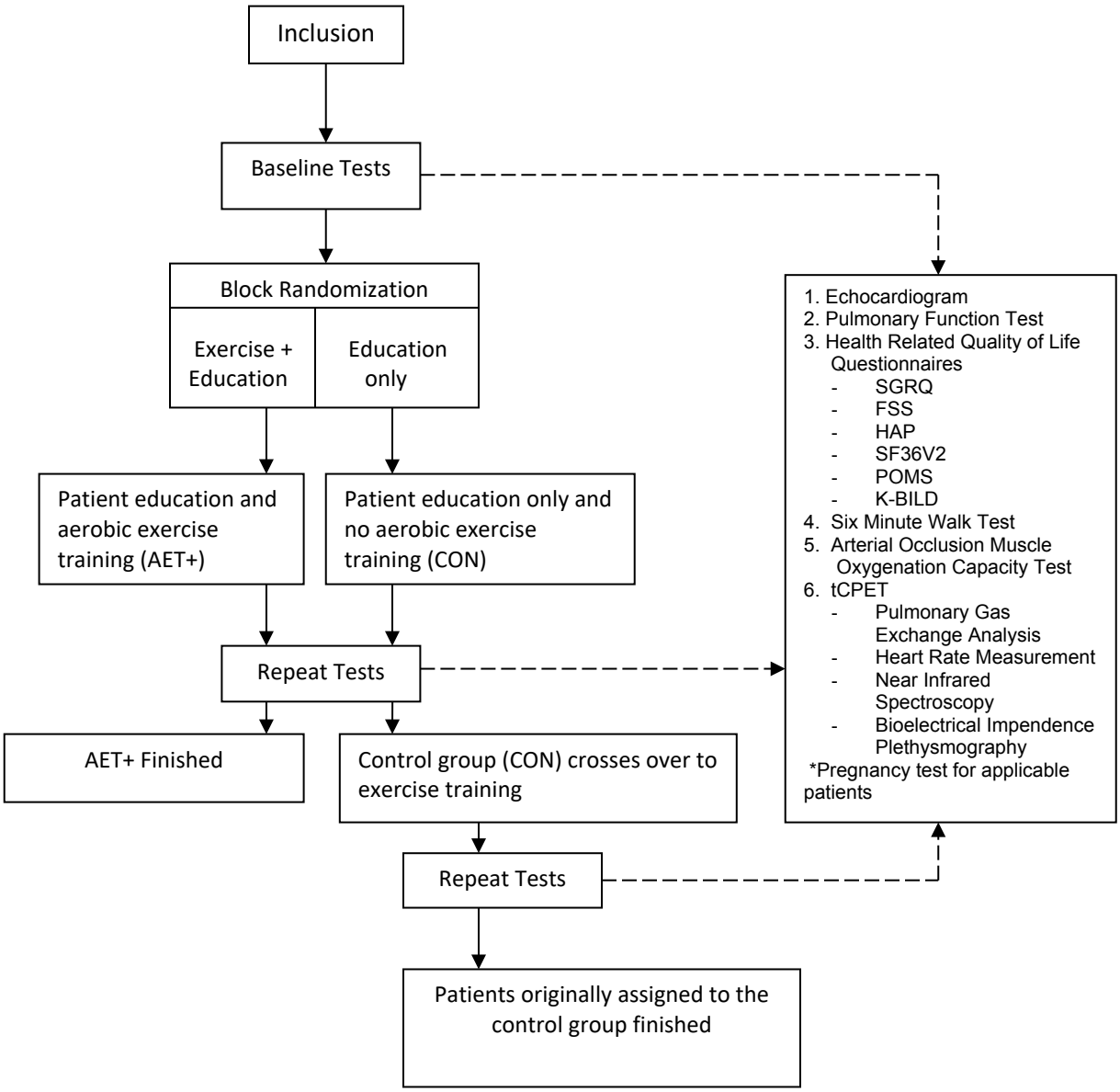
2. "Characterization of the Cardiorespiratory Adaptation to AET in Patients with ILD."
   Specific Hypothesis: After AET+, significant increases in AT-time and muscle oxygenation will be observed over control.
   "Sub-study On Crossover:" After completing the education-only regimen and subsequently completing the AET regimen, improvements similar to AET+ will be observed in AT-time and muscle oxygenation capacity.

3. Determination of the Influence of AET on Patient-reported Measures of Fatigue, Physical Activity, and Other HRQoL Domains in Patients with ILD."
   Specific Hypothesis: After AET+, patients will report decreased fatigue severity measured by the Fatigue Severity Scale, increased physical activity measured by the Human Activity Profile, and improvement in other HRQoL domains measured by the St. Georges Respiratory Questionnaire and SF-36v2 over control.
   "Sub-study On Crossover:" After completing the education-only regimen and subsequently completing the AET regimen, improvements similar to AET+ will be observed in fatigue severity, physical activity and other HRQoL domains.

4. "One-year Follow Up on Hospitalization, Lung transplant, and Mortality."
   This is a descriptive analysis to examine health outcomes of frequency, length and severity of hospitalizations, acceptance onto a lung transplant waiting list, and mortality occurring over the year after completion of the main study.

Study Design and Methods

Overview of the Research Paradigm



1-year Follow-up

Patients will be contacted monthly for 1 year following completion of exercise training to determine continued exercise habits, the amount of re-hospitalizations, acceptance to a lung transplant waiting list, and mortality rate.

To qualify for participation, subjects will undergo physical evaluation by a credentialed member of the Rehabilitation Medicine Department's medical staff to determine if they meet the inclusion and exclusion criteria. At this time, subjects must answer "no" to the question "do you currently participate, or within the past six months have you regularly participated, in a structured exercise program greater than 30 minutes a day for 3 or more days a week." Subjects answering "no" to this question, and meeting other inclusion/exclusion criteria will then undergo an EKG and Doppler echocardiography to rule out pulmonary hypertension and right and left ventricular dysfunction. In addition, they will have pulmonary function testing with DLCO to rule out COPD and to assess lung diffusion capacity. Subjects will also undergo a blood draw for two tests: Nt ProBNP and Complete Blood Cell Count with Differential. Qualified participants will then receive the baseline research test battery, which includes 6MWT, tCPET with cardiac output and muscle oxygenation measurements, and questionnaires to measure patient-reported fatigue severity, physical activity, and other HRQoL domains.

After completion of the baseline research test battery, subjects will be randomized to one of two groups. The randomization design will be a 2x2 block randomization in which subjects will be randomized in pairs. The first subject will be assigned to either a control group that receives 10-weeks of patient education lectures (1 day per week, 1 hour each lecture) with no AET or an intervention group participating in AET, 3 days per week for 10 weeks, in addition to the educational lectures (AET+). The second subject of the pair will be assigned to the opposite group.

After completion of the AET+ or control regimens, subjects will undergo the follow up research test battery. The follow up battery consists of echocardiogram, pulmonary function test, arterial occlusion muscle oxygenation test, 6MWT, tCPET, and questionnaires identical to those included in the battery at baseline. Subjects in the control group will subsequently participate in a 10-week AET regimen identical to AET+ except without the educational lectures, since participation in the lectures was completed as the control condition. A second identical, follow up test battery will be completed by this group after the crossover AET regimen is completed. After completion of their AET+, subjects will be contacted monthly with regard to continued exercise habits, the frequency, length, and severity of hospitalizations, or acceptance to a lung transplant waiting list. Mortality will also be assessed at this time.

Specific Aim 1: "Determination of the Influence of AET+ on PWC in Patients with ILD".
The main outcome variable for this project is 6MWT distance, which is the most frequently used measured of physical performance for evaluating patients with ILD and other advanced lung diseases. A minimal clinically important difference (MCID) for 6MWT distance has been determined to be approximately 30 meters in ILD [2]. Additional measures of PWC used in this study are peak WR on the tCPET, and performance and perceived fatigability as measured by a modification of the method used by Schnelle and coworkers in an older cohort. We will measure all 4 of these variables at baseline and after the AET+ and control regimens, as well as after the crossover regimen. We hypothesize that:

1.1. An increase in 6MWT distance of at least 30 meters longer than control will be observed after AET+.
1.2. A significant increase in peak WR will be observed after AET+ compared to control.
1.3. A significant decrease in performance fatigability will be observed after AET+ compared to control.
1.4. A significant decrease in perceived fatigability will be observed after AET+ compared to control.

1.5 In the Sub-study on Crossover we hypothesize that AET will result in improvements over baseline in all of the variables of interest including 6MWT, peak WR, and performance and perceived fatigability that are similar to AET+.

Specific Aim 2: "Characterization of the Cardiorespiratory Adaptation to AET in Patients with ILD." Measures of cardiorespiratory capacity are often influenced by subjective factors such as motivation and confidence. Our measures of cardiorespiratory capacity in this project are AT-time, and muscle oxygenation capacity. Neither of these physiological measures is influenced by subjective factors. We will measure AT-time during tCPET and muscle oxygenation by arterial occlusion testing at baseline and after the AET+ and control regimens. We will also measure Qt, peak VO2, PETO2 and PETCO2 during tCPETs at baseline and after the AET+ and control regimens. We will measure all of the variables again after the group initially completing the control regimen completes the crossover AET regime. We hypothesize:

2.1. After the AET+ regimen, AT-time will be significantly prolonged over controls.

2.2 After AET+, a significant increase in muscle oxygenation capacity will be observed over controls.

2.3 Qt, peak VO2, PETCO2 and PETO2 will remain unchanged following both AET+ and control regimens.

2.4 In the Sub-study on Crossover we hypothesize that AET will result in improvements over baseline in all of the variables of interest including AT-time and muscle oxygenation that are similar to AET+. We also hypothesize that Qt, peak VO2, PETO2 a PETCO2 will remain unchanged over baseline after AET.

Specific Aim 3: "Determination of the Influence of AET on Patient-reported Measures of Fatigue, Physical Activity, and Other HRQoL Domains in Patients with ILD." We will use the Fatigue Severity Scale (FSS) to assess fatigue severity, Human Activity Profile (HAP) to assess participation in physical activities, SF-36v2 to assess general HRQoL, Profile of Mood States (POMS) to assess changes in mood, and Kings Brief Interstitial Lung Disease Health Status Questionnaire (K-BILD) to assess HRQoL specific to ILD. We will also use the St. Georges Respiratory questionnaire to assess HRQoL specific to IPF. Subjects will answer the questionnaires before and after the AET+ and control regimens. Subjects in the group receiving the control regimen will again answer the questionnaires after completing the crossover AET regimen. We hypothesize

3.1. After AET+, fatigue severity will be diminished over control.

3.2. After AET+, participation in physical activity will be increased over control.

3.3. After AET+, overall mood will be increased over control.

3.4 After AET, general HRQoL and HRQoL specific to ILD and IPF will all be improved over control.

3.5 In the Sub-study on Crossover we hypothesize that AET will result in improvements over baseline in all of the variables of interest including fatigue severity, physical activity, mood state, and HRQoL that are similar to AET+.

Specific Aim 4: "One-year Follow Up on Hospitalization, Lung transplant, and Mortality." In this follow up sub-study, patients will be contacted monthly for one year after completing AET+ regarding frequency and type of exercise subjects have continued; number and nature of hospitalizations; days spent in the hospital; and the severity of their condition causing hospitalization. Subjects' acceptance onto transplants lists and patient mortality will also be determined. We will examine potential associations among these variables and our variables of interest to determine plausibility of relationships between study outcomes and clinical endpoints.

Two corollary hypotheses will be examined: i) poor clinical outcomes are associated with the severity of cardiorespiratory impairment, and ii) AET-induced improvements in these outcomes are associated with improvements in cardiorespiratory capacity

Methods

Medical Tests:

The following tests will be performed to determine a subject's eligibility for this study:

Electrocardiogram: All subjects will be screened for signs/symptoms of coronary artery disease, cardiomyopathy, or any other underlying cardiovascular diseases that may increase the subject's risk of performing an exercise based intervention by screening all patients with a 12 lead electrocardiogram (EKG). This will be performed in the National Institutes of Health Electrocardiography Laboratory prior to the subject's inclusion in the study. Subjects will be required to lay supine on an examination table while 10 electrodes are placed on the subject's chest and then connected to an electrocardiogram by an EKG technician. A cardiologist will interpret all electrocardiograms prior to the performance of any exercise testing.

Blood Draw: Patients will undergo a blood draw in the National Institutes of Health Phlebotomy Laboratory or the Department of Rehabilitation Medicine. Two tests will be run with approximately 4 tablespoons of blood taken via a standard blood draw technique. 1) Nt ProBNP: N-terminal pro b-type natriuretic peptide assays will be performed before and after the intervention period to objectively monitor for potential myocardial damage. Recent data suggests that high levels of NT-proBNP indicate acute heart failure. As studies have not yet demonstrated the safety of exercise in patients with ILD, this assay may be informative. This test is used as a standard of care in many emergency departments when patients exhibit symptoms of heart failure such as shortness of breath and fatigue. 2) Complete Blood Count with Differential: Using the same sample of blood we will perform a test to separate the red blood cells, white blood cells and platelets from the plasma which will help us learn more about the oxygen carrying capacity the blood. 3) Glucose (diabetic subjects only): 4 mL of blood may be drawn to validate the accuracy of subject's glucometer to be used before and after NIH testing and training sessions.

Pregnancy Testing: Female patients of childbearing potential will undergo urine dip stick pregnancy testing at the National Institutes of Health Phlebotomy Laboratory during baseline testing following blood draw. Follow-up pregnancy tests will be performed at subsequent testing visits to the National Institutes of Health. In order for a patient to be enrolled or continue with this study, this test must be negative.

Echocardiogram: Cardiac echo is required for this protocol. Subjects must be without a pulmonary hypertension (PH) diagnosis and have an estimated left ventricular ejection fraction (LVEF) of $\geq$50%. To evaluate both of these measures, all subjects will be required to undergo a Doppler echocardiogram prior to inclusion in the study. This may be performed at the National Institutes of Health Echocardiogram Laboratory. A transducer placed on the subject's chest will allow us to measure the subject's right ventricular size/thickness and systolic pressure. 1) PH causes a retrograde flow of blood from the pulmonary arteries into the right ventricle which, when chronic, results in ventricular remodeling, increasing the size and thickness of the myocardium, thus increasing the chronic RV systolic pressure. To determine the probability of pulmonary

hypertension we will use the guidelines as presented in the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. These guidelines suggest using tricuspid regurgitation velocity (TRV) at rest and the presence of additional pre-specified echocardiographic variables suggestive of PH. The probability of PH may then be judged as low, intermediate, or high (Table A). Echocardiographic 'PH signs' used in addition to criteria based on TRV provide an assessment of the RV size and pressure overload, the pattern of blood flow velocity out of the RV, the diameter of the PA and an estimate of RAP (Table B). Based on echocardiogram interpretation, the patient will be admitted to the study if the probability of pulmonary hypertension is low or intermediate [57].

Table A

Peak tricuspid regurgitation velocity (m/s)	**Presence of other echo 'PH signs'***	**Echocardiographic probability of pulmonary hypertension**
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9-3.4	No	
2.9-3.4	Yes	High
>3.4	Not required	

Table B

A. The ventricles [a]	**B. Pulmonary artery**	**C: Interior vena cava and right atrium**
Right ventricle/left ventricle basal diameter ratio > 1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

a. Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

2) LVEF will be estimated through echocardiogram volumetric measurements of the left ventricle. Placing the transducer over the subject's left ventricle allows for the measurement of the chamber's size in end -systolic and end-diastolic states thus giving an estimation of LVEF by comparing the difference in size. Subjects in this protocol will be required to have an estimated LVEF of ≥50%, because a decreased LVEF will increase the risk of exercise testing/training in this study population. Additional follow-up echocardiograms will be performed following completion of the exercise training for the AET group and following both the education phase and exercise training phase for the ED-only group.

Pulmonary Function Test: Forced Vital Capacity (FVC), Maximal Voluntary Ventilation (MVV), and Diffusion Capacity (DLCO) tests will be assessed for all subjects. These tests will be performed at the National Institutes of Health Pulmonary Function Laboratory prior to inclusion in the study. FVC is used to evaluate the degree of obstructive and restrictive lung disease. MVV is used to evaluate the subject's ventilatory limitation. Both tests will be obtained while the subject is at rest. We will determine whether subjects' exercise capacity is limited by ventilation by computing the ratio between expired minute ventilation (Ve) measured at maximum exercise and MVV (Ve / MVV must be 0.90 or greater). To perform the FVC and the MVV test the subject will be instructed to stand, plug their nose with their free hand (or wear a nose clip) and create an airtight seal over the mouth piece. For the FVC, the subject will be asked to take in three regular breathes, followed by a deep inhalation and a quick and complete exhalation, blowing air until there is nothing left to expire. This test will be performed 2-3 times. Completion of the test will be when two test results are within 5% of each other. For the MVV, the subject will be asked to breathe in and out normally three times followed by breathing in and out rapidly (90-100 breaths·min^{-1}) for 12-15 seconds. The teeth and tongue must refrain from blocking air flow. ILD results in a decreased ability for the interstitial lung tissue to exchange gases across the respiratory membrane wall. Therefore, a DLCO test is used to determine the lungs' ability to exchange gases across this respiratory membrane wall. Using a mouthpiece and nose clip, the subject will be required to inhale air containing a small amount of carbon monoxide and then exhale rapidly for 10 seconds. Exhaled air is then measured to determine the amount of carbon monoxide that was absorbed by the lung tissue and as such determine the subject's diffusion capacity. Additional follow-up pulmonary function tests will be performed following completion of the exercise training for the AET group and following both the education phase and exercise training phase for the control group.

Research Tests

Once the inclusion and exclusion criteria have been satisfied, the enrolled subject will undergo the following tests:

Six-minute Walk (6MWT) and Fatigability Tests: Subjects will rest in a seated position for a minimum of 30 minutes during which they complete the study questionnaires prior to beginning the 6MWT. Resting blood pressure, pulse rate, and oxygen saturation will then be recorded in the seated position. The subject will then be asked to stand and instructed to walk as far as possible around a pre-measured walking course over a time period of six minutes. Oxygen saturation and pulse rate will be measured throughout the test using a portable pulse oximeter. Oxygen saturation, pulse rate, rating of perceived dyspnea, rating of perceived exertion will be recorded upon completion of each lap of the walking course. Distance covered will be recorded at 1.5 minutes and the end of 6 minutes. The Fatigue/Fatigability Scale[30] will be completed before the test begins and immediately after. Immediately upon completion of the six minutes the subject will be asked to stop and immediate post-exercise pulse rate and oxygen saturation will be recorded. The subject will then be asked to rest in a seated position and pulse rate will be recorded during each minute of recovery for a total of ten minutes to evaluate the subject's ability to recover from intense activity. Supplemental oxygen will be provided for those patients that require supplemental oxygen while exercising and/or resting. Those subjects requiring supplemental oxygen will be provided supplemental oxygen with the same delivery device and flow pre/post intervention to maintain consistency. The target endpoint for this test is the completion of the six minutes of walking however symptomatic endpoints for stopping the tests will be those recommended by the American College of Sports Medicine. Additionally should any subject's oxygen saturation desaturate to ≤80% the patient will be required to stop walking at this point with or without the presence of symptoms of severe dyspnea. The patient will rest, while the timer continues to run, until oxygen saturation returns to baseline values or above 90% at which point the patient will resume walking again. The main outcome variable for this project is the change in 6MWT distance from before to after the AET+ and control regimens. The performance fatigability index will be calculated as the ratio of the 1.5-minute walking speed to the walking speed calculated over the entire 6 minutes of the test divided by the total distance covered on the test. The perceived fatigability index will be calculated by having the subject rating their feeling of tiredness prior to the 6MWT and measuring the change in tiredness after the 6MWT. The change in tiredness divided by the total distance walked will be computed as the perceived fatigability index.[30]

Fatigue Scale Items (Use before Walking Test)	Score	Fatigability Scale Items (Use After WalkingTest)
Extremely Tired	7	Extremely More Tired
Somewhat Tired	6	Somewhat More Tired
A Little Tired	5	A Little More Tired
Neither Tired Nor Energetic	4	Neither More Tired Nor More Energetic
A Little Energetic	3	A Little More Energetic
Somewhat Energetic	2	Somewhat More Energetic
Extremely Energetic	1	Extremely More Energetic

Schnelle, et al. J Am Geriatr Soc 60:1527–1533, 2012.

Blood glucose of diabetic patients will be monitored before and after testing, and as clinical necessary. Testing will be performed by qualified staff using NIH glucometer or patient's own glucometer. In order to use patient's own glucometer, it must first be validated for accuracy through the NIH Department of Laboratory Medicine.

Treadmill Cardiopulmonary Exercise Test (tCPET): Subjects will complete a tCPET using the standard modification of the Naughton protocol for individuals with low oxidative capacity.[31-33] The 6MWT and tCPET are separated between morning and afternoon testing to allow patients adequate rest following the completion of the 6MWT so that fatigue will not skew the tCPET data. This protocol was selected because it provides two additional work stages with small increments in intensity at the beginning of the test to ensure an adequate number of data points can be obtained for interpretation of the results, while minimizing the potential for bias due to early fatigue that could result from large increases in work rate. These tests will be performed on a computerized treadmill allowing programmed adjustment of both speed and inclination components of the work rate. The treadmill was chosen as the method of testing because it is well known to evoke higher values of VO_2 at maximal exercise, compared to other standard methods, and we are well experienced in treadmill testing in this patient subset. Treadmill walking is also task specific to the exercise training protocol and similar to the 6MWT. Supplemental oxygen will be provided through a Rudolph valve using a Douglas reservoir bag and high flow regulator for those patients that require supplemental oxygen while exercising and/or resting. Those subjects requiring supplemental oxygen will be provided supplemental oxygen with the same delivery device and flow pre/post intervention to maintain consistency.

Primary data obtained from the symptom limited treadmill exercise tests includes VO_2 from pulmonary gas exchange analysis, heart rate (HR) from EKG, cardiac output from bioelectrical impedance cardiography (ZCG), and muscle oxygenation from near infrared spectroscopy (NIR). Additional supporting data will also be available from these devices. Infrared pulse oximetry and blood pressure will also be monitored during the treadmill tests. Data from the pulmonary analysis system, EKG, ZCG, and NIR will be collected continuously throughout the tests. This is a symptom-limited test in which the target stopping point is volitional exhaustion, defined as the subject's expressed desire to stop despite strong encouragement from the testing staff. Other symptomatic endpoints for stopping the tests will be those recommended by the American College of Sports Medicine. Additionally should any subject's oxygen saturation desaturate to ≤80% the test will be terminated at this point with or without the presence of symptoms of severe dyspnea.

Blood glucose of diabetic patients will be monitored before and after testing, and as clinical necessary. Testing will be performed by qualified staff using NIH glucometer or using patient's own glucometer. In order to use patient's own glucometer, it must first be validated for accuracy through the NIH Department of Laboratory Medicine.

Pulmonary Gas Exchange Analysis: Pulmonary gas analyses will be performed using computerized system including rapid response oxygen and carbon dioxide analyzers, and a pneumotachometer interfaced with a microprocessor will be used for measurement of cardiorespiratory gas exchange. Subjects will interface the system using a mouthpiece or facemask that is connected to a plastic pneumotachometer. A plastic tube connects the pnemotachometer to the gas analysis system. When using a mouthpiece, subjects will also wear a nose clip to prevent expired air from escaping through the nostrils. Gas exchange variables measured during the tests will be measured continuously, on a breath-by-breath basis. Data reduction methods may utilize numbers bin or serial rolling averages. The dependent variable of interest obtained from gas analyses is VO_2. VO_2 will be determined from the Haldane equation. Volume of expired carbon dioxide (VCO_2) will also be measured and used in the calculation RER, where $RER = VCO_2/VO_2$. Attainment of an RER of at least 1.10 is one of criteria indicating that oxidative metabolism is approaching a physiologically maximum level at volitional exhaustion[34,35].

Heart Rate Measurement: Heart rate will be obtained from EKG recordings. Electrodes will be placed on the subjects' chests in the standard Mason-Likar exercise-testing configuration. EKG will be monitored and recorded continuously throughout the maximum exercise test.

Near Infrared Spectroscopy: Muscle microcirculatory reactivity and muscle tissue oxygen extraction will be measured by spatially resolved near infrared spectroscopy (NIRS). Near Infrared (NIR) light is emitted into the muscle tissue at known distances from a sensor by a NIR emitting diode. The amount of NIR light returning to a photo-sensing diode is measured and processed according to two wavelengths of the NIR spectrum, and the absorption and scattering coefficients of the medium are calculated. Oxygenated ([O2-Hb]) and de-oxygenated hemoglobin ([H-Hb]) concentrations are then determined as an interaction between their corresponding wavelengths and the amount of light that is collected by the NIR sensors. These calculations are however influenced by oxygenated and deoxygenated myoglobin concentrations, which in this project may introduce some conservative bias. In general, oxy and doxy hemoglobin and myoglobin dynamics tend to fluctuate in the same direction, often making the influence of myoglobin on the analysis superfluous. Myoglobin concentration in muscle is small compared to hemoglobin and most accounts have indicated that the myoglobin signal accounts for less than 10% of the total NIR absorption, rendering its influence less confounding. Spatially resolved measurements of total tissue hemoglobin, ([Tot-Hb], [O2-Hb] and [H-Hb] are absolute measures and desaturation rates are time constant based kinetic indices. A single infrared transducer containing both infrared laser emitting diodes and frequency specific light sensors will be attached to the gastrocnemius muscle and worn by the subjects during the symptom limited treadmill exercise test. The lasers are cool lights and will not be felt by the subjects. Reports of burns or other tissue damage occurring with the use of these devices are not found. NIR measurements of muscle oxygenation will be made during tCPET as well as during an arterial occlusion test.

Bioelectrical Impedance Plethysmography: Measurements of cardiac output will be made using a bioelectrical impedance cardiograph (ZCG). Silver/silver chloride electrodes are placed on the subjects' chests at known distances and the electrocardiographically-gated rate of change in electrical conductance is measured. This produces a waveform that is the inverse of the pulse tracing obtained from Doppler ultrasound analyses. The first derivative of the waveform is then used to estimate cardiac output. This can occur because air in the lung provides no resistance to electrical current leaving impedance to vary only with changes in fluid volume. Additional data accurately obtained by ZCG includes pre-ejection period, dz/dt, which is analogous to the dv/dt of the Doppler blood flow graph, the dz/dt second derivative, an index of cardiac inotropicity analogous to Doppler measured peak ascending aortic acceleration, and left ventricular ejection time. Changes in total peripheral resistance can be determined when brachial artery blood pressure is measured (TPR= [1/3(SBP-DBP)+DBP]/cardiac output).

Arterial Occlusion Muscle Oxygenation Capacity Test: NIR light source and receiving sensors will be placed on the belly of the dominant gastrocnemius muscle to record muscle oxygen-hemoglobin flux. A blood pressure cuff will be placed around the distal hamstrings of the dominant leg. Using a Hokanson® rapid inflation vascular testing system, the cuff will be rapidly inflated to a pressure that totally occludes blood flow into the gastrocnemius, typically between 60 and 80 mmHg above systolic pressure. The occlusion will be maintained for up to 10 minutes and tissue saturation will be measured over the time course. The tissue saturation index will be calculated as STI= [O2-Hb] / Tot-Hb. The rate of decline in STI will be the main muscle tissue saturation measure.

Health Related Quality of Life: Overall, improvement in HRQOL is one of the primary goals of rehabilitation and a clear understanding of the relationships amongst HRQOL, exercise, and psychosocial health is essential in a clinical practice. The proposed research addresses this information by using a battery of quantitative, objective and subjective measures to examine physical activity and a range of psychosocial and behavioral patient characteristics. Below is a list of the self-report tools that will be utilized in the proposed research. Associations among these and the measured physiological data will also be examined to determine on the effect of aerobic exercise training on psychosocial and behavioral functioning and other HRQOL components. The tools to be used include:

- St. George's Respiratory Questionnaire – Idiopathic Pulmonary Fibrosis Specific Version (SGRQ-I): The SGRQ-I is an IPF specific version of the original SGRQ designed to measure and quantify health-related health status for patients with chronic airflow limitations. It has been shown to correlate well with established measures of disability, disease level, and symptom level.[36]
- Fatigue Severity Scale (FSS): The FSS can be used to monitor change in fatigue in response to therapeutic interventions. The Fatigue Severity Scale is composed of nine items with a seven-point response format. Clinical improvements in fatigue were associated with reductions in scores on the FSS. The FSS is also a practical measure due to its brevity and ease of administration and scoring.[37]
- Human Activity Profile (HAP): The HAP was designed to measure activities of patients in rehabilitation programs. It is a self-report measure of energy expenditure or physical fitness. The Human Activity Profile appears to be a useful indicator of physical activity levels in people with various neurological and cardiorespiratory conditions, as well as in healthy older people.[38]
- Short Form 36-Item Health Survey Version 2 (SF36v2): The SF36v2 is widely used throughout the world as an instrument to measure general HRQOL. It assesses HRQOL in eight scales or domains. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.[39]
- Profile of Mood States (POMS): The Profile of Mood States (POMS) measures present mood state by a list of adjectives. POMS measures six dimensions of affect or mood, including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. [40]
- King's Brief Interstitial Lung Disease Health Status Questionnaire (K-BILD): The K-BILD is designed to measure health status in patients with interstitial lung disease through three domains (breathlessness and activities, chest symptoms, and psychological). The questionnaire has 15 items in total.[41]

Randomization: Once the subjects have completed baseline testing they will be randomized to one of the two conditions: AET+ or CON. We will use block randomization to keep groups as equal in number as possible and to avoid early filling of one of the groups. An independent randomizer (Diane Brandt, P.T., Ph.D., RMD, Epidemiology and Biostatistics Section) who is not affiliated with this study in any other way, will perform randomization of subjects. The AET+ and CON procedures will occur in the Clinical Center at The National Institutes of Health. The education regimen will be conducted at separate times for the AET+ and CON groups to avoid cross contamination.

Educational Sessions: The education portion is comprised of 13 separate lectures. Subjects in the AET+ arm will receive 1-2 lectures per week as needed following their exercise session to fulfill the education requirement within 10 weeks. Subjects in the CON arm will receive the 13 lectures within the 10-week education period. Many classes will take more than one class session to cover the material. For example, inhaler use/lung medications will require at least 2 sessions to cover.

The lectures will include the following topics:

Lung Anatomy/Physiology/Breathing Retraining
Lung Diseases and Medications Part 1
Lung Diseases and Medications Part 2
Oxygen Therapy/Sleep Disorders
Preventing Infection/Airway Clearance
Diagnostic Testing
Advance Care Planning/Energy Conversation
Emotional/Social Well Being
Panic Control/Relaxation
Nutrition/Fall Prevention
Benefits of Exercise/Disease Management/Community Resources
Home Recommendations (excluding exercise recommendations)

Exercise Training: The AET+ regimen will consist of 10 weeks of supervised treadmill or track walking. Exercise session duration will be 30 minutes and will progress to 45 minutes per session over the 10 weeks. The sessions will be continuous unless the patient cannot tolerate the regimen, in which case exercise bouts will be alternated with rest intervals until the total time of the exercise bouts equals the 30-45 minute total exercise time target. The intensity of the exercise will be between 70 and 80% of the heart rate reserve, defined as 0.70 and 0.80 (maximum heart rate – resting heart rate) + resting heart rate, as determined during the baseline tCPET. Should the target heart rate range be considered insufficient (i.e. subject stopped the CPET prematurely due to dyspnea and/or O_2 saturation <80%, or subject achieved a higher heart rate on the 6MWT than on the CPET), an RPE of 4 to 6 can be used to progress exercise intensity. ECG monitoring will be used as appropriate to ensure proper RPE rating for the heart rate response in these subjects. The frequency of the sessions will be three times per week, unless make up sessions are needed in order to attend 80% or 24 sessions in ten weeks. The target endpoint for each session will be the completion of the prescribed training time, however symptomatic endpoints for stopping the training session will be those recommended by the American College of Sports Medicine. Additionally should any subject's oxygen saturation desaturate to ≤80% the patient will be required to stop walking at this point with or without the presence of symptoms of severe dyspnea. The patient will rest until oxygen saturation returns to baseline values or above 90% at which point the patient will resume walking again. The session timer will be stopped during rest breaks and will only resume once the patient returns to their target heart rate zone. Those patients requiring supplemental oxygen will continue to use their supplemental oxygen throughout the duration of exercise training. Additionally those patients who previously did not require supplemental oxygen prior to exercise training but deteriorate to the point of requiring supplemental oxygen at any point during the training will be allowed to begin supplemental oxygen use based on their oxygen needs. However regardless of whether or not any changes were made to the patient's supplemental oxygen

use or the patient began using supplemental oxygen during the exercise training, all post-training exercise tests will be performed with the same oxygen device/flow used in the baseline testing to maintain consistency between tests.

Blood glucose of diabetic patients will be monitored before and after training, or as clinically appropriate. If training at NIH CC, glucose monitoring will be performed by qualified staff using NIH glucometer or patient's own glucometer (if first validated for accuracy through the NIH Department of Laboratory Medicine). If training at Inova Fairfax, blood glucose monitoring will be performed per Inova policy.

The locations for this intervention will be Inova Fairfax Hospital and the NIH CC. At NIH, the intervention will take place in the Clinical Center Fitness Center located in room 7-3551 on the 7th floor of the Clinical Center and will be led by trained NIH AI staff. This room has three treadmills that are currently used for aerobic training of CC patients.

Participant Inclusion and Exclusion Criteria

See Appendix 2 for the Inclusion/Exclusion Checklist that will be used.

Inclusion Criteria

ILD Groups: Subjects in this study will include individuals with ILD who are referred for Pulmonary Rehabilitation. The following list provides more specific inclusion criteria:

- Between age 21-80 years.
- NYHA functional class II or III, will accept NYHA functional class I and IV based on 6 minute walk test results (≤400 meters for Class I and ≥50 meters for Class IV)
- No episodes of syncope or significant chest pain for at least one month.
- No prior Pulmonary Rehabilitation received within the last 6 months and not currently in a maintenance program.
- Physically inactive, no participation in a structured exercise program as defined as more than 30 minutes of exercise 3 or more days a week within the last 6 months.
- Patients may qualify if they have any one of the following conditions:
  Interstitial lung disease, including idiopathic pulmonary fibrosis (IPF), non-specific pulmonary fibrosis (NSIP), sarcoidosis or other form of chronic lung fibrosis based on clinical context via clinic note from primary pulmonologist
- Low to intermediate probability of pulmonary hypertension as determined by tricuspid regurgitation velocity (TRV) at rest on echocardiogram and the presence of additional echocardiographic variables such as right ventricular size and pressure, pattern of blood flow velocity out of the right ventricle, the diameter of the pulmonary artery and an estimate of right atrial pressure. If the patient has had a recent right heart catheterization showing a mean PAP <25 mmHg, ruling out pulmonary hypertension..

Exclusion Criteria

Since the goal is to examine exercise responses and adaptations as affected by ILD, patients will have no other medical conditions that would impair aerobic capacity or the ability to engage in

physical activity. These conditions would include any of those affecting the cardiovascular, pulmonary, metabolic, neurological, or musculoskeletal systems. Specific exclusion criteria are:

- Inability to maintain a resting oxygen saturation ≥90% SpO2, measured by pulse oximetry, on supplemental oxygen.
- Inability to complete a treadmill cardiopulmonary exercise test based on the specified criteria.
- Diagnosis of ischemic heart disease.
- Left ventricular dysfunction with the ejection fraction <50%.
- Acute cor pulmonale.
- Dilated or hypertrophic cardiomyopathy.
- Non-idiopathic cardiomyopathy.
- Significant hepatic or renal dysfunction.
- Metastatic cancer with a life expectancy of less than one year.
- Disabling stroke.
- Active substance abuse.
- Severe psychiatric disease.
- Patients on antiretroviral therapy.
- Uncontrolled diabetes mellitus with a history of DKA.
- Mitochondrial disease.
- Pregnancy.
- Ongoing tobacco use.
- Acceptance onto a lung transplant waiting list.
- No participation in active ILD drug trials prior to enrolling in this study and throughout the duration of their participation in this study. Patients may continue to take any currently prescribed medications throughout the entire protocol. However, any changes to current medications or addition of other medications during the course of the study must be reported within one week to the PI or associate investigator.
- General medical complications that pose a risk to exercise testing or training as determined by the PI (for example, severe peripheral vascular disease).
- Inability to read English.

Other Exclusions:

- The age range of the subjects will be limited to those between 21 and 80 years because the normal adaptive processes to aerobic exercise are generally less well understood in the childhood, adolescent, and aged subset of the population, and reference ranges for many of the exercise response variables are less well accepted than in the general adult subset. The age range of 21 to 80 encompasses the range generally referred to in the Inova Fairfax pulmonary rehabilitation program, which is one of the few pulmonary rehabilitation programs in existence serving patients who have advanced lung disease
- Subjects will not typically include individuals in Class I because patients are usually in Class II or III at the time of diagnosis.

- Subjects in NYHA Class IV will typically be excluded as the instability of their symptoms is a contraindication for exercise testing or training by nearly all published guidelines.
- Subjects in Class I may be included if they walk less than 400 meters during a six-minute walk test.
- Subjects in Class IV may be included if they are able to walk at least 50 meters during a six-minute walk test.
- Subjects with severe Raynaud's phenomenon will be excluded from participation in the arterial occlusion muscle oxygenation capacity test.

New York Heart Association Functional Classification

Class	**Patient Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Monitoring Subjects and Criteria for Withdrawal from the Study: Subjects will be followed carefully during the study. At the start of each study day, subjects will be asked whether they are experiencing any unusual symptoms, and vital signs will be measured (pulse rate, oxygen saturation, resting blood pressure). All subjects will undergo EKG and echocardiography before and during the symptom limited exercise test. We will monitor heart function in the rehabilitation medicine exercise lab during exercise, and stop the exercise if there are any signs of heart problems.

Subjects enrolled who subsequently meet the exclusion criteria above at any time during the protocol will be excluded (off-study exclusion criteria).

Dr. Leighton Chan, as the Principal Investigator, will make the decision to include or exclude potential participants based on their meeting inclusion, exclusion or off-study exclusion criteria.

Unanticipated Problems, Adverse Events, and Protocol Deviations:

NIH IRB and CD reporting

Definitions: The PI or designee will refer to definitions of reportable events per Policy 801.

Expedited reporting: Events requiring expedited reporting will be submitted to the IRB per Policy 801 "Reporting Research Events.

Reports to the IRB at the time of continuing review: The PI or designee will refer to HRPP Policy 801 "Reporting research events" to determine IRB reporting requirements. In addition, an independent medical monitor will monitor all adverse events. (See section on Data and Safety Monitoring.)

Analysis

Our statistical model for specific Aims 1-3 will compare variables of interest between and within the AET+ and CON groups at baseline and post-intervention with a 2-way mixed model analysis of variance (2-way ANOVA). Should there be baseline differences in the specific variable of interest or in demographic characteristics, we will use an analysis of covariance (ANCOVA) to control for the group equality, but the study will be powered under the assumption that no informative covariates are identified and using 6MWT as the primary outcome.

In Specific Aim 1 we will test the hypothesis that AET+ will improve scores on measures of PWC. The dependent variables for this Aim include total distance covered and fatigability index on the 6MWT, and peak WR achieved on the tCPET. 6MWT distance is the primary outcome variable for this RCT and thus our project is powered on the sample size estimated to achieve a significant outcome on this variable (See Sample Size below).

In Specific Aim 2, we will test the hypothesis that after AET+, significant increases in AT-time and muscle oxygenation will be observed over CON. The main dependent variables for this aim are AT-time and measures of muscle oxygenation which include [Tot-Hb], [O2-Hb], [H-Hb], and StO2 measured during tCPET and muscle arterial occlusion cuff tests. Additional dependent variables will include Qt and its components HR and SV measured during tCPETs.

In Specific Aim 3 we will test the hypothesis that patients will report decreased fatigue severity, increased physical activity, and improvements in other HRQoL. The dependent variable score for fatigue severity will be the Fatigue Severity Scale score. The dependent variable score for physical activity will be the Human Activity Profile maximum and average scale scores, and the scores for HRQoL will be composite and domain scores for the SGRQ-I, SF-36v2, and K-BILD.

In the crossover sub-study, we will determine if AET+ induces significant improvements in the variables of interest in the CON group. For this analysis we will use repeated measures ANOVA's to determine differences in the variables of interest among baseline, 10-week post control, and 2-week post crossover AET data points. Dependent variables will be those in each of the specific aims characterized above.

In Specific Aim 4, relationships between the post-study physiological variables and health outcome variables will be determined using Pearson product moment correlations and appropriate nonparametric procedures.

In all of the analyses, statistical significance will be interpreted as the probability of making a type 1 error equal to or less than 5% ($p \leq 0.05$).

Sample Size:

The broad objective of the proposed work is based on identifying effects of exercise on, and relationships among, measures of physical work capacity, fatigability, oxidative metabolism, tissue oxygen extraction, and clinical outcomes. The proposed study builds upon the PI's preliminary study of the feasibility and safety of exercise treatment for patients with ILD in which the 6MWT was the primary improvement metric. Many of the hypotheses proposed under this objective require measurement of variables not included in prior studies of the ILD population. Conversely, there are established standards for clinically relevant changes in the 6MWT and multiple studies of ILD patients with which to inform our sample size decisions and 6MWT is the primary outcome variable for the proposed study. For these reasons we will power the study on 6MWT. Specifically, changes in 6MWT distance between baseline and the second testing period are compared for ILD patients randomized to the AET+ and CON arms using a 2-way mixed model ANOVA. From this, we have determined our goal is to recruit 60 patients with ILD (30 into each group) over the duration of this study, with details below.

The prior information, assumptions, and calculation for the power analysis that was conducted are as follows. An increase in 6MWT distance of 54 to 80 m exceeds the MCID in patients with ILD[2]. Previous studies by Holland et al.[21] and Nishiyami et al.[20] on exercise interventions in ILD patients have observed in post-hoc independent t-test an effect size between experimental and control groups of 0.65 and 0.86, respectively, with an increase in 6MWT distance of 31 to 42 m in the experimental group. Effect sizes in this range are associated with high-moderate to large differences.

In order to translate the existing literature's results into predictions of effect size of the 2-way mixed model ANOVA we will use as our primary statistical test, simulations were run in STATA. Simulations were drawn from normal distributions for each of control and exercise groups with equal mean and variance chosen as the average of the mean and variance observed in the control and exercise groups in Holland et al.[21] Specifically, both groups were assumed to have mean 6MWT of 385 m and standard deviation 127 m at baseline in the simulation. The control group was assumed in all samples to show no change between baseline and retest, while different simulations were run for improvement in the exercise group of 25, 30, 35, and 40 m between baseline and retest. We did not simulate differences smaller than 25 m as this is below the MCID. At each level of improvement from treatment we simulated 3000 samples from both control and exercise groups at test-retest correlations of 0.25, 0.30, 0.35, and 0.40.

It was not possible to determine from the previously published ILD literature what level of correlation to expect between test and retest. The preliminary study performed by NIH observed a correlation of 0.840 between pre and post-treatment 6MW distances. We expect a weaker correlation between patients assigned to the CON arm of the proposed study, however, due to the conflicting effects of education and possible decline from the progression of ILD. Additionally, informal study of the plots of pre-post test change in Elia et al.[55] also suggest the range of correlation simulated is conservative. As we are powering on only one of the multiple study aims due to the limitations of prior data and the hierarchy of study goals, we feel it prudent to risk overpowering on this outcome by using overly conservative estimates as it may ensure proper power for the other study aims.

The ranges of improvement in the treatment group and test-retest correlations considered give rise to 16 simulated data sets of 6000 observations each. Each data set was then tested with a 2-way mixed model ANOVA and the effect size recorded. Simulated effect sizes increased across the

range of correlation under consideration at each level of improvement in 6MWT distance. The observed effect sizes were 0.16-0.17 at 25 m, 0.18-0.20 at 30 m, 0.21-0.23 at 35 m, and 0.24-0.265 at 40 m. As we expect to have underestimated correlation, even at the given improvement levels the predicted effect sizes are highly conservative. With either correlation modestly above 0.40 and 30 m improvement, correlation of 0.25 and 35 m improvement, or some point in between these two at a sample size of n=60 the simulated effect sizes predict a power above 80% at a significance level of 0.05. Modestly higher improvement, in the range of 35-38 m, and correlation of 0.38-0.45 will result in the study having a power of approximately 95%. This range is compatible with the observed effect sizes in the literature in the moderate to large range, using Cohen's conventions for effect sizes where these ranges are 0.25-0.4 for ANOVA and 0.5-0.8 for t-tests.

To support the results from simulation, we finish by observing how power is maintained at a slightly less conservative estimate of effect size and correlation but under the additional assumption of significant subject withdrawal from the study. Assuming an effect size of 0.25 and test-retest correlation of 0.40 then a minimum of 33 patients in each group are necessary to achieve the desired power of 0.95. Even then, if only 20 patients complete the protocol in each group post-hoc analysis predicts a not-unacceptable power of 0.803.

Our recruitment goal was therefore set at 60 patients, however, completion rates to date for this study suggest that 80 subjects may need to be consented and screened in order to achieve 60 completed subjects. Therefore, the enrollment goal remains the same at 60 patients in total (30 in each group) over the course of the study as it ensures high power for comparison of 6MWT distance between AET+ and CON groups, with a buffer for moderate patient dropout. However, recruitment will remain open until 30 subjects in each of the AET+ and CON cohorts have completed the entire protocol.
Based on this recruitment goal we have agreed upon the following strategy to maintain an effective end power. At which point we attain 45 completed subjects (total) an analysis of the standard deviations in 6MWD from pre to post will be determined in the control and intervention cohorts. To maintain the blinding controls of the study as much as possible, this analysis will be performed by our statistician only. Based on this analysis our sample size will be adjusted thereafter to reflect a more accurate sample size needed to maintain an effective end power.

Human Subject Research Protections (HSRP)

Subject Selection

Rationale: Patients referred from the Baltimore/Washington/Northern Virginia area will be potential subjects for this study. All subjects will be classified by the New York Heart Association Functional Classification System (NYHA) in Class II or Class III, which relates symptoms of cardiorespiratory dysfunction to daily activity participation. No participants will be excluded based on race, gender, or ethnicity.

Recruitment: Subjects will be primarily recruited from the pool of subjects available at Inova Fairfax Hospital (Associate Investigators Drs. Nathan, Ahmad, Brown, Shlobin, and NIH Associate Investigators).

Other recruitment efforts will be directed toward presentations to ILD support groups and an introductory study letter for local private pulmonary practices. We will also utilize NIH Clinical Center-sponsored digital media resources such as Twitter, Facebook, CC Radio, CC TV, Photo Gallery; databases such as NIH Search the Studies, ClinicalTrials.gov, and Research Match; and local newspapers such as the Washington Post to disseminate information about the study to potential participants and their healthcare providers.

Pre-screening at Inova Fairfax Hospital as an Activity Preparatory to Research

Inova will refer the patients to NIH after patient signs release of information authorization. The NIH Associate Investigator and Study Coordinator will have physical access to the medical records of the Inova Advanced Lung Disease (ILD) Clinic and Pulmonary Rehabilitation Department referral patients for purposes of pre-screening Inova patients and patient referrals for this study. NIH investigators represent that (1) the use or disclosure of these records is solely to review PHI as necessary to aid study recruitment, (2) the PHI will not be removed from the covered entity (Inova Fairfax Hospital) in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

Pre-Screening Process in the Inova Fairfax Advanced Lung Disease Clinic:

If NIH Associate Investigators are at Inova Fairfax Hospital and Dr. Steven Nathan or his associates at the Inova Advanced Lung Disease (ALD) Clinic feel a patient would be a good candidate for enrollment into this study based on inclusion/exclusion criteria, the NIH associate investigator will be introduced to the patient after a brief overview of the study. If the patient is interested, he or she will sign an Inova Authorization to Release and Disclose PHI form. If the patient meets initial eligibility criteria, an appointment will be made for the patient to come to NIH for NIH consent and testing.

If the NIH Associate Investigator is not at the Inova Fairfax Hospital at the time of a patient visit and Dr. Steven Nathan or one of his associates at the Inova ALD Clinic feel a patient would be a good candidate for enrollment into the study based on the inclusion/exclusion criteria, the ALD clinic research staff will introduce the patient to the study, and the research team will have the patient sign an Inova Authorization to Release and Disclose PHI form. Once the form has been signed the NIH Investigator may contact the patient directly for follow-up.

Pre-Screening Process in the Inova Pulmonary Rehabilitation Outpatient Department:

Patient will sign release of record authorization then the patient will be referred to NIH Associate Investigator and Study Coordinator in the Pulmonary Rehabilitation Outpatient Clinic. Then referral records of patients referred for pulmonary rehabilitation for the purposes of prescreening for the study may be reviewed. When a possible patient is identified, the Inova Pulmonary Rehabilitation registrar will contact the patient by telephone to schedule pulmonary rehabilitation. The patient will be informed about the study and will be given the NIH Associate Investigator's contact information if the patient states they are interested. The Inova Fairfax Pulmonary Rehabilitation registrar will state the following to the patient referral after beginning the process of registering the patient for pulmonary rehabilitation:

"You may be eligible for an NIH study examining the benefits of pulmonary rehabilitation for patients with interstitial lung disease. Would you like the contact information for the NIH study coordinator for more information about the study?"

If the NIH Study Coordinator interviews a potential subject from any source the following script will be followed:

"Thank you for your interest regarding the research we are conducting to determine the benefits of a walking program for patients with interstitial lung disease. We are accepting volunteers between the ages of 21 and 80 who have been diagnosed with interstitial lung disease and who have been referred by their physician for pulmonary rehabilitation. If you are enrolled in the study we would ask that you come to NIH for a day of testing which would include a test to determine how far you can walk in 6 minutes, breathing tests and a treadmill exercise test. During the treadmill test you will have 16 electrodes on your chest, we will ask that you wear a neoprene mask to collect data on the amount of oxygen you breathe in and out, as well an electrode on your calf to determine the amount of oxygen your muscle utilizes for energy.

After testing you will be randomized into one of two groups, group 1 will receive exercise and education simultaneously 3 days a week for 10 weeks concluding with repeat testing at NIH. Group 2 is a 20 week group where you will receive education one day each week for 10 weeks, return to NIH for testing followed by 10 weeks of exercise 3 days a week and finally one last testing session at NIH. We do not have control over which group you are assigned to. You will be put into a group by a process called "randomization" where you have a 50-50 chance of landing in either group. Does this sound like something that you would like to participate in?"

If they answer "yes," we ask if they have time to answer a short questionnaire that would allow us to evaluate their eligibility and safety for inclusion into the study. (Please see Appendix 2 of the protocol to compare the inclusion/exclusion criteria with the questions we would be asking.)

If, based on this interaction, we think the subject might meet the inclusion criteria for the study, we will request medical records (recent history, medication list, pulmonary function test, resting EKG, six minute walk and echo) to further evaluate their eligibility for the study. Potential participants can either send us their medical records or they can fill out a medical release document and we will request this information from their physician prior to their visit to NIH. Their medical records will be reviewed and, if it appears that the patient meets the inclusion criteria, we will set

up an appointment for the patient to come to the NIH Clinical Center for consent and testing. If, after obtaining a patient's medical records it is clear that the patient does not meet inclusion criteria, the information may be used to refine our inclusion and exclusion criteria; however, these medical records will not be used for any research purposes.

To prepare for the visit, we will enter their personal information into the NIH Admissions Travel and Vouchers system and an NIH patient number will be assigned to them. Upon arriving at the NIH, the patient will proceed through admissions and then consented to the study, followed by a history and physical, blood draw, ECG, transthoracic echocardiogram, pulmonary function testing, arterial occlusion muscle oxygenation capacity test, cardiopulmonary exercise test, questionnaires, and six minute walk test.

Exclusions:

Exclusion of Children: Individuals younger than 21 years will not be included in the protocol because reference ranges for normative aerobic capacity and aerobic fitness have not been established for these age ranges. The objectives of this project do not include establishing these normative reference ranges. Moreover, far less is understood about advanced lung disease in children and the mechanisms by which it occurs. This lack of information could introduce critical levels of bias into the interpretation and cause the interpretation of our results to be misleading. Exercise response and adaptation in children with advanced lung disease should be studied in separate and specific protocols.

Exclusion of Pregnant Women:

Women of childbearing age will undergo urine pregnancy testing during screening and follow-up visits and will be excluded from the study should results be positive. Pregnant women will necessarily be excluded from the study for safety reasons. Women who do not exercise before pregnancy should not begin a rigorous exercise during pregnancy and would not be able to achieve the target heart rate required as part of the testing and training.

Exclusion of Those Who Are Unable to Obtain Informed Consent:

Individuals unable to give informed consent will necessarily be excluded from the study because of the risk to subject safety and the need to maintain integrity of the study. Subjects must be able to comprehend and follow directions, and express their own needs adequately during all testing and retesting procedures, and exercise and educational training sessions.

Benefits and Risks/Discomforts:

A previous study found that participation in an aerobic exercise training program improved 6MW distance, peak VO2, and resting pulmonary artery systolic pressure. No less is expected for patients completing the proposed study. In particular, 6MWD has been used as an endpoint in

clinical trials of medications used to treat advanced lung diseases because it correlates indirectly with the mortality and may correlate directly with quality of life.

The risks of this study are those associated with aerobic exercise testing and training in patients who have circulatory disorders. These include sudden cardiac arrest, myocardial infarction, angina and electrocardiographic abnormalities, shortness of breath, dizziness, early onset of fatigue and exhaustion, near-syncopal or syncopal episodes, and muscle or joint pain. Many of these symptoms may occur during the immediate, post-exercise recovery phase, which is generally thought to be the first six minutes following strenuous exercise. Risk of injury also includes those related to falling on a moving treadmill belt such as abrasions, contusions, cuts, sprains, fractures, or muscle strain. The likelihood that any of these injuries would occur is small and preventive measures will be enforced to insure that the risks remain at a minimum.

Many subjects will experience delayed onset muscle soreness after the treadmill exercise tests or after beginning the exercise-training phase. This soreness will be mild to moderate in intensity and may be felt immediately after exercise or up to 48 hours following the exercise session. It will typically subside within seven days. Many subjects will also experience increased levels of fatigue that are sustained for up to 24 hours following the exercise sessions. This fatigue will typically subside after one to three weeks.

In order to minimize the possibility of an attack exacerbated by the arterial occlusion muscle oxygenation capacity test, subjects diagnosed with severe Raynaud's phenomenon will be excluded from participation in that test. Otherwise, the risk of exercise in this population is similar as for other ILD patients. These subjects were exercised safely with no adverse events in our previous study examining the benefits of exercise in patients with pulmonary hypertension. Included in that study were patients with ILD with connective tissue disorders who had Raynaud's [56].

Subjects with uncomplicated diabetes will be monitored before and after exercise testing and training for glucose levels and glycemic responses to exercise. Physical activity generally reduces glycemic levels and intense activity can cause transient blood glucose elevations in individuals with diabetes. Thus, the risks of hypoglycemia and hyperglycemia are associated with exercise in individuals with diabetes. The acute risks of exercise for individuals with diabetes must be weighed against the potential long-term benefits such as a reduction in cardiovascular disease risk and improved hemodynamic function. In order to reduce risks and avoid the onset of diabetic symptoms during participation in the study, glucose monitoring will be performed per standard of care.

Exercise is a very low risk intervention in this population. The most serious risks for those participating in exercise are cardiovascular abnormalities. These risks are slight even in individuals with known coronary atherosclerosis during maximal exercise testing. In studies that include known heart disease as well as patients in whom the presence of heart disease is unknown, morbidity and mortality during maximal exercise testing remains low at 0.0 to 8.3 per 100,000 and 0.0 to 1.0 per 100,000 respectively[53-62]. Morbidity and mortality remain at similar lows for maximal exercise testing environments that are attended by a physician and those supervised by a physician but operated without physician attendance [54, 57, 60, 63, 64]. Exercising at sub-maximal intensities carries with it even lower risk of adversity. Therefore, we would consider **a single study related death, myocardial infarction, or stroke** to be a reason to consider stopping the study. Should one of these *unanticipated serious* adverse events occur, the PI will notify the

Clinical Director, IRB, and our independent medical monitor within the time frame and according to the policies specified in the currently approved NIH OHSRP SOP Policy 801 ("Reporting Research Events"). Following the completion of the SAE review and the determination of the IRB we will consider stopping the protocol if the IRB deems it necessary.

To minimize risk and maximize safety, exercise tests and classes will be carried out in laboratories that are in clinical settings with immediate response backup at the NIH Clinical Center and Inova Fairfax Hospital. The Principal Investigator, Dr. Leighton Chan, a physician board certified in Physical Medicine and Rehabilitation, will supervise the medical and safety aspects of the study and will be available should an emergent need arise. If for any reason Dr. Chan is not immediately available should an emergency arise then the RMD medically responsible physician of the day will be available to assist. In addition, all subjects will be screened by medical history and examination to exclude those with contraindications to exercise. Subjects will be monitored during the exercise tests by an EKG. Subjects will be informed of the signs and symptoms of heart disease and questioned frequently during the test regarding the presence of symptoms of cardiovascular, neurological, or musculoskeletal conditions. Subject's oxygen saturation will be monitored by infrared pulse oximetry. Safety procedures will be rehearsed by the laboratory personnel and emergency precautions will be observed continuously. A fully equipped emergency response team will be readily available to respond to life threatening events. The current response time is less than three minutes. Dr. Chan will be briefed frequently and routinely regarding all testing and training operations. As recommended by the American Heart Association and the American College of Sports Medicine, exercise will be overseen by personnel appropriately trained to extend physician services in the form of exercise testing and training[43,44,46,54] for populations included in this study (non-cardiac disease). Additional clinical consults, e.g, cardiology or pulmonology, along with laboratory testing may be performed in order to help ensure safety for exercise.

Health risks during exercise are very small. In fact may decrease the risk as we are doing intensive peak and submaximal exercise evaluations, performed under controlled and safe clinical conditions as well as other medical tests and examinations related to defining the seriousness of the patients' conditions. Improvement in aerobic capacity enables individuals to accomplish a given amount of activity or work at a lower percentage of maximum capacity and with less fatigue. Moreover, improvement of exercise tolerance generally increases quality of life by permitting individuals to engage more easily in daily physical activities. It is anticipated that the potential benefits of participating in a program of aerobic exercise conditioning outweigh the minimal risks associated with exercise in this group of patients who have advanced lung disease. Thus, this protocol involves more than minimal risk to study patients, with the prospect of direct benefit to individual subjects.

Participants from Inova Fairfax Hospital's Advanced Lung Disease Clinic will be identified and referred to the protocol by one of the physician associate investigators. the use and disclosure of patient medical records as an "activity preparatory to research", the NIH Associate Investigator and Study Coordinator may assist the Inova Principal Investigator, Dr. Steven Nathan, by reviewing medical records of the Inova Advanced Lung Disease (ILD) Clinic and Pulmonary Rehabilitation Department referral patients for purposes of pre-screening Inova patients and patient referrals for this study.

Consenting: NIH research staff will interview interested candidates. Those deemed appropriate will both read and sign the NIH approved consent form. A copy of the signed informed consent shall be given to the individual signing the consent and the original consent document will be

retained in the medical record. Upon giving consent, the subject will undergo a full examination by a physician, and a review of available medical records will be performed to confirm their suitability for the trial. After this, they will begin the baseline research tests including: treadmill cardiopulmonary exercise test, arterial occlusion muscle oxygenation capacity test, pulmonary gas exchange analysis, heart rate measurement, bioelectrical impedance plethysmography, near infrared spectroscopy, six-minute walk and fatigability tests, and patient self-report instruments. All tests will be performed again post rehabilitation for outcome comparisons.

Data and Safety Monitoring Plan:

As the PI, Dr. Chan will closely monitor patient safety throughout the duration of the study. However, this protocol has several characteristics that suggest a more extensive data monitoring procedure. First, the risk of performing several exercise tests on patients with interstitial lung disease is unknown. We suspect that the risk is a minor increase over minimal risk, but we are not sure. Second, the protocol involves randomization and blinding. Patients will be randomized, to either education or exercise + education. In addition, while the subjects will not be blinded to their treatment allocation, the study personnel will be blinded to the extent that is possible with exercise intervention trials. Study personnel will be blinded through initial baseline screening/testing and randomization, however following randomization due to the nature of exercise training and the time points involved in this study the blinding process will no longer be possible. Finally, this study involves one extramural site: Inova Fairfax Hospital..

Given these additional factors, we feel that our plan may need more than just PI monitoring, but fails to meet the criteria for the involvement of a full DSMB. Therefore, we have enlisted the assistance of Matthew N Bartels, MD, MPH, Chairman of the Department of Physical Medicine and Rehabilitation at the Montefiore Medical Center/Albert Einstein College of Medicine, New York, as the independent medical monitor (IMM) for this study. He will be apprised of all significant adverse events. In addition, this monitor will also have access to the study data. RMD's Epidemiology and Biostatistics Department will examine the results on an interim basis. If, at any point, they feel that the study should be stopped because of concern for safety of study subjects, they will inform the PI, the IRB, and the clinical and scientific directors of CC and NHLBI.

Conflicts of Interest:

This study does not include any commercial interests, technology transfer, or any products made by a commercial interest. No conflicts of interest have been identified for any NIH employees associated with this study.

Subject compensation:

Subjects will be compensated $300 for each completed testing session at the NIH. For those in the concurrent exercise and education group of the randomized trial, this will amount to $600 because participants will come to the NIH for initial testing and again for retesting at the end of the study. For those in the education only group the amount of compensation will be $900 because participants will come to the NIH for initial testing, then again for a second testing after the

completion of 10 weeks of education, and again for a third time after 10 completed weeks of exercise.

Data Management Plan:
Data will be collected using appropriately calibrated computer-assisted instrumentation, commercial software programs, data collection sheets and self-reported outcome questionnaires.

Clinical Trials Survey System (CTSS) will be used to manage data collection of the following subject self-reported outcome questionnaires and subjects will have the choice of using an NIH mobile device or paper format to complete the questionnaires. All digital CTSS forms will be considered source documentation.

CTSS	Source
Fatigue Severity Scale	Digital or Paper
Human Activity Profile	Digital or Paper
King's Brief ILD Questionnaire (K-BILD)	Digital or Paper
Profile of Moods	Digital or Paper
St. George's Respiratory Questionnaire	Digital or Paper
SF-36	Digital or Paper

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Clinical Trials Database (CTDB) will be used to manage data collection and tracking of the intervention through the use of an NIH mobile device. Paper source may be used should capability of digital entry not be available. All Digital CTDB forms will be considered source documentation.

Upon enrollment, subjects will be assigned a protocol number that will be used as a subject identifier for all subject files and data collection sheets. All computer software with associated data files is kept on password-protected computers that are off-network and are stored in a locked laboratory with restricted access. Paper data collection sheets will be kept in de-identified subject folders in locked filing cabinets in secure areas. Patient consent forms and other relevant medical records with patient names and other identifiable data are kept in separate folders and locked in separate filing cabinets. No information will be kept in either folder that could be used to link a subject's medical record file to a subject's study data file.

Electronic data collected in the laboratory will be transferred to a restricted access folder on the Clinical Center network with appropriate firewall protection. Only study PIs and AIs will have access to this folder. A password protected USB device will be used to transfer data. Email communication with patient information or data will be transmitted via encrypted email as per NIH guidelines. Data will be analyzed as discussed in the Data Analysis section of this document.

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List of Abbreviations

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
A-VO_2	Arteriovenous Oxygen Difference
AET	Aerobic Exercise Training
AET+	Aerobic Exercise Training Group
AI	Associate Investigator
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AT-Time	Anaerobic Threshold
ΔVO_2	Amplitude of Change in Oxygen Consumption from Baseline
CON	Control Group (Education Only)
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
DBP	Diastolic Blood Pressure
DKA	Diabetic Ketoacidosis
DLCO	Diffusion Capacity
EKG	Electrocardiogram

FIO2	Fraction of Inspired Oxygen
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GET	Gas Exchange Threshold
HAP	Human Activity Profile
HRQOL	Health Related Quality of Life
HRR	Heart Rate Reserve
ILD	Interstitial Lung Disease
IMM	Independent Medical Monitor
IPF	Idiopathic Pulmonary Fibrosis
K-BILD	King's Brief Interstitial Lung Disease Health Status Questionnaire
LVEF	Left Ventricular Ejection Fraction
MCID	Minimal Clinical Important Difference
MRT	Mean Response Time
MVV	Maximal Voluntary Ventilation
NIRS	Near Infrared Spectrometry
NYHA	New York Heart Association
ORI	Oxidative Response Index
PA	Pulmonary Artery
PAH	Pulmonary Arterial Hypertension
$PETCO_2$	Partial Pressure of End-Tidal Carbon Dioxide
$PETO_2$	Partial Pressure of End-Tidal Oxygen
PH	Pulmonary Hypertension
PI	Principal Investigator
POMS	Profile of Mood States
PPH	Primary Pulmonary Hypertension
PWC	Peak Work Capacity
QOD	Quantifiable Oxygen Deficit
QOL	Quality of Life
Qt	Cardiac Output
r	Correlation Coefficient
r^2	Coefficient of Determination
RAP	Right Atrial Pressure
RCT	Randomized Control Trial
RER	Respiratory Exchange Ratio
RHC	Right Heart Catheterization
RMD	Rehabilitation Medicine Department
RV	Right Ventricle
RVSP	Right Ventricular Systolic Pressure
SGRQ-I	St. George's Respiratory Questionnaire-IPF Specific Version
SBP	Systolic Blood Pressure
SF36v2	Short Form 36 Health Survey Version 2
SpO2	Saturation of Peripheral Oxygen
SSQ	Social Support Questionnaire
tCPET	Treadmill Cardiopulmonary Exercise Test
TPR	Total Peripheral Resistance
TRV	Tricuspid Regurgitation Velocity

VCO_2	Volume of Expired Carbon Dioxide
Ve	Expired Minute Ventilation
VO_2	Oxygen Consumption (Volume of Oxygen Consumed per Minute)
Vs (or SV)	Stroke Volume
Vt	Tidal Volume
WHO	World Health Organization
WR	Work Rate
ZCG	Impedance Cardiogram