***For COPD patients undergoing lung transplant, would pre- and post-transplant pulmonary rehabilitation versus post-transplant pulmonary rehabilitation alone, improve functional outcomes 1-year post-surgery?***

**Introduction**

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the United States.1 This term refers to two lung diseases which often co-exist, chronic bronchitis and emphysema, that are characterized by obstruction to airflow that interferes with normal breathing.1 In the United States alone, 13.1 million adults (aged 18 and over) were estimated to have COPD in 2008.1 COPD leads to decreased physical activity and increased morbidity and disability as well as an economic burden to the healthcare system.1 Common symptoms experienced by COPD patients include chronic cough, increased mucus, frequent clearing of the throat, exercise intolerance, and dyspnea with exertion.1 Smoking is the primary risk factor for COPD followed by occupational exposure to industrial pollutants, heredity, history of childhood infections, and socioeconomic status.1

Lung transplantation (LTx) is an ultimate treatment option for patients with chronic lung diseases whose life expectancy after the intervention is exceeding the predicted survival without treatment.2 Aggressive treatment efforts such as bronchodilator medications, supplemental oxygen, and smoking cessation can improve symptoms, however COPD lung damage is irreversible.1 Once preventative treatments are exhausted, COPD patients are considered for LTx as a last option to improve lung function. One-year survival is between 70% and 80% for both single lung transplantation (SLT) and bilateral lung transplantation (BLT).2 Lung transplantation not only improves lung function in patients with COPD, it provides a better health-related quality of life.

Even though the life expectancy has increased over the years from LTx procedures, survival after transplantation depends on prognostic factors of candidates such as age, underlying diagnosis, and exercise capacity, among others.3 The American Thoracic Society, the American College of Chest Physicians, and the American Association of Cardiovascular and Pulmonary Rehabilitation all recommend exercise training in the treatment and rehabilitation of patients with COPD.4,5 Several studies have examined the use of outcome measures while others have looked at the long-term maintenance of these benefits.6 Despite the fact that exercise training does not affect measures of lung function, compelling evidence demonstrates improved physical function with exercise training.1 The participation in pre-transplant pulmonary rehabilitation is encouraged and often required for patients undergoing such surgeries, with the goals of optimizing quality of life, functional capacity, and overall surgical outcomes.7

Pulmonary rehabilitation is a multidimensional continuum of services directed to persons with pulmonary disease and their families, usually by an interdisciplinary team of specialists, with the goal of achieving and maintaining the individual’s maximum level of independence and functioning in the community.7 Ultimately, pulmonary rehabilitation should result in a better quality of life, increased participation in physical and social activities, and decrease health care use.7 The overall goal of pre-transplant pulmonary rehabilitation is to maximize the advantages derived from the planned surgical procedure.7 In addition, COPD patients can benefit from pre-operative rehabilitation to improve tolerance for surgery, increase ability to clear secretions, and decrease work of breathing as a result of improvement in diaphragmatic function.7 Lastly, pulmonary rehabilitation can contribute to the reduction of post-operative complication rates, improve adherence to exercise regimens, and improve tolerance of the time spend waiting for surgery.7

The purpose of this review of literature is to outline the benefits of pre- and post-lung transplant pulmonary rehabilitation on functional outcomes 1-year post-surgery. Many studies have examined the benefit of lung transplantation on lung function in COPD patients; however, lung transplantation alone does not predict improved physical function 1-year post-surgery. Pre-surgical disease progression as well as exercise capacity contributes to the outcome in COPD patients post-lung transplant. With the support of pulmonary rehabilitation intervention for COPD patients pre-transplant, clinicians will be able to better prepare their clients for surgery and increase their chances of improved outcome 1-year post-transplant.

**Presentation Of The Literature**

Reviews of literature related to the benefits of pre- and post-transplant pulmonary rehabilitation outcomes contained four areas of overlapping information. These themes include inclusion and exclusion criteria, physical activity participation, outcome measures, and short-term vs. long-term exercise programs.

***Inclusion and Exclusion Criteria***

To begin, numerous studies in this review examined the qualifications of COPD patients who were awaiting or who had received lung transplantation. Laporta et al. specifically reviewed the clinical and functional characteristics of patients who were accepted for lung-transplantation.8 COPD patients who were in the advanced stages of their disease most often led to lung transplant when compared to other diagnosis.8 COPD patients had the lowest 6-Minute Walking Distance (6-MWD) scores compared to patients with pulmonary fibrosis or bronchiectasis and 74% of those COPD patients had a BODE index score of 7 or higher which qualified them to be placed on the waiting list for transplant.8 Important criterion for pulmonary rehabilitation and lung transplantation include patient motivation, age, and smoking history or cessation.7 Compliance of patients enrolled in pulmonary rehabilitation is an important determinant on the outcome of physical function and behavioral modification. Some authors debate whether smoking cessation should be a goal of rehabilitation or a prerequisite.7 Patients with other comorbidities, particularly if unstable or symptomatic could interfere with the rehabilitative process; however, patients denied based on criteria related to the surgical procedure can benefit from the referral to pulmonary rehabilitation to potentially improve these reversible factors resulting in reconsideration as surgical candidates upon completion of the program.7

***Physical Activity Participation***

Langer and Brossenbroek both assessed determinants affecting participation in physical activity in lung transplant candidates and recipients.3,9 Langer examined 96 patients awaiting single or double lung transplant over a 4-day period by measuring physical activity, functional exercise capacity, and self-reported function.3 Candidates for lung transplant were markedly inactive in daily life and showed severe reduction in functional exercise capacity and both respiratory and peripheral muscle force.3 When these candidates were compared to COPD patients not listed for lung transplant, they were more sedentary and less anxious or depressed than those not listed.3 One explanation of this may be due to the fact that patients are anticipating improvements in health status after transplantation, therefore candidates are less motivated to improve their outcomes. The strongest determinant of activity behavior was concluded to be functional exercise capacity (6-MWD) among COPD lung transplant candidates.3

Brossenbroek assessed daily physical activity, pulmonary function, and fear and motivation to exercise in COPD patients in which 47 were lung transplant recipients and 15 were lung transplant candidates.9 Results showed that lower body strength was the most important determinant in the difference in daily physical activity in lung transplant recipients compared to candidates.9 Overall, lower body strength, pulmonary function, and number of months after transplantation contributed significantly to a higher daily physical activity level in lung transplant recipients.9 In addition to Langer’s conclusion of lack of motivation in candidates3, Brossenbroek found that recipients who were not physically active prior to lung transplant had poor outcomes resulting in the inability to establish an active lifestyle or death9. To sum up, determinants affecting participation in physical activity highly correlate with the functional outcome post-transplant in COPD patients who do or do not participate in pre-transplant exercise programs. Therefore, pulmonary rehabilitation can benefit COPD candidates for lung transplant by identifying modifiable risk factors of sedentary behavior and increasing daily activity participation, resulting in better outcomes post-transplant.

***Outcome Measures***

Functional exercise capacity, health related quality of life (HRQoL), and lung function measures were the main outcome measures used within the literature. Functional exercise capacity was by far the strongest determinant measure of outcome in patients with COPD either awaiting lung transplant or who received lung transplant. The 6-MWD was the most common measure of functional exercise capacity used by Langer, Troosters, Laporta, and Berry.3,6,8,1 Troosters and Berry found similar gains in 6-MWD scores post-outpatient exercise programs >3 months in duration which helped forstall early morbidity and mortality as well as improved long-term benefits.6,1 Langer and Laporta used pre-transplant 6-MWD scores as a determinant in decreased physical activity and poor outcomes in disease progression.3,8 Overall the 6-MWD was the largest determinant in the outcome of functional exercise capacity in COPD patients either pre- or post-transplant.

The use of outcome measures, such as the 6-MWD, can greatly benefit patient interventions developed in pre-transplant pulmonary rehabilitation. Enfield et al. evaluated the relationship between 6-MWD and survival in a cohort of patients with severe COPD who participated in inpatient pulmonary rehabilitation.11 Results demonstrated that inpatient pulmonary rehab significantly increased 6-MWD with a mean change of 86.39 meters.11 Limited exercise capacity is the hallmark of disability in patients with COPD and is associated with poor HRQoL, increased morbidity, and higher mortality.11 Therefore, this study demonstrates that increased post-6-MWD and amount of change in 6-MWD from pre- and post-inpatient pulmonary rehabilitation improves survival rates in patients with severe COPD.11

Martinu et al. specifically assessed the effect of baseline 6-MWD pre-lung transplant on survival rate in 176 transplanted patients (48% COPD).12 Results indicated greater than 50% reduction in mortality during the 28-month follow-up period for every 500-foot increment in the baseline 6-MWD.12 This study collectively found that the 6-MWD is a useful measure of both urgency and utility among patients awaiting lung transplantation.12 Patients with higher walk distances pre-transplant might have an enhanced ability to fully participate in postoperative pulmonary rehabilitation leading to reduced atelectasis, improved muccocillarly clearance, and increased reserve should complications develop.12

HRQoL measures including Chronic Respiratory Disease Questionnaire,6 Hospital Anxiety and Depression Scale (HADS),3,10 SF-36,3 Questionnaire to Assess Health-enhancing Physical Activity (SQUASH),9 Exercise Self-Regulation Questionnaire (SRQ-E),9 and Borg Dyspnea and Borg Leg Fatigue Scores3 were taken in listed studies. Lung function measures most commonly taken using spirometry, others including FEV1, FVC, TLC, CO2 output and O2 input.

***Short-term vs. Long-term Exercise Programs***

In the comparison of Arnardottir, Troosters, and Berry, each study examined the effects of short- and long-term training programs.10,6,1 Arnardottir et al. compared two groups who were each trained 8 weeks 2x/week, (A) exercise program including endurance and resistance training, and calisthenics, and (B) exercise program including endurance and calisthenics.10 Results indicated that group A had increased exercise capacity (12-MWD) at 6-months and baseline 12-MWD at 1-year post training, group B was below baseline at 1-year follow-up.10 Conclusions indicate that short-endurance training slowed the decline for functional exercise capacity for 1-year, which supports the use of exercise programs for patients with COPD awaiting lung-transplantation.

Troosters et al. examined short- and long-term effects of a 6-month outpatient training program (3x/week 1st 3 months, 2x/week 2nd 3 months) compared to usual care (control) in 70 patients with COPD.6 Training group was measured for exercise capacity (6-MWD) and HRQoL at baseline, 6 months and 18 months post-training.6 Results showed the improved 6-MWD, max O2 uptake, and increased muscle force and QOL at 6-months, with benefits of training persisting for 12 months after training program ended (measured at 18 months).6 Conclusions from this study indicate that a long-term exercise program can have persistent benefits for LTx candidates who have longer waiting periods. The improvement of baseline functional exercise capacity prior to LTx can increase their pulmonary function post-transplant.

In addition, Berry et al. conducted a randomized control trial comparing short- (3 months) and long-term (18 months) exercise in 140 patients with COPD.1 All subjects completed the short-term program, while only 70 subjects continued with the long-term program.1 The long-term intervention group reported 12% less disability, walked 6% farther during 6-MWD, climbed steps 11% faster, and completed overhead tasks 8% faster than the short-term group.1 Conclusions from this study indicate that the early identification and intervention in patients with COPD is needed to prevent or forstall morbidity and mortality while awaiting for lung-transplantation. Therefore, pre-transplant pulmonary rehabilitation can benefit individuals with decreased functional exercise capacity to increase their chances of improved outcome post-surgery.

Lastly, Serres and Reinsma examined the effects of improved skeletal muscle performance and force post-exercise training programs before and 1-year after lung transplantation.13,14 Serres et al. specifically determined whether patients with COPD were able to achieve a peripheral training effect after an individualized exercise training program.13 A control group participated in physical therapy 1 hour/day for 3 weeks, and a training group participated in 1 hour/physical therapy, 50 minutes of cycling, and 1 hour/walking outside for 6 days/week for 3 weeks.13 The training group increased exercise tolerance, maximum voluntary contraction of quads, and critical power. Conclusions indicate that after training, greater muscle strength and endurance is achievable in patients with COPD, which suggests better recruitment and improved oxidative capacity in the exercising muscles. Reinsma et al. specifically evaluated maximal exercise capacity and peripheral muscle force before and 1-year post-transplant.14 Post-LTx, patients showed improved exercise capacity and muscle force with limited exercise instruction.14 It was concluded that the early presence of peripheral muscle weakness contributes to the limitation of exercise capacity and reflects a peripheral deficit post-LTx.14 Therefore, it can be concluded from this study that the improvement of peripheral skeletal muscle strength and endurance can improve post-LTx outcome with the addition of improved lung function secondary to transplantation.

**Discussion**

In the review of literature comparing the effects of pre- and post-transplant pulmonary rehabilitation vs. post-transplant pulmonary rehabilitation alone and the affect on outcomes 1-year post lung transplant in patients with COPD, several conclusions were determined. Within the evidence presented, pre- and post-lung transplant pulmonary rehabilitation suggests better outcomes 1-year post-surgery in patients with COPD. With the examination of improved skeletal muscle recruitment, increased exercise capacity, long-term maintenance of training benefits, and reduction of post-transplant decline, pulmonary rehabilitation shows positive influence on survival and functional outcomes 1-year post-surgery.

**Limitations Of The Evidence**

There were several common limitations mentioned throughout the evidence related to the research question at hand. However, the most common limitation mentioned was the effect of sample size related to drop out rates and compliance, which had influences on the studies’ external validity. One study had 14 drop outs in the training group and 8 drop outs in the control group with no justification or explanation, therefore those who complied the most had the greatest improvements.1 The second study had two groups of 50, a control and training group, in which the final numbers were 37 subjects in the training group and 33 in the control group.6 Drop outs occurred due to refusal of testing, refusal of participation in training, refusal of follow-up, and death.6 Third, of the original 63 subjects included in the study separated into 2 groups (n=42, n=21), 21 subjects did not complete the study, 10 due to exacerbation, 8 due to lack of motivation or psychological problems, and 3 due to back pain.10 During the follow-up an additional 10 subjects dropped out, 3 subjects died, 1 moved, and 6 got other serious diseases.10

**Recommendations For Additional Research**

Studies that included exercise programs with lower intensity suggested that other studies be conducted with higher intensity to determine the effects of long-term benefits of resistance training.10 Other studies suggested that duration was a factor to be further examined based on intensity level due to their use of high intensity but shorter duration.6 Several studies mention the importance of examining other factors related to physical activity participation including environmental or behavioral factors such as expected health benefits, self-efficacy, social support, and access to facilities.3 Lastly, additional research should aim to examine larger sample groups of patients with COPD and the relation to supplemental interventions along with already examined exercise interventions.1

**Clinical Conclusions**

COPD is the third leading cause of death in the United States.1 With the continued research and interventions for patients with COPD, this disease can hopefully be better prevented, maintained, and treated. As physical therapists, or other allied health professionals, participating in pulmonary rehabilitation, it is vital to understand the importance of improving functional outcomes in patients with lung disease. Specifically for patients with COPD awaiting lung transplantation, the improvement of baseline functional exercise capacity can improve survival rates post-transplant.12 Providing individualized training programs for LTx candidates and monitoring functional outcomes can help determine future benefits. Targeting the improvement of skeletal muscle recruitment and exercise capacity during a long-term (>3-months) pulmonary rehabilitation intervention can not only improve quality of life, but also increase quantity of life 1-year post-lung transplantation in patients with COPD.

One could use the conclusions of this literature review to supplement a Capstone project focusing on similar determinants affecting outcomes post-lung transplantation. An example of another comorbidity effecting functional outcomes post-transplant is osteoporosis. Osteoporosis is common in advanced COPD and worsens rapidly after transplantation.15 Increased high-density lipoprotein cholesterol (HDLc) has been observed in patients with COPD and linked with osteoporosis in the general population.15 This association could be further examined in the literature to determine the effects of health outcomes and quality of life post-lung transplantation.

**References:**

1. Berry MJ, Rejeski WJ, Adair NE, Ettinger WH, Zaccaro DJ, Sevick MA. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation*. 2003; 23: 60-68.
2. Lahzami S, Bridevaux PO, Soccal PM, et al. Survival impact of lung transplantation for COPD. *Eur Respir J*. 2010; 36: 74-80.
3. Langer D, Cebria i Iranzo MA, Burtin C, et al. Determinants of physical activity in daily life in candidates for lung transplantation. *Respir Med*. 2012;106(5):747-754. doi: 10.1016/j.rmed.2012.01.003.
4. American Thoracic Society. Standards for diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1995; 152: S77-S152.
5. American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation Pulmonary Rehabilitation Guidelines Panel. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Panel. *Chest*. 1997; 112: 1363-1396.
6. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: A randomized trial. *Am J Med*. 2000; 109: 207-212.
7. Takaoka ST, Weinacker AB. The value of preoperative pulmonary rehabilitation. *Thorac Surg Clin*. 2005; 203-211.
8. Laporta R, Ussetti P, Mora G, López C, Gómez D, de Pablo A, Lázaro MT, Carreño MC, Ferreiro MJ. Clinical and functional characteristics of patients prior to lung-transplantation: report of experience at the Clínica Puerta de Hierro. *Arch Bronconeumol*. 2008; 44(8): 424-7.
9. Brossenbroek L, ten Hacken NH, van der Bij W, Verschuuren EA, Koeter GH, de Greef MH. Cross-sectional assessment of daily physical activity in chronic obstructive pulmonary disease lung transplant patients. *J Heart Lung Transplant*. 2009;28(2):149-155. doi: 10.1016/j.healun.2008.11.905.
10. Arnardottir RH, Sorensen S, Ringqvist I, Larsson K. Two different training programs for patients with COPD: A randomized study with 1-year follow-up. *Respir Med*. 2006;100(1):130-139. doi: 10.1016/j.rmed.2005.03.043.
11. Enfield K, Gammon S, Floyd J, Falt C, Patrie J, Platts-Mills TA, Truwit JD, Shim, YM. Six-minute walk distance in patients with severe end-stage COPD. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2010; 30: 195-202.
12. Martinu T, Babyak MA, O’Connell CF, Carney RM, Trulock EP, Davis RD, Blumenthal JA, Palmer SM. Baseline 6-min walk distance predicts survival in lung transplant candidates. *American Journal of Transplantation*. 2008; 8: 1498-1505.

1. Serres I, Varray A, Vallet G, Micallef JP, Prefaut C. Improved skeletal muscle performance after individualized exercise training in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil*. 1997;17(4):232-238.
2. Reinsma GD, ten Hacken NH, Grevink RG, van der Bij W, Koeter GH, van Weert E. Limiting factors of exercise performance 1 year after lung transplantation. *J Heart Lung Transplant*. 2006;25(11):1310-1316. doi: 10.1016/j.healun.2006.08.008.
3. Reed RM, Wise RA, Dobs AS, Lechtzin N, Girgis RE. Elevated HDL cholesterol levels are associated with osteoporosis in lung transplant candidates with chronic obstructive pulmonary disease. *Respiratory Medicine*. 2010; 104: 1943-1950.