STRENGTH TRAINING IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

By

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DEDICATION

This thesis is dedicated to my Mama and Daddy, Terri and Bob Correll. Thank you so much for your unconditional love and never ending support. You were there to see me through every trial or celebrate with me for every triumph. I can honestly say that I am the person I am today because of your great values, kindness and the occasional bout of tough love. I am truly very fortunate to have such loving, involved and dedicated parents. Thank you for your faith in me. I love you always.
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Amanda Leigh Correll

ABSTRACT

STRENGTH TRAINING IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Thesis under the direction of Michael J. Berry, Ph.D., Department Chair and Professor of Health and Exercise Science

The purpose of this study was to obtain pilot data comparing aerobic exercise to strength training exercise on measures of physical function in COPD patients. Participants included seven patients who participated in the REACT II trial. REACT II was completed in April of 2006 and consisted of a 12-week aerobic training program. These same patients also partook in the current study of a 12-week high intensity progressive resistance training program that met three times a week. Each participant completed, in both the REACT II and current study, the six minute walk test, stair climb test, short physical performance battery and a self-reported physical function questionnaire. A two factor factorial Analysis of Variance (ANOVA) with two within factors was used to examine differences in outcome measures. The two within factors were time (baseline and three months) and intervention (aerobic and strength). Results of this study found no significant interactions between aerobic and strength training in COPD patients for the six minute walk distance, stair climb time, short physical performance battery or self-reported physical function. There was a trend (p = 0.07) towards significance for the difference between aerobic and strength intervention six minute walk distances (488.2 ± 45.4 versus 397.9 ± 80.1, respectively). There was also a trend (p = 0.08) towards significance for the difference between aerobic and strength intervention SPPB scores (11.3 ± 0.5 versus 10.3 ± 0.9, respectively). And lastly, there was a trend (p = 0.07)
towards significance for the difference between baseline and three month physical function questionnaire scores (1.4 ± 0.1 versus 1.3 ± 0.1, respectively). In conclusion, neither aerobic or strength training demonstrated significant improvements in measures of physical function in this study. However, both training groups elicited changes in the expected direction for the measures studied. Further research is needed with a larger sample size to determine the optimal training program for COPD patients.
Introduction

Chronic obstructive pulmonary disease (COPD), a group of lung diseases including chronic bronchitis and emphysema, is a preventable and treatable disease characterized by an airflow limitation that is not fully reversible. COPD is a leading cause of morbidity and mortality and is expected to increase in upcoming years. According to the Centers for Disease Control and Prevention, COPD was the fourth leading cause of death in the United States in 2004 and is projected to become the third leading cause of death by 2020.

The signs and symptoms most commonly associated with this disease are dyspnea (shortness of breath), chronic cough, sputum production and exercise intolerance. While decreases in pulmonary function were traditionally thought to be associated with exercise intolerance and disability in these patients, recent evidence suggests that decreases in pulmonary function are not predictive of physical function. COPD has recently been recognized as a multi-system disease affecting organs of the body other than the lungs. In particular, COPD patients experience skeletal muscle dysfunction characterized by decreases in strength, endurance, efficiency and an earlier production of lactic acid at a given work load. This muscular dysfunction leads to decreased exercise capacity, loss of physical function and decreased quality of life.

There are many treatment options for this disease including pharmacological therapy such as bronchodilators or glucocorticosteroids, oxygen therapy, surgical treatments such as lung transplantation or lung volume reduction surgery and pulmonary rehabilitation. Pulmonary rehabilitation, which includes exercise training, is a standard
mode of care for these patients and has been shown to improve exercise intolerance, physical function and health related quality of life. Many large studies have shown that aerobic exercise in COPD patients is efficacious. Benefits from this type of training include increases in exercise tolerance and exercise endurance time, improvements in physical function and overall shortness of breath, decreased muscle fatigue and improved self-efficacy for walking. Despite conclusive support for aerobic training as an effective treatment in this population, results generally show no improvements in lung function or cardiovascular function, as measured by VO₂. However, COPD patients do display improvements in physical function, suggesting exercise may ameliorate the skeletal muscle dysfunction seen in these patients. In order to better target skeletal muscle, strength training has been proposed as a more efficient mode of exercise therapy for COPD patients.

There have been studies that demonstrated the benefits of strength training in the COPD population, but many limitations remain in the literature. Discrepancies exist as to what is the most effective regimen for strength training in these patients. Limitations within the strength training research include: varying training durations and intensities, inclusion of mostly male participants, training programs that focus on either the upper or lower body and programs that combine both aerobic and strength training. Due to the lack of conclusive evidence supporting strength training as a treatment for COPD patients, a randomized clinical trial comparing strength training to aerobic training (the current standard of care) is needed. Therefore, the purpose of this study is to obtain pilot data comparing aerobic exercise to strength training exercise on measures of physical function in COPD patients. These data may then be used to support a larger randomized
controlled trial comparing the effects of these two interventions on physical function in COPD patients.
REVIEW OF LITERATURE

Definition of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), a group of lung diseases including chronic bronchitis and emphysema, is defined as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The American Thoracic Society (ATS) and European Respiratory Society (ERS) describe this airflow limitation as usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gas. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) also states that COPD is accompanied by extrapulmonary effects, such as weight loss, nutritional abnormalities and skeletal muscle dysfunction, which contribute to the severity of the individual. Disease severity depends on the degree of airflow limitation as well as symptoms such as shortness of breath, decreased exercise capacity, systemic effects and other comorbidities.

Chronic bronchitis is defined as the presence of a chronic productive cough for three months in each of two successive years, provided that all other causes of chronic cough have been ruled out. Emphysema is a pathological condition resulting in the destruction of alveolar walls and permanent enlargement of the air spaces distal to the terminal bronchioles. Although chronic bronchitis and emphysema can exist independently, COPD patients often present with both diseases. In COPD patients, inflammation in the lungs causes narrowing and remodeling of the small airways which leads to the airflow limitation. Inflammatory processes also cause destruction of the lung parenchyma which leads to loss of alveolar attachments to the small airways and
decreased lung elastic recoil resulting in an airflow limitation\textsuperscript{5}. Although COPD can be accompanied by asthma, the airflow inflammation in these two diseases is very different. Airflow limitation is normally reversible in asthma patients; however for patients with COPD symptoms and asthma symptoms, it is often difficult to distinguish the two diseases\textsuperscript{45}.

The signs and symptoms most commonly characteristic of COPD are dyspnea (shortness of breath), chronic cough, and sputum production. The American Thoracic Society defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity\textsuperscript{51}.” Cough and sputum production may be evident before airflow limitation or airflow limitation may precede cough and sputum production.

**Staging the severity of COPD**

In order to diagnose COPD, spirometric measures are needed to assess the severity of the airflow limitation\textsuperscript{13}. Spirometry measures include an individual’s forced vital capacity (FVC) and forced expiratory volume in one second (FEV\textsubscript{1}). FVC is the maximum volume of air that a patient can forcefully exhale after a maximum inhalation and FEV\textsubscript{1} is the volume of air that can be forcefully exhaled in one second. The ratio of FEV\textsubscript{1}/FVC and FEV\textsubscript{1}, as a percent of predicted, are used in determining the extent of lung obstruction. Spirometric measures should be obtained in all individuals who have a history of exposure to cigarettes, environmental or occupational pollutants or in the presence of COPD symptoms\textsuperscript{13}. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages severity of COPD into four categories based on spirometric results\textsuperscript{45}. Stage I (mild COPD) corresponds with an FEV\textsubscript{1}/FVC <70% and FEV\textsubscript{1}≥80% of
predicted. There may be symptoms of chronic cough and sputum production. Stage II (moderate COPD) corresponds with an $\text{FEV}_1/\text{FVC} < 70\%$ and $50\% \leq \text{FEV}_1 < 80\%$ of predicted. In this stage, dyspnea is exhibited upon exertion and there may be symptoms of cough and sputum production. Stage III (severe COPD) corresponds with an $\text{FEV}_1/\text{FVC} < 70\%$ and $30\% \leq \text{FEV}_1 < 50\%$ of predicted. Symptoms exhibited in this stage can range from dyspnea, reduced exercise capacity, fatigue and repeated exacerbations. Stage IV (very severe COPD) corresponds with an $\text{FEV}_1/\text{FVC} < 70\%$ and $\text{FEV}_1 < 30\%$ of predicted or $\text{FEV}_1 < 50\%$ of predicted with the presence of chronic respiratory failure.

**Etiology**

The most common risk factor for COPD is cigarette smoking. However, smoking is not the only important risk factor. Other risk factors for COPD include: inhalation exposures, occupational exposures, indoor and outdoor air pollution, lung growth and development, oxidative stress, gender, infections, socioeconomic status, nutrition and asthma\(^5\). As such, non-smokers can also develop chronic airflow limitation characteristic of COPD. The development of COPD as a result of exposure to risk factors depends upon a genetic and environmental interaction\(^{45}\). Genetic predisposition can cause an individual to be more susceptible to COPD than other smokers.

**Epidemiology**

COPD is a leading cause of morbidity and mortality throughout the world and is expected to increase in upcoming years due to increases in exposure to COPD risk factors. Although the prevalence of COPD is often under recognized due to variable definitions of the disease, prevalence surveys from around the world estimate that one quarter of adults over 40 years of age may have an airflow limitation equivalent to Stage I COPD\(^{45}\).
According to The Global Burden of Disease Study, COPD was the sixth cause of death worldwide in 1990 and is projected to become the third leading cause of death by 2020\textsuperscript{35}. There were approximately 2.7 million deaths globally from COPD in 2000, and in the United States there were approximately 141,000 deaths from COPD in 2002\textsuperscript{35}.

Additionally, the mortality trends for females have changed significantly. In 1980, 20.1 out of 100,000 women and 73.0 out of 100,000 men died from COPD in the United States\textsuperscript{5}. In 2000, the death rate for women had increased to 56.7 out of 100,000 while the death rate for men had only increased to 82.6 out of 100,005\textsuperscript{5}. Historically, men have had higher rates of cigarette smoking, however in the past several decades, smoking has become as common or more common in women\textsuperscript{14}. Smoking trends are most likely the cause of an increase in female mortality, but there is growing evidence that women may be more susceptible to the effects of inhaling tobacco smoke\textsuperscript{56}. Research has shown that in women, COPD becomes clinically evident at an earlier age than men\textsuperscript{56}. Women also present with similar lung function as age-matched men despite a shorter smoking history\textsuperscript{56}. Not only is COPD prevalence increasing, but economic burden is increasing as well. In 2007, the total economic costs of COPD in the US were $42.6 billion, as compared to $23.9 billion in 1993\textsuperscript{40}.

Pathophysiology

Respiratory System

Chronic obstructive pulmonary disease results in changes to four compartments of the lung. These compartments include the central airways (cartilaginous airways larger than 2 mm in diameter), peripheral airways (noncartilaginous airways smaller than 2 mm in diameter), lung parenchyma and pulmonary vasculature\textsuperscript{45}. Within the central airways
there is an increased proportion of mucus glands and goblet cell metaplasia resulting in the inflammation which is characteristic of chronic bronchitis. In the peripheral airways, similar goblet cell metaplasia occurs, as well as metaplasia of the smooth muscle and deposition of collagen. These changes in the airways result in mucous hypersecretion, ciliary dysfunction and metaplasia of epithelial cells. The lung parenchyma, which consists of the bronchioles, alveoli and capillaries, also undergo pathological changes as a result of COPD. Emphysema, which is a result of changes to the lung parenchyma, is characterized by an abnormal enlargement of the air spaces distal to the terminal bronchioles. More specifically, there is destruction of the alveolar wall attachments leading to a loss of elastic recoil and alveolar wall support. These anatomical changes are a cause of the collapse of peripheral airways and the resulting hyperinflation. Lastly, there are pulmonary vasculature changes which occur in the early stages of COPD. These changes consist of thickening of the vessel wall and endothelial dysfunction followed by an increase in vascular smooth muscle and inflammatory cells in the vessel wall. Eventually, these changes can lead to the loss of pulmonary capillaries and an increase in pulmonary arterial pressure or pulmonary hypertension. The net effect of all these changes is an airflow limitation which leads to gas exchange abnormalities and hyperinflation of the lungs.

Pulmonary hyperinflation compounds the airflow limitation by imposing a mechanical disadvantage on the inspiratory muscles of the respiratory system. The length of the diaphragm is shortened and the external intercostal muscles are lengthened, therefore altering the muscles optimal length for contraction. This abnormal muscular arrangement leads to weaker inspiratory muscles in COPD patients. While expiratory
muscles must work against an increased load, dysfunction of these muscles is usually due to systemic or intrinsic factors of the muscle and not anatomical changes.\textsuperscript{22}

**Pathophysiology of Skeletal Muscle**

Chronic obstructive pulmonary disease has recently been recognized as a multi-system disease. Although decreases in pulmonary function are associated with physiological limitations in COPD, they do not accurately predict disability in patients.\textsuperscript{9} COPD can manifest in systems other than the pulmonary, thus affecting organs of the body other than the lungs. Inflammatory processes and systemic manifestations of COPD lead to skeletal muscle dysfunction and muscle wasting of appendicular and diaphragmatic skeletal muscle. These changes ultimately contribute to a decreased exercise capacity, a loss of physical function as well as decreased quality of life.\textsuperscript{22,54}

Skeletal muscle dysfunction is characterized by decreases in strength, endurance, efficiency and an earlier appearance of lactic acid at a given work load.\textsuperscript{39} Generally, muscles of the lower extremities are most affected by COPD, while those of the upper extremities are the least affected and remain better preserved throughout the disease progression.\textsuperscript{39} COPD patients tend to be sedentary and reduce their physical activity because of ventilatory limitations. This decrease in activity contributes to the muscle dysfunction and leads to further losses of exercise capacity, physical function and quality of life.\textsuperscript{39}

Other factors thought to contribute to skeletal muscle dysfunction are systemic inflammation, oxidative stress, nutritional abnormalities, hypoxia and hypercapnia and certain drugs.\textsuperscript{39} Inflammatory mediators decrease the contractility of muscle fibers and also influence protein degradation.\textsuperscript{39} Oxidative stress affects the physiology of muscle
fibers by damaging enzymes, proteins and lipids that are needed for a muscle fiber to survive\textsuperscript{39}. Nutritional abnormalities lead to loss in body weight and fat free mass. Hypoxia causes reductions in stored energy and protein synthesis in muscles while hypercapnia leads to decreases in muscle contractility\textsuperscript{39}. Systemic corticosteroids which are often prescribed in the management of COPD patients can also cause skeletal muscle myopathy in COPD patients.

\textit{Loss of Skeletal Muscle and Strength}

Structural alterations lead to skeletal muscle dysfunction in COPD patients. These alterations are apparent in muscle mass and muscle fiber types and sizes\textsuperscript{19}. In 1994, Engelen and colleagues investigated body composition and respiratory and peripheral skeletal muscle function in 72 COPD patients\textsuperscript{19}. Of these patients, 14\% experienced loss of both body weight and fat-free mass, while 7\% of the patients experienced either a loss of body weight or a loss of fat-free mass. Results showed that fat-free mass loss was related to lower values of respiratory and skeletal muscle strength. Engelen and colleagues concluded that patients who lost fat-free mass displayed lower values of skeletal muscle strength as compared to those who maintained their fat-free mass\textsuperscript{19}. Additionally, peripheral skeletal muscle strength was affected more than respiratory muscle strength.

More recently, in 2007, Hopkinson and colleagues completed a prospective investigation of COPD patients examining change in body composition and maximum isometric quadriceps strength over a one year period\textsuperscript{29}. Bioelectrical impedance analysis (BIA) was used to determine fat-free mass in 64 patients with stable COPD. At baseline, 36\% of the COPD patients had fat-free mass loss determined by BIA and a disease
specific regression equation\textsuperscript{53}. These same patients also had significantly weaker quadriceps strength. At the one year follow-up period, fat-free mass loss was shown to be correlated with a greater amount of fat-free mass at baseline. Fat-free mass loss was also correlated with lower quality of life score, poorer lung function, prednisone use and more frequent exacerbations\textsuperscript{29}. Additionally, at the one year follow-up, results showed that the mean maximum isometric quadriceps strength decreased significantly from 34.8 kg (66.3\% predicted), to 33.3 kg (62.3\% predicted)\textsuperscript{29}. These authors conclude that over one year, COPD patients experience significant losses in fat-free mass and strength. This population averaged a yearly loss of quadriceps strength of 4.3\%, which is significantly greater than the 1-2\% predicted in normal aging populations determined from a 12-year longitudinal study completed by Frontera and colleagues in 2000\textsuperscript{21}.

Rossi and colleagues investigated changes in body composition, fat distribution and pulmonary function in 77 COPD patients and found that the loss of skeletal muscle coincides with a decline in lung function\textsuperscript{50}. Their study included 47 women and 30 men with baseline BMI values of 24.96 ± 3.28 and 27.04 ± 3.35 kg m\textsuperscript{2} respectively. Measurements obtained were body weight, waist circumference, sagittal abdominal diameter, fat-free mass and fat mass as determined by dual energy x-ray absorptiometry (DEXA), forced expiratory volume in 1 second (FEV\textsubscript{1}) and forced vital capacity (FVC). Over a 7 year follow up period, investigators found that there was a significant decrease in fat-free mass for both men and women. Results also showed that a decline in fat-free mass and an increase in the sagittal abdominal diameter were associated with a decline in FEV\textsubscript{1} and FVC\textsuperscript{50}.
In 2002, Marquis and colleagues examined the cross sectional area of the mid-thigh muscle in 142 stable COPD patients\textsuperscript{38}. Measurements obtained were a CT scan of the thigh, pulmonary function tests, arterial blood gases and peak work rate. Mortality data were subsequently collected on these patients. The mean mid-thigh cross sectional area of the COPD patients was $73 \pm 18 \text{ cm}^2$, as compared to $102 \pm 18 \text{ cm}^2$, the mean cross sectional area of healthy individuals of similar age ($65 \pm 5$ years)\textsuperscript{38}. All of the measurements obtained were correlated with mortality. However, when included in a multivariate analysis, cross sectional area of the thigh proved to the strongest predictor of mortality. The authors concluded that cross sectional area of the thigh was a better predictor of mortality than body mass index, and that cross sectional area had the greatest impact on mortality for COPD patients with an FEV$_1 < 50\%$ predicted\textsuperscript{38}.

Peripheral muscle weakness has been shown to contribute to the decreased exercise capacity in COPD patients\textsuperscript{28}. Hamilton and colleagues in 1995, investigated respiratory and skeletal muscle strength in 4,617 subjects that were referred for clinical exercise testing\textsuperscript{28}. This large investigation found that 70\% of the patients with a chronic lung disease had lower quadriceps strength as compared to normal age-matched subjects. Of the four exercises studied (knee extension, knee flexion, seated press and seated row), the COPD patients had scores that were, on average, 81\% of the healthy control group scores\textsuperscript{28}. Results also showed that when compared to age matched healthy controls, COPD patients had a 20-30\% reduction in quadriceps strength\textsuperscript{28}.

In 1998, Bernard and colleagues examined muscular strength of the quadriceps, pectoralis major and latissimus dorsi in 34 males with moderate to severe COPD\textsuperscript{7}. Results from this investigation corroborated those of Hamilton et al.\textsuperscript{28} in that quadriceps
strength was found to be reduced in Bernard and colleagues’ sample. These investigators also found that the decrease in quadriceps strength was proportionally greater than the decrease in pectoralis major and latissimus dorsi strength. The authors postulated that this was most likely because the upper body muscles are more commonly used in activities of daily living. Additionally, the authors stated that the pectoralis major and latissimus dorsi muscles may serve as accessory muscles of inspiration.7

Gosselnik and colleagues investigated the role of peripheral muscle weakness on multiple measures of exercise capacity and lung function in 41 COPD patients.26 The measurements obtained were VO₂ max, 6 minute walk distance (6MWD), lung function, diffusing capacity, isometric quadriceps force, hand grip force and maximum inspiratory and expiratory pressures. The patients scored poorly on 6MWD, VO₂ max, and respiratory and peripheral muscle force. Walking distance was significantly correlated with quadriceps force (0.63), hand grip force (0.53), maximal inspiratory pressure (0.49), and diffusing capacity (0.38).26 In a stepwise multiple regression analysis, quadriceps force and maximum inspiratory pressure were significant predictors of 6MWD. Therefore, the authors concluded that both lung function and peripheral muscle strength are determinants of exercise capacity in COPD patients.26

Eisner and colleagues compared adults with COPD from the Function, Living, Outcomes and Work (FLOW) study (n = 1202) to age, sex and race matched referent subjects (n = 302) to examine the impact of COPD on physical function measures.17 Results from this study showed that COPD is associated with worse performance in the six minute walk test as compared to healthy controls (-102 meters; 95% CI, -117 to -86
meters). Results also showed that COPD was associated with decreased performance (-1.0 points) on the SPPB as compared to the referent subjects.  

Structural Changes in Skeletal Muscle of COPD Patients

Alterations in skeletal muscle of COPD patients are also apparent at the cellular level. When compared to age-matched healthy control subjects, COPD patients experience a decrease in the percent of type I muscle fibers of the vastus lateralis as well as an increase in the percent of type IIb muscle fibers. The cross sectional area of type I, IIa and IIb muscle fibers are also decreased in patients with COPD. However, upper limb type I fibers remain relatively unchanged in COPD patients as compared to healthy age-matched control subjects. Capillarity is also decreased in COPD patients. More specifically, when compared to healthy subjects, COPD patients have a significantly lower number of capillaries per square millimeter of muscle. When compared to age-matched adults, COPD patients also have lower levels of oxidative enzyme activity in the vastus lateralis muscle. Alterations at the cellular level have been attributed to inactivity of the COPD patient and hypoxemia, a decrease of oxygen in arterial blood.

In 2002, Gosker and colleagues compared skeletal muscle fiber types and metabolic profiles in both COPD patients and healthy control subjects. The COPD patients had significantly lower proportions of type I muscle fibers (16% compared to 42% in the control subjects) as well as oxidative enzymes. The authors concluded that the low oxidative capacity was related to the proportion of type I muscle fibers, but there was an additional reduction of oxidative capacity within type IIa muscle fibers.

Gosker and colleagues in 2007 examined whether a reduction in mitochondrial volume density also contributes to a decrease in oxidative capacity in COPD patients.
Muscle biopsies were obtained from the vastus lateralis muscle of six COPD patients and four healthy control subjects and on the tibialis anterior muscle of six COPD patients and six healthy control subjects. Mitochondrial number and fractional area were determined for both groups. When comparing COPD patients to the controls, both the mitochondrial number (0.34 versus 0.63 n·µm\(^{-2}\), respectively) and fractional area (1.95 versus 4.25%, respectively) were reduced\(^{24}\). Even though there was a reduced mitochondrial number in the tibialis anterior of the COPD patients as compared to the controls (0.65 versus 0.88 n·µm\(^{-2}\), respectively), the fractional area remained unchanged\(^{24}\). The authors concluded that a reduced mitochondrial fractional area in the vastus lateralis contributes to a decrease in oxidative capacity, whereas a maintained fractional area may explain the normal oxidative capacity in the tibialis anterior\(^{24}\).

Jobin and colleagues, in 1998, examined capillarity and fiber type proportions in 15 male subjects\(^{31}\). Eight COPD patients and seven healthy subjects completed a symptom limited maximal exercise test as well as a transcutaneous biopsy of the vastus lateralis muscle. Results showed that the COPD patients had a lower number of capillaries per square millimeter (92.6 ± 16.1) as compared to the healthy subjects (213.3 ± 33.5)\(^{31}\). Also, the capillary to fiber ratio was less in the COPD patients (0.83 ± 0.05) than in the healthy subjects (1.56 ± 0.10)\(^{31}\). The authors concluded that COPD negatively affects fiber type and capillarization in the lower limbs of these patients.

Jakobsson and colleagues, examined glycolytic and oxidative enzyme activity in the quadriceps femoris muscle of COPD patients\(^{30}\). A muscle biopsy of the quadriceps femoris muscle was performed on 18 COPD patients and seven healthy control subjects. Phosphofructokinase was higher in the COPD patients (+34%), than in the control group,
indicating improved glycolysis\textsuperscript{30}. Citrate synthase was lower in the COPD patients (-29\%), than in the control group, indicating decreased aerobic metabolism\textsuperscript{30}. The authors attributed the decrease in citrate synthase to physical inactivity and the increase in phosphofructokinase to chronic hypoxia which leads to increased anaerobic metabolism capacity\textsuperscript{30}.

Chronic obstructive pulmonary disease has been recognized as a multi-system disease, where pulmonary function is not the only predictor of mortality. Systemic manifestations of this disease lead to skeletal muscle dysfunction. This muscular dysfunction leads to decreased exercise capacity, loss of physical function and decreased quality of life\textsuperscript{22,54}. COPD patients also experience a loss of body weight and/or loss of fat-free mass. Skeletal muscle dysfunction encompasses peripheral muscle weakness, causing COPD patients to have a 20-30\% reduction in quadriceps strength as compared to their healthy age-matched counterparts\textsuperscript{28}. Changes on the cellular level are also present in this disease. These patients experience a decrease in type I muscle fibers with an increase in type IIb muscle fiber proportion. Muscle biopsies of COPD patients have also shown irregularities in the muscle fibers such as low oxidative capacity, decreased capillaries per square millimeter and metabolic enzyme changes. Due to the deleterious effects of COPD, exercise training has been introduced as a treatment option to counteract further deconditioning in these patients.

Exercise Training

Exercise training has been established as an effective treatment for patients with chronic obstructive pulmonary disease. Pulmonary rehabilitation, which includes exercise training, is a standard mode of care for these patients and has been shown to
improve exercise capacity, physical function and health related quality of life. Possible mechanisms of improvement following exercise training include improved aerobic capacity, increased motivation, reduction in dyspnea, and improved mechanical skill when performing activities of daily living. While research has shown exercise training to be an effective treatment for COPD patients, the optimal training program has yet to be established. For example, research has also shown that COPD patients can train at a relatively high intensity in order to induce skeletal muscle improvements seen in healthy adult populations that partake in a training program. However, whether patients will adhere to such a program has not been determined.

Aerobic training, including walking and cycling, was the first mode of exercise to be established as efficacious for these patients. In 1994, Goldstein and colleagues found that following 8 weeks of pulmonary rehabilitation, COPD patients experienced improvements in 6 minute walk distance and submaximal cycle time but no change in lung function. They studied 38 severe, stable COPD patients that completed thrice weekly sessions of interval training consisting of treadmill walking, upper extremity endurance training and leisurely walking. When a participant could walk for 20 minutes, the speed was then increased by 10-20%, with the ultimate goal of being able to walk up to 40 minutes. Sixteen weeks following the conclusion of the pulmonary rehabilitation program, patients still exhibited significant improvements, from baseline, in 6 MWD (37.9 meters) and submaximal cycle time (4.7 minutes). There were also no changes in pulmonary function.

Ries and colleagues conducted a randomized controlled trial in 1995 which provided the strongest evidence to date for the benefits of exercise training in patients.
with mild to severe chronic obstructive pulmonary disease\textsuperscript{49}. There were 119 stable COPD patients that were randomly assigned to an 8-week comprehensive pulmonary rehabilitation program or an 8-week education program. The pulmonary rehabilitation group received education sessions, physical and respiratory care instruction, psychosocial support and supervised exercise training, while the education group received lecture and discussion classes. The exercise training consisted of walking at a symptom limited level on a treadmill, using an isokinetic upper body ergometer and a progression of arm lifts with weights at home. Results showed that when compared to the education only group, the pulmonary rehabilitation group showed significantly greater improvements in maximal exercise tolerance (1.5 versus 0.6 METS), exercise endurance time (10.5 versus 1.3 minutes), symptoms of perceived breathlessness following an exercise test (score of -1.5 versus +0.2), muscle fatigue (score of -1.4 versus -0.2), overall shortness of breath (score of -7.0 versus +0.6) and self-efficacy for walking (score of 1.4 versus 0.1)\textsuperscript{49}. However, improvements in lung function, depression and quality of life did not differ significantly between groups. Due to the improvements in outcomes deemed important to COPD patients, the authors concluded that pulmonary rehabilitation programs which include exercise training are an effective treatment for these patients.

Casaburi and colleagues also observed improvements in peak and constant work rate and more efficient exercise breathing in COPD patients following 6 weeks of cycle ergometer training\textsuperscript{12}. There were 25 participants that met three times a week for 45 minutes sessions of cycle ergometer training. Based on an incremental exercise test at baseline, the exercise intensity was set at 80\% of peak work rate. Participants were also encouraged to walk one hour a day at home. Contrary to other studies, results did show
significant increases in FEV$_1$ (9\%, p<0.05), peak work rate (35\%, p<0.001) and peak VO$_2$ (16\%, p<0.001)$^{12}$. This research was unique in comparison to earlier research because of the high exercise intensity. However, it is questionable if this level of exercise can be used in maintenance programs for COPD patients.

Despite conclusive support for aerobic training as an effective treatment in this population, results generally show no improvements in lung function or cardiovascular function, as measured by VO$_2$. However, COPD patients do display improvements in physical function, suggesting exercise may ameliorate the skeletal muscle dysfunction seen in these patients. In order to target these organs, strength training has been proposed as a more efficient mode of treatment for COPD patients.

It is well known that strength training will increase skeletal muscle mass and strength in older adults$^{34}$. However, the use of strength training in the treatment of COPD is not as well documented. Clark and colleagues, in 2000, completed a randomized controlled trial examining the effects of a 12-week strength training program in COPD patients$^{15}$. The participants were 43 COPD patients (26 were in the training group and 17 were in the control group) and 54 healthy sedentary control subjects. The strength training intervention was twice a week for 12 weeks. Each session consisted of patients performing three sets of 10 repetitions for eight different strength training exercises at 70\% of the patient’s one repetition maximum. Results showed that the training group experienced significant improvements in strength on four of the five lower body exercises and one of the three upper body exercises. Quadriceps strength increased by 7.6 ± 7.2 kg as compared to 0.4 ± 4.8 kg in the control group. Whole body endurance during treadmill walking also improved in the training group with a mean difference of
4,205 joules from baseline (95% CI: 1,404 - 5,650) as compared to a mean difference of 344 joules from baseline (95% CI: 109 - 579) in the control group\textsuperscript{15}. The limitations of this study were that there was no aerobic group to compare to the strength training group and only mild COPD patients were included (mean FEV\textsubscript{1} of 77 ± 23\%)\textsuperscript{15}.

There has been some research examining both aerobic and strength training in COPD populations. Normandin and colleagues, in 2002, completed a prospective, randomized, un-blinded trial, comparing the efficacy of aerobic and strength training in COPD patients\textsuperscript{41}. The participants consisted of 40 symptomatic COPD patients of whom 20 were randomized to a high intensity, lower extremity aerobic program and 20 were randomized to a low intensity, peripheral muscle training program. The training programs lasted for eight weeks and met twice weekly. The aerobic group trained on a stationary bicycle and treadmill for 30 minutes, with the goal of training at greater than 80\% of the maximum level obtained from an incremental exercise test\textsuperscript{41}. The strength training group completed “classroom exercises” for 30 minutes each session, such as chair exercises, upper body exercises with weights, and standing exercises. Results showed that the aerobic group had greater increases in treadmill endurance (8.4 ± 1.3 minutes as compared to 2.7 ± 1.4 minutes in the strength training group). The strength training group showed greater increases in arm endurance testing (12.2 ± 2.0 repetitions per minute compared to 6.5 ± 1.9 repetitions per minute in the aerobic training group)\textsuperscript{41}. While both groups showed significant improvements in exercise variables, overall dyspnea, functional performance and health status, there are many shortcomings in this study. The study was un-blinded, lasted only 8 weeks, and there was no control group. Additionally, the strength training protocol was poorly defined and modified from a
home exercise program. From the article, it is unclear what the exact nature of what the
strength training exercises were.

Ortega and colleagues performed a randomized controlled trial with an aerobic
training group, strength training group, combined aerobic and strength training group and
a control group\textsuperscript{42}. The participants were 47 moderate to severe COPD patients who
trained thrice weekly for 12 weeks. The aerobic training group completed 40 minutes
sessions on a calibrated cycle ergometer at 70\% of their peak work rate which had been
obtained from an incremental exercise test. The strength training group completed four
sets of six to eight repetitions on five different exercises at 70 - 85\% of their one
repetition maximum load. The combined training group performed 20 minutes of cycling
and two sets of six to eight repetitions of the strength training exercises. Results showed
that only the strength training group had significant improvements in the shuttle walking
test (from 457 ± 150 to 561 ± 204 meters)\textsuperscript{42}. At the end of the 12-week training
programs and at the 12-week follow-up period following the completion of the program,
all training groups had significant improvements in strength. The authors concluded that
strength training was an acceptable mode of exercise for COPD patients and was better
than aerobic training to develop muscle strength. The authors also concluded that aerobic
training was better to develop exercise endurance, while a combined training program
was best to produce results seen in both the individual training modalities\textsuperscript{42}. The
limitations with this research are that there were small sample groups and only the
strength training group had improvements in the shuttle walk test. The shuttle walk test
is incremental (each minute the walking speed increases), therefore making it more of a
measure of exercise capacity than endurance\textsuperscript{42}. 

21
In 2004, Panton and colleagues performed a randomized controlled trial that compared the effects of a combined strength training and aerobic training program (n=9) to that of an aerobic training program (n=8) in COPD patients44. Results showed that the combined training group had significant improvements in upper and lower body strength and improvements in the 12 minute walk test. Three of the eight activities of daily living also improved in the combined training group44. The aerobic group had no significant changes. Limitations in this study were that there was a small sample size and the lack of a strength training only group made it hard to determine if the training effect was due to the combination of training regimens or to strength training alone.

Bernard and colleagues also compared the effects of an aerobic versus a combined, aerobic and strength training program in COPD patients8. There were 36 patients randomized to aerobic training alone (n=19) or aerobic and strength training (n=17) for 12 weeks. While quadriceps strength increased in both training groups, the improvement was significantly greater in the combined group. The thigh muscle cross sectional area also significantly increased in the combined group as compared to the aerobic only group8. Changes in peak exercise work rate, six minute walk distance and quality of life were similar in both groups. Similar to the results of Panton and colleagues44, it is difficult to determine if the training effect was due to strength training alone or to the combination of the training programs.

Mador and colleagues in 2004 produced conflicting results when compared to previous research36. When comparing an aerobic training only to a combined aerobic and strength training group in COPD patients, combined training led to significant improvements in quadriceps and latissimus dorsi strength. Aerobic training alone did not
result in significant improvements in muscular strength. However, six minute walk distance, exercise endurance time and quality of life, as measured by the Chronic Respiratory Questionnaire, improved significantly in both training groups\textsuperscript{36}. The problems with this study were that even though combined training did improve muscular strength, this type of training did not prove significantly better than aerobic training alone at improving exercise endurance and quality of life. The sample size was small (n=24) and perhaps a larger sample size was needed to exclude the additional effect of strength training\textsuperscript{36}.

Kongsgaard and colleagues investigated heavy resistance training in elderly male COPD patients\textsuperscript{32}. There were 6 patients in a 12-week heavy progressive strength training program and 7 patients in the control group which performed breathing exercises for 12 weeks. The strength training group met twice weekly for 60 minutes. Each participant in this group performed four sets of eight repetitions at 80% of their one repetition maximum and was also asked to complete each concentric phase as explosively as possible. Measures that improved in the strength training group were as follows: strength, physical function, power, cross sectional area of the quadriceps, maximal gait speed, stair climb time and self-reported health\textsuperscript{32}. In the control group there were no changes found. Limitations found here were that only a small number of men were included in the study and the heavy progressive strength training program made it questionable as to whether COPD patients could maintain the high level of intensity for a longer duration than 12 weeks.

Spruit and colleagues examined strength versus aerobic training in COPD patients on the outcome measures of peak knee extension torque, maximal knee flexion force,
elbow flexion force, six minute walk distance, maximal workload on a cycle ergometer and health related quality of life. After a 12-week training program, both groups showed significant improvements in peripheral muscle strength, six minute walk distance, maximum workload and health related quality of life. With this research, unexpected results were reported. More specifically, the strength training group showed improvements in peak workload and six minute walk distance, while the aerobic training group showed improvements in peripheral muscle strength. The authors concluded that aerobic training, like strength training, may be a sufficient mode of exercise for combating peripheral muscle weakness in COPD patients.

There are many common limitations found in strength training research for COPD populations. For example, the training programs range from three weeks to 12 weeks and the number of sessions per week range from one to three. This variability makes the optimal training duration unclear. There is also an uncertain definition as to the optimal training intensity for these patients. Male subjects were predominantly included in the research and most strength training programs focused on either the upper or lower body. And finally, the majority of strength training programs were a combination of aerobic and strength training. This makes direct comparisons between aerobic and strength training programs difficult.

**Purpose**

The purpose of this study is to obtain pilot data comparing aerobic exercise to strength training exercise on measures of physical function in COPD patients. These data may then be used to support a larger randomized controlled trial comparing the effects of these two interventions on physical function in COPD patients.
It is hypothesized that strength training will result in greater improvements in physical function as compared to aerobic training in COPD patients. More specifically, it is hypothesized that strength training will result in greater improvements in six minute walk distance, stair climb time, short physical performance battery and self reported physical function.
METHODS

Study Design

This thesis was a pilot study designed to test the effects of strength training on measures of physical function in patients with COPD. The goal of this study was to produce data to support a larger randomized controlled trial that will examine aerobic training and strength training in COPD patients. After participants were screened for eligibility and baseline assessments were obtained, they began a center-based, supervised, progressive strength training intervention 3 days a week for 3 months after which follow-up assessments were made.

Participants

Participants for the current study were individuals with COPD who were previously enrolled in the Reconditioning Exercise and COPD Trial (REACT II). Recruitment for REACT II ended in November 2005 with the final participants closing out of the study in April of 2006. The primary purpose of the REACT II study was to compare two different approaches to prescribing exercise on activity levels in COPD patients. Participants were eligible for REACT II if a non-reversible airflow limitation, defined as an FEV₁/FVC < 70% and FEV₁ > 20% of predicted was present as determined by a pulmonary function test. The exclusion criteria were as follows: FEV₁/FVC > 70%, FEV₁ < 20% of predicted or absence of reported disability, inability to perform exercise due to physical disability, living more than 35 miles from center, unwilling and/or unable to participate in all aspects of the study, or undergoing active treatment for cancer; severe congestive heart failure, stroke, peripheral vascular disease, coronary artery disease,
valvular heart disease, major psychiatric disease, severe anemia, liver or renal disease, uncontrolled diabetes or hypertension, and orthopedic impairment.

**REACT II**

The Reconditioning Exercise and Chronic Obstructive Pulmonary Disease Trial II (REACT II) was a single center, single blind, randomized controlled trial. Recruitment began in 2001 and took place over 4 years, where patients started in waves of approximately 12 to 15 patients per wave via community based advertising in the local media and physician referral. Patients within each wave were randomized to either the Lifestyle Activity Program (LAP) or the traditional exercise therapy (TET) following baseline visits. All participants were informed that they could drop out of the study at any time and no financial reward was offered to patients for their participation. Data collection occurred at baseline and at 3, 6 and 12 months post-randomization. Staff members blinded to the participant’s treatment assignment completed all data collection.

Both the LAP and the TET groups received exercise treatment and bimonthly education classes during the first three months of the study. Both groups received 36 hours of interventionist and participant contact over the course of each intervention. The TET group met for one hour sessions thrice weekly for 12 weeks. Each session consisted of a warm-up, 30 – 35 minutes of walking at a rating of perceived dyspnea of 3 – 5 (moderate to somewhat hard) on the Borg categorical scale, 10 – 15 minutes of strength training using elastic resistance bands and a cool-down. After completion of the 36 center-based sessions, participants were encouraged to continue exercising on their own.
The LAP also consisted of 36 hours of participant contact. LAP participants progressively reduced their center-based activity over the first three months of the intervention after which time participants were encouraged to increase their levels of physical activity outside of the center. Both group and individual behavior change procedures were used to encourage these participants to self-regulate their levels of physical activity. The goal of this approach was to promote independent physical activity by gradually tapering participants from interventionist and center dependency while promoting independent self regulation of physical activity. Counseling was offered to participants during months 4-11, to review and evaluate their ability to sustain long-term physical activity. During the first three months, LAP participants had 14 center based exercise sessions identical to the sessions in which the TET participated and during months 4-11, there were 8 more identical center based exercise sessions. To minimize the potential for measurement bias, the schedule was organized so that the 6 and 12 month testing appointments and patient contacts were separated by at least a two week interval.

**Procedures**

After successfully completing three baseline visits, eligible participants began a 12-week strength training program. Follow up testing was performed over two days at the end of 12 weeks. Data obtained at the baseline and follow up visits will be used in this study. Recruitment consisted of two letters mailed to all of the REACT II participants. If a potential participant was interested, they were then administered a brief screening questionnaire over the telephone. Participants who met the inclusion/exclusion criteria attended screening visit one. The first baseline visit was used to determine
eligibility into the study. During this visit, participants read and signed an informed consent approved by Wake Forest University’s Health Science Institutional Review Board. Participants also completed a medical history form and a treadmill graded exercise test with a supervising physician. The informed consent is presented in Appendix A. During the second baseline visit, participants completed pulmonary function tests, strength testing, a health related quality of life questionnaire, self-reported physical function questionnaires and physical performance tests at the Wake Forest University Human Performance Laboratory. Baseline visit three was completed at the General Clinical Research Center of Wake Forest University Health Sciences, where participants completed a muscle biopsy, a dual energy X-ray absorptiometry scan (DEXA), a computed tomography scan (CT) and blood draw. Participants that were on an anti-coagulant therapy did not complete a muscle biopsy. Follow up visit one was conducted at Wake Forest University Human Performance Lab where pulmonary function tests, strength testing, a health related quality of life questionnaire, self-reported physical function and physical function tests were performed. The second follow up visit took place at the General Clinical Research Center of Wake Forest University Health Sciences where the participant completed a muscle biopsy, DEXA scan, CT scan and blood draw. Data for this thesis was obtained from baseline visit two and three and follow up visit one and two.

Pulmonary Function Testing

All pulmonary function tests were completed using a Medical Graphic Plethysmograph (Model 1085). The tests were performed according to American Thoracic Society\(^4\) standards and met reproducibility and acceptability requirements. Prior
to each test, all equipment was calibrated according to manufacturer’s guidelines. Obtained values include each participant’s FEV₁/FVC (%) and FEV₁ (% predicted).

**Graded Exercise Testing**

The incremental graded exercise test was performed using a modified Naughton protocol where the speed and/or grade increased every two minutes. The protocol is presented in Appendix B. The procedures, purpose and endpoints of the test were also explained to each participant. The American College of Sports Medicine criteria for exercise test termination were followed³.

Oxygen saturation (SpO₂) was measured during the graded exercise test using a Nonin pulse oximeter (Model 9500). Oxygen saturation values were measured at rest, prior to starting the graded exercise test, at the end of each two minute stage and during recovery. A twelve lead electrocardiogram was monitored throughout the test. Tracings were recorded at rest in the supine position, standing, at the end of each stage and during the recovery phase.

**Exercise Intervention**

All the participants completed a center based, supervised, 12-week high intensity progressive resistance training program. The strength training intervention met three times a week. Before each exercise session, blood pressure and oxygen saturation levels were recorded. Participants then completed a 3-5 minute warm-up and 5 minutes of flexibility exercises. The strength training exercises targeted these major muscle groups: abductors (overhead press) and horizontal adductors (bench press) of the shoulders; flexors (bicep curls) and extensors (triceps extensions) of the elbows; trunk flexors; hip extensors; and the extensors and flexors of the knee. A one-repetition maximum was
measured for each of the eight exercises at the beginning of the intervention and at weeks two and seven. This procedure included a warm-up or familiarization trial on each machine at a low amount of resistance. Each participant then lifted a moderate amount of weight. If this weight could be lifted more than once, 10 pounds were added each time until only one repetition could be completed. If the initial weight could not be lifted, the weight was decreased by 10 pounds. Adequate rest periods were allowed between attempts, depending upon individual participant needs. The goal of each participant was to be able to lift 80% of their 1-RM for three sets of eight repetitions. The suggested progression of the strength training intervention is shown in Table 1 and was based on ACSM guidelines. Adjustments to this schedule were made for each individual participant dependent upon his/her ability to perform the recommended progression. The participants recorded the weight lifted and repetitions completed in a log book.

Adherence with the exercise training will be computed and defined as the number of exercise session completed/total possible number of sessions times 100.

### Outcome Measures

**Six Minute Walk Testing**

The 6-minute walk testing was performed according to the American Thoracic Society. Participants were instructed to walk as long as possible within a six minute time limit. The 6-minute walk test was performed in a dedicated gymnasium that measured 8 meters by 14 meters. Oxygen saturation (SpO₂) was also measured at rest,

<table>
<thead>
<tr>
<th>Week</th>
<th>Intensity</th>
<th># of Sets (8 reps/set)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>40-50 %1RM</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>40-50</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>60-70</td>
<td>2</td>
</tr>
<tr>
<td>4-7</td>
<td>60-70</td>
<td>3</td>
</tr>
<tr>
<td>8-12</td>
<td>70-80</td>
<td>3</td>
</tr>
</tbody>
</table>
every lap and at recovery, using a Nonin pulse oximeter (Model 9500). No feedback or encouragement was given to the participants during the walk. If needed, the participant was allowed to stop at any time during the test, while time continued. If oxygen saturation dropped below 88%, participants were asked to stop and recover until oxygen saturation was above 88%.

**Stair Climb Time**

The timed stair climb test was performed at the Wake Forest University Human Performance Lab. Participants were asked to ascend two flights of stairs as quickly as possible. In order to standardize testing, all participants were asked to hold onto the handrail. The elapsed time started at floor level and ended at the top of the second flight of stairs. The first flight of stairs had 10 steps and the second flight of stairs had 11 steps. Each step had a seven inch rise and a 12 inch run. The total vertical ascent was 12.6 feet. The participants did not receive encouragement or feedback on their performance.

**Short Physical Performance Battery**

The short physical performance battery based on timed short distance walk, repeated chair stands and balance test, as described by Guralnik et al. was performed with all participants. Lower extremity function was determined using three performance-based tests that assess walking speed, time to rise from a chair and sit down five times (chair stands) and standing balance.

*Walking speed.* Walking speed was assessed by asking the patient to walk at their usual pace over a 4 meter course. Patients were instructed to stand with both feet touching the starting line and to start walking after a specific verbal command. Patients were allowed to use walking aids (cane, walker, or other walking aid) if necessary, but not the
assistance of another person. Timing began when the command was given, and the time in seconds needed to complete the entire distance was recorded. The faster of two walks was used to compute walking speed.

Chair stands. The repeated chair stands test was performed using a straight-backed chair placed with its back against a wall. Patients were first asked to stand from a sitting position without using their arms. If they were able to perform this task, they were then asked to stand up and sit five times as quickly as possible. The time to complete the task was recorded.

Standing balance. For the test of standing balance, patients were asked to maintain balance in three positions characterized by a progressive narrowing of the base of support: feet together (side by side position), the heel of one foot beside the big toe of the other foot (semi tandem position), and the heel of one foot in front of and touching the toes of the other foot (tandem position). For each of the three positions, patients were timed to a maximum of 10 seconds. Scores were summed for the measure of balance for a range of 0 to 30 seconds. These three physical performance measures were then used to calculate summary scores by using a quantile and an arithmetic approach.

Quartile summary performance score. Each of the three performance measures was assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. For the test of balance, participants were assigned a score of 1 if they could hold a side by side standing position for 10 seconds, but were unable to hold a semi-tandem position for 10 seconds; a score of 2 was assigned if they could hold a semi-tandem position for 10 seconds, but were unable to hold a full tandem position for more than 2 seconds; a score of 3 was assigned if they could stand in full
tandem position for 3 to 9 seconds; a score of 4 was assigned if they could stand in full tandem position for 10 seconds.

Four categories were computed for walking speed and chair stands, according to cutoffs based on quartiles of the time to perform each task assessed in the Established Populations for Epidemiologic Studies of the Elderly (EPESE). The speed of the faster of two walks was scored as follows: < 0.42 m/sec = 1; 0.41 to 0.59 m/sec = 2; 0.58 to 0.75 m/sec = 3; > 0.75 m/sec = 4; a score of 0 was assigned to participants unable to perform the test. The time required to perform five chair stands was scored as follows: > 16.7 sec = 1; 13.7 to 16.6 m/sec = 2; 11.2 to 13.6 m/sec = 3; < 11.1 = 4. A score of 0 was assigned to participants unable to perform the task. A summary performance score ranging from 0 (worst performers) to 12 (best performers) was calculated by adding walking speed, chair stands and standing balance scores. This scale has proven valid for predicting institutionalization, hospital admission, mortality and disability27.

Self-Reported Physical Function

Participants completed a self-reported physical function questionnaire at screening visit two. This questionnaire was a 23-item questionnaire that assessed the physical disability of the participant. It was a modified version of the form used in the Fitness and Arthritis in Seniors Trial (FAST). For each item, participants were asked to indicate how much difficulty they experienced while performing physical activities during the past month. The questionnaire is scored on a 6-point scale with a score of one indicating “usually did with no difficulty” and a score of six indicating “usually did not do for other reasons.” The questionnaire is presented in Appendix C.
Statistical Analyses

Data for this investigation will be obtained from participants who completed both the REACT II investigation (an aerobic training intervention) and the present investigation (a strength training intervention). Descriptive statistics are presented as means ± standard deviations. Differences at baseline for the aerobic and strength training treatments were determined by a Repeated Measures T-test. A two factor factorial Analysis of Variance (ANOVA) with two within factors was used to examine differences in outcome measures. The two within factors were time (baseline and three months) and intervention (aerobic and strength). Alpha was set at 0.05, and all analyses were done using the Statistical Package for Social Sciences (SPSS version 16.0).
RESULTS

Participant flow is described in Appendix D. First, 176 letters were mailed to REACT II participants. Interested participants were then screened for eligibility. The 119 participants that were not screened either did not respond, the letter was returned in the mail or the participant had passed away. Of the 45 people screened, 29 were excluded due to failure to meet pulmonary function criteria, cardiac condition or other various reasons. The 16 participants that were included began the current study. There were four participants that did not comply for various reasons and five participants are currently in the study. Seven participants completed the current study.

Descriptive data for subjects prior to the start of the aerobic and the strength intervention are shown in Table 2. Significant differences between treatments at baseline are noted by an asterisk. During aerobic training, the participants attended 86% of the sessions (31 ± 3.5 sessions). During strength training, the participants attended 94% of the sessions (34 ± 2.2 sessions).

Table 2. Participant Descriptive Data.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Aerobic</th>
<th>Pre-Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female, n</td>
<td>6/1</td>
<td>6/1</td>
</tr>
<tr>
<td>Age, yr</td>
<td>62 ± 10.0</td>
<td>66.4 ± 12.0*</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>203.3 ± 61.6</td>
<td>206.4 ± 78.3*</td>
</tr>
<tr>
<td>Height, in</td>
<td>67.5 ± 3.8</td>
<td>66.1 ± 3.6*</td>
</tr>
<tr>
<td>BMI</td>
<td>31.1 ± 7.8</td>
<td>32.7 ± 10.0*</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>65.0 ± 17.4</td>
<td>70.3 ± 27.6*</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>62.0 ± 5.9</td>
<td>64.4 ± 9.2</td>
</tr>
</tbody>
</table>
Six Minute Walk

Mean (±SEM) baseline aerobic, baseline strength, three month aerobic and three month strength data for the six minute walk are shown in Figure 1. Results from the ANOVA revealed no significant interaction between time and intervention, p = 0.68. Additionally, there was no significant difference between baseline and three month six minute walk distances (430.8 ± 63.1 versus 455.3 ± 61.6, respectively, p = 0.11). There was a trend (p = 0.07) towards significance for the difference between aerobic and strength intervention six minute walk distances (488.2 ± 45.4 versus 397.9 ± 80.1, respectively).

Figure 1. Six Minute Walk Distance.
Stair Climb Time

Mean (±SEM) baseline aerobic, baseline strength, three month aerobic and three month strength data for the timed stair climb are shown in Figure 2. Results from the ANOVA revealed no significant interaction between time and intervention, p = 0.40. Additionally, there were no significant differences between baseline and three month stair climb times (13.0 ± 2.8 versus 12.4 ± 2.8, respectively, p = 0.47) or between aerobic and strength intervention stair climb times (13.7 ± 3.2 versus 11.8 ± 2.4, respectively, p = 0.20).

Figure 2. Stair Climb Time.
Short Physical Performance Battery

Mean (±SEM) baseline aerobic, baseline strength, three month aerobic and three month strength data for the short physical performance battery are shown in Figure 3. Results from the ANOVA revealed no significant interaction between time and intervention, \( p = 0.58 \). Additionally, there was no significant difference between baseline and three month SPPB scores (10.4 ± 0.9 versus 11.3 ± 0.5, respectively, \( p = 0.15 \)). There was a trend (\( p = 0.08 \)) towards significance for the difference between aerobic and strength intervention SPPB scores (11.3 ± 0.5 versus 10.3 ± 0.9, respectively).

Figure 3. Short Physical Performance Battery.
Self-Reported Disability

Mean (±SEM) baseline aerobic, baseline strength, three month aerobic and three-month strength data for self-reported disability determined by a physical function questionnaire are shown in Figure 4. Results from the ANOVA revealed no significant interaction between time and intervention, $p = 0.75$. Additionally, there was no significant difference between aerobic and strength intervention physical function questionnaire scores (1.4 ± 0.1 versus 1.3 ± 0.1, respectively, $p = 0.34$). There was a trend ($p = 0.07$) towards significance for the difference between baseline and three-month physical function questionnaire scores (1.4 ± 0.1 versus 1.3 ± 0.1, respectively).

Figure 4. Self-Reported Disability.
DISCUSSION

The current study sought to obtain pilot data comparing aerobic exercise to strength training exercise on measures of physical function in COPD patients. Previous research has shown no improvements in lung or cardiovascular function following an aerobic exercise intervention, yet there have been improvements in physical function. Additionally, recent findings demonstrate that COPD patients experience a skeletal muscle myopathy; therefore, it was hypothesized that strength training would result in greater improvements in physical function as compared to aerobic training in COPD patients. More specifically, it was hypothesized that strength training would result in greater improvements in six minute walk distance, stair climb time, short physical performance battery and self-reported physical function. Results of this study found no significant differences between aerobic and strength training in COPD patients for the six minute walk distance, stair climb time, short physical performance battery or self-reported physical function.

The six minute walk test is a commonly used exercise test to determine functional exercise capacity and to measure the response of exercise interventions in patients with COPD\(^1\). Even though the results from this study did not show differences between the aerobic and strength training groups, both groups experienced a change in the expected direction and there was a trend towards significance favoring the aerobic training group. This trend could be due to the fact that the aerobic group started at a higher baseline value than the strength training group. The aerobic group improved an average of 19.4 meters and the strength training group improved an average of 29.4 meters. According to
the research completed by Redelmeier and colleagues in 1997, a clinically significant improvement in the six minute walk distance is 37 to 71 meters or an average of 54 meters. Therefore, in the current study, results showed that there were no clinically significant improvements in six minute walk distance in either the aerobic or strength training groups.

The failure to show statistically or clinically significant improvements in the six minute walk test following both exercise interventions is in contrast with other studies, Goldstein et al. reported significant improvements from baseline to the end of an eight week intervention in six minute walk distance in a COPD population. The treatment group underwent eight weeks of interval training and improved significantly on the six minute walk test (37.9 meters) as compared to the control group (n = 40). Clinically significant improvements were barely reached in this sample. Bernard et al. found similar findings in both an aerobic training group and a combined aerobic and strength training group. Both the aerobic and combined training groups increased the mean six minute walk distance by 66 and 88 meters, respectively, following 12 weeks of training. Additionally, Mador et al. reported statistically significant improvements in six minute walk distance following eight weeks of either aerobic training, (27 meters) or combined training (34 meters). It should be noted that the average improvements in both of these groups were less than 54 meters, indicating a failure to reach clinically significant improvements.

In an investigation by Dourado et al., participants were either randomized into a strength training group (n = 11), a low intensity general training group (n = 13) or a combined training group of strength and low intensity training (n = 11) for 12 weeks.
The strength training group increased six minute walk distance by an average of 43 meters (p <0.05) from baseline, the low intensity general training group increased an average of 31 meters from baseline and the combined training group increased an average of 48 (p<0.05) from baseline. A minimally clinical significant improvement was seen in a portion of the strength training group (n = 6) (54.5%) and in a portion of the combined training group (n = 4) (36.4%)\(^{16}\).

Reasons for the lack of statistically and clinically significant findings with either intervention in the current study could have been due to the small sample size and the variability in each participant’s responses to the training. Previous research has demonstrated that in the COPD population, a more individualized exercise program is needed in order to tailor intensity, intervals and duration to each patient’s exercise ability\(^ {57}\). This may account for the variability in response to each intervention.

The second outcome measure evaluated was the stair climb time test which is an appropriate tool to determine physical function in the COPD population\(^ {47}\). This measure has good test re-test reliability and utilizes a mode of mobility to which most participants are accustomed\(^ {47}\). Results from the current study did not show a significant interaction between time and intervention nor were there statistically significant differences for time or intervention. Both the aerobic and strength training interventions climbed the stairs faster (a change in the expected direction), indicating potential improvements, however the changes were not significant.

Berry and colleagues have shown that patients with mild COPD can achieve improvements in the timed stair climb following an exercise intervention\(^ {11}\). Mild (n = 99), moderate (n = 36) and severe (n = 16) COPD patients underwent 12 weeks of
walking, upper body strength training and stretching exercises. Following the intervention the mild COPD group climbed the steps .57 seconds faster\textsuperscript{11}. Berry and colleagues also compared short term (3 months) and long term (18 months) exercise programs in COPD patients with regards to stair climb time\textsuperscript{10}. Participants in the long term intervention group climbed two flights of stairs 11\% faster than the short term intervention group.

Kongsgaard and colleagues reported improvements in stair climb time with nine elderly male COPD patients who partook in a 12-week heavy strength training program (only one flight of stairs was completed for this study as opposed to two flights of stairs in the current study)\textsuperscript{32}. The strength training group made significant improvements in the stair climb time (0.8 seconds) as opposed to the control group (0.3 seconds). Again, reasons for the lack of significance within the current study could be due to the small sample size or variability within each participant’s response to the training intervention.

The short physical performance battery is a widely used, standardized measure of lower extremity function that predicts mobility disability in older adults\textsuperscript{43} and has been used to assess the impact of COPD on physical function\textsuperscript{17}. Results from the current study did not show a significant interaction between time and intervention; however, there was a main effects trend (p = 0.08) towards significance favoring the aerobic training group to the strength training group. Both the aerobic and strength training groups demonstrated changes in the expected direction, with improvements from baseline to post-intervention.

The Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study examined the effects of an exercise intervention of aerobic, strength, balance and flexibility exercises versus a successful aging intervention consisting of health education
on SPPB scores. Over one year of follow-up, SPPB scores were significantly higher in the exercise group (8.5 units) than in the successful aging group (7.9 units). At both the six month and one year follow-up, a higher number of participants in the exercise group improved by greater than one point and a higher number of participants in the successful aging group declined by greater than one point. This research indicates that being physically active does maintain lower extremity function in older adults. In agreement with the LIFE-P results with older adults, both the aerobic and strength training interventions had changes in the expected direction, indicating potential improvements, however the changes were not significant. The improvements in the current investigation were 1.0 and 0.67 units for the aerobic and strength training groups, respectively. These changes are greater than the differences between the exercise and successful aging group from the LIFE-P study yet are not statistically significant; again, most likely due to the small sample size. However, these differences can be considered clinically significant in light of the LIFE-P findings.

Eisner and colleagues examined the effect of COPD on SPPB scores in the FLOW study. Results showed that COPD was associated with decreased performance (-1.0 points) on the SPPB as compared to the referent subjects. Therefore, the one point improvement seen in this study, while not statistically significant, could be of clinical importance to these patients.

Finally, self-reported physical function was the fourth outcome evaluated. Results revealed no significant interaction between time and intervention, however, there was a trend (p = 0.07) towards significance for the main effect of time favoring three month to baseline physical function questionnaire scores. Both the aerobic and strength
training groups demonstrated changes in the expected direction, with improvements from baseline to post-intervention. The aerobic group improved an average of 0.2 units and the strength training group improved an average of 0.1 units from baseline to the end of the respective intervention.

Other studies have shown similar results, for example, Berry et al. compared the effects of a short term (3 month) and long term (18 months) aerobic and upper extremity strength training exercise intervention on self-reported physical function in COPD patients\textsuperscript{10}. Both groups decreased their scores on the questionnaire after 3 months of an exercise intervention. These results coincide with others who found that older adults with knee osteoarthritis decreased their self-reported disability following an aerobic or strength training intervention\textsuperscript{20}.

There are several limitations with this study, the most significant being a small sample size. Due to the fact that this research is based on data from a pilot study, there are a small number of participants. Recruitment in the COPD population is often difficult. Research has shown that individuals who smoke, a common etiology in COPD, are less likely to lead physically active lifestyles as compared to non-smokers\textsuperscript{18, 55}. Additionally, smokers are less likely to be considering increasing their levels of physical activity as compared to non-smokers\textsuperscript{18}. Therefore, recruiting these patients into exercise interventions can prove difficult. Additionally, patients in the later stages of the disease might not be willing to partake in an exercise program for fear of increased dyspnea or an exacerbation. Due to the small sample size there is very little statistical power which allows for the possibility of a type II error. Including more participants in these analyses might have allowed for statistically significant findings instead of trends towards
significance. Also because of the size of the sample, there was only one female included. This may have affected the results due to differences in gender responses to exercise and thus further limits these findings.

Another limitation is the lack of a control group. Due to the nature of this pilot study, there was no control group to compare with the aerobic and strength training group. Some might recognize the lack of a control group as a limitation, while others might see this omission as unethical, due to the proven benefits of an exercise intervention in this population.

Future directions in the study of strength training in COPD patients could include several factors. A large sample size will need to be analyzed in order to achieve statistical power and allow for variance in exercise responses in this population. Ideally, an equal proportion of COPD stages should be included, ranging from Mild to Very Severe. An equal number of males and females should be included in the sample. Finally, an examination of factors responsible for the individual variability to the responses to exercise training needs to performed.
CONCLUSIONS

The current study found that there were no significant interactions between time (0 and 3 months) and treatment (aerobic and strength training) in COPD patients for the six minute walk distance, stair climb time, short physical performance battery or self-reported physical function questionnaire. Both training groups demonstrated improvements in the expected direction for all of the outcomes measured, thus indicating improvements in physical function and self-reported physical function despite clinically or statistically significant differences. The current results are inconclusive in determining the optimal training program for COPD patients.
REFERENCES


APPENDIX A

Informed Consent

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE
CONSENT FORM

Strength Training in Patients with
Chronic Obstructive Pulmonary Disease

Principal Investigator: Michael Berry, Ph.D.
Sponsor: National Institute on Aging

You are being invited to participate in a research study to determine the effects of a strength training exercise program (weight lifting) in older adults with shortness of breath and chronic lung problems. Please read this form and ask any questions you may have before you agree to be in the study. If there are words you do not understand in this form, please ask and the study staff will explain them to you. If you would like the study staff to read this form to you, please ask and they will be happy to do so.

Introduction & Background Information.

People with chronic lung problems, such as chronic bronchitis or emphysema, often lose arm and leg muscle mass and are weaker. The purpose of this research study is to find out what effect strength training (weight lifting) has on muscle strength and how easily you can do everyday things. We are also studying certain genes. Genes are pieces of your genetic material that determine many things like your hair color or how tall you are. We think genes may determine how you respond to exercise, too. The gene we are studying is the angiotensin converting enzyme (ACE) gene. People have different forms of this gene. Recently there has been some research to suggest that people with one form of ACE genes (the DD genotype) may get more benefits from strength training; people with another form of ACE genes (the II genotype) may get more benefits from aerobic type training (walking, cycling, swimming). We want to compare the differences in muscular strength following a three month strength training exercise program between people with COPD with the different ACE genotypes. We can tell what your genotype is by doing tests on your blood.

Number of People Who Will take Part in this Study

A total of 32 people will take part in this study. The study will take place at the Geriatric Research Center (GRC) and the General Clinical Research Center (GCRC) at Wake Forest University Health Sciences, the Department of Health and Exercise Science at Wake Forest University and at the Clinical Research Center near Wake Forest University.
How the study works.

If you agree to be in this study, you will have three screening visits to find out if you qualify to be in the study. If you do qualify for the study, you will begin the strength training exercise program. After you finish the four months of the strength training exercise program, you will come back for two follow-up visits.

This is what you can expect at the screening visits.

Screening Visit 1 at the Clinical Research Center, Wake Forest University:

- You will learn about the study in more detail. You will be given time to ask questions about the study and have them answered. You will be asked to sign this informed consent form if you are interested in participating in the study.
- You will complete a breathing test where we have you blow into a tube as hard and as fast as you can for 10 to 15 seconds. This is to see if you qualify for the study.
- If you do qualify for the study based on the breathing test, you will complete some questionnaires to give us some background information about you.
- You will have a Graded Exercise Test to make sure it is safe for you to be in an exercise program. During this test, you will walk on a treadmill. You will have sticky pads with wires attached to your chest so that we can watch your heart beat. You will wear a blood pressure cuff so that we can take your blood pressure during the test. Every two minutes the treadmill will go a little faster and be raised (so that you are walking uphill) until you can’t walk anymore and want to stop

Screening Visit 2 at the Human Performance Lab, Wake Forest University:

- You will be asked to complete a questionnaire asking about how easily you can do everyday activities and to perform more breathing tests.
- You will answer some questionnaires asking about your quality of life.
- We will test the strength of your hands by having you grip and squeeze a device called a dynamometer. We will test the strength of your knee and leg by having you sit in a special chair and push and pull against it with your leg.
- You will also complete some physical performance tests.
  - We will measure how far you can walk in six minutes.
  - We will measure how fast you walk by asking you to walk at your normal pace for 15 to 20 yards (about 50 feet). You will do this test two times.
  - We will measure how fast you can stand up from and sit down in a chair.
  - We will test your balance by asking you to stand with your feet in different positions.
- This visit will take about an hour and a half.
- If you still want to participate, you will be asked to return for a third screening visit.
Screening Visit 3 at the Sticht Center, Wake Forest University Medical Center:

- You will come fasting for at least 12 hours (nothing to eat or drink except water).
- You will have a whole body DEXA (dual energy x-ray absorptiometry) scan. A DEXA scan is a painless scan of your body that measures how much bone, fat, and muscle you have. You will lie on a padded table while the scanner moves over your body.
- You will have a CT (computed tomography) scan of your thigh. A CT is a painless scan that will measure the amount of muscle and fat in your thigh. For this scan, you will lie on a table that moves into the scanner.
- You will have about 3 tablespoons of blood drawn. We will freeze some of your blood sample for future research and will use some to determine your ACE genotype.
- You will have a muscle sampling procedure.
  - To reduce the chance of bleeding, you cannot take aspirin, certain other pain relievers (like ibuprofen, Motrin™, Advil™, Aleve™) or other medications that may affect bleeding, platelets, or bruising for 1 week before and for 3 days after the procedure. It is OK to use acetaminophen (Tylenol™ or Extra-strength Tylenol™).
  - You will also be asked to avoid strenuous physical activity for 36 hours before and after the procedure.
  - The skin of one of your thighs will be thoroughly cleaned and a local anesthetic (numbing medicine similar to what a dentist uses) will be used to numb your skin first and then your thigh muscle. After the numbing medicine takes effect, a very small incision (1/4 inch long) will be made in the skin of your thigh and a needle inserted to remove a small piece of muscle (about the size of a small pea). Sometimes, the doctor doesn’t get enough muscle tissue the first time and will ask if you will allow the needle to be inserted for a second try.
  - After the needle is removed, the doctor will apply pressure to your leg to prevent bleeding into the tissue and will close the incision with small pieces of sterile tape. This muscle sample will be frozen and stored so that we can later study it to measure factors that affect muscle function, strength, endurance, and metabolism.
- You will be given a snack after the sampling and blood draw. This visit will take about 2 hours.
- You cannot be in the study if you refuse to have this muscle sampling procedure.

After the third screening visit, you will participate in a strength training exercise program which is described below.
This is what you can expect at the exercise program

Once you have completed all of your screening visits, you will then begin your 12 week program of strength exercise training. You will come to the Clinical Research Center located near Wake Forest University 3 days per week for about one hour. This is what will happen at each session:

- Your heart rate and blood pressure will be measured.
- You will warm-up by walking or cycling on a stationary bicycle for 3 to 5 minutes at a slow pace.
- You will do some flexibility (stretching) exercises for about 5 minutes.
- You will lift weights for about 45 minutes. During this time you will do weight lifting exercises using all parts of your body. You will do 8 exercises, and each exercise will be done 6 to 8 times (repetitions). At first, you will do each exercise 6 to 8 times only once (1 set). As you get stronger, you will be asked to increase the number of sets that you do, until you can do 3 sets of 6 to 8 repetitions of each exercise. From time to time we will test your strength on the different exercises and change your workout based on how well you do on the tests.

This is what you can expect at the follow-up visits

After you finish the 12 week exercise program you will have follow-up testing done. These visits will be done over three days and will be very similar to the screening visits. You will answer questionnaires about your activities and perform exercise tests. You will also have another DEXA and CT scan done and another sampling of your leg muscle.

Risks and discomfort.

The risks of the testing you will have are very small. Each testing procedure will be explained to you in detail by the staff before it happens. If you have any side effects or health problems during your participation of this study, you should immediately contact Dr. Berry at 336-758-5847.

Breathing Tests - You may experience some tightness in your chest or short bouts of coughing. If you do experience this tightness, it usually improves a few minutes after completing the test. Coughing usually is temporary and can be relieved by drinking some water.

Blood Draw - There is a small amount of pain sometimes when your blood is drawn. There is a small risk of bruising and/or infection at the site of the blood draw. Occasionally some people become dizzy, lightheaded or feel faint. Infection may occur on rare occasions. Only trained staff will collect blood samples. All DNA samples are coded and personal information that identifies your sample is kept in a locked file by the investigators. The results will not be given to you, your physician, family members, or others. It will not be included in the medical records, or made available to anyone other than the investigators. Once we have tested your samples for this study as described
above, your samples will be “de-identified” which means that the link between the code on the sample and your personal information will be destroyed.

Treadmill Test, Strength Tests, Physical Function Tests and Exercise Program - There is a very small chance (1 in 10,000) that you could suffer a heart attack during the testing procedures or during the exercise program. You may experience increased shortness of breath while doing some of the exercise testing procedures, such as the walking test on the treadmill and the physical performance tests. This shortness of breath should improve at the end of the testing or exercise training session, or with rest. There is also a small chance that you could be injured during the testing or during the exercise intervention. Examples might include injury from falls while walking or doing the balance test, muscle soreness, and joint soreness. Muscle and joint soreness are common effects of exercise, especially when beginning an exercise program. To prevent or lessen the muscle and joint soreness, the exercise program will be tailored to your current fitness level, and we will increase the amount of weight you lift slowly as you get stronger. Also, our trained staff will watch you very carefully during the testing and the exercise program at Wake Forest. Emergency equipment and trained personnel will be available to deal with any unusual situation that may arise. Testing and exercise programs like this one are an important part of the treatment of patients with COPD. Although our experience has shown that the testing procedures and exercise programs are low risk, even for severely disabled patients, there is no guarantee against injury or illness from problems we can’t predict. During the treadmill test, strength tests, physical function tests and the exercise program, there is a chance that the amount of oxygen in your blood may decrease. Because of this, we will monitor the amount of oxygen in your blood using a devise that has a clip that fits over the top of your finger. If the amount of oxygen in your blood begins to decrease, we will stop the testing and/or the exercise. You will be advised to talk with your personal physician to obtain supplemental oxygen. If you are already prescribed supplemental oxygen, you will be advised to consult with your personal physician to increase the amount you get.

CT and DEXA Scan - This research study involves exposure to radiation from two whole-body DEXA scans and two CT scans of the thigh. The risk of these procedures is small and is similar to that received from clinical x-ray and nuclear medicine studies. The amount of radiation exposure that you will receive from these procedures is equivalent to a uniform whole body exposure of 226 millirem. This is equal to 0.75 times the amount of background radiation that the average person in the United States receives each year (annual background = 300 millirem). Other than minimal exposure to radiation, there are no risks associated with the CT or DEXA scans. Please be aware that this radiation exposure is necessary for this research study only and is not essential for your medical care. The Wake Forest University Baptist Medical Center’s Radiation Safety Committee, a group of experts on radiation matters, has reviewed the use of radiation in this research study and has approved this use as being necessary to obtain the research information desired. The potential long-term risk from these radiation doses is uncertain, but these doses have never been associated with any definite adverse effects. Thus, the risk to you, if any, is estimated to be slight.
Muscle Biopsy - The numbing medicine injected into your muscle will reduce the discomfort felt during removal of the small muscle sample. Temporary numbness of the skin near the sampling site can rarely occur, and very rarely, this numbness can persist. Bruising can occur. You may feel pain or soreness in the area of the sampling after the local anesthetic wears off. There is a slight risk of bleeding into the tissue and infection however, pressure is applied to stop the bleeding and this procedure is done under sterile conditions to protect against infection. You will be given instructions on how to care for the incision and treat any pain or discomfort before you leave the clinic. A very small scar (1/4 inch) may develop. If you are allergic to the local anesthetic, you may experience dizziness, anxiousness, numbness of the lips and tightness of the throat. Medications to treat your reaction are kept close by if needed. If you are allergic or sensitive to the adhesive tape, you may experience skin irritation or a rash where the tape was applied. These reactions go away within a short time.

Taking part in this research study may mean that you give us information that is confidential or private. We will use a code to identify your research records, keep your research records locked up and allow only approved people who are working on this research to see your records so that we can keep your information safe.

A Safety Committee, an independent group of experts, will be reviewing safety information from this research throughout the study.

Possible benefits from participating in the study.

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. You will receive health and medical screening examinations and the results will be discussed with you. Programs like this one have been shown to increase strength and the ability to perform certain everyday activities in healthy older adults. The exercise program and all testing are free of charge. At your request, we will provide your doctor with a copy of your breathing, treadmill, and DEXA tests. In addition, you will add to what we know about chronic obstructive pulmonary disease, rehabilitation, and disability.

Alternative to participation.

This is not a treatment study. Your alternative is not to participate.

What Are the Costs?

There are no costs to you or your insurance company for taking part in this study. All the study costs, including the costs of testing and the exercise program, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

Who is Sponsoring this Study?
This study is being sponsored by the National Institutes of Health. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor.

**Compensation for Study Participation**

You will be compensated $50 for your time and travel after the completion of each muscle sampling. There will be two muscle samplings, so you will receive a total of $100. You will receive your compensation by check that will be mailed to you after each procedure.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

**Use and Storage of Blood and Tissue Samples**

You will have your blood drawn once. Part of the sample will be stored for up to 20 years under the supervision of Dr. Barbara Nicklas at the Central Blood Repository at Wake Forest University School of Medicine in Winston-Salem, NC. The sample will be used in the future by researchers chosen by the study investigators to better understand how factors in your blood relate to physical health, mood, memory and attention, and your responses to the group program. Your name, address, phone number and other personal information will not be disclosed to these researchers.

By consenting to participate, you authorize the use of your blood and tissue samples for the research described above. The results from future tests will only be used for research purposes and will not be given to you or to your physician. It is very unlikely, but, if future testing of your stored sample has commercial value, you would not share in any profits that occur. You cannot be in this research study if you don’t agree to long-term storage of your blood and tissue samples.

**Significant Findings**

We will tell you about any important findings that happen during this study that could change your mind about participating.

**Compensation for research-related injury.**

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and
necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center’s Director of Risk and Insurance Management, at (336) 716-3467.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Michael Berry at 336-758-5847 (days) or 336-946-2098 (evenings).

Questions

Any questions about this study are welcome. If you have any doubts or questions, please feel free to ask for more information. If you have questions about any of the testing procedures before, during, or following testing or the exercise program, you may call Dr. Michael Berry at 336-758-5847 (days) or 336-946-2098 (evenings). For questions regarding research subject rights, you may call the Chairman, Institutional Review Board, at 336-716-4542.

Use, disclosure, and confidentiality of health information.

By taking part in this research study, your personal health information, as well as information that directly identifies you, may be used and disclosed. Information that identifies you includes, but is not limited to, such things as your name, address, telephone number, and date of birth. Your personal health information includes all information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images, photographs/videotapes/audiotapes and information from study visits, phone calls, surveys, and physical examinations.

Your personal health information and information that identifies you (“your health information”) may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health
information are the National Institute on Aging of the National Institutes of Health which funds this project through the Claude D. Pepper Older Americans Independence Center, the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; the General Clinical Research Center of Wake Forest University and their designated investigators; and the members of the Data Safety and Monitoring Board established for the study.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

If this research study involves the treatment or diagnosis of a medical condition, then information collected or created as part of the study may be placed in your medical record and discussed with individuals caring for you who are not part of the study. This will help in providing you with appropriate medical care. In addition, all or part of your research related health information may be used or disclosed for treatment, payment, or healthcare operations purposes related to providing you with medical care.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

When you sign this consent and authorization form you authorize or give permission for the use of your health information as described in the consent form. You can revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address: Michael Berry, Ph.D., Department of Health and Exercise Science, PO Box 7868, Wake Forest University, Winston-Salem, NC 27109-7868

If you withdraw your authorization you will not be able to be in this study. If you withdraw your authorization, no new health information that identifies you will be
gathered after that date. Your health information that has already been gathered may still
be used and disclosed to others. This would be done if it were necessary for the research
to be reliable. You will not have access to your health information that is included in the
research study records until the end of the study.

This authorization is valid for five years after the completion of the study or a total of six
years, whichever is longer.

Your rights as a research study participant.

Your participation in this research study is voluntary. You may choose not to take part in
this study, or withdraw from participating in this study at any time. Refusing to
participate or leaving the study will not result in any penalty or loss of benefits to which
you are entitled. If you do not participate in the study or withdraw from the study, your
future medical care by the staff of the Wake Forest University Baptist Medical Center or
your opportunities for employment by any branch of Wake Forest University will not be
affected.

If you decide to leave the study, you should talk to the study investigators or staff first to
make sure there are no safety concerns. You should tell the study project manager if you
decide to leave the study, either by telephone, (336) 758-3618, or by written letter
addressed to: Strength Training and COPD Project Manager, PO Box 7868, Reynolda
Station, Winston-Salem, NC 27109.

The study staff also has the right to stop your participation in the study at any time. This
could be because it is in your best medical interest, your medical condition worsened, we
find out new information about the study interventions or testing procedures, or because
the entire study has been stopped. Also, if we find out something that might change your
mind about being in the study, we will tell you about it.

Test Results.

We can send copies of your test results to your personal physician. If you don’t want us
to send any of your results to your physician, you can still be in this research study.

Do you want us to send important medical findings from your study tests/exams to your
personal physician?

[ ] Yes       [ ] No       ___________ Initials

Consent.

I will be given a signed copy of this consent form.

I agree to take part in this study. I authorize the use and disclosure of my health
information as described in this consent and authorization form. If I have not already
received a copy of the Privacy Notice, I can ask for one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

________________________________________
Printed Name of Participant

________________________________________
Signature of Participant               Date/Time

________________________________________
Signature of Person Administering Consent  Date/Time
# APPENDIX B

## REACT TREADMILL PROTOCOL

MODIFIED NAUGHTON

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration (Minutes)</th>
<th>Speed (mph)</th>
<th>Grade (%)</th>
<th>METS</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2:00</td>
<td>1.5</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
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APPENDIX C

REACT II Data Collection Form Information

1. **Form Name:** REACT II Physical functioning questionnaire

2. **Form Abbreviation:** pfq1

3. **Type of Form:** ☒ Paper ☐ Electronic

4. **Administration format:** ☒ Self-report ☐ Interview ☐ Completed by staff

5. **Collection timepoints:**

- ☒ Baseline ....................... ☒ SV:1 ☐ SV:2 ☐ SV:3 ☐ GCRC 0
- ☒ 3 Months...................... ☒ FU3:1 ☐ FU3:2 ☐ FU3:3 ☐ GCRC 3
- ☒ 6 Months...................... ☒ FU6:1 ☐ FU6:2
- ☒ 12 Months..................... ☒ FU12:1 ☐ FU12:2 ☐ FU12:3 ☐ GCRC 12

6. **Summary / procedure:**

This form assesses the physical disability of the respondent. It is a modified version of the form originally used in the Fitness and Arthritis in Seniors Trial (FAST) and consists of 23 items in which respondents are asked to indicate how much difficulty they experienced performing physical activities during the past month. Responses are scored on a 6-point scale ranging from “Usually did with no difficulty” [score value = 1] to “Usually did not do for other reasons” [score value = 6]. The form measures physical disability across five discrete domains or subscales: B=basic; T=transfer; A=ambulation/climbing; UE=upper extremity; and C=complex.

**Scoring**

1. Code items 1 – 23 “Usually did with no difficulty” =1 … “Usually did not do for other reasons” = 6.

2. Scores are computed as the mean for items comprising each subscale. Items coded with a 6 are excluded from the scoring calculations (valid response range for each subscale is 1 to 5).
   a. B (basic): items 4, 9, 13, 15, 21
   b. T(transfer): items 8, 11, 14, 16, 17
   c. A (ambulation/climbing): items 2, 6, 19, 23
   d. UE (upper extremity): items 3, 7, 12, 20
   e. C (complex): items 1, 5, 10, 18, 22
7. Reference:
How much difficulty, if any, do you have with each of these activities? Think about the past month. How hard was it to do the activity because of your health?

1. Doing light housework (such as washing dishes, dusting, etc.)?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons

2. Walking several blocks?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons

3. Lifting heavy objects?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons

4. Preparing your own meals?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons
5. Participating in community activities such as religious services, social activities, or volunteer work?

<table>
<thead>
<tr>
<th>Usually did with no difficulty</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
<th>Usually did with alot of difficulty</th>
<th>Unable to do</th>
<th>Usually did not do for other reasons</th>
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6. Walking one block?

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<th>Usually did with no difficulty</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
<th>Usually did with alot of difficulty</th>
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7. Lifting or carrying something as heavy as 10 pounds, such as a bag of groceries?

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<th>Usually did with no difficulty</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
<th>Usually did with alot of difficulty</th>
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8. Moving in and out of a chair?

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<th>Usually did with no difficulty</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
<th>Usually did with alot of difficulty</th>
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9. Managing your money, such as paying bills?

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<th>Usually did with no difficulty</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
<th>Usually did with alot of difficulty</th>
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10. Visiting with relatives or friends?

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<thead>
<tr>
<th>Difficulty</th>
<th>Usually did</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
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<th>Usually did not do for other reasons</th>
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11. Moving in and out of a bed?

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<th>Difficulty</th>
<th>Usually did</th>
<th>Usually did with a little difficulty</th>
<th>Usually did with some difficulty</th>
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<th>Usually did not do for other reasons</th>
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12. Gripping with your hands?

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<th>Difficulty</th>
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<th>Usually did with some difficulty</th>
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<th>Usually did not do for other reasons</th>
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13. Using the telephone?

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<th>Difficulty</th>
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<th>Usually did with a little difficulty</th>
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14. Using the toilet including getting on and off of the toilet?

<table>
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<tr>
<th>Difficulty</th>
<th>Usually did</th>
<th>Usually did with a little difficulty</th>
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15. Dressing yourself?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons

16. Getting in and out of a car?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons

17. Bathing or showering?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons

18. Taking care of a family member?

- Usually did with no difficulty
- Usually did with a little difficulty
- Usually did with some difficulty
- Usually did with a lot of difficulty
- Unable to do
- Usually did not do for other reasons
19. Climbing several flights of stairs?

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20. Raising your arms above your head (to comb your hair or put away groceries)?

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21. Feeding yourself?

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22. Doing errands, such as grocery shopping or shopping for personal items?

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23. Climbing one flight of stairs?

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Participant Flow through the study

Number of letters mailed to REACT II participants
n = 176

Excluded (n = 131)
Letters returned: 12
No Response: 117
Deaths: 2

Screened for Eligibility
n = 45

Excluded (n = 29)
Did not meet PFT criteria: 1
Not Interested: 4
Cardiac condition: 9
Non-compliant after SV1: 1
Transportation: 2
Too Active: 9
Other: 3

Entered REACT III-p
n = 16

Excluded (n = 4)
Transportation: 1
Health issues: 2
Other: 1

Completed for this Thesis
n = 7