LONG-TERM FOLLOW-UP OF EXERCISE REHABILITATION OUTCOMES IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

By

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DEDICATION

This thesis is dedicated to my mom and dad, A.K.A. Gongo and Bubba, who have always believed in me, supported me in every possible way, showed me the value of determination and hard work, inspired me to dream big and go after whatever I wanted, and encouraged me to be the best person that I could possibly be.

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LIST OF ABBREVIATIONS

ADL(s)	activity(s) of daily living	mg	milligram(s)
ANCOVA	analysis of covariance	mmHg	millimeter(s) of Mercury
ATS	American Thoracic Society	n	number
ATT	alpha$_1$-antitrypsin	NOTT	Nocturnal Oxygen Therapy Trial
BMRC	British Medical Research Council	NPPV	non-invasive positive pressure ventilation
cAMP	cyclic adenosine monophosphate	$PaCO_2$	arterial partial pressure of carbon dioxide
CET	cycle ergometry training	PaO_2	arterial partial pressure of oxygen
cm(s)	centimeter(s)	PASE	Physical Activity Scale for the Elderly
COPD	chronic obstructive pulmonary disease	PDE	phosphodiesterase
CRQ	Chronic Respiratory Index Questionnaire	$P_E$max	maximum expiratory pressure
et al.	and others	PFQ	Physical Function Questionnaire
F(s)	female(s)	PFT (s)	pulmonary function test(s)
FAST	Fitness and Arthritis in Seniors Trial	$P_I$max	maximum inspiratory pressure
FEV_1	forced expiratory volume in 1 second	REACT	Reconditioning and Chronic Pulmonary Disease Trial
FU	follow-up	RV	residual volume
FVC	forced vital capacity	SEM	standard error of the mean
HRQOL	health-related quality of life	SPSS	Statistical Package for the Social Sciences
kg(s)	kilogram(s)	ST	short-term
L(s)	liter(s)	TLC	total lung capacity
LT	long-term	TV	tidal volume
LTOT	long-term oxygen therapy	U.S.	United States
LVRS	lung volume reduction surgery	V_E	minute ventilation
m(s)	meter(s)	VMT	ventilatory muscle training
M(s)	male(s)	VO_2max	maximal oxygen uptake
min(s)	minute(s)	yr(s)	year (s)

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ABSTRACT

LONG-TERM FOLLOW-UP OF EXERCISE REHABILITATION OUTCOMES IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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

The purpose of this study was to compare the long-term outcomes in pulmonary function, self-reported health–related quality of life, physical activity, and disability, along with functional exercise capacity in COPD patients either completing a 3-month (short-term, ST) or an 18-month (long-term, LT) exercise rehabilitation program at 58 months. Thirty-nine patients completed the follow-up study, including 12 from the ST and 27 from the LT groups. There were no significant differences between the ST and the LT groups in the adjusted means of FEV_1 % predicted, (57.6 ± 3.1 versus 56.6 ± 2.1%), FEV_1/FVC ratio, (51.5 ± 2.1 versus 52.1 ± 1.4%), RV/TLC ratio, (53.7 ± 4.2 versus 58.4 ± 2.8%), CRQ: dyspnea (4.9 ± 0.4 versus 5.1 ± 0.2 units), mastery (6.3 ± 0.2 versus 6.4 ± 0.1 units), emotion (5.6 ± 0.2 versus 5.7 ± 0.1 units), fatigue (4.3 ± 0.3 versus 4.7 ± 0.2 units), PASE (103.0 ± 12.2 versus 92.2 ± 8.8 units), PFQ (35.0 ± 3.8 versus 39.4 ± 2.5 units), or 6-minute walk distance, (500.7 ± 26.6 versus 517.9 ± 18.8 m) respectively, measured at the 58-months. These results showed that at 58 months there are no significant differences between the ST and the LT exercise rehabilitation groups in any of the outcome variables. Therefore, an additional 15 months of participation in an exercise rehabilitation program did not result in a difference in the level of benefits maintained at 58 months.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a condition of progressive deterioration of the respiratory system characterized by the obstruction of pulmonary airways and decreased airflow, is a major health problem worldwide. COPD is currently the fourth leading cause of death in the United States (U.S.), following heart disease, cancer, and stroke, (95) and is the only leading cause of death which has increased in prevalence (by 71%) over the last several years (68). COPD also has a major influence on morbidity, accounting for an estimated 668,362 hospital discharges at a rate of 24.5 per 10,000 individuals in 1998 (95).

Individuals with COPD experience functional capacity limitations that adversely impact the physical activity level and the performance of activities of daily living (ADL's) in these patients. A recent national survey of 573 individuals with COPD given by Schulman, Ronca, and Bucuvalas, Incorporated, and supported by the American Lung Association (100) revealed that 70% of respondents experienced limitations in activities requiring physical exertion, 51% had limitations in their occupational abilities, and 56% were limited in performing household chores. The survey also showed that social activities and family activities were limited in 53% and 46% respectively, while normal sleeping patterns were disturbed in 50% of respondents.

As a result of these physical limitations, the quality of life for many COPD patients and their families is significantly compromised. Twenty-three percent of respondents described themselves as "invalid", while 8% remained homebound due to dyspnea (100), not only because of its physical effects, but also due to the fear and the

anxiety associated with the thought of experiencing the sensation of breathlessness outside of the home.

The medical treatment of individuals with COPD centers on the management of the current symptoms and the prevention of future exacerbations. Various drug therapies, supplemental oxygen, pulmonary rehabilitation programs, and surgical interventions all are currently available treatment options. Smoking cessation is paramount to any successful treatment plan in COPD patients who continue to smoke, and many alternative strategies are available to assist with this difficult process (29, 91, 94).

Multidisciplinary pulmonary rehabilitation programs have been successful in enhancing the physical function and the health related quality of life (HRQOL) in individuals with COPD. A meta-analysis of 14 randomized controlled clinical trials looking at the effectiveness of pulmonary rehabilitation revealed that significant improvements occurred in maximal exercise capacity, functional exercise capacity, and HRQOL in pulmonary rehabilitation participants as compared to individuals in the control groups (72).

The long-term (greater than one year post intervention) benefits of participation in pulmonary rehabilitation programs have also been analyzed (13, 21, 61, 81, 102, 123, 146, 147). The outcomes typically measured in these long-term follow-up studies include physical performance parameters, HRQOL, morbidity as shown by the number of hospitalizations or by the total number of days of hospitalization, mortality, as well as the total utilization of healthcare dollars. In a randomized control trial (128) the long-term benefits achieved by 50 COPD patients who underwent a 6-month outpatient exercise therapy only regimen were compared to 50 COPD patients who received “usual care”

treatment. The significant improvements in the 6-minute walk test distance, maximal oxygen uptake (VO_2max), quadriceps strength, and HRQOL made by the exercise therapy group (n=37), as compared to the control group (n=33), were still present and clinically relevant at the LT follow-up visit.

Strijbos et al. (123) examined the long-term outcomes of COPD patients participating in a 12-week home-based or a hospital-based outpatient pulmonary rehabilitation program, as compared to that of a control group that did not receive an exercise intervention. Their findings showed that both the hospital-based and the home-based rehabilitation groups had similar significant improvements in exercise capacity, perceived dyspnea, and well-being at the 6-month follow-up as compared to the control group. At 18 months, the improvement in exercise capacity began to diminish in the hospital-based rehabilitation group, as compared to that of the home-based rehabilitation group. The benefits achieved in both rehabilitation groups were still statistically significant when compared to the control group at 18 months.

A randomized control trial by Ries et al. (102) found that many of the significant physical and psychological benefits achieved from participating in an 8-week outpatient comprehensive pulmonary rehabilitation program diminished within one year of follow-up. Results from the Reconditioning and Chronic Pulmonary Disease Trial (REACT) study by Berry et al. (21) also showed that the improvements in self-reported disability, physical function, and HRQOL made by COPD patients following the completion of a 3-month exercise therapy program had greatly diminished by 18 months, while the 18-month exercise therapy group maintained and improved upon the benefits achieved at the end of the initial 3-month program.

Maintenance exercise programs initiated after the completion of a structured pulmonary rehabilitation program have been successful in postponing the decline in benefits achieved following the initial intervention. A study by Guell and colleagues (61) compared the long-term effects of a 3-month exercise training program followed by a 6-month maintenance program in 30 COPD patients (exercise group) to that of 30 COPD patients who received standard care only (control group). The results revealed that a 6-month supervised one-time-a-week maintenance therapy program consisting of breathing and arm/leg coordination exercises helped maintain the benefits achieved in 6-minute walk distance, dyspnea, and HRQOL in the exercise group at 24 months. This study also showed that the exercise group experienced significantly fewer COPD exacerbations ($p<0.0001$) and a trend for fewer hospitalizations than the control group. Groisbois et al. (59) investigated the effects that a maintenance exercise regimen had on 58 COPD patients who had completed an initial 7-week outpatient pulmonary rehabilitation program. The patients were self-selected into 1 of 4 groups who had continued supervised exercise training either once or twice a week, continued an independent home exercise program, or did not continue any type of exercise program. Improvements in maximum workload and dyspnea ratings occurred in all patients following completion of the initial program, but remained significant only in the once-a-week supervised exercise training group and the independent home exercise group at the LT follow-up. The non-exercisers showed diminished benefits approaching baseline measures at 18 months.

The duration of an exercise intervention may also influence the magnitude of benefits achieved as well as the length of time that they are maintained in COPD patients.

The REACT study, a recent unpublished investigation by Berry and colleagues (21) compared the effects of a 3-month (short-term, ST) versus an 18-month (long-term, LT) exercise rehabilitation program on self-reported disability, physical function, and HRQOL in 140 COPD patients. The results showed that both the ST and the LT groups had similar improvements in these outcomes at 3 months. At 18 months, those patients randomized into the LT exercise group (n=62) maintained the improvements in self-reported disability, physical function, and HRQOL obtained at 3 months. Those patients in the ST exercise group (n=56), showed declining benefits at 18 months, which approached baseline values. The results of this study present a case for prolonged exercise rehabilitation programs (greater than 3 months), but also showed that the benefits achieved from short-term exercise rehabilitation programs are not permanent.

While the results of the REACT study showed diminished benefits in COPD patients who completed a ST exercise rehabilitation program at 18 months, it is not known whether this decline in benefits persisted beyond 18 months. It is also not known whether the improvements made by those patients participating in the LT exercise rehabilitation program were maintained. Therefore, it was the primary purpose of this thesis to describe and compare the outcomes of COPD patients who participated in either a ST or a LT exercise rehabilitation program at 58 months.

LITERATURE REVIEW

Definition of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized primarily by airway obstruction and decreased airflow. Chronic bronchitis and emphysema are 2 distinct components of COPD, but may occur simultaneously in the same individual. Chronic bronchitis is defined as "the presence of a chronic cough for 3 months in each of 2 successive years in a patient in whom other causes of chronic cough have been excluded" (3). Chronic bronchitis is characterized by chronic inflammation and edema of the peripheral airways, excessive mucus production and accumulation, bronchospasm, bronchial airway obstruction hyperinflation of the alveoli distal to the obstructed airways.

Emphysema is defined as "the abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by the destruction of their walls and without obvious fibrosis" (3). Emphysema is characterized by alveolar deterioration and hyperinflation, destruction of pulmonary capillaries, weakened respiratory bronchioles, and air trapping.

Depending upon the degree of pulmonary system damage and airway hyperresponsiveness, the following may all occur in an individual with COPD: obstructed airflow, lung hyperinflation, mismatched ventilation/perfusion ratio, decreased maximum inspiratory pressure ($P_I max$), increased work of breathing, and a decreased gas diffusion capacity (33). The primary physical manifestations that result from these pathophysiologic changes include dyspnea (the sensation of breathlessness), persistent

cough, excessive sputum production, fatigue, decreased exercise tolerance, hypoxemia, and deconditioning. Malnutrition and osteoporosis may also occur, especially in advanced cases of COPD (54, 109).

Although COPD is a progressive disease that worsens in severity with time, it is characterized by recurrent "exacerbations" of varying intensity. A COPD exacerbation commonly occurs following a bacterial infection (in 50% to 70% of cases) (117, 120) or due to a repeated exposure to an environmental pollutant such as suspended particulate matter, carbon monoxide, sulfur dioxide, and nitrogen dioxide (in up to 5% of cases). An acute COPD exacerbation is characterized by any combination of worsening dyspnea, an increase in sputum production, and/or an increase in sputum purulence (120). Eighteen to 34% of all COPD exacerbations may be related to upper respiratory tract viral infections (117), while changes in ambient temperature may also trigger an exacerbation (54). In the U.S. it is estimated that individuals with COPD experience anywhere from 1-4 acute exacerbations of the disease each year (117).

Thus, exacerbations are detrimental to a COPD patient's HRQOL and may result in either temporary or permanent disability, increased emergency room visits and hospital admissions, respiratory failure, or even death. An important goal of COPD management therefore is to decrease the number and the severity of exacerbations experienced by COPD patients, through comprehensive patient education, early aggressive medical management, and proper follow-up care

Etiology

The etiology of COPD can be attributed to smoking in 80-90% of all cases, to exposure to second-hand smoke and/or environmental pollutants, to having a history of

recurrent respiratory infections in childhood, as well as to a genetic influence in 1-5% of cases (12). Approximately 15% of all individuals who smoke will develop COPD (117) and they are 10 times more likely to die of COPD than nonsmokers (11). Smoking cessation has been related to a decreased number of recurrent respiratory symptoms and infections in former smokers, as compared to those individuals who continued to smoke (30).

Smoking is not the only etiology related to the development of COPD, hereditary influences also play a role in the onset of COPD early in life. The most common genetic cause of COPD is related to an inherited deficiency in $alpha_1$-antitrypsin (ATT), a protein that is normally produced by the liver that plays a role in the inhibition of several proteases, including neutrophil elastase (106). Neutrophil elastase, an enzyme that degrades lung elastin, causes destruction of lung tissue, which results in many of the characteristic structural and functional changes associated with emphysema. The deficiency in ATT results in unchecked elastase activity and further damage to lung tissue. $Alpha_1$-antitrypsin deficiency is responsible for the early onset of COPD (usually before the age of 50 years) in approximately 50-100,000 individuals in the U.S., many of whom are Caucasians of northern European descent (3, 12).

The remaining causes of COPD include prolonged exposure to second-hand smoke and/or environmental pollutants and recurrent respiratory infections during childhood. Second-hand smoke can be just as harmful to nonsmokers as smoking is to smokers. Second-hand smoke contains 200 poisonous chemicals that can cause serious health problems including respiratory infections, COPD exacerbations, asthma, and coronary artery disease (11). Other environmental pollutants such as carbon monoxide,

sulfur dioxide, nitrogen oxide, the ozone, and suspended particulates may initiate the inflammatory process and contribute to the development of COPD.

Recurrent respiratory infections during childhood have also been suggested as a cause of COPD. Early recurrent infections in childhood can stunt the growth of lung tissue and result in decreased forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in adulthood (114). Permanent damage and fibrotic scarring of the airways may occur as a result of the excessive inflammatory response (airway hyperresponsiveness) potentiated by frequent lower respiratory tract bacterial infections in childhood (113). Chronic mucus hypersecretion and poor control of lung elastase activity causing increased lung tissue damage both occur, which contribute to the development of chronic bronchitis and/or emphysema. All of these pathologic changes caused by recurrent childhood infections make the individual even more susceptible to the further lung damage caused by cigarette smoke and other pollutants.

Epidemiology

The World Health Organization ranks the U.S. 12th in COPD mortality for men and 7th in COPD mortality for women when compared to 28 other industrialized countries (148). COPD is currently the fourth leading cause of death in the U.S. and is the only cause of death that has increased in prevalence over the last several years (68). Approximately 113,000 deaths in the U.S. were attributed to COPD in 1998, while it encompassed almost 9 million cases of chronic bronchitis and 3 million cases of emphysema (12). The combined chronic bronchitis and emphysema age-adjusted

mortality rates for 1998 were 24.7 per 100,000 men and 16.5 per 100,000 women. Hospital discharge rates varied among age groups, with 68% of all 1998 discharges (a rate of 133.3 per 10,000 individuals) attributed to those who were 65 years and older. Over 16 million physician visits related to COPD occurred in 1995, with chronic bronchitis accounting for approximately 10 million visits and chronic airways obstruction accounting for approximately 4 million visits (11, 84).

The economic impact of COPD is tremendous, costing the U.S. approximately $30.4 billion annually, including $14.7 billion for direct healthcare expenditures and $15.7 billion in indirect costs (12). An estimated 73% of these healthcare expenditures were utilized by only approximately 10% of all COPD patients (142).

Pathophysiology

The major pathological consequences of COPD include decreased elastic recoil and increased compliance of the damaged lung tissue which results in increased work of breathing, lung hyperinflation both at rest and dynamically during exercise, fixed expiratory airflow obstruction, decreased inspiratory muscle strength, and decreased maximum inspiratory pressure (33). Gas exchange and diffusion capacity are also affected, with arterial hypoxemia commonly occurring mainly due to a combination of ventilation-perfusion mismatch, alveolar hypoventilation, and low mixed venous partial pressure of oxygen. Hypercapnia and chronic respiratory acidosis also can occur due to the inability of individuals with COPD to maintain adequate minute ventilation (V_E), and also due to an increased respiratory dead space to tidal volume ratio. All of these physical

manifestations contribute to the intolerance of increased physical activity and exercise as well as to dyspnea.

Dyspnea is a complex symptom related to many of the above-mentioned physical manifestations of COPD. Several sensory input mechanisms are involved with the development of dyspnea including increased activity of central and peripheral chemoreceptors, along with increased afferent input from various receptors in the pulmonary system, upper airways, and respiratory muscles (3, 6). Fatigue, as well as the perceived level of breathlessness that results "when the demand for ventilation is out of proportion to the patient's ability to respond to that demand" also plays a role in the development of dyspnea (144). The quality and the severity of dyspnea experienced by COPD patients are also influenced by each individual's experience, emotional state, and expectations (6). A number of studies have shown that desensitization to dyspnea occurs following pulmonary rehabilitation programs, allowing an individual with COPD to show improvement in physical function, ADL's, and HRQOL (125, 146). Exercise interventions have been shown to decrease V

acidosis as factors involved with peripheral muscle dysfunction in COPD patients (26). Maltais et al. (76) suggest aging, electrolyte imbalances, and systemic inflammation as other factors that may play a role in the development of this muscle dysfunction. The muscles of ambulation are especially affected (18, 25, 58), and may result in decreased functional mobility, reliance on an assistive device for safe ambulation, or loss of independent living all together, which would significantly impact the quality of life in affected COPD patients.

Medical Management

The medical management of COPD is multifactorial and may include all of the following interventions: smoking cessation, appropriate medications, oxygen therapy, surgery, and pulmonary rehabilitation programs.

Smoking Cessation

Smoking exposes the bronchial linings to several toxic chemicals including carbon monoxide, nicotine, hydrocarbons, and other tars, causing irritation and chronic inflammation. The alkaloid nicotine is the primary addictive compound in cigarette smoke and is responsible for the feeling of euphoria via a rapid increase in the release of the central nervous system neurotransmitter, dopamine. Other effects of nicotine include an antidepressant effect and a feeling of enhanced performance, especially for mundane activities that rely on memory and focused attention (81). These seemingly "beneficial" effects of nicotine, coupled with the considerably uncomfortable symptoms of nicotine withdrawal are what make this addiction so difficult to overcome.

In individuals with mild to moderate COPD, smoking cessation has been shown to slow the annual age-related rate of decline in FEV_1 to that of healthy nonsmokers

(107). Therefore, smoking cessation is imperative for individuals with COPD. However, only 2.5% of all smokers who try to quit are successful (38). Physician counseling on the negative effects of the continued use of tobacco products and encouragement for smoking cessation was lacking in 85.7% of all COPD patient office visits in 1996 (38, 83). This occurred despite the National Cancer Institute's Recommendation of the "four A's" program: "Ask about smoking; Advise about smoking cessation; Assist with smoking cessation intervention; and Arrange for follow-up" (110).

Several aides for quitting smoking are available including various nicotine delivery systems (gum, patches, inhalers, and nasal sprays), and pharmacological agents such as the antidepressants Zyban (bupropion hydrochloride) and Buspar (buspirone hydrochloride), or the antihypertensive, Catapres (clonidine hydrochloride), (29, 94). The nicotine patch was found to be the most successful smoking cessation intervention in 1998 (38) and has the lowest potential for continued nicotine addiction due to the slow delivery rate of nicotine (time to maximum effect= 500 minutes (min)) (94), as compared to the other systems (time to maximum effect= 10-30 min). A double-blind clinical trial by Jorenby et al. (45) showed that the combination of Zyban along with a transdermal nicotine patch, as compared to the use of Zyban alone, had significantly higher abstinence rates at 1 year than treatment with the nicotine patch or placebo alone ($p<0.001$). Behavioral interventions also play an important role in smoking cessation, with abstinence rates approaching 20% in the most aggressive programs (45).

Medications

Medications commonly used in the management of COPD include bronchodilators (anticholinergic, sympathomimetic, and xanthine derivatives), anti-

inflammatories (steroidal and non-steroidal), antibiotics, antitussives, expectorants, and mucolytics (43, 90). The primary therapeutic goals of the pharmacological management of COPD are to increase bronchodilation and mucus expectoration, and to decrease inflammation along the bronchial linings. Replacement of ATT may also be part of the medical regimen in patients with ATT deficiency emphysema (43).

Bronchodilators are commonly used in COPD patients but are not as effective as when used in patients with asthma. Three main classes of bronchodilators are utilized in COPD patients including anticholinergic, sympathomimetic, and xanthine derivatives (methylxanthines). Each class of bronchodilator has an independent mechanism for inducing bronchodilation along with varied primary locations of action. For example, anticholinergic bronchodilators primarily affect the larger central airways while sympathomimetic bronchodilators primarily affect the smaller distal airways (89).

Anticholinergic bronchodilators such as Atrovent (ipratropium bromide), and tiotropium (not approved for use in the U.S.) function by preventing acetylcholine from binding to the muscarinic receptor sites located in the airway smooth muscle tissue. This results in decreased bronchoconstriction, mucus secretion, and nocturnal oxygen desaturation, as well as in improved dyspnea, exercise performance, and quality of sleep in patients with COPD (43, 79). Atrovent is normally delivered as an inhaled medication and the recommended dosage is 2 puffs of a metered dose inhaler 4 times per day.

Sympathomimetic bronchodilators are also regularly recommended for COPD patients, and are administered as inhaled, oral, subcutaneous, or intravenous medications. The smooth muscle tissue lining the bronchial airways contains beta-2 receptors that respond to circulating levels of catecholamines by causing smooth muscle relaxation and

therefore bronchial dilation. Selective beta-2 agonists function by increasing the formation of cyclic adenosine monophosphate (cAMP), which results in altered intracellular calcium concentration (103). Smooth muscle intracellular calcium ion concentration is a primary regulator of smooth muscle contraction, thus the actions of sympathomimetic medications result in decreased bronchoconstriction, plus decreased airway hyperresponsiveness, and decreased inflammatory mediator release by basophils and mast cells (43). Some examples of sympathomimetic bronchodilators include Proventil and Ventolin (albuterol), and Serevent (salmeterol xinafoate).

Xanthine derivatives including the methylxanthine, theophylline, have historically been the first line of medical defense in COPD patients, but their use has significantly declined since 1993 (132). The exact mechanism of theophylline's therapeutic effect is unknown, but there is some evidence to suggest that theophylline acts as a phosphodiesterase (PDE) inhibitor at higher dosages, causing increased levels of cAMP and bronchial smooth muscle relaxation (135). Another proposed mechanism of action is the direct inhibition of selective PDE receptors, which also results in bronchodilation, as well as improved diaphragm function, vital capacity, cardiac output, and exercise performance (43). Decreased dyspnea and a decreased inflammatory reaction have also been found to be associated with theophylline use. Toxicity and serious side effects such as seizures, cardiac arrhythmias, and respiratory arrest, especially in the elderly and in individuals with hepatic pathology may occur during the use of theophylline. The narrow therapeutic range of serum theophylline is 8-15 milligrams (mg) per liter (L), but seizures have occurred in elderly patients with serum levels as low as 14 mg/L (115).

Theophylline or Theo-Dur is commonly administered orally, but can also be given intravenously.

The combination of anticholinergic and sympathomimetic medications in metered dose inhalers has also been shown to decrease symptoms, exacerbations, and healthcare costs in individuals with stable COPD (17, 43). One example is Combivent (albuterol/ipratropium). The xanthine derivative, theophylline, has also been added to some bronchodilator inhalers as well. The addition of theophylline to inhaled bronchodilators has resulted in the reduction in the severity of COPD symptoms (87) and may also decrease healthcare costs by preventing future COPD exacerbations.

Anti-inflammatory medications are frequently utilized by COPD patients with the goal of treatment being the reduction of chronic bronchial inflammation, which has been suggested as an etiology of COPD. Both steroidal and non-steroidal anti-inflammatories can be prescribed, and are usually administered either orally or inhaled. Corticosteroids such as prednisone and methylprednisolone, are commonly recommended for COPD patients experiencing a severe, acute exacerbation requiring hospitalization, but should not be used for longer than 2 weeks (81). Inhaled corticosteroids have been shown to be effective in increasing $FEV_{1,}$ reducing COPD symptoms, and shortening the duration of hospitalization in patients experiencing an acute exacerbation (81, 86). A meta-analysis of 3 studies by Van Grunsven et al. (133) revealed that relatively high doses of inhaled corticosteroids utilized by patients with moderate to severe COPD resulted in improved FEV_1 at 2 years and improved long-term prognosis. In contrast, systemic corticosteroids have not been shown to slow the rate of decline in FEV_1 in patients with COPD (24, 81). Chronic use of systemic corticosteroids has been associated with the development of

adverse side effects such as dermal thinning, peptic ulcer disease, adrenal insufficiency, osteoporosis, diabetes mellitus, hypertension, and myopathy. Despite these risks, systemic corticosteroids are utilized continuously in approximately 4-10% of "steroid-dependent" patients with severe COPD (82).

The non-steroidal anti-inflammatory medications, NasalCrom (cromolyn) and Tilade (nedocromil), have limited success in the treatment of COPD patients, but may be beneficial when a respiratory tract allergy is present. Newer non-steroidal anti-inflammatory medications such as PDE 4 inhibitors that inhibit macrophages, neutrophils, and cytotoxic T-lymphocytes, may be successful in the management of COPD by decreasing the overall inflammatory response. The results of a clinical trial involving COPD patients undergoing treatment with the PDE 4 inhibitor, SB 207499, demonstrated improvement in lung function, symptoms, and quality of life (126). Several other non-steroidal anti-inflammatory medications are currently under development, which may prove to be beneficial in the long-term management of COPD.

Antibiotics are not routinely prescribed for patients with COPD, but have been shown to decrease the duration of acute COPD exacerbations especially when excessive purulent sputum is present (13). A 10-day cycle of antibiotics, such as tetracycline, amoxicillin, or erythromycin, is usually recommended for treatment of an acute COPD exacerbation (89). In COPD patients who experience frequent recurrent infections, the prolonged use of antibiotics may be justified. The common bacteria involved in acute respiratory infections include *Streptococcus pneumoniae, Hemophilus influenzae*, and *Moraxella catarrhalis* (3, 89). Patients with COPD who have frequent infections are at high risk for developing pneumonia, which may result in hospitalization, the use of

supplemental oxygen and/or assisted mechanical ventilation, or even respiratory failure. A meta-analysis of 20 cohort studies (111) revealed that the influenza vaccine was 56% effective in preventing respiratory illness, 50% effective in preventing hospitalization, and 68% effective in preventing death in elderly COPD patents. This provides a strong incentive for the recommendation that all COPD patients obtain yearly immunizations and vaccinations for protection against both bacterial and viral infections (43, 90).

Antitussives, expectorants, and mucolytics may all be used in the treatment of COPD patients but are of limited, if any, benefit. The routine use of these medications in patients with COPD is not recommended, though oral acetylcysteine, a mucolytic, may decrease the frequency of exacerbations experienced by these patients through its antioxidant effects (3, 43).

Supplemental Oxygen Therapy

Supplemental oxygen therapy has been shown to improve mortality and HRQOL in COPD patients with chronic hypoxemia (125). Long-term oxygen therapy (LTOT) is utilized in 800,000-1 million individuals with COPD in the U.S. (92) and should be delivered at a rate that maintains an arterial oxygen saturation (SaO_2) level of at least 90% or an arterial partial pressure of oxygen (PaO_2) of 60 millimeters of Mercury (mmHg) (51, 125). By maintaining an adequate SaO_2 level, supplemental oxygen helps to decrease pulmonary hypertension (lowers pulmonary artery pressure and pulmonary vascular resistance), reverses the associated polycythemia, and improves cardiac function (125). Selinger et al.(110) showed that the removal of LTOT from hypoxic COPD patients resulted in increased pulmonary vascular resistance and stroke volume index at rest and during exercise, as well as causing variable effects on oxygen consumption,

dependent upon each patient's resting partial pressure of arterial carbon dioxide ($PaCO_2$). Long-term oxygen therapy is also associated with increased body weight, improved physical and neuropsychological function, and prolonged survival (54).

Indications for LTOT according to Medicare guidelines include: PaO_2 </= 55 mmHg or SaO_2 </= 89% while breathing room air, or PaO_2 = 56-59 mmHg or SaO_2 = 89% with any of these accompanying signs: evidence of cor pulmonale by electrocardiogram, erythrocytosis (hematocrit > 56%), or PaO_2 >/= 60 mmHg or SaO_2 >/= 90% with "compelling medical justification" (92). Oxygen delivery systems typically involve oxygen provided via a nasal cannula by home oxygen concentrators, and either stationary or portable liquid oxygen tanks, via trans tracheal oxygen, or by non-invasive positive-pressure ventilation (NPPV) mask systems.

The effect of supplemental oxygen on long-term survival in COPD patients was the primary focus of 2 early studies, the Nocturnal Oxygen Therapy Trial (NOTT) (1) and the British Medical Research Council (93) study on domiciliary oxygen. The NOTT investigated the effects of continuous (17.7 hours/day) versus nocturnal (12 hours/day) supplemental oxygen therapy on the neuropsychological function, quality of life, and survival in patients with COPD. The BMRC study looked at the effect of supplemental oxygen therapy (15 hours/day) versus no supplemental oxygen on survival in COPD patients. The findings of both of these studies revealed that supplemental oxygen therapy was effective in improving 3-year (NOTT) and 5-year (BMRC) survival along with demonstrating that the longer the duration of oxygen therapy per day resulted in better survival. It was also noted that the availability of a portable ambulatory oxygen supply was clearly more beneficial for participants in the NOTT continuous oxygen therapy

group as compared to a stationary oxygen supply utilized by the BMRC oxygen therapy group at the 3-year follow-up, in terms of survival.

Patients with COPD who exhibit hypoxia at rest, are typically hypoxic during periods of increased activity and have been found to benefit from supplemental oxygen during exercise. A study by Garrod et al. (50) revealed that hypoxic COPD patients who utilized supplemental oxygen (4 L/min) during a 6-week exercise rehabilitation program had significant decreases in dyspnea ($p=0.02$), but not in other outcome measures as compared to those patients receiving a placebo, though this decrease may have been related to initial baseline differences. Other studies show improvement in V_E and exercise tolerance at submaximal workloads, as well as increased maximum exercise level when hypoxemic COPD patients use supplemental oxygen during exercise training (50, 70).

Adverse medical consequences can occur in patients using LTOT including the development of oxygen toxicity, which may lead to adult respiratory distress syndrome, and also increased carbon dioxide retention, which can actually cause a depressed respiratory drive in select COPD patients (3). Physical hazards of LTOT include the possibility of fires and explosions, due to the high flammability of oxygen. However, the benefits of LTOT for hypoxemic COPD patients clearly outweigh these potentially deleterious effects.

Ventilatory Muscle Training

Ventilatory muscle training (VMT) encompasses several techniques that are performed by individuals with COPD to attempt to increase the strength and endurance of the respiratory musculature. Maximum inspiratory pressure produced by the muscles of

inspiration, especially the diaphragm, is reduced in individuals with COPD as compared to normal healthy controls. Maximum expiratory pressure ($P_E$max) may also be reduced in individuals with COPD, but is not as common a finding (87).

Structural alterations in the chest wall, changes in respiratory physiology, and overall physical deconditioning associated with COPD all impact the function of the muscles of inspiration (77). The primary muscle of inspiration is the diaphragm, which is a thin, dome-shaped muscle with a central tendon. The pathologic changes of COPD, specifically hyperinflation, cause alterations in total muscle length and the zone of apposition of the diaphragm, resulting in a decrease in the contractile mechanical advantage and reduced inspiratory pressure generated during inspiration. This mechanism may also affect the mechanical advantage of the parasternal intercostals, another important set of inspiratory muscles. Other changes associated with COPD include an altered muscle morphology and cellular environment surrounding the muscle tissue. Studies of the diaphragm in patients with severe COPD show increased type I and decreased type IIb muscle fibers, as well as muscle atrophy, with up to a 40-60% reduction in muscle mass (117). Both of these alterations would result in decreased inspiratory muscle contractile force and thus decreased production of inspiratory pressure. Electrolyte imbalances, hypercapnia, and/or increased levels of tumor necrosis factor alpha in the immediate cellular environment surrounding the muscle tissue may negatively affect contractile function also resulting in decreased inspiratory pressure production.

Other factors associated with COPD which may have a detrimental influence on inspiratory pressure production are the increased resistive load, caused by airway

resistance and decreased dynamic compliance, along with an altered central control of respiratory drive and pattern of muscle recruitment, involving both inspiratory as well as expiratory muscle activation (77).

Improvement of respiratory muscle function may occur either when the resistive load is decreased or the muscle contractile force and resultant pressure production is increased. Ventilatory muscle training primarily involves working toward increasing the force generated by the respiratory muscles by applying the "overload principle" via resistive exercise training. Inspiratory muscle training may result in improved strength and endurance of the respiratory muscles both in healthy individuals (110) and in those with COPD (73, 105, 108, 141). In COPD patients, these strength and endurance improvements may lessen the perception of dyspnea during rest or exercise and improve HRQOL (41, 73, 105). The relationship between improved inspiratory muscle strength and decreased perception of dyspnea may be due to the decrease in motor output (efferent stimuli) from a smaller proportion of stronger muscle tissue activated in comparison to the same level of sensory input (afferent stimuli) (37).

Many studies have assessed the efficacy of various techniques of VMT in COPD patients (20, 73, 105, 108, 141). A randomized control study by Rierra et al. (105) investigated the effect of target-flow inspiratory muscle training in 20 patients with severe COPD. The training group underwent a progressive 6-month VMT program beginning at 60-70% of $P_I$max, while the control group trained at 0% load. No significant differences were noted in spirometry, VO_2max, exercise ventilation, or workload achieved in or between the 2 groups, while the maximum sustained inspiratory pressure, the $P_I$max, and functional capacity as determined by the shuttle walking test were all

significantly increased in the training group as compared to baseline measures and to the control group. Dyspnea improved and HRQOL was significantly higher in the training group at 6-months.

A study by Scherer et al. (108) compared the effectiveness of normocapnic hyperpnea (increased rate and depth of respiration with normal blood gases) versus incentive spirometry VMT in an 8-week program completed by 30 COPD patients. Ventilatory muscle training involving normocapnic hyperpnea resulted in significant improvements in $P_E$max, VO_2max, respiratory muscle endurance, 6-minute walk test distance, dyspnea, and the physical component of the Medical Outcomes Survey Short Form-12 questionnaire. All of these variables were significantly better in the training group as compared to the control group.

In a study involving 30 patients with advanced COPD, Weiner et al. (141) investigated the effect of adding a 30-minute VMT session to an existing exercise therapy program for 6-weeks. Significant improvement was noted in dyspnea, $P_I$max, and inspiratory muscle endurance, but FEV_1 and the 6-minute walk distance were minimally affected. A study by Larson et al. (73) randomized 53 patients with moderate to severe COPD into 1 of 4 groups, VMT, cycle ergometry training (CET), CET+VMT, or health education. Ventilatory muscle training was performed using a threshold loaded breathing device for 4 months with progressive resisted settings up to 60% of $P_I$max. The results showed that the addition of VMT to aerobic CET did improve inspiratory muscle strength but did not improve the perception of dyspnea during exercise, the training effect, or exercise performance in this group of COPD patients.

Berry et al. (20) conducted a similar 12-week study in which 25 patients with moderate COPD were randomized into 3 groups, a general exercise group, VMT group, an exercise group + VMT group, and a placebo VMT control group. Ventilatory muscle training and placebo VMT were performed on a spring-loaded inspiratory muscle trainer. No significant differences were demonstrated in $P_I$max, PFT's, or VO_2max following the intervention in any of the groups. In addition, a meta-analysis of 17 randomized clinical trials on the effectiveness of VMT by Smith and colleagues (119) revealed that VMT alone did not result in significant clinical improvement in COPD patients.

Lung Surgery

In patients with advanced or end-stage COPD significant disability and poor quality of life may persist despite maximal medical management. Surgical interventions that may benefit these individuals include: bullectomy, single or bilateral lung volume reduction, and single or bilateral lung transplantation surgery. The surgical intervention recommended for each patient varies according to the type and the severity of COPD, the level of physiologic and functional disability, associated comorbidity, and other patient characteristics such as motivation, compliance, and availability of social support. International guidelines have been established for patient selection for lung transplant surgery (39) with regard to specific inclusion and exclusion criteria.

Bullectomy

Bullectomy involves the surgical resection of bullae, which are enlarged, thin-walled, fluid-filled alveoli that are incapable of normal gas exchange and respiration. Giant bullae may occupy a significant volume of the thoracic cavity resulting in increased

alveolar deadspace, the compression of normal lung tissue, and inhibited ventilation. The removal of this abnormal non-functional lung tissue allows for increased normal lung tissue expansion during inspiration and improved ventilation.

Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) or pneumonectomy involves the removal of 20-30% of the emphysematous lung tissue from one or both lungs (7, 34). Various surgical techniques can be utilized including median sternotomy, standard thoracotomy, video-assisted thorascopic surgery, and laser ablation surgery (47). Single or bilateral LVRS may be performed, though bilateral LVRS is usually preferred, and bilateral LVRS may be completed in one or more stage. The primary indications for LVRS include: age < 75 years; significant disability despite exhausted medical therapy; ex-smoker >3-6 months; FEV_1 < 35-40% predicted post bronchodilator; lung hyperinflation; residual volume (RV) > 200-250%; and total lung capacity (TLC) > 120% predicted (47).

The significant benefits of LVRS on pulmonary physiology involve the promotion of increased static lung recoil pressure, allowing for increased expiratory airflow and decreased hyperinflation, as well as improved dynamic compliance (42, 52, 131). Thus the surgically induced decrease in lung volume and total lung capacity facilitates improvement in lung function, gas exchange, dyspnea scores, exercise capacity, and quality of life post-operatively (116). Supplemental oxygen therapy and chronic oral steroid use is also decreased in many COPD patients following LVRS (47).

Lung volume reduction surgery is not without its inherent risks though, as shown by post-operative mortality rates at 30 days ranging from 0-15% (47). Common post-operative complications include air leaks, pneumonia, pneumothorax, prolonged

mechanical ventilation, and gastrointestinal disturbances (112). Long-term survival rates post LVRS vary among studies, but are approximately 85-87% at 1 year and 81-82% at 2 years (109). Gelb et al.(53) demonstrated 4-year and 5-year survival rates of 64% and 42% in a sample of 26 patients with moderate to severe COPD who had undergone bilateral LVRS.

An interesting study by Criner et al. (34) investigated the benefits of LVRS as compared to pulmonary rehabilitation on lung function, functional exercise capacity, and quality of life in patients with severe COPD. All patients completed an 8-week pulmonary rehabilitation program, then were randomized into 2 groups: the surgery group (bilateral LVRS with stapling resection), or the medical group, which completed an additional 3 months of maintenance pulmonary rehabilitation. Thirteen subjects from the medical group eventually crossed over into the surgery group following the completion of the additional ST maintenance program. Outcomes were measured at baseline, at the completion of the 8-week program, and 3 months post either completion of the maintenance program or LVRS. The results revealed that following the 8-week rehabilitation program, both groups showed significant improvement in total maximal exercise time ($p<0.001$) and a trend toward improved 6-minute walk test distance ($p=0.14$), as well as improved quality of life as shown by the scores on the Sickness Impact Profile. There were no significant changes in any of the variables in the medical group following an additional 3 months of pulmonary rehabilitation. Three months post LVRS, subjects in the surgical group demonstrated significant improvement in lung function, maximum V_E, maximum tidal volume (TV), and quality of life as compared to the pre-operative measures taken at the end of the 8-week pulmonary rehabilitation

program. The overall mortality rates for the surgical group and for the medical group were 9.4% and 2.7% respectively. Thus, LVRS in conjunction with appropriate medical therapy and pulmonary rehabilitation was more beneficial for COPD patients than the combination of the 2 non-surgical modalities alone.

Despite the numerous studies supporting the efficacy and safety of LVRS, many studies reviewed by Flaherty and Martinez (47) demonstrated less positive results. This has lead to the development of the National Emphysema Treatment Trial (7), which is a multicenter, prospective, randomized investigation of the outcomes of LVRS. The primary outcomes of the Nocturnal Emphysema Treatment Trial include maximum exercise capacity and survival, while the secondary outcomes include pulmonary function, HRQOL, long-term cost-effectiveness, and comparisons of surgical technique, patient risk profiles, and patient selection criteria. Early results have demonstrated that COPD patients who had a pre-operative FEV_1 of less than 20% of predicted and either homogenous emphysema or a very low transfer factor do not benefit from surgical intervention and exhibit a very high mortality rate (7). As a result of these findings, patients meeting the above criteria will no longer be randomized into the surgical intervention (LVRS) group.

Lung Transplantation

For certain individuals with severe COPD symptoms and disability despite maximal medical management, lung transplant surgery may be an optional treatment. The Registry of the International Society for Heart and Lung Transplantation reported that 1412 lung transplant surgeries were performed worldwide in 2000, including approximately 672 single and 740 bilateral lung transplants (10). The number of lung

transplant surgeries performed annually represents only a fraction of the number of patients waiting on a transplant list for an appropriate donor organ. As of April 12, 2002 there were 3811 patients on the national lung transplant waiting list (10), and even with the acceptance of transplant organs from older donors, the supply of organs simply cannot keep up with the demand.

Lung transplantation surgery has been performed since 1963, but has been much more successful since the development of cyclosporine, an immunosuppressive agent, in 1983 (130). Single lung transplants were performed initially, but postoperative complications and deteriorating pulmonary function occurred due to the native emphysematous lung becoming even more hyperinflated following surgery. This increased hyperinflation resulted in the compression of and decreased ventilation in the allograft. Thoughts of bilateral lung transplantation were initiated as early as 1970 but came to light in 1986, which technically resolved the native lung hyperinflation issue.

Lung transplant surgery is expensive as shown by the average estimated hospital cost for bilateral lung transplant surgery alone being $108,000, and the associated monthly cost for medications being $1000 in 1998 (124). This does not take into account other charges for postoperative care such as physician fees and ancillary hospital charges. Patients with severe COPD (FEV_1 < 25-30% of predicted), significant hypoxemia and/or hypercapnia, pulmonary hypertension, life-threatening exacerbations, or an abnormally rapid deterioration of overall pulmonary function despite maximal medical management should be referred for lung transplant surgery (5).

The benefits of lung transplantation surgery include improved lung function, tolerance to physical activity, physical function, and HRQOL (15, 60). The improvement

in lung function usually peaks 3-6 months post surgery (15) and is significantly greater following bilateral lung transplantation as compared to single lung transplantation (55, 16). HRQOL as measured by the Medical Outcome Health Survey 20 revealed that lung transplant recipients exhibited significantly higher HRQOL in all dimensions except for pain post transplant, as well as when compared to the HRQOL of transplant candidates on a waiting list (60). These improvements in HRQOL were maintained over a period of 3 years post surgery.

Pulmonary Rehabilitation

Pulmonary rehabilitation programs are multidisciplinary in nature, and include proper medical management, patient education, exercise therapy, VMT, relaxation and stress management programs, nutritional advice, and psychological counseling. Pulmonary rehabilitation programs have varied in the frequency and the duration of intervention, with the majority of programs being offered 2-3 days per week for 6-8 weeks (75).

The primary goal of pulmonary rehabilitation programs is to "achieve and maintain an individual's maximum level of independence and functioning in the community" (46) by "relieving symptoms, particularly dyspnea; improving functional ability; and enhancing HRQOL" (75). Many studies have shown that participation in pulmonary rehabilitation programs is beneficial for individuals with COPD independent of disease severity (56, 85, 102, 145) and results in decreased health-care costs, primarily through a decreased number of future hospital readmissions (41, 67, 69, 74) as well as decreased emergency room and physician office visits. Objective improvement in overall

health status, physical activity performance, exercise tolerance, quality of life, and psychological well being following the completion of pulmonary rehabilitation programs has been shown by numerous studies (27, 44, 66, 72, 73, 122, 139, 141). However, lung function as represented by FEV_1, which has been shown to be the most significant predictor of survival in individuals with COPD (14, 102, 127), typically does not improve following the completion of such programs (51, 102). Other predictors of survival in COPD patients such as the severity of symptoms and functional status (23, 102) can be improved following pulmonary rehabilitation programs and thus provide support for participation in such programs.

Exercise therapy is the cornerstone of any pulmonary rehabilitation program and has been shown to be the primary modality for improving physical performance and tolerance to activity (32), although many studies have not isolated exercise therapy from the multidisciplinary approach of pulmonary rehabilitation when analyzing and interpreting the results. Aerobic exercise involving the lower extremities has been the mainstay of exercise therapy for COPD patients. More recently, programs have incorporated upper extremity resistance training and even more recently, resistive training for both the upper and lower extremities into the exercise therapy program. Ventilatory muscle training has also been utilized, but alone has not been proven to promote significant improvement in lung function or exercise tolerance (119). The primary purpose of an exercise therapy program is to improve functional exercise capacity thereby offsetting the detrimental effects of deconditioning, which most individuals with COPD experience as a consequence of the disease.

Deconditioning due to a lack of physical activity is a primary characteristic associated with COPD, and can be depicted as the "dyspnea spiral" (96). This concept is based on the effect of the pulmonary impairment causing dyspnea upon physical exertion, which encourages a more sedentary lifestyle, for example decreased physical activity level. In turn, the decreased activity level leads to overall deconditioning and then eventually to the individual with COPD experiencing greater dyspnea upon even very low levels of physical exertion. Further deconditioning occurs and the process may continue until functional independence is lost resulting in individuals with COPD requiring assistance for the most basic of self-care activities. Exercise training has been shown to decrease the subjective experience of dyspnea at a given workload (125, 146) allowing the individual with COPD to better tolerate increased physical activity, thereby disrupting the vicious downward spiral of deconditioning and preventing functional dependence.

The detrimental effects of physical deconditioning include: decreased muscle tissue oxidative enzyme levels, decreased numbers of mitochondria, muscle atrophy and weakness, altered neuromuscular control, decreased blood volume, decreased stroke volume and cardiac output, and increased resting heart rate (36). As mentioned previously, the pathophysiologic changes that occur due to COPD include: obstructed airflow, lung hyperinflation, mismatched ventilation perfusion ratio, decreased $P_I max$, increased work of breathing, and decreased capacity for gas diffusion. Increased pulmonary vascular resistance and edema may lead to right-sided ventricular hypertrophy and/or failure (cor pulmonale), further compromising cardiac output and tolerance to increased activity. The deficits of deconditioning along with the pathophysiologic

changes associated with COPD all contribute to a poor tolerance to increased activity and exercise, early fatigue, and dyspnea in these patients. Other factors that can reduce tolerance to exercise in COPD patients are anemia, carboxyhemoglobinemia, chronic metabolic acidosis, and malnutrition (138). In general, the physical benefits of exercise training for COPD patients are associated with changes in skeletal muscle morphology and enzymes, decreased sensitivity to dyspnea, improved ventilation, and the delayed onset of lactic acidosis. Specific physiological responses to exercise training in COPD patients include: increased VO_2max, increased maximal workrate, decreased heart rate at submaximal workloads, decreased blood lactate levels, and decreased muscle half-time phosphocreatine recovery time (104). A study of rigorous exercise training in COPD patients by Casaburi et al. (27) also showed a reduction in V_E and respiratory rate along with an increased TV, which improved the ventilatory deadspace to tidal volume ratio thus increasing the potential for more efficient pulmonary gas exchange and better oxygenation. These benefits of training promote improved exercise performance and a decreased perception of dyspnea. Two additional mechanisms of positive training responses in COPD patients are the improved mechanical efficiency in the performance of an activity, which decreases oxygen demand, and the improved respiratory muscle function (88), which improves ventilation.

In looking at the evidence for the efficacy of pulmonary rehabilitation programs, Lacasse et al. (72) performed a meta-analysis of pulmonary rehabilitation studies in 1996. Fourteen randomized control trials were included in this meta-analysis, which revealed that pulmonary rehabilitation programs were successful in improving maximum exercise capacity and the HRQOL in individuals with COPD. Functional exercise capacity, as

measured by the 6-minute walk test, improved by 55.7 meters (m) on average, which is greater than the minimal clinically important distance of 50 m as determined by Goldstein et al. (57) and the minimal clinically important distance of 54 m as determined by Redelmeier et al. (98). Improvement in functional exercise capacity was significantly higher in programs that were 6 months or greater in duration as compared to those less than 6 months in duration.

Benefits achieved from participation in exercise rehabilitation programs may be dependent upon the initial level of severity of the COPD. Wedzicha et al. (139) investigated the effect of an 8-week exercise plus education program versus an 8-week education only program in 126 randomly assigned COPD patients. These patients were further grouped according to the severity of dyspnea, either into the moderate or severe category. Health status and shuttle walking test distance improved significantly in the exercise plus education group of moderately severe COPD patients, while no significant improvements were seen in the severely dyspnic exercise plus education group. The education only groups showed no improvements following intervention. Another study (73) demonstrated that patients with all stages of COPD (mild, moderate, and severe based on FEV_1) showed significant improvement in functional capacity as determined by the 6-minute walk test, as well as in the dyspnea and fatigue domains of the Chronic Respiratory Disease Questionnaire (CRQ) (63) following a 12-week exercise therapy program. In addition, the mild and moderate COPD patients demonstrated significant improvement in total treadmill time and overhead task time, while those in the severe stage did not. This study provided solid evidence that even patients with mild COPD can benefit from exercise therapy in pulmonary rehabilitation programs.

Lower Extremity Exercise

Many early studies on the effects of exercise training in pulmonary rehabilitation programs involve interventions that primarily utilize lower extremity aerobic exercise training, either via walking or stationery cycling. Notable dyspnea and impaired endurance during functional ambulation in COPD patients seems to have prompted this focus (22). A majority of these studies have demonstrated improvement in exercise tolerance and endurance as well as in maximal workload and decreased leg fatigue following exercise training. The results of several randomized controlled trials using various protocols and modalities have reinforced these results (20, 66, 72, 97, 102, 123, 140).

Weiner et al. (141) utilized supervised outpatient cycle ergometer exercise training for 6 months in patients with moderate COPD to assess the effects on exercise endurance and functional capacity. The results demonstrated a significant increase in cycle ergometer endurance at constant load but did not show an increase in 12-minute walk test distance. Another study involved 119 COPD patients participating in an 8-week outpatient multidisciplinary pulmonary rehabilitation program followed by 1 visit monthly for a year (102). Walking was the primary exercise modality and the results of this study demonstrated a 9% increase in VO_2max, a 33% increase in treadmill maximal workload, and an 85% increase in treadmill endurance, as well as decreased dyspnea in the intervention group. Strijbos et al. (123) examined the results of a 12-week outpatient versus home-based exercise program involving walking, stationary cycling, and stair climbing exercise intervention. Both groups made improvements in the 4-minute walk test, maximum cycle ergometry workload, and dyspnea ratings. These benefits were

better maintained in the home-based group at 18 months. Berry and colleagues (20) looked at the effect of a 12-week outpatient exercise therapy walking program on both functional and treadmill exercise performance in a small sample of COPD patients. Significant improvement was noted in the 12-minute walk distance, while no significant changes were seen in total treadmill time or dyspnea ratings. Another study (97) compared the effects of 2 different 8-week walking programs, one supervised and the other self-monitored, on the physiological outcomes in 41 COPD patients. The results revealed that both groups had significant increases in $FEV_{1,}$ VO_2max, and exercise endurance, as well as decreased leg fatigue ratings. There were no significant changes in dyspnea in either of the 2 groups. Hernandez et al. (66) used a 12-week home-based, paced walking program to assess the effects of exercise training on a group of COPD patients. An increase in exercise endurance accompanied by a decreased level of dyspnea was noted in the intervention group, along with an improved quality of life.

Upper Extremity Exercise

Upper extremity strength and endurance are very important for the independent performance of ADL's such as bathing and dressing. COPD patients who rely on accessory muscle assistance for breathing commonly experience increased dyspnea when activities involving the use of upper extremities are performed. This is due in part to the shoulder girdle stabilizing role that some of these accessory muscles play when elevation of the upper extremities occurs. More of the respiratory burden is then shifted onto the mechanically disadvantaged, weakened diaphragm (28). The diaphragm, which is unable to generate sufficient inspiratory pressure for adequate ventilation, becomes overworked and fatigued which then contributes to the perception of increased dyspnea. Increased

dyspnea may also be related to the fact that when upper extremity musculature is active, oxygen uptake and carbon dioxide production is increased as compared to the metabolic changes during activity of the lower extremity musculature. This is related to the upper extremity musculature being smaller in mass and cross-sectional area, composed of more type 2 than type 1 muscle fibers, and having smaller capillary beds as compared to lower extremity musculature (143). This increased muscle metabolism results in an increased ventilatory demand (80) and the increased perception of breathlessness. Another factor is that dyssynchronous thoracoabdominal breathing, resulting in further compromised ventilation, is associated with upper extremity activity in some COPD patients (28).

Upper extremity exercise in COPD patients typically involves cranking an upper body ergometer or performing repetitive therapeutic exercises, either with or without resistance. Upper extremity exercise may be performed with or without support as well, though open chain, unsupported activities more closely simulate the performance of ADL's and may be more effective (80). Most studies have shown that upper extremity exercise results in a decreased metabolic and ventilatory requirement specifically for activities that require arm elevation, but this training effect does not always translate into improved performance of ADL's (101). Even so, the ATS recommends that upper extremity exercise be included in any pulmonary rehabilitation or exercise therapy program in which patients with COPD are involved (8).

Total Body Resistance Training

More recently pulmonary rehabilitation programs have incorporated both upper and lower extremity resistance exercise into the training regimen. Peripheral muscle dysfunction leading to atrophy, weakness, increased fatigue, and decreased endurance is

prominent in patients with COPD. Resistance training has been shown to improve muscle strength and endurance in healthy older adults (4) and has the potential to do the same in COPD patients.

In fact, resistance training in COPD patients has been shown to improve not only muscle strength, but also overall endurance. Simpson et al. (118) studied 14 patients with COPD who performed an 8-week upper and lower extremity resistive exercise program. Their results demonstrated that those patients who participated in the resistive training program had a significant (73%) increase in cycling endurance time, while the control group showed no change. There was also a significant improvement in perceived dyspnea in the weight-training group but no significant improvements in cycling VO_2max or 6-minute walk test distances were observed in either group. Clark and colleagues (31) investigated the effect of a 12-week outpatient weight-training program on exercise tolerance and skeletal muscle function in 43 patients with mild COPD. These COPD patients exhibited decreased upper and lower extremity muscle strength and endurance as compared to healthy sedentary individuals at baseline except for upper extremity sustained contraction. Following the weight-training intervention, significant improvements were noted in maximal strength in 4 of 5 lower extremity exercises, as well as in the 60-second sustained isokinetic contractions in both the upper and lower extremity. Maximal workload, VO_2max, TV, and V_E were all significantly greater in the training group as compared to the controls following the intervention. Both the training group and the controls showed improved treadmill endurance, but the training group's improvement was significantly higher than the controls' improvement. The change in treadmill endurance correlated with the change in isokinetic sustained muscle strength.

Gosselink et al. also found a correlation between quadriceps muscle strength and functional capacity, as determined by cycle ergometer VO_2max and the 6-minute walk test in 41 patients with moderate COPD (58).

In contrast to the above studies, the results of a study conducted by Bernard et al. (19) demonstrated that the addition of strength training to an aerobic exercise training program did not result in significant overall increased endurance above that obtained by the aerobic exercise only group. Patients with COPD were randomized into either 1 of 2 treatment arms, aerobic exercise plus strength training or aerobic exercise alone. Following the 12-week intervention, both groups showed significantly increased quadriceps strength, but the aerobic plus strength training group demonstrated significantly greater quadriceps strength, thigh muscle cross-sectional area, and pectoralis major strength than the aerobics only group. Maximal work rate, 6-minute walk test distance, and quality of life improved from baseline in both groups but were not significantly different between the groups at the completion of the intervention.

The long-term benefits of resistive training can both be maintained for at least 3 years as well as be improved by participating in a comprehensive exercise therapy program that includes weight training a minimum of 2 days per week (122). Other studies are underway to assess the long-term maintenance of strength gains made by resistive exercise training in patients with COPD.

The recommended resistive exercise program for COPD patients involves a frequency of 2-3 days per week, performing 1-3 sets of 6-10 repetitions beginning with 50-60% of the 1 repetition maximum progressing up to 85% of the one repetition maximum, by adding a 5-10% increase in lower extremity and a 5-7% increase in upper

extremity load as tolerated (122). A resistive exercise program that simulates ADL's should be incorporated in order to promote not only improved muscle strength and endurance, but also improved performance of ADL's.

Safety considerations for resistive exercise programs in COPD patients include utilizing proper breathing technique, avoiding the Valsalva maneuver, monitoring SaO_2, dyspnea level, and blood pressure periodically, as well as patient observation for proper lifting technique in order to protect arthritic joints and osteoporotic bones from possible injury (122).

PURPOSE

The purpose of this study was to compare the long-term outcomes in pulmonary function, self-reported HRQOL, self-reported physical activity, self-reported disability, and functional exercise capacity in COPD patients either completing a ST (3-month) or a LT (18-month) exercise rehabilitation program at 58 months.

HYPOTHESIS

There will be no significant differences in the long-term outcomes between the ST and the LT exercise rehabilitation groups at the 58-month follow-up.

METHODS

Reconditioning Exercise and Chronic Obstructive Pulmonary Disease Trial

The Reconditioning Exercise and Chronic Obstructive Pulmonary Disease Trial (REACT) (21) served as the original research study from which COPD patients were recruited for the current follow-up study. The REACT study was conducted from August 1995 through July 1999 and involved 140 patients with COPD (non-reversible airflow limitation with a FEV_1 >/= 20% of predicted and a FEV_1/FVC ratio of </= 70%). All patients participated in a supervised, 3-time per week, facility-based aerobic and upper extremity resistive group exercise intervention lasting 3 months. Following the 3-month exercise intervention, the patients were randomly assigned to either one of 2 groups, those who received an additional 15 months of supervised exercise training (long-term, LT) or those who did not (short-term, ST). Outcome measures were taken at baseline, 3, 9, 15, and 18 months and included self-reported disability, physical function (as determined by 6-minute walk test, stair climb time, and overhead task time), pulmonary function tests (PFT's), self-reported physical activity, and HRQOL.

Participants

All participants were volunteers recruited from COPD patients who had completed the initial REACT study. Of the 140 original REACT participants, 39 agreed to participate in the follow-up study, 5 were known to have expired, while the remainder of subjects either declined to participate or were unable to be contacted. Informed consent

for the follow-up study was obtained from all participants and the Wake Forest University Institutional Review Board approved the study protocol.

Procedures

All follow-up testing was completed during a 1-time visit to the Wake Forest University Human Performance Laboratory. Subjects were asked to refrain from using bronchodilator inhalers within 4 hours prior to testing, but were instructed to take all other medications as usual. Subjects completed a comprehensive medical history questionnaire, physical activity readiness questionnaire (9), and a current medication form.

Each subject's height and weight (in shoes) were determined using a sliding balance scale. Pulmonary function tests were then performed using a Medical Graphics Corporation (St. Paul, MN) 1085D plethysmograph according to the guidelines set by the ATS (2). Following the PFT's, subjects completed the physical activity scale for the elderly (PASE) (137) and the physical function questionnaire (PFQ) (78). A trained examiner then administered the CRQ (63). Performance of the 6-minute walk test to assess the functional capacity of each subject completed the follow-up testing protocol. The 6-minute walk test was not performed in those subjects who had a history of chest pain while walking or at rest, or who currently had musculoskeletal conditions that compromised the safe completion of the test.

Outcome Measures

Pulmonary Function Tests

Pulmonary function tests determined each subject's forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), residual volume (RV), and total lung capacity (TLC). Forced expiratory volume was expressed as a percent of predicted, based on the equations of Knudson and colleagues (71) and also as a percent of FVC. All subjects met reproducibility and acceptable requirements for testing as described by the ATS (2).

Physical Activity Scale for the Elderly

The PASE (137) is a self-administered questionnaire that is based on a 7-day recall of occupational, household, and leisure activities. The frequency and duration of occupational and leisure activities were assessed. The total PASE score is based on summing the totals of each activity's empirically derived weight times the duration of performance, or participation (136). The PASE has been validated and shown to be reliable as an indicator of physical activity in older adults (136, 137).

Physical Function Questionnaire

The PFQ is a self-administered tool used to measure the level of physical disability experienced by subjects due to their health over the past month. It is a modified version of an original questionnaire used in the Fitness and Arthritis in Seniors Trial (FAST) (99) and is composed of 23 items describing common daily activities. Each item of the PFQ is scored on a 1-6 scale, with 1 representing "usually did with no difficulty", and 6 representing "usually did not do for other reasons". The scores were categorized into five activity subscales including basic, transfer, ambulation/climbing, upper

extremity, and complex. An overall score was determined by a composite average of responses for all 23 items.

Chronic Respiratory Disease Index Questionnaire

The CRQ (63) is a disease specific, examiner administered tool that measures the change in HRQOL over time. The HRQOL is categorized into four categories including dyspnea, fatigue, emotional function, and mastery of the disease. With respect to the dyspnea category, subjects listed five important activities in which they experienced shortness of breath or dyspnea to individualize the baseline CRQ. The same five activities were used on each subsequent administration of the CRQ to assess the change in dyspnea over time. Subjects were informed of the answer given for each item during the previous administration of the CRQ in order to decrease the randomness of their current responses. The answers were scored on a 1-7 scale, with 1 representing "extremely short of breath" and 7 representing "not at all short of breath". The remainder of the questions were not individualized and dealt with fatigue, emotional function, and mastery of the disease. These questions were scored on a 1-7 scale, with choices ranging from "all of the time" to "none of the time". Scoring is based on the mean responses of each of the 4 categories. The minimal clinically important difference has been shown to be 0.5 units per question per dimension (62, 72). Torres and colleagues (35) have determined that the CRQ is one of the best practical tools for measuring the efficacy of pulmonary rehabilitation due to its simplicity to administer and sensitivity to detect clinically important differences in COPD patients.

6-Minute Walk Test

The 6-minute walk test was performed to assess the functional capacity of each subject. Subjects were instructed to cover the greatest distance possible by walking for 6 minutes around the perimeter of a gym that measured 70'x 88'. Subjects' walking pace was self-determined and rest periods were allowed if needed. Verbal encouragement was not provided and subjects were not permitted to time or pace themselves by using a watch. Performance was based on the measured total distance walked. The minimal clinically important distance has been established to be 54 m in patients with COPD (98). The 6-minute walk test has been deemed a reliable and valid measure in evaluating the physical response of COPD patients to pulmonary rehabilitation programs (35). Although the 6-minute walk test is considered a submaximal exercise test, positive correlations of between 0.51 and 0.90 have been demonstrated between total walk distance and VO_2max (121), thus making the 6-minute walk test a good measure of functional exercise capacity when properly performed.

Statistical Analysis

Descriptive statistics were determined for all variables measured in the ST and LT groups at baseline and 58 months. Independent t-tests were utilized to compare the means for the ST and LT groups' descriptive statistics. Independent t-tests were also performed on selected variables of physical function and disease severity using the original baseline REACT data. Comparisons of these variables were made between the group of participants who returned for the 58-month follow-up study and the group of participants who did not return. Analysis of covariance (ANCOVA), using baseline scores as the

covariate, was performed on the PFQ, CRQ, and PASE scores, as well as the PFT values and the 6-minute walk test distance. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software for Windows 98 (version 10.1, SPSS, Incorporated, Chicago, IL). The significance level was set at $p = 0.05$.

RESULTS

A total of 39 (23 M/16 F) participants completed the REACT 58-month follow-up study, with an average age of 72.4 ± 6.2 yrs (range = 62-85 yrs) and average follow-up time of 58.5 ± 6.2 months, (range = 48-72 months). Table I shows participant demographic and clinical characteristics. Overall, there were no significant differences in the demographic characteristics between the ST and the LT groups at 58 months. The most common associated comorbidities included hypertension, arthritis, and coronary artery disease respectively, which is very similar to a sample of 290 COPD patients studied by Van Manen (134). Using the original REACT data set, a comparison of the functional exercise capacity between those participants who returned (returnees) for the 58-month follow-up study and those who did not return (non-returnees) revealed that the returnees demonstrated significantly higher ($p=0.01$) functional exercise capacity as determined by the 6-minute walk test distance at 18 months than the non-returnees (518 ± 13 m versus 474 ± 10 m respectively).

TABLE I*

PARTICIPANT DEMOGRAPHICS/CLINICAL INFORMATION

PARTICIPANTS	ST (3-MONTH)	LT (18-MONTH)
Completed REACT, n	56	62
Completed 58 mos FU, n (%)	12 (21.4)	27 (43.5)
Unable to contact	11 (19.6)	8 (12.9)
Contacted but refused FU	17 (30.4)	12 (19.4)
Expired	5 (8.9)	0 (0)
CHARACTERISTICS		
Weight, kg	79.4 ± 4.5	79.1 ± 3.7
Gender, M, n (%)/ F, n (%)	6 (50)/6 (50)	17 (63)/10 (37)
Age, yrs	71.3 ± 1.8	72.9 ± 1.2
Height, cm	168.3 ± 3.4	171.7 ± 1.6
FU time, mos	59.3 ± 1.8	58.2 ± 1.2
COMORBIDITY		
Arthritis, n (%)	5 (41.7)	14 (51.9)
Cancer, n (%)	2 (16.7)	3 (11.1)
Circulatory problems, n (%)	1 (8.3)	3 (11.1)
Coronary artery disease, n (%)	4 (33.3)	6 (22.2)
Diabetes mellitus, n (%)	1 (8.3)	2 (7.4)
Hypertension, n (%)	6 (50.0)	13 (48.1)
Transient ischemic attack, n (%)	2 (16.7)	2 (7.4)
SMOKING STATUS		
Current, n (%)	0 (0)	3 (11.1)
Past, n (%)	8 (75)	25 (92.6)

*values for FU time, age, height, weight, and pack yrs are means ± SEM; ST= short-term, LT= long-term, mos=months, FU= follow-up, n= number, kg= kilograms, M= male, F= female, yrs= years, cm= centimeters, SEM= standard error of the mean.

Pulmonary Function Tests

Mean FEV_1 % predicted scores for both the ST and the LT groups at 0, 3, 18, and 58 months are shown in Figure 1. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (57.6 ± 3.1 vs. 56.6 ± 2.1%, respectively). Mean FEV_1/FVC scores for both the ST and LT groups at 0, 3, 18, and 58 months are shown in Figure 2. No significant differences were found when comparing adjusted mean scores between the ST and LT groups at 58 months, (51.5 ± 2.1 vs. 52.1 ± 1.4 %, respectively). Mean RV/TLC ratio scores for both the ST and the LT groups at 0, 3, 18, and 58 months are shown in Figure 3. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (53.7 ± 4.2 versus 58.4 ± 2.8%, respectively).

Figure 1

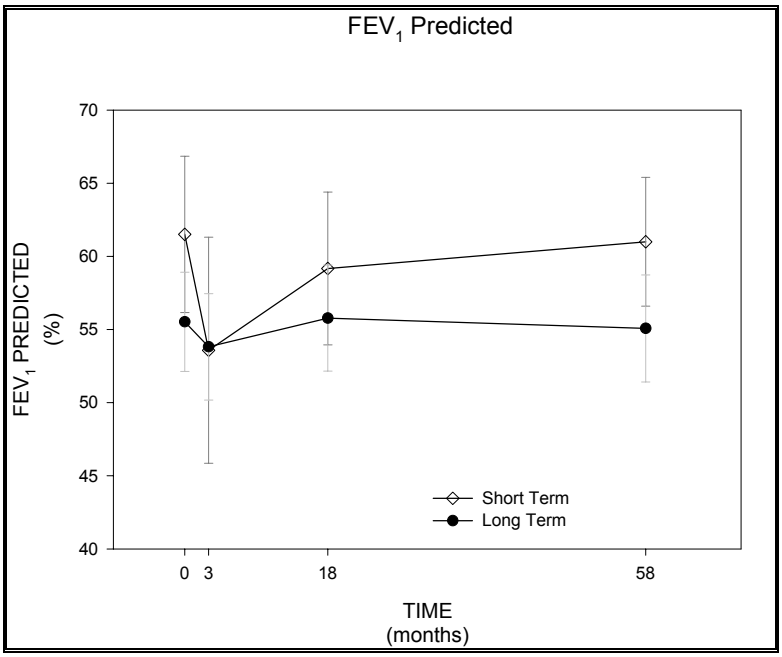


Figure 2

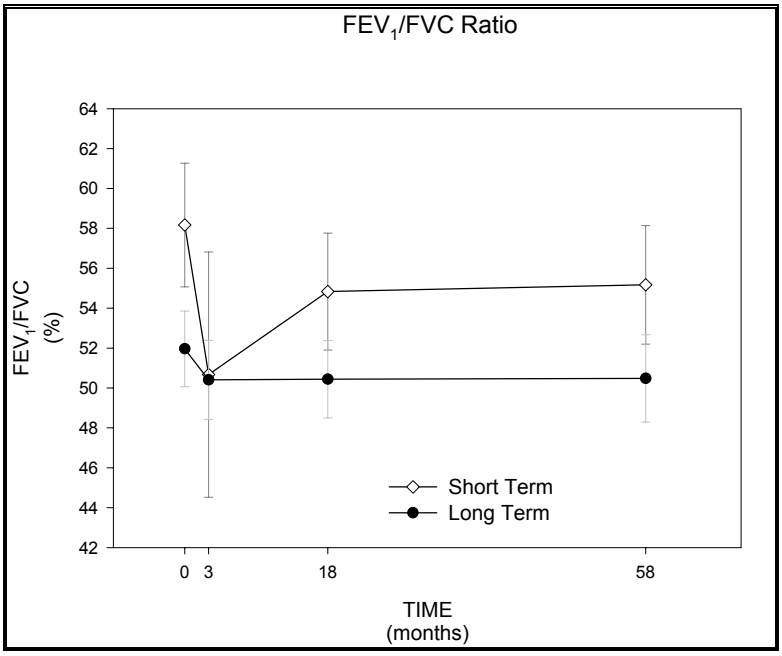
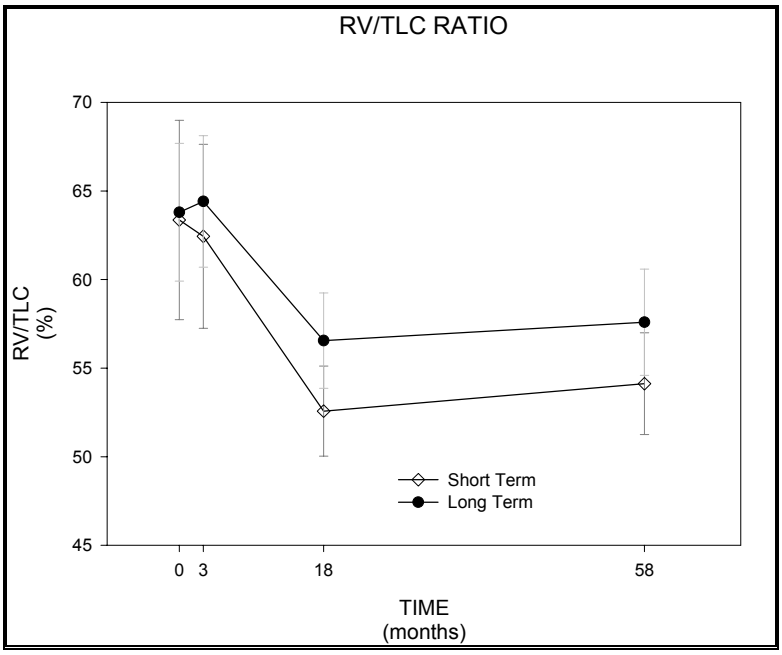


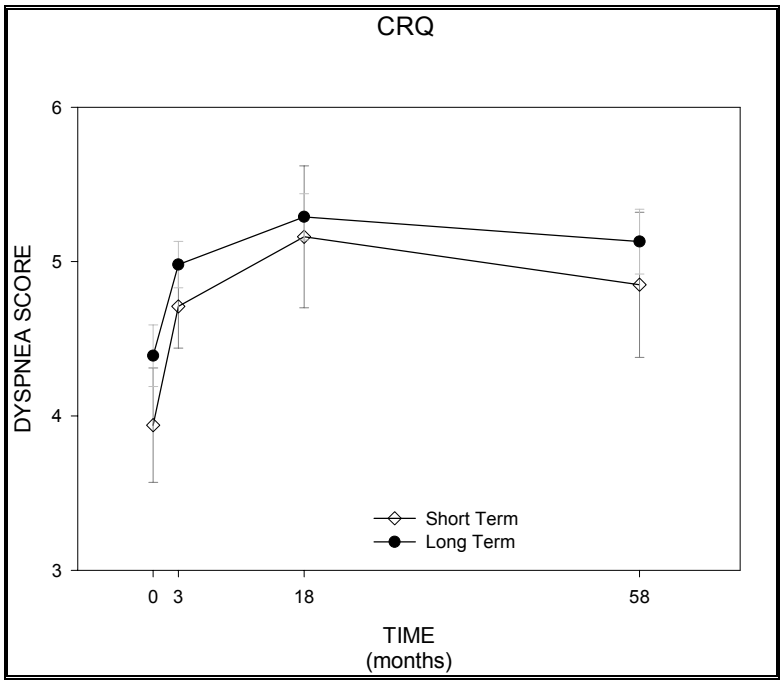
Figure 3



Chronic Respiratory Index Questionnaire

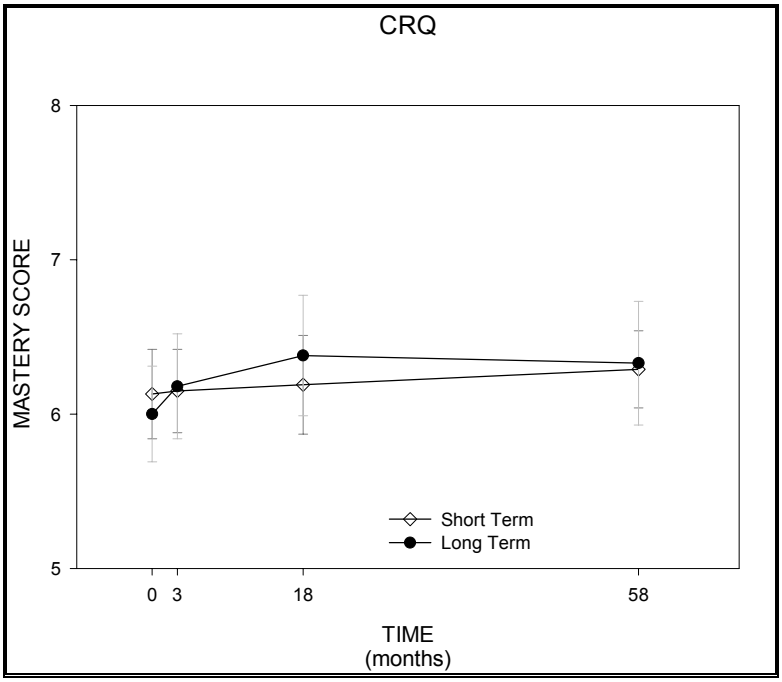
With respect to the CRQ, no significant differences were observed between the ST and the LT groups in any of the individual domain scores (dyspnea, mastery, emotion, or fatigue) at 58 months. Mean dyspnea scores for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 4. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (4.9 ± 0.4 versus 5.1 ± 0.2 units, respectively)

Figure 4



Mean mastery scores for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 5. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (6.3 ± 0.2 versus 6.4 ± 0.1 units, respectively).

Figure 5



Mean emotion scores for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 6. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (5.6 ± 0.2 versus 5.7 ± 0.1 units, respectively). Mean fatigue scores for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 7. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (4.3 ± 0.3 versus 4.7 ± 0.2 units, respectively).

Figure 6

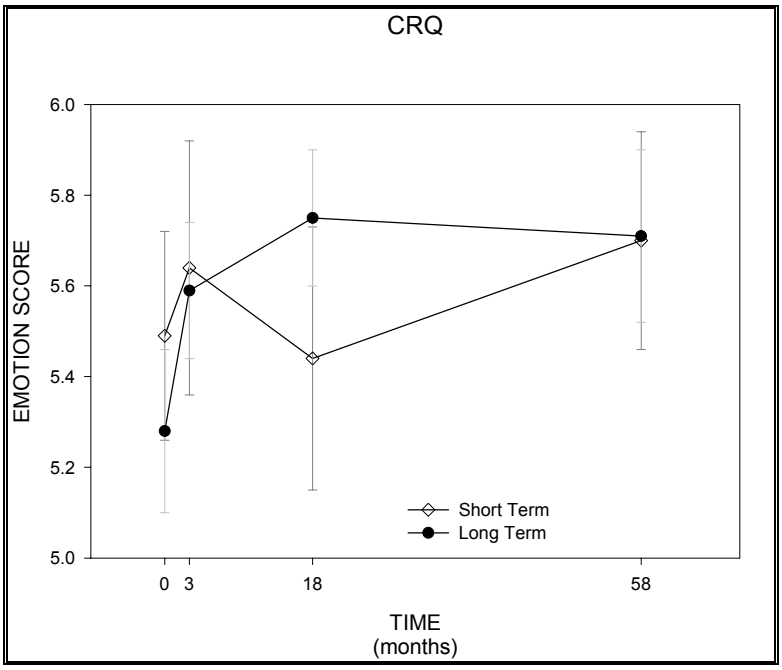
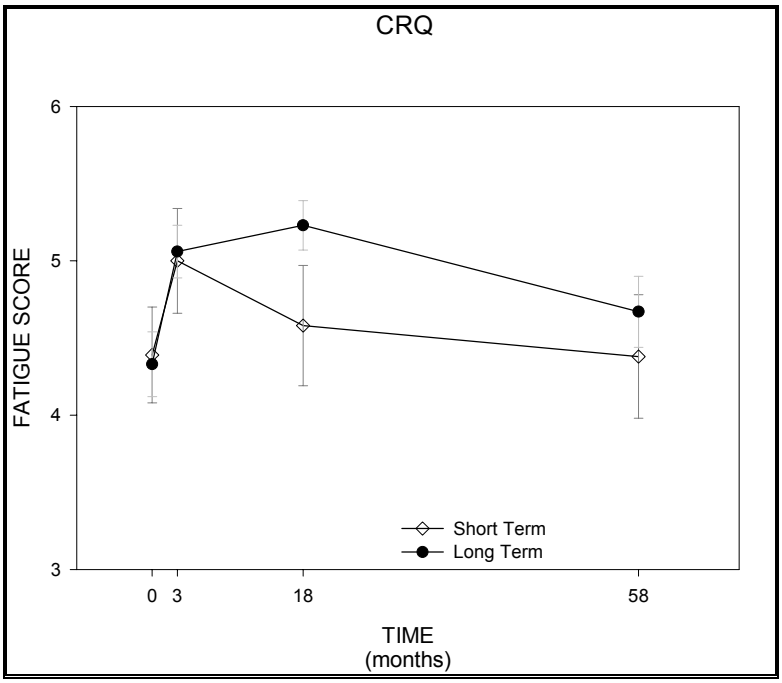


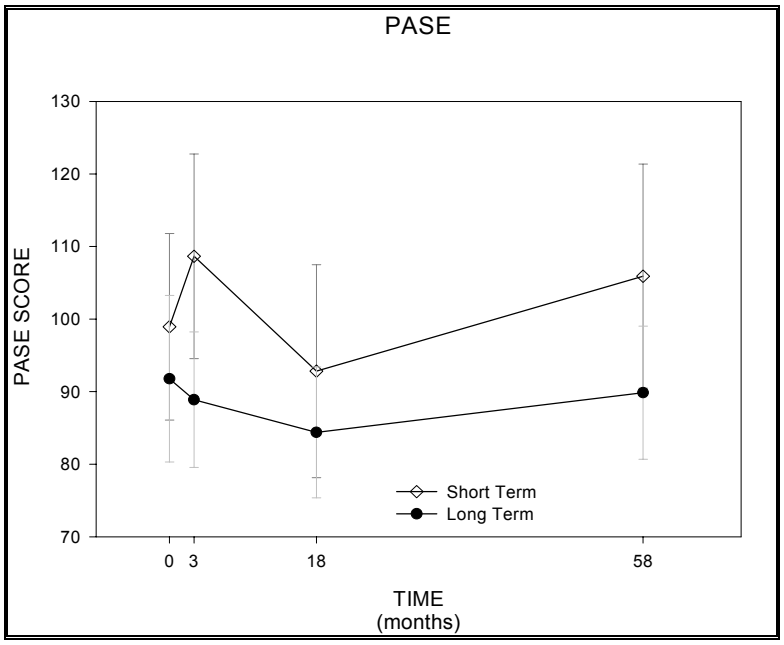
Figure 7



Physical Activity Scale for the Elderly

Mean PASE scores for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 8. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (103.0 ± 12.2 versus 92.2 ± 8.8 units, respectively).

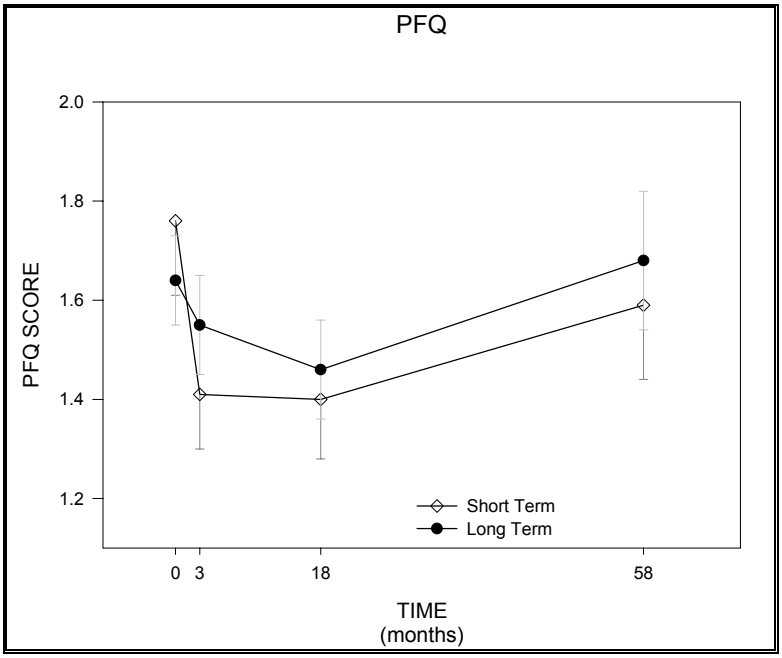
Figure 8



Physical Function Questionnaire

Mean PFQ scores for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 9. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (35.0 ± 3.8 versus 39.4 ± 2.5 units, respectively). No significant differences were observed when comparing adjusted mean scores between the ST and the LT groups in any of the activity subscales at 58 months: (basic: 1.1 ± 0.1 versus 1.3 ± 0.1, transfer: 1.3 ± 0.2 versus 1.3 ± 0.1, ambulation/climbing: 2.1 ± 0.3 versus 2.3 ± 0.2, upper extremity: 1.7 ± 0.2 versus 1.9 ± 0.1, or complex: 1.7 ± 0.3 versus 1.8 ± 0.2 units, respectively).

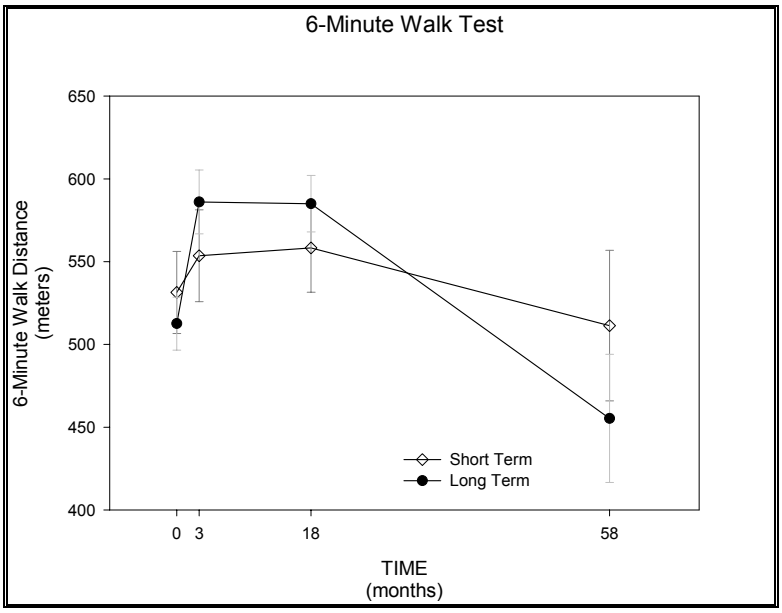
Figure 9



6-Minute Wal Test

Mean 6-minute walk test distance values for both the ST and the LT groups at time 0, 3, 18, and 58 months are shown in Figure 10. No significant differences were found when comparing adjusted mean scores between the ST and the LT groups at 58 months, (500.7 ± 26.6 versus 517.9 ± 18.8 m, respectively).

Figure 10



DISCUSSION

The original REACT study was a clinical trial in which patients with COPD participated in a 3-month facility-based exercise therapy program and then were either randomized to continue the supervised program for an extra 15 months or were encouraged to continue to exercise on their own, independent of the study. At 18 months, study participants returned for follow-up assessments. In general, the results of the REACT study revealed that both the ST and the LT exercise therapy groups showed improvements in the HRQOL, self-reported disability, and functional exercise capacity at the completion of the initial ST exercise therapy program. At 18 months, these benefits were maintained in the LT group, but were not maintained in the ST group whose outcome variables approached the initial baseline measures. The primary purpose of this follow-up study was to describe and compare the long-term outcomes of COPD patients who had participated in either a ST or an LT exercise rehabilitation program (REACT) at 58 months. The outcomes assessed included: lung function (PFT's- FEV_1 % predicted, FEV_1/FVC ratio, and RV/TLC ratio); HRQOL (CRQ); self-reported physical activity (PASE); self-reported disability (PFQ); and functional capacity (6-minute walk test). Overall, the results of this study showed no significant differences between the ST and the LT groups in any of these variables measured at 58 months. These findings suggest that even patients who participated in a long-term formal exercise rehabilitation program will not maintain the benefits achieved once the program ends.

Research has demonstrated that the benefits gained from participation in pulmonary rehabilitation programs that include exercise therapy, can be maintained for

up to 2 years (48)and even 3 years in select COPD patients (122). Other studies have shown that the benefits gained from participation in pulmonary rehabilitation programs diminish by 18 months following completion of these programs (21;102;123). To our knowledge, this is the first study to look at the long-term (58 months) outcomes in COPD patients following completion of an 18-month exercise rehabilitation therapy program.

Lung function (FEV_1% predicted, FEV_1/FVC ratio, and RV/TLC ratio), as measured by PFT's, was not significantly different between the ST and LT groups at 58 months. Many studies investigating the efficacy of pulmonary rehabilitation programs demonstrate that lung function is typically not affected by exercise therapy interventions (51;102).

Results from the present investigation show that HRQOL, as measured by the four domains of the CRQ (dyspnea, mastery, emotion, and fatigue) was not significantly different between patients from the ST and the LT exercise therapy groups at 58 months. More specifically, the results of this follow-up study showed that the dyspnea, mastery, and emotion scores were similar between the 2 groups at 58 months. Results from the original REACT study showed a significant difference in all domains of the CRQ when comparing the ST and the LT exercise therapy groups at the 18-month follow-up (49). Given the fact that the differences seen at 18 months between the 2 groups were not seen at 58 months, it does not appear that those patients participating in an 18-month exercise therapy program will maintain long-term benefits to any greater degree than those participating in a short-term exercise therapy program.

Self-reported activity, as measured by the PASE, was not significantly different between the ST and the LT groups at 58 months. Older adult volunteers were recruited

from community centers and retirement homes in order to assess the value of the PASE in measuring physical activity in a study conducted by Harada et al. (65). The mean PASE score was 50 ± 44 units in 36 adults recruited from retirement homes, while the mean PASE score for 51 adults recruited from community centers was 158 ± 65 units, respectively. The adjusted mean PASE scores from the ST and the LT groups this follow-up study were 103 ± 12 and 92 ± 9 units, which demonstrates that our participants were more active than those individuals residing in retirement homes and somewhat less active than those individuals recruited from community centers. The subjects in each study were all of similar age. These results support the idea that individuals with COPD are less active on a regular basis than independent-living older adults without COPD.

Self-reported disability, as measured by the PFQ, was not significantly different between the ST and the LT groups at 58 months. The PFQ was developed specifically for the Fitness Arthritis and Seniors Trial (FAST), which investigated the effects of aerobic and resistive exercise training, as well as osteoarthritis education on self-reported disability in patients with knee osteoarthritis (40)**.** The baseline adjusted mean PFQ score in this sample of 439 patients was approximately 1.8 units, while the sample of COPD patients in the current study had an adjusted mean PFQ score of 1.5 units in the ST group and 1.7 units in the LT group. Thus, patients with COPD reported similar, but slightly less disability than age-matched patients with knee osteoarthritis. The results of these 2 studies also suggest that COPD patients had less self-reported disability associated with the transfer and the ambulation/climbing domains than the osteoarthritis patients, and similar self-reported disability in the remaining domains.

Functional capacity, as measured by the 6-minute walk test, was not significantly different between the ST and the LT groups at 58 months. The participants in this follow-up study had a mean 6-minute walk test distance of 511 ± 45 m in the ST group, and 455 ± 39 m in the LT group. In healthy age-matched individuals the mean 6-minute walk distance has been reported to be 631 ± 93 m (129), though these subjects had standardized verbal encouragement every 30 seconds, which may have positively influenced the total distance walked (64). In the present study, the participants had no such verbal encouragement. Our participants were also older which may have also limited the total distance walked given that age has been shown to be an independent predictor of the 6-minute walk test distance (129). Gibbons et al. (55)also established reference 6-minute walk test distance values for 20 healthy older adults aged 61-80 years. The mean distance covered was 635 ± 71 m, which again is higher than that of our study participants.

The limitations of this study include: small sample size with a disproportionate number of subjects representing the LT versus the ST group. This discrepancy somewhat biases the sample and can be possibly explained by idea that the LT group felt more dedicated to the study because of participation in the longer initial exercise intervention. Another potential source of bias involves the inclusion criteria for the original REACT study. Subjects had to be able to complete the 6-minute walk test and must have not been consistently exercising prior to entry into the study. These criteria exclude low level functioning COPD patients as well as those COPD patients who were motivated and already active, which may have influenced adherence to exercise behavior following the study intervention resulting in differences in the current follow-up study. The follow-up

study participants were probably also higher functioning than those individuals who did not return for follow-up testing. The original REACT data analysis at 18 months showed that the 58 month follow-up participants had significantly higher 6-minute walk test distances as compared to the participants which did not return for the 58-month follow-up study. This finding lends support to the possibility that similar differences between the returnees and the non-returnees may have also been present at 58 months as well resulting in a somewhat biased sample. Also, of the original REACT participants that were contacted, several were no longer able to live independently at home and/or required assistance for routine activities. Many did not feel it was appropriate to participate in the follow-up testing and/or were unable to arrange for assistance and transportation to the campus. An additional limitation of this study, as well as the original REACT study, is that there was no control group of healthy individuals involved in order to track the overall age-associated decline in the different outcome variables.

Further research is indicated to identify the ideal parameters of pulmonary rehabilitation programs in order to maximize benefits and minimize patient healthcare costs. Long-term follow-up studies (greater than 2 years) looking at morbidity and mortality in COPD patients need to be completed in order to provide further evidence for the efficacy of pulmonary rehabilitation programs. Alternative strategies for developing more cost effective exercise interventions and social support that could be more accessible to a larger number of COPD patients need to be developed. Programs that offer a behavioral component that would promote exercise adherence and individual accountability along with exercise therapy may be more successful in maintaining benefits gained from short-term participation in pulmonary rehabilitation programs. The

Reconditioning and Chronic Disease Trial 2 (REACT 2**)** a new study that will incorporate behavioral change strategies into an exercise therapy program for COPD patients will attempt to discover the answers to these questions.

Conclusion

Overall, the results of this 58-month follow-up study involving a group of 39 COPD patients who had completed either a 3-month or an 18-month exercise therapy program demonstrated that there were no significant differences in lung function, self-reported physical activity level, self-reported disability, self-reported HRQOL, or functional exercise capacity between the 2 groups. These results indicate that the benefits gained from participation in either a ST or LT exercise rehabilitation program are not permanent and diminish considerably over time. Future research must continue to assess the cost effectiveness of pulmonary rehabilitation programs in order to make the most efficient use of limited healthcare resources.

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2002	Long-Term Follow-Up of Exercise Rehabilitation Outcomes in Patients with Chronic Obstructive Pulmonary Disease
2002	Peripheral Arterial Disease Rehabilitation: A Summary of the Premier Scientific Symposium
2002	The Acute and Chronic Medical Complications of Diabetes Mellitus
2001	Chronic Obstructive Pulmonary Disease
2001	Epidemiology of Physical Activity and Sudden Cardiac Death
2000	The Effect of Phrenic Nerve Injury and Diaphragmatic Dysfunction on the Mechanics of Breathing Following Coronary Artery Bypass Surgery
2000	The Effects of Orientation Interventions on State-Anxiety in New Phase II Cardiac Rehab Participants

ABSTRACTS:

Oxygen Desaturation During Symptom-Limited Maximal Graded Exercise Tests in Cardiac Patients.
T.M. Arrowood, J.H. Ross, M.J. Berry, FACSM, P.H. Brubaker, FACSM. (To be presented at the American College of Sports Medicine Annual Meeting, St. Louis, MO, May/June, 2002).

A Comparison of Fasting Blood Glucose Values Measured with Cholestech And One Touch Glucometer.
J.H. Ross, P.H. Brubaker, FACSM, T.M. Arrowood.
(To be presented at the American College of Sports Medicine Annual Meeting, St. Louis, MO, May/June, 2002).