THE COMBINED EFFECT OF TIOTROPIUM AND FORMOTEROL ON THE FUNCTIONAL STATUS OF PATIENTS WITH MODERATE-TO-SEVERE COPD

by

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This has been a long journey and a personal quest in my life. Early in my nursing career I would occasionally remark that I would “never get my Ph.D. in nursing”. But as life and passing time prove, many changes occur along the way, and you often regret hasty comments. It has been an interesting trek with many twists and turns culminating to this final and terminal degree. I am much wiser for this experience and hope to give back what I have learned over a lifetime career in many different nursing roles.

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volunteered for my study and helped me complete my research. Without them this dissertation would not be possible.

“No matter where you are in life, there is always more journey ahead.”

Nelson Mandela

On to my next adventure…

April 19, 2010

ABSTRACT

THE COMBINED EFFECTS OF TIOTROPIUM AND FORMOTEROL
ON THE FUNCTIONAL STATUS OF PATIENTS WITH
MODERATE-TO-SEVERE COPD

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This double blinded placebo controlled pilot study examined the use of combined inhaled medication for patients with moderate-to-severe COPD. The inhalation of formoterol versus placebo was studied when combined with the routine use of tiotropium. Maximizing bronchodilitation through the use of combination inhaler therapy is felt to be superior to the use of a single inhaled medication, yet few studies are found in the literature. Currently the Global Initiative for Obstructive Lung Disease (GOLD) recommends the use of combination inhaled therapy in patients with moderate-to-severe COPD.

This study of 18 patients with moderate-to-severe COPD measured the effects on the functional status of patients as determined by FEV_1 and FVC via spirometry, the distance walked during a six-minute walk test, and the patients' perception of dyspnea and fatigue via the Modified Borg Scale. *Statistically* significant improvement was demonstrated in all measures except the Modified Borg Scale. *Statistically* significant spirometric changes of both the FEV_1 and FVC

occurred, but were not increased by the 12% and 200 mL change stated as *clinically* significant by the American Thoracic Society. One patient was found to have a clinically significant change in FEV_1, and five patients obtained clinically significant changes in their FVC with formoterol. The distance walked in six-minutes was found to be *statistically* significant, but did not achieve the commonly accepted *clinically* significant change of 35 meters. Only two patients were able to walk a clinically significant distance after inhaling formoterol. Demographic data was not found to identify discerning characteristics that would be beneficial for distinguishing which patients benefitted most from the combined therapy.

This study found improvements in both the six-minute walk test and in spirometry that were *statistically* but not *clinically* significant. Subjective dyspnea and fatigue with the use a Modified Borg Scale was not found to be statistically significant. It is recommended that patients continue to take the combined therapy of formoterol and tiotropium until research contradicts this evidence. More research is needed to ascertain the best measurement of functional status for patients with COPD and to identify which patients will benefit from combination therapy.

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CHAPTER 1

INTRODUCTION

Dyspnea is the hallmark symptom of chronic obstructive pulmonary disease (COPD). The American Thoracic Society (ATS) (1999) defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”. In other words, dyspnea means shortness of breath. Patients with COPD experience symptoms of dyspnea with physical exertion and, in the later stages of the disease process, become dyspneic even at rest. Dyspnea occurs secondary to a mismatch between the central nervous system motor command and the incoming afferent information from airway, lung and chest wall receptors (Mahler, 2007). The pathophysiology involves primarily expiratory airflow limitation but patients report inspiration is more difficult than exhalation (Mahler). As the disease progresses, dyspnea intensifies and the patients’ ability to perform daily activities diminishes as does their quality of life.

Inhaled bronchodilators (beta agonists and/ or anticholinergics) are the current national and international choice for first-line therapy for COPD because they directly relax airway smooth muscles and improve symptoms (Hanania & Donohue, 2007). The degree of improvement, however, has been based on relatively few studies using primarily spirometry as the evaluative measurement. Spirometry measures the patient’s Forced Expiratory Volume in one second (FEV_1) and generally has only a weak correlation with symptoms of dyspnea or functional status—the two outcome measures for drug therapy. Functional status encompasses four dimensions which include functional capacity, performance, reserve and capacity utilization (Leidy, 1994; Wang, 2004). Functional capacity is defined as the maximum potential to perform

physical activity at a standardized level (Wang, 2004); performance is the ability to perform the physical activity required for daily living; reserve is the difference between capacity and performance; and capacity utilization is the "extent to which capacity is called upon in the selected level of performance" (Leidy, 1994).

Background and Significance

In the year 2000, COPD accounted for approximately 1.5 million emergency department visits and 726,000 hospital admissions (NHLBI, 2003). The direct and indirect cost for the year of 2002 was $32.1 billion (NHLBI, 2003). COPD is dramatically under-diagnosed in at-risk patients, and more than 12 million adults in the U.S. are identified as having the disease. It is estimated that approximately 24 million have symptoms of the disease without the benefit of a diagnosis (ALA, 2005). COPD is the fourth leading cause of death in the United States, accounting for approximately one in 20 deaths in 2005. With approximately 126,005 individuals dying from this disease in 2005, COPD is the only major chronic disease with an increasing mortality rate (CDC MMWR, 2008).

COPD is a chronic disease that slowly progresses over time and gradually diminishes functional status. This was demonstrated in a national survey of patients conducted by the American Lung Association (2001). The findings showed that 44% of patients were breathless while washing and dressing, and 46% were dyspneic while performing light housework. Close to 60% of the patients admitted to being short of breath every day, and 70% felt limited in their usual physical exertion. COPD profoundly impacts the quality of life.

In clinical practice, symptomatic patients will typically seek health care when approximately 50% of their lung function is lost. Using spirometric staging, this means patients will be classified with moderate-to-severe COPD at first diagnosis. Because there is no cure for COPD; the primary goal of care is to maximize the functional status by pharmacologic management. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines (2008) (Table A.1) developed by the National Institutes of Health and the World Health

Organization, give the health care provider a stepwise approach to pharmacologic management, which primarily involves inhaled medications. The first step is to start with a short acting bronchodilator (usually a short acting $beta_2$ agonist) for relief of intermittent symptoms. The next step is to add a long acting bronchodilator, which in current practice is a long acting anticholinergic agent such as tiotropium. If symptoms persist, a long acting $beta_2$ agonist should be added, and lastly an inhaled corticosteroid.

Combining inhaled medications from two different classes such as anticholinergics and $beta_2$ agonists is considered to be superior to solo medication even though few studies have been done to support this practice. For example, the GOLD guidelines, derived by consensus of pulmonary experts, are based on just 15 published double-blind placebo controlled studies. The majority of studies used changes in pulmonary function tests as the primary outcome measurements with a variety of other measurements used for assessing functional status. Only three of the 15 studies included a six-minute walk test to evaluate the functional change in performance that occurred with inhaled medications and only one study measured the effect of combination therapy of long acting beta agonists and anticholinergic while assessing a six-minute walk test.

All bronchodilators increase performance to varying degrees, but that may or may not correlate to a significant change in spirometry (GOLD, 2008). That is, performance may increase and perception of dyspnea may decrease—even when significant changes in spirometry are not demonstrated.

As an example, Vogelmeier et al. (2008) evaluated combined inhaled therapy with an anticholinergic agent plus a long acting $beta_2$ agonist by using a six minute walk test. The six minute walk test was performed at the beginning of the study and after 24 weeks of therapy. Formoterol, tiotropium and the two combined were studied and compared with placebo. All treatments were statistically superior to placebo in terms of the primary endpoint, which was the FEV_1 two hours post-dose after 24 weeks of therapy. The change in FEV_1 necessary to meet the standard for reversibility or significant bronchodilitation requires a change of 12% and 200

milliliters (Pellegrino et al., 2005), and this change was not demonstrated between the groups other than when they were compared with the placebo group. The six minute walk test was statistically significant, by 17 meters (56 ft) with combination therapy as compared to placebo. Whether this translates into a functional improvement in symptoms is questionable. This distance of 17 meters was considerably lower than the distances reported to be clinically significant by Puhan et al. (2009) and Redelmeier et al. (1997) i.e., 35 meters (115.5 ft) and 54 (178.2 ft) meters respectively.

Framework

The framework that guides this dissertation is based upon the disease state of COPD and the functional status of patients as defined by Weaver, Richmond & Narsavage (1997) (Appendix B.1) and Yeh, Chen, Liao & Liao (2004) (Appendix C.1). Both groups of authors published their concepts of functional status models but for reasons to be described, it is a combination of each of these studies that most appropriately represents this disease. Multiple variables that influence functional status were identified by Weaver and Narsavage in 1992, with a secondary analysis yielding a new explanatory model of functional status (Weaver et al., 1997). The purpose of Weaver's study was to verify and extend prior work concerning functional status and to develop a model that more comprehensively reflected the factors specific for COPD. A sample of 104 patients with COPD were included in the study and informational data collected by the use of demographic and specialized questionnaires, spirometry, dyspnea subscale from the Pulmonary Functional Status Scale, oximetry, and a 12 minute walk test. A Pulmonary Functional Status Scale was utilized to measure six different domains of functional status e.g., self-care, transportation, household tasks, grocery shopping, meal preparation and relationships. Other questionnaires focused on a Self-Esteem Scale and a Multiple Affect Adjective Check List Revised (MAACL-R) for psychological evaluation.

After eliminating several extraneous variables by statistical multiple regression analysis, only the variables that were statistically significant ($p < 0.05$) and with beta weights greater than

0.05 were kept in the final model. Excluded were variables of length of illness, age and oxygen desaturation with exercise. Functional status was an inter-play between identified physiological and psychological variables as shown in Appendix B.1 Authors Weaver et al. concluded that if functional status was to be improved with COPD, the focus needed to be on interventions that influenced performance, dyspnea, anxiety, and depressed mood.

A limitation to the model by Weaver et al. (1997) is the unfortunate omission of fatigue because it is a major symptom of COPD. Fatigue was later added to the model by Yeh et al. (2004), (Appendix C.1) who extended Weaver's model to test their hypothesis for functional status. In their study, 138 individuals were included and data was collected using questionnaires, a 6-minute walk test and spirometry obtained from prior medical records. Study instruments included a Functional Performance Inventory (FPI) developed by Leidy in 1999 and translated into Chinese, The Hospital Anxiety and Depression Scale (HADS) by Zigmond and Snaith (1983) to evaluate negative moods, and the SF-36 by Ware and Sherbourne (1992) to evaluate health perception and fatigue in patients. A Borg Scale was used to evaluate perceived dyspnea. Yea et al. found age to be related to exercise tolerance and functional performance but unrelated to the other variables. Also, fatigue and exercise tolerance showed no significant relationship.

Unlike Weaver et al. (1997), Yeh et al. (2004) found age to be an important variable, but the age range in the study was large—from 35 to 89 years of age. Yea et al. study utilized a convenience sample from a teaching medical hospital in Taiwan that included younger patients who potentially had a genetic deficiency of alpha-1 antitrypsin or a history of asthma. Neither one is representative of the general population because COPD is typically manifested in the fifth and sixth decade of life.

In summary, functional status is a multifaceted concept involving multiple components as indicators of health status that vary according to different disease states. For patients with moderate-to-severe COPD, the severity of disease and dynamic hyperinflation, manifested, in part, by symptoms of dyspnea and fatigue, is the reason for the classification of prescribed medications i.e., inhaled bronchodilators. The bronchodilators used in this study have no

influence on anxiety or mood, and so the psychological aspects from Weaver et al. (1997) and Yea et al. (2004) models, which included anxiety, self-esteem, depressed mood, negative mood and health perception, were eliminated from this model.

The goal is to relieve symptoms that interfere with activities of daily living and improve the functional status of patients. Therefore, the model for this dissertation has included only those specific components of functional status as described by Leidy (1995), Weaver et al. (1997) and Yeh et al (2004) that appear (at this time) to be the more relevant for patients with COPD. Dynamic hyperinflation is represented in the model because of its significance to functional status but due to technical difficulties inherit in clinical measurement, it is beyond the scope of this pilot study.

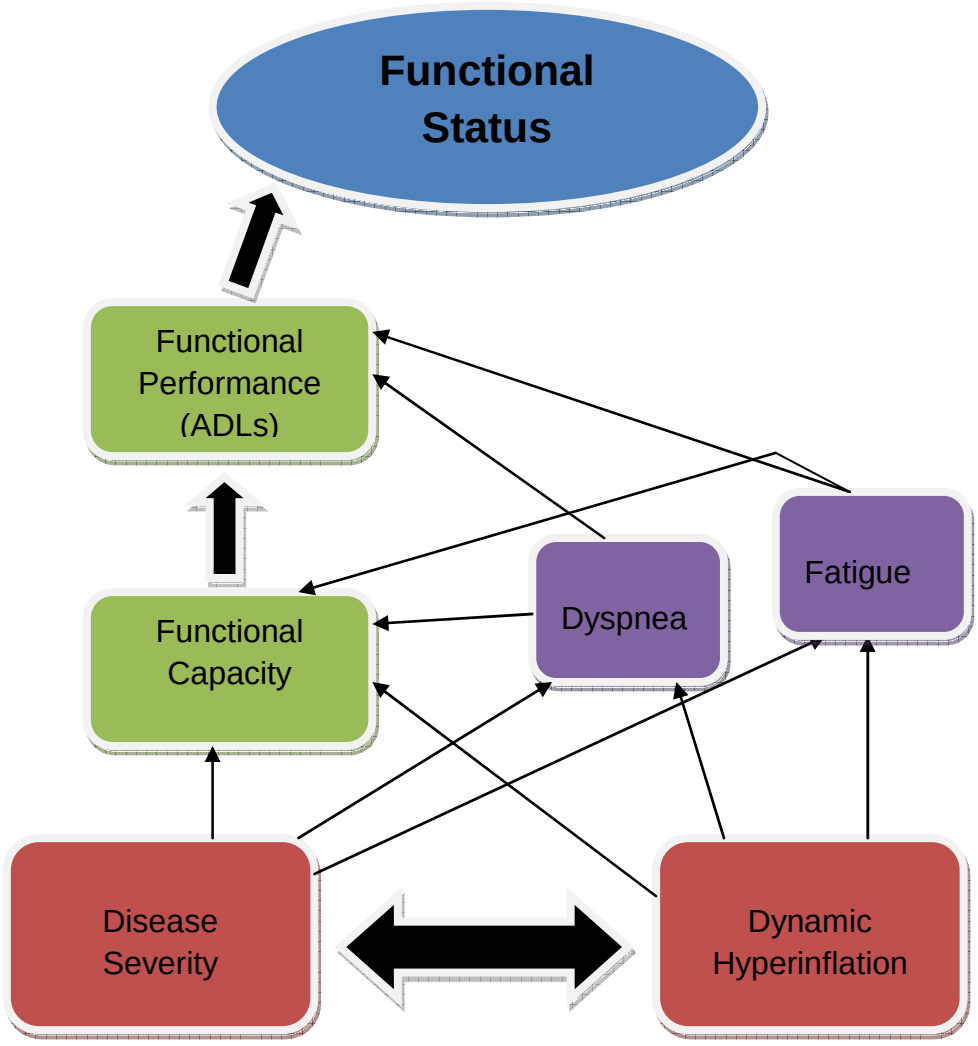

Figure 1.1. Functional Status Model

Purpose

The proposed study is to evaluate the combined effect of tiotropium and formoterol on the functional status of individuals with moderate-to-severe COPD. The two primary goals of drug

therapy that are most directly associated with improved functional status are improvements in functional performance and reduction in the perceptions of dyspnea.

Study Hypotheses

Patients with moderate-to-severe COPD will show significant improvements in functional status as measured by the six minute walk test and/or spirometry after the addition of inhaled formoterol to their current inhaled tiotropium therapy. Patients with moderate-to-severe COPD will show significant reduction in the perception of dyspnea and the perception of fatigue as measured by the Modified Borg Scale after the addition of inhaled formoterol to their current inhaled tiotropium therapy.

Assumptions

Dyspnea is a cognitive/perceptual variable rather than a physiologic one. The level of dyspnea is widely variable in patients with similar levels of lung function. Functional capacity, performance and status are interrelated. Improved functional status is a desired goal for patients with COPD.

Summary

Patients with COPD experience a diminished functional status due to the nature of their disease. Dyspnea limits activities of daily living and decreases performance. Interventions to improve functional status are important, but very few studies have been published using combined long acting bronchodilators. Functional performance is more accurately assessed by an additional standard six-minute walk test rather than spirometry alone.

CHAPTER 2

REVIEW OF LITERATURE

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation, chronic inflammation, and a range of pathologic changes that are not completely reversible (GOLD, 2008). The pulmonary system is primarily involved but extra-pulmonary effects and comorbidities may also exist e.g., skeletal muscle wasting, and lactic acidosis. COPD develops from the persistent exposure of the airways (bronchi and bronchioles) and lung parenchyma (alveoli) to inhaled noxious particles or gases. The most common risk factor for COPD is cigarette smoking, present in 85% of the cases, with the remaining percent attributed to other environmental exposures and/or genetic predispositions i.e. alpha-1 antitrypsin deficiency (Croxton et al., 2003).

Traditionally, chronic obstructive bronchitis and emphysema have been the two disorders associated with COPD; each disorder indicative of pathophysiologic changes in distinct anatomic areas of the lungs—airways and lung parenchyma respectively. However, since many patients have overlapping features of both, the terms (chronic bronchitis and emphysema), are now discouraged for the more encompassing term COPD. The purpose is to facilitate consistency in the early diagnosis of airflow limitation, irrespective of the involved site(s), so the appropriate therapy (inhaled bronchodilators) will be prescribed in a timely and uniform manner (Croxton et al., 2003). Although not curable, current therapies reduce symptoms and improve quality of life, and if the noxious agents such as cigarette smoking are discontinued early, progressive lung

destruction will be markedly diminished or eliminated. With few exceptions COPD is “preventable and treatable” (Celli, 2008).

Pathogenesis of COPD

Chronic inflammation occurs throughout the pulmonary system. The two prevailing hypotheses which account for the inflammation are (1) an oxidant/antioxidant imbalance and (2) a protease/antiprotease imbalance (Croxton et al., 2003). Cigarette smoke, for example, releases reactive oxygen species (free radicals) that if not adequately detoxified will directly or indirectly damage cells especially the respiratory epithelium (Figure 4). Normally the lung contains adequate amounts of antioxidants to keep oxidative damage to a minimum but should antioxidant mechanisms become depleted, tissue damage can occur. Cigarette smoke alone contains more than 10^{14} free radicals per puff (Jones & Metcalf, 2007). Obviously this poses tremendous oxidative stress to cells. The physiologic response is the accumulation and activation of inflammatory immune cells—particularly the neutrophils and macrophages but also the CD4+ and CD8+ lymphocytes. Combined, these immune cells release a variety of proteolytic enzymes and chemical mediators which initiate and/or exacerbate tissue damage. Examples include: elastase, metalloproteinases, TNF-α, interleukins, chemotactic and growth factors. Neutrophils and macrophages are even potent producers of free radicals.

The protease/antiprotease imbalance, aided and supported by imbalance of oxidants and antioxidants, is considered to account for the destruction of the connective tissue within the alveolar walls. Elastin and other structural proteins are the principle components of the elastic fibers. Should these proteins become destroyed by proteolytic enzymes released by neutrophils and macrophages the result will be loss of elastic recoil, airway collapse, and carbon dioxide retention (MacNee, 2007).

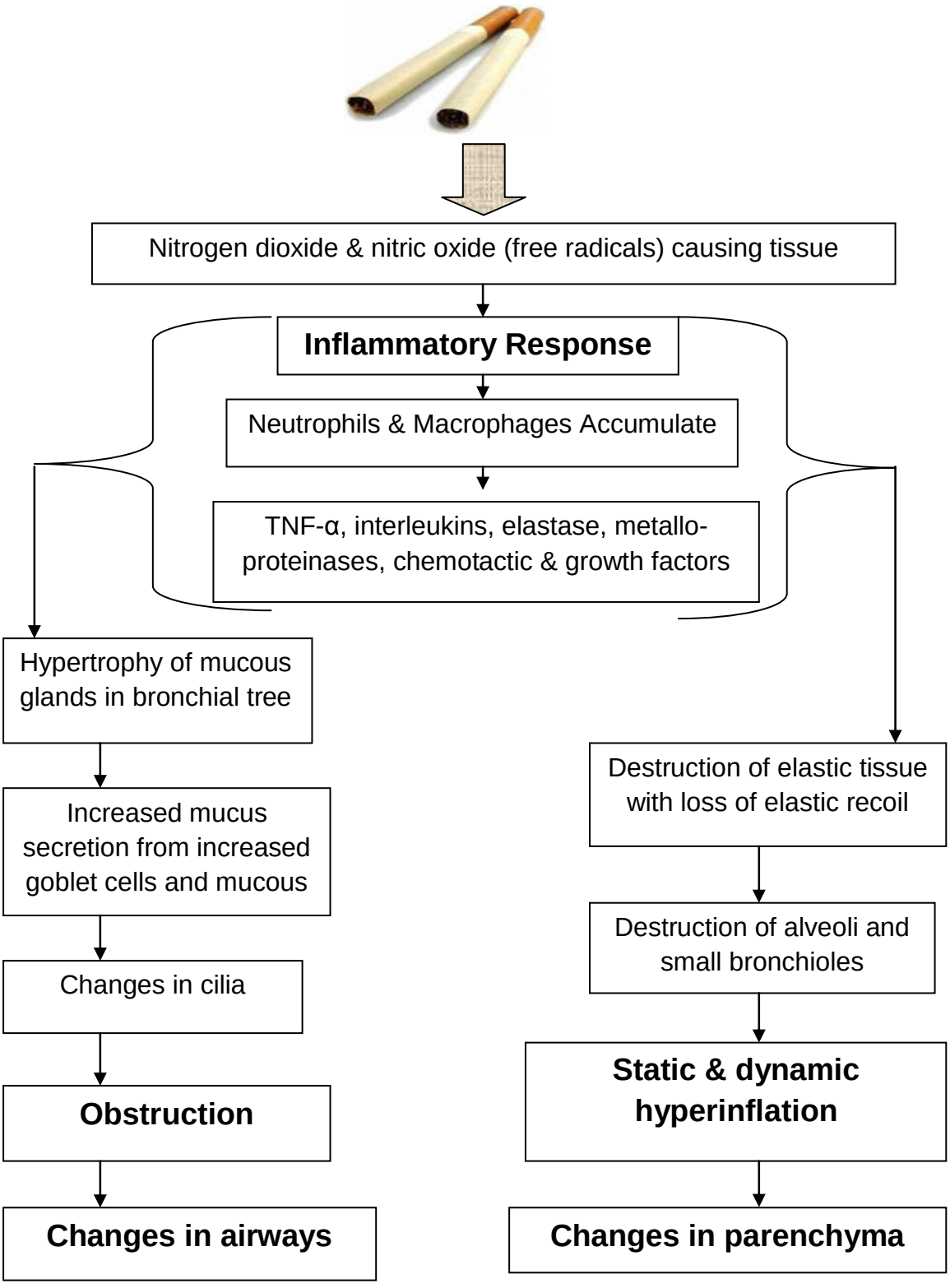

Figure 2.1. Pathophysiologic changes of COPD.

Pathophysiologic Changes of COPD

Pathophysiologic changes resulting from chronic inflammation, recurrent injury, and repair mechanisms may be found in the central airways, peripheral airways, lung parenchyma (alveoli) and pulmonary vasculature (Celli et al., 2004). Depending on the anatomic site(s) and the extent of disease, the physiologic changes may vary. These will be briefly addressed relative to (1) changes in the airways, and (2) changes in the parenchyma. Physiologic changes in the airways include mucus hypersecretion, ciliary dysfunction, and airflow limitation secondary to obstruction. Airways are compromised by hypertrophy of the mucous glands and goblet cells in the bronchial tree in areas greater than 2 mm in diameter. Smoking, for instance, decreases the number and length of cilia and disrupts their effectiveness in clearing mucus from the airways.

Destruction of the parenchyma involves the airspace walls of the alveoli and the smaller bronchioles that become distended and enlarged. This process may be thought of as similar in effect to pouring bleach onto a sponge and watching it dissolve. Loss of alveolar attachments and numerous alveoli leads to the loss of elastic recoil, air trapping, impaired gas exchange, and airflow limitation (GOLD). The primary abnormality is a decrease in the maximal expiratory flow rate (Niewoehner, 2007). Two major processes considered to be responsible are a decrease in the elastic recoil of the lung (as with parenchymal destruction) and restriction to airflow in the bronchi and bronchioles due to airway narrowing (as with airways disease). Airflow limitation or obstruction is believed to be responsible for hyperinflation and uneven ventilation (Niewoehner, 2007).

Static Hyperinflation from Destruction of Alveoli and Small Airways

Destruction of the alveolar walls and damage to the surrounding connective tissue leads to a loss of lung elastic recoil and associated airway tethering (Mason, 2005). Loss of the alveolar-bronchiolar attachments may progress to collapse of the involved airways, particularly during exhalation (Jeffery, 2001). The elastic recoil of the lung refers to the “intrinsic tendency to

deflate after it has been inflated" (Niewoehner, 2007). Lung elastic recoil is diminished with normal aging and is also reduced with COPD (Niewoehner, 2007). As the elastic recoil of the lung is lost, a premature collapse of the airways in mid exhalation leads to air trapping (Doherty, 2004).

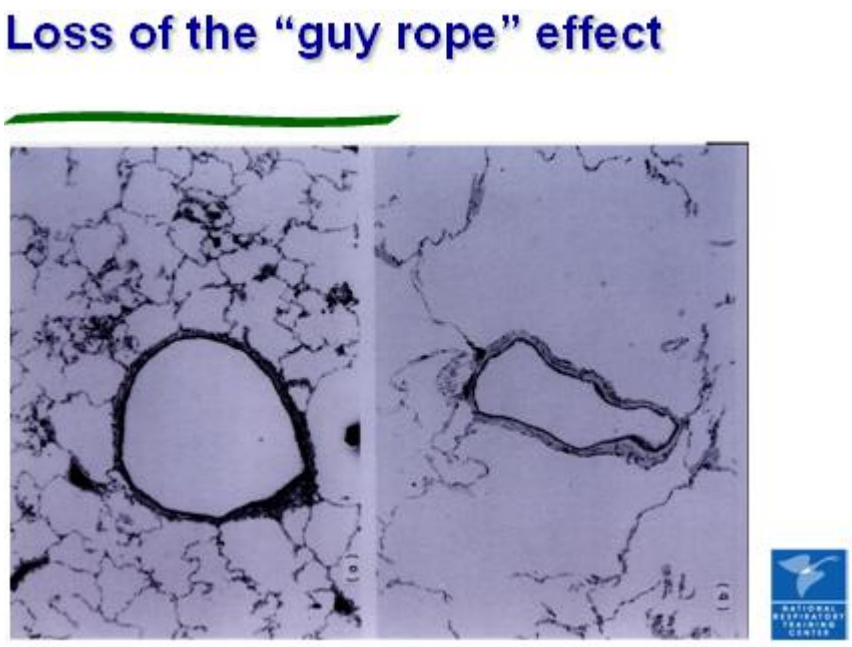

Figure 2.2. Loss of "guy rope" effect. (National Respiratory Training Center, n.d.).

Static hyperinflation is a consequence of air trapping, and is an important physiologic abnormality in patients with COPD (Niewoehner, 2007). Loss of elastic lung recoil and increased peripheral airway resistance are interrelated, leading to an increase in static lung volumes, with resultant hyperinflation (Niewoehner, 2007). Simply stated, emphysema is a destructive process, with many of the structural proteins being dissolved by neutrophil elastase and other proteases (Barnes, 2000). This leads to loss of the "guy rope effect" as seen in Figure 2.2, with resultant airway collapse and increased resistance to airflow. Additionally, loss of these structural proteins means that a lung stretched to its maximum size loses the force that normally tends to drive the

lung back to its normal resting state; much like a rubber band that has been overstretched loses its ability to snap back to its original size. This is referred to as loss of elastic recoil. The lung loses its tendency to return to a normal resting size and when combined with collapsed airways resist air exiting. Air is trapped in the lung, causing the lung volumes to increase.

Normal Lung Volumes and Changes with COPD

Figure 2.3 illustrates normal lung volumes determined by spirometry and plethysmography. Brief definitions of each of the important normal lung volumes are included.

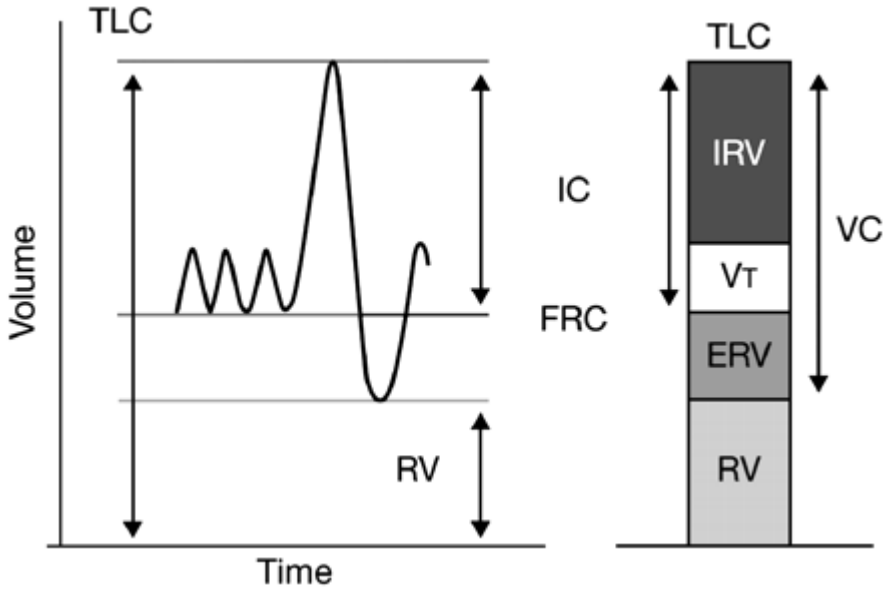

Figure 2.3. Normal lung volume measurements
Illustration from Ferguson, G.T. (2006) & definitions from Cherniack, R.M. (1977).

Normal inspiration and exhalation (tidal breathing or tidal volume V^T) is shown by the three breaths on the left side of the graph. Spirometry cannot measure total lung capacity (TLC), functional residual capacity (FRC) or residual volume (RV). These three measurements can only

be obtained by complete pulmonary lung function testing or plethysmography. Inspiratory capacity (IC) is inversely related to functional residual capacity (FRC).

FRC = functional residual capacity = ERV + RV

IRV = inspiratory reserve volume = the maximal volume of air that can be inhaled, over and above the tidal volume.

ERV = expiratory reserve volume = the maximum volume of air that can be exhaled beyond the functional residual capacity.

Figure 2.4 illustrates the concepts of static and dynamic hyperinflation. Note the left-most border of the rectangles illustrating typical lung volumes at rest in healthy individuals and in patients with COPD. In this portion of the diagrams, end-expiratory lung volume (EELV) is equivalent to functional residual capacity (FRC). Note that in the resting patient with COPD, the EELV is significantly increased, the inspiratory capacity (IC) is diminished, and the total lung capacity (TLC) is supra-physiologic. This is static hyperinflation.

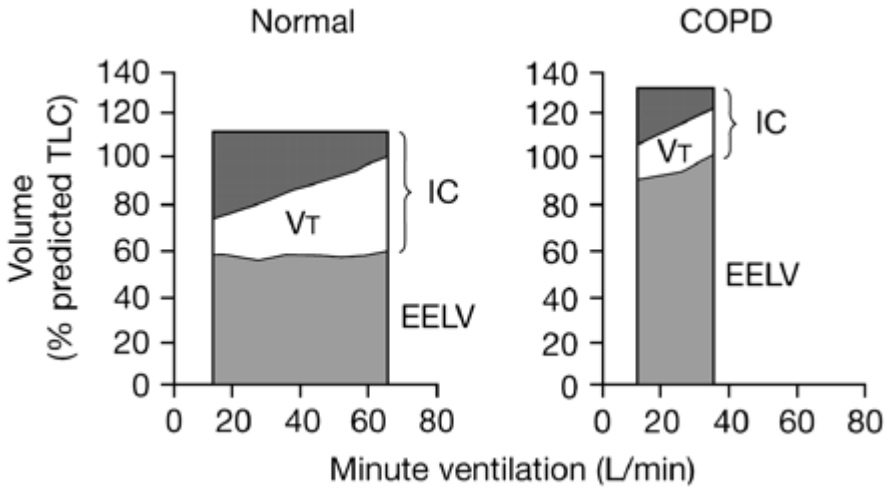

Figure 2.4. Dynamic changes in lung volumes during exercise in healthy lungs & COPD.

Dynamic changes in lung volumes occur during exercise in normal lungs and COPD. The left hand side of the bar graphs represents breathing at rest while the right hand side of the graphs represents breathing with exercise. Note that end-expiratory lung volume (EELV) remains relatively constant in normal lungs as minute ventilation increases. Tidal volume (VT) is able to expand, since inspiratory volume (IC) remains constant. In COPD, increases in EELV force VT closer to the total lung capacity (TLC) and IC is reduced even at rest. Dynamic hyperinflation further increases EELV and reduces IC as minute ventilation increases. VT is unable to expand and patients cannot achieve high minute ventilations before breathing becomes so restricted that patients have to stop activity.

Static hyperinflation is defined as an abnormally large total lung capacity (TLC), functional residual capacity (FRC) or residual volume (RV) (Niewoehner). Residual volume is the amount of air left in the lungs after complete exhalation, or the volume of trapped air (Niewoehner). Residual volume increases more than total lung capacity, so the ratio of RV/TLC increases as COPD progresses (Celli, 2007). As illustrated in Figure 2.4, this increase in the RV/TLC ratio occurs at the expense of a decrease in inspiratory capacity, i.e., the size breath that the patient can inspire is diminished.

Dynamic Hyperinflation

Normally, as individuals exercise their tidal volume increases, and lung volumes remain stable as long as this tidal volume is completely exhaled prior to the beginning of the next breath (Kohlhaufl, 2007). Expiratory muscles are utilized during exercise and individuals increase both pleural and alveolar pressures in order to keep tidal volumes completely exhaled prior to each next breath (Kohlhaufl). In contrast, for patients with COPD, their airways collapse during expiration and complete exhalation cannot be achieved prior to the next breath (Kohlhaufl). This inability to exhale completely before taking another breath while exercising leads to dynamic hyperinflation and increased work of breathing (Kohlhaufl). With exertion or any process that

causes tachypnea, dynamic hyperinflation leads to breathlessness and greatly reduced quality of life (Casaburi & Porszasz, 2006).

Dynamic hyperinflation of the lungs is considered to be one of the major mechanisms of exertional dyspnea (O'Donnell, 1994). With the increased minute ventilation required by exertion, and in the presence of expiratory airflow limitation, expiratory time is insufficiently long. This causes inspiration to begin before the lung volume has declined to the normal passive functional residual capacity. Dynamic hyperinflation of the lungs develops when patients are unable to reduce their end-expiratory lung volume (EELV) below passive functional residual capacity (O'Donnell, 1994). This process is due to limitation in expiratory flow and loss of elastic recoil (Mahler, 2007). Healthy individuals decrease EELV with exertion, but due to the loss of elastic recoil and flow limitation described above, this does not occur with COPD (Mahler). This is illustrated by the right border in Figure 2.4.

Changes in the Diaphragm

The diaphragm is the primary muscle of inspiration, and is affected by the changes in lung volume that occur with COPD, i.e., hyperinflation pushes the diaphragm inferiorly and into a less mechanically advantageous position (De Troyer, 1997). The diaphragm becomes shorter and flatter and in a lower or more caudal position (De Troyer). Static and dynamic hyperinflation causes impairment in the ability of the diaphragm to generate pressure changes (Sinderby et al., 2001) and to increase lung volume. Since the impaired diaphragm is less effective with inspiratory breathing, accessory muscles such as the scalene and inspiratory intercostal muscles make a greater contribution to breathing (De Troyer). Thus, the consequences of dynamic hyperinflation are loss of diaphragmatic effectiveness, recruitment of relatively inefficient accessory muscles, and a progressive decline in vital capacity as the increasing residual volume impinges on inspiratory capacity.

Ventilation and Perfusion

Ventilation and gas exchange are disturbed with COPD but unfortunately the mechanisms involved are not well understood (Niewoehner, 2007). Even in healthy lungs, not all alveoli are equally ventilated, i.e. ventilation throughout the lung is not uniform. This is attributed to the effects of gravity on pleural pressure gradients and complex effects of normal lung structure on gas distribution (Mason, 2005).

Ideally, ventilation of alveoli with gas should match up closely with perfusion of blood at the alveolocapillary membrane. However, this does not always occur because of "dead space" ventilation. Anatomic dead space refers to the volume of gas in conducting airways (trachea, major bronchi, and bronchioles proximal to respiratory bronchioles), a part of the lung that plays no role in the transfer of oxygen and carbon dioxide. If alveoli are ventilated but have little or no perfusion, the amount of lung receiving incoming air but playing no role in oxygen uptake or carbon dioxide excretion is increased, i.e., the "dead space" is increased. Such dead space is referred to as "physiologic dead space" (Mason). Anatomic and physiologic dead space should be relatively equal but with ventilation/perfusion mismatching, physiologic dead space is increased with COPD (Mason).

The process of emphysema is not necessarily uniform throughout the lung tissue. Areas are either over or under ventilated, as well as, under perfused with blood because of a loss of vasculature in the capillary bed. In narrowed airways, alveoli may be perfused with blood but under ventilated and thus return poorly oxygenated blood to the left heart. Alternatively, as the destructive forces of emphysema dissolve alveolar tissue, some regions may be adequately ventilated, but contribute little to oxygenation due to lack of an intact alveolar-capillary membrane. Both of these examples are referred to as ventilation-perfusion mismatch. As COPD progresses, the mismatch in ventilation and perfusion becomes increasingly more abnormal (Rodriguez-Roisin, Echazarreta, Gomez & Barbera, 2007).

Dyspnea and Exercise

Tidal volume (normal inspiration and exhalation), consists of air that ventilates alveoli (alveolar ventilation that causes gas exchange) and air that makes no contribution to gas exchange (dead space ventilation). Dead space ventilation consists of air that fills conducting airways such as trachea and major bronchi, and air that goes to areas of the lung with poor perfusion (ventilation-perfusion mismatch). Exertion causes muscles to demand increased oxygen delivery and generates increased carbon dioxide production. In order for more oxygen to be delivered and more carbon dioxide excreted, alveolar ventilation must be increased.

All individuals who exercise require an increase in minute ventilation. If a healthy individual and a patient with COPD have muscles with the same level of conditioning, and both perform an equal amount of exercise, the oxygen and carbon dioxide demands would be equal. However, the patient requires a larger minute ventilation because of a much larger physiologic dead space and more of each breath is wasted ventilation. To maintain a normal pH and $PaCO_2$, all individuals must achieve the same alveolar ventilation but because of the increased physiologic dead space in patients, they must have a larger total minute ventilation to achieve the same alveolar ventilation. Hypoxemia, early onset lactic acidosis and/or weakness of the extremity muscles, may also cause an increase in the ventilatory demand (Mahler, 2007). At any given level of exertion a patient with COPD must have greater minute ventilation, and the central nervous system motor commands a higher efferent output so dyspnea with exertion is perceived (Mahler).

Static and dynamic hyperinflation are considered a significant cause of dyspnea. The relationship between clinical dyspnea and the physiologic factors that cause shortness of breath are multifactoral (O'Donnell & Webb, 1992). However, the ability to precisely measure these factors is poor. For instance, the level of dyspnea is widely variable between patients with similar levels of lung function and spirometry and lung volumes are poorly predictive of the degree of perceived dyspnea (O'Donnell & Webb). Even determinants of dynamic hyperinflation do not

discriminate between severely dyspneic and moderately dyspneic patients (O'Donnell & Webb). Hypoxemia contributes to dyspnea, but the exact mechanism by which this perception occurs is unknown (O'Donnell & Webb). Obviously, more research is needed to understand the physiology and to design methods to relieve this distressing symptom.

Systemic Effects on Skeletal Muscle

COPD is a systemic disease, not limited to pulmonary pathology. This systemic involvement is particularly apparent when assessing the peripheral skeletal muscles. Peripheral muscle wasting is estimated at thirty percent, and wasting increases as disease severity progresses (Gayan-Ramirez & Decramer, 2007). The loss of skeletal muscle mass is associated with weakness and poor tolerance to exercise. Structural and biochemical changes in the muscles have also been noted (Gayan-Ramirez & Decramer), including a decrease in capillary density and in concentrations of aerobic (but not glycolytic) enzymes. Muscles take up oxygen much more slowly than do muscles in healthy individuals, creating an oxygen debt during exercise (Casaburi, 2000). Studies of the vastus lateralis muscle show less type I fibers and more type II and myosin heavy chain type 2B fibers (Casaburi). These changes and others lead to poor aerobic muscle function (Casaburi). One consequence of impaired aerobic muscle function is that lactic acidosis occurs at a lower work rate as compared with healthy individuals (Casaburi). Lactic acid is produced when oxygen transport to peripheral skeletal muscles is inadequate, necessitating energy production via anaerobic glycolysis. This results in the excess production of lactic acid and metabolic acidosis. As the minute ventilation increases in an effort to correct the acidosis, it will further impede exercise tolerance and increase dyspnea (Casaburi). It is important to note that the transport of bulk oxygen to the lower extremities has been shown to be normal even in the presence of lactic acidosis suggesting metabolic defects intrinsic to muscles may be the problem rather than inadequate tissue perfusion (Casaburi).

Deconditioning plays a major role in muscle dysfunction. Dyspnea imposes a sedentary life style, leading to muscular atrophy, and eventually leading to further inactivity and deconditioning. Thus, a sedentary lifestyle and breathlessness are often blended into a vicious cycle that leads to deconditioning of the peripheral muscles. The role of malnutrition with disease progression may also contribute to muscle wasting, as may inadequate levels of anabolic hormones, the frequent therapeutic use of corticosteroids, and perhaps a systemic inflammatory myopathy specifically related to COPD (Casaburi, 2000).

Clinical Manifestations: Dyspnea and Cough

Dyspnea is an interaction between components that are physiological, psychological, social and environmental in nature (ATS). Shortness of breath may diminish both functional status and quality of life (ATS). The gradual downward spiral of deconditioning and dyspnea is repeatedly observed with COPD as represented in Figure 2.5.

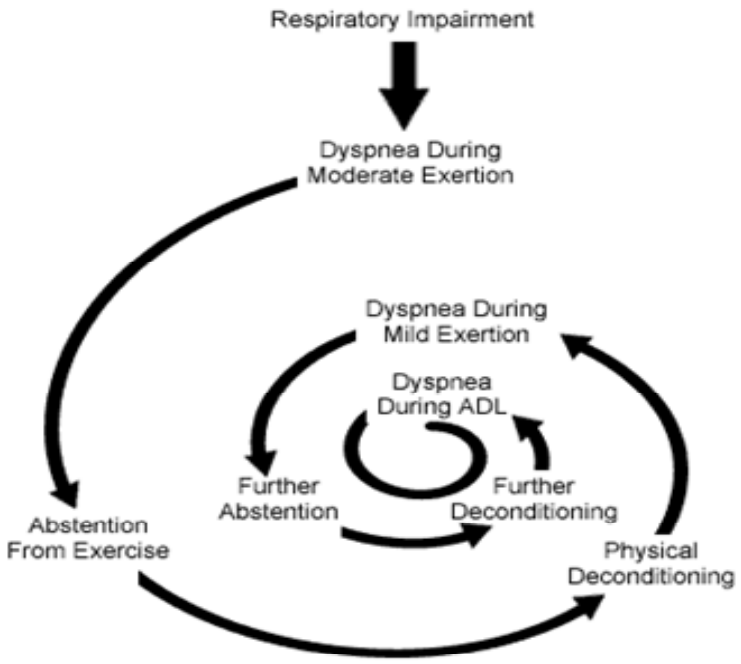

Figure 2.5. Dyspnea and deconditioning.

Reprinted from Haas F, Salazar-Schicchi J, Axen K. Desensitization to dyspnea in chronic obstructive pulmonary disease. In: Casaburi R, Petty TL, eds. Principles and Practice of Pulmonary Rehabilitation. Philadelphia, PA, WB Saunders Company; 1993:241-25.

Individuals commonly experience a daily productive cough often attributed to a “smoker’s cough”. While a persistent cough is frequently a symptom of smokers, obstructive changes in the airways need to be documented before this symptom can be attributed to COPD.

Diagnosis of COPD with Spirometry

For diagnosing and staging of lung disease, spirometry is the measurement tool of choice (Niewoehner, 2007). Spirometry is able to differentiate the lung function of individuals with normal, obstructive or restrictive patterns and may be performed in an outpatient setting. Table 2.1 presents the most frequently utilized values for COPD and their respective definitions.

Table 2.1. Lung Volume Measurements and Definitions.

Lung Volume Measurement	Definition
FEV_1 = forced expiratory volume in one second.	The volume of air exhaled in one second during a forced exhalation following a full inspiration.
FVC = forced vital capacity	The total volume of air exhaled during a forced exhalation after a full inspiration.
FEV_1/FVC = ratio or % FEV_1	The ratio of FEV_1/FVC of the individual.
IC = inspiratory capacity	The maximum volume of air that can be inhaled from the end of an ordinary expiration.
FRC = functional residual capacity	The volume of air remaining in the lungs at the end of an ordinary expiration.

(Cherniack, 1977)

Everyone being tested with spirometry is evaluated in relation to a population of individuals with normal lung function by comparing age, height, gender and ethnicity (Booker, 2005). By utilizing an individual's specific lung function value and evaluating this result in relation to normal values, a percent predicted can be obtained. A healthy individual or an individual with a restrictive pattern will have a FEV_1/FVC ratio of greater than 70%. By definition, obstruction occurs when the individual has a FEV_1/FVC ratio of less than 70% (GOLD, 2008). After a diminished ratio is established, attention to the percent predicted of the FEV_1 will stage the individual into one of four stages of severity for COPD (GOLD). Classifications for the levels of severity of COPD are shown on Table 2.2.

Table 2.2. Spirometry guidelines for the classification of COPD (GOLD, 2008)

Stage I: Mild	$FEV_1/FVC < 0.70$ FEV_1 > or = 80% predicted
Stage II: Moderate	$FEV_1/FVC < 0.70$ FEV_1 < 80 % predicted but > or = 50 % predicted
Stage III: Severe	$FEV_1/FVC < 0.70$ FEV_1 < 50% predicted but > or = 30% predicted
Stage IV: Very Severe	$FEV_1/FVC < 0.70$ FEV_1 < 30% predicted or FEV_1 < 50% predicted plus chronic respiratory failure

The spirometric values used for the diagnosis and staging of COPD are measurements obtained after the administration of an inhaled bronchodilator (GOLD, 2008). Although spirometry is essential for the diagnosis of COPD, there is only a weak correlation between FEV_1 and symptoms of dyspnea or exercise endurance (Laveneziana & O'Donnell, 2007). The ATS defines reversibility or significant response to bronchodilators as a change in the FEV_1 or FVC of greater than 12% and also an improvement in lung volume of 200 milliliters (Pellegrino et al., 2005). However, if this level of improvement in *spirometric* lung volume is not achieved, this does not necessarily indicate that the *clinical* response to inhaled bronchodilators is insignificant (Pellegrino et al.). Post-bronchodilator expiratory lung volumes without the evaluation of inspiratory capacity may not show significant change, but a decrease in lung hyperinflation (which would be manifest indirectly as an increase in inspiratory capacity) may be of real benefit (Pellegrino et al.). Improvement in the inspiratory capacity correlates well with positive changes in dyspnea and exercise tolerance (Laveneziana & O'Donnell, 2007); even though inspiratory capacity is measured more accurately with complete pulmonary function testing rather than

spirometry alone. Post-bronchodilator spirometry testing is typically performed 30 minutes after inhalation of albuterol and 45 minutes after inhalation of ipratropium bromide.

Redelmeier, Goldstein, Min and Hyland (1996) attempted to determine the minimal change in FEV_1 that would be associated with a perceptible change in the level of dyspnea. They determined that in patients with a FEV_1 of approximately one liter, an increase in the FEV_1 of 112 milliliters was the threshold beyond which improvement in dyspnea occurred. They also report that the FEV_1 was not a good predictor of dyspnea. Additional objective measurements of dynamic hyperinflation such as inspiratory capacity as well as measurements of exercise endurance should be evaluated for the efficacy of bronchodilators (O'Donnell, 2000).

Treatment with Bronchodilators

Inhaled and oral bronchodilators relieve dyspnea by one or more mechanisms: increasing ventilatory capacity, reducing dynamic airway compression, and/or reducing resting and dynamic hyperinflation (which consequently increases the length of the vertical muscles of the diaphragm with resultant improved diaphragmatic efficiency) (Mahler, 2007). Inhaled bronchodilators are preferred to oral agents because they act locally in the airways, rather than systemically, and side effects are minimized. Additionally, because the agents are inhaled directly into the lung, the medications are better able to target the diseased organ (GOLD, 2008).

According to Poiseuille's Law, resistance to airflow is inversely related to the fourth power of the radius (Johns Hopkins School of Medicine, 1995). For example, if the radius of the bronchi was cut in half, without altering the length, the resistance would increase 16-fold. Thus, small changes in the radius of the bronchi may cause dramatic changes in resistance to airflow and perceived work of breathing. If the airway can be pharmacologically dilated, resistance will decrease by the fourth power of the change in the radius. By decreasing resistance, airflow will improve. Even minimal improvements in airflow may provide considerable benefit for patients; so maximizing airway diameter (bronchodilation) is the cornerstone of therapy (Doherty, 2004).

Direct relaxation of the airway smooth muscles is the primary physiologic effect of inhaled bronchodilators (Hanania & Donohue, 2007). Bronchodilation improves FEV_1 and other lung volumes, decreases air trapping and dynamic hyperinflation and improves mucociliary transport or clearance (Hanania & Donohue). The prime objectives guiding use of inhaled bronchodilators are decreasing dyspnea and increasing functional performance.

The patency of airways at the end of exhalation is primarily controlled by the parasympathetic smooth muscle innervations of the bronchioles, with peribronchial ganglion cells releasing acetylcholine (Doherty). Acetylcholine causes smooth muscle constriction (bronchoconstriction) and induces mucous gland secretion. Inhaled anticholinergics and β_2-agonists or a combination of both are the choices for managing the undesirable effects of acetylcholine.

Anticholinergics

Two inhaled anticholinergic bronchodilators are ipratropium and tiotropium bromide. Although both drugs bind and act on all three muscarinic receptors, tiotropium bromide quickly dissociates from M_2 receptors which potentially results in less sustained bronchoconstriction. Anticholinergics block the action of acetylcholine (anticholinergic agents) to oppose bronchoconstriction and decrease mucous gland secretion. Anticholinergics act by blocking muscarinic receptors in the smooth muscles of airways, and three subtypes of muscarinic receptors are involved (Barnes, 2000). M_1 receptors are found in the parasympathetic ganglia and aid with cholinergic neurotransmission, thereby augmenting cholinergic mediated bronchoconstriction (Barnes). M_3 receptors located on airway smooth muscle cells and glands also influence bronchoconstriction and secretion of mucus (Barnes). M_2 receptors located on postganglionic parasympathetic nerve endings inhibit the release of acetylcholine and act as feedback inhibitors (Barnes). An ideal anticholinergic bronchodilator medication would bind to and inhibit the parasympathetic M_1 and M_3 receptors (thus causing bronchodilation and decreasing

mucous production) while sparing the M_2 receptors (thus allowing inhibition of acetylcholine and preventing acetylcholine-mediated bronchoconstriction) (Gross).

Tiotropium bromide monohydrate (Spiriva®) is an inhaled anticholinergic that has been available in Europe and the United Kingdom since approximately mid-2002, and was approved for use in the United States in January 2004 (Gross, 2004). Prior to tiotropium, the only available inhaled anticholinergic was ipratropium. Tiotropium bromide is used once daily. It is approximately 10-fold more potent than ipratropium, and superior to ipratropium in bronchodilation (Barnes, 2000). Two year-long studies (Casaburi et al., 2002 & Vincken et al., 2002) have shown multiple benefits from tiotropium. Casaburi et al. reported that tiotropium decreased both dyspnea and exacerbation frequency and improved health status. Exacerbations were fewer and occurred after a longer time period, and hospitalizations were decreased (Casaburi et al.). The mechanisms for decreasing exacerbations are not clear (Casaburi et al.). Vincken et al. (2002) found that tiotropium improved dyspnea, lung function and health related quality of life while diminishing exacerbations. Tiotropium increased the time to the first exacerbation and also reduced the number of exacerbations experienced (Vincken et al.). Vincken et al. recommended tiotropium as first-line maintenance therapy for COPD.

Tiotropium has little systemic absorption, thus a greater margin of safety (Barnes, 2000). No significant cardiovascular or respiratory adverse effects have been reported, as well as, no significant changes in heart rate or blood pressure (Barnes). The major side effect in all of the studies has been dry mouth, but patients rarely stopped the medication because of this**.** Dry mouth is due to the anticholinergic activity at the M_3 muscarinic receptor sites, which causes reduction in salivation (Scully, 2003). No interactions between tiotropium and other medications have been reported (Gross, 2004). Delivery of 18 micrograms of tiotropium is via a capsule containing a dry powder and utilizing a HandiHaler® inhaler (Chodosh et al., 2001). A study by Chodosh et al. showed that the inspiratory flow rates of patients with various levels of COPD were sufficient to adequately deliver this medication into the tracheobronchial tree.

Beta$_2$ Agonists

Beta$_2$ agonists (β_2-agonists) exert influences upon mucociliary function, airway inflammation, cytological structural changes and respiratory muscle contractility (Johnson, 2007). The distribution of β_2-receptors can be found in the smooth muscle cells, airway epithelial cells, vascular endothelial cells, inflammatory cells, type II alveolar epithelial cells, skeletal muscle cells and fibroblasts (Johnson). β_2-agonists produce effects by "binding to and temporarily stabilizing receptors in their activated state" (Johnson). The primary therapeutic effect of β_2-agonists is bronchodilation through smooth muscle relaxation. Only two long acting β_2-agonists (LABAs) are available in the U.S. and these are salmeterol (Serevent®) and formoterol (Foradil®), and they were developed for maintenance therapy for obstructive lung diseases.

Formoterol (Foradil®) is an inhaled long acting Beta$_2$ (β_2) agonist with a duration of action of greater than twelve hours (Donohue, 2008). It is delivered via an Aerolizer® inhaler device at a dose of 12 micrograms per capsule twice a day. Formoterol is comparable to salmeterol (Serevent®) in many ways since they are both inhaled long acting β_2 agonists. Inhaled β_2 agonists activate adenyl cyclase and produce cyclic 3'5' adenosine monophosphate, which relaxes airway smooth muscle and causes bronchodilation (Donohue).

Formoterol and salmeterol were compared in a study (Celik, Kayacan, Beder & Durmaz, 1999) involving individuals with COPD who had partially reversible airway obstruction. Formoterol was found to have a more rapid onset of action at ten minutes versus salmeterol at twenty minutes (Celik et al.). Peak bronchodilator effects for formoterol occurred at 60 minutes as compared to salmeterol at 120 minutes (Celik et al.). Both formoterol and salmeterol had comparable bronchodilation with minimal side effects (Celik et al.). Authors Maesen, Westermann, Duurkens and van den Bosch (1999) found formoterol to provide long lasting improvements in measured work of breathing and airway resistance even in patients with poorly reversible COPD (as judged by changes in FEV_1). Therefore, poor reversibility of lung function

with bronchodilators as demonstrated with spirometry does not justify withholding therapy (Maesen et al.).

The most common side effects experienced with inhaled β_2 agonists are tremors and tachycardia. Testing formoterol at doses of 12 and 24 micrograms showed that the higher dose had a lower safety margin (Cazzola et al., 1998). Only the dose of 12 micrograms of formoterol has been approved for use in the United States. In the study by Cazzola et al. the mean maximum heart rate increased only six beats per minute.

Short acting β_2 agonists such as albuterol drive potassium into the cells by increasing Na-K-ATPase activity (Rose, 2007). This lowers the plasma potassium levels and increases the risk of hypokalemia (Rose). Short acting β_2 agonists are even used therapeutically to treat hyperkalemia (Rose). The link between hypokalemia and short acting β_2 agonists initially caused concern that the same may be true for long acting β_2 agonists. Fortunately, this has not been demonstrated. In a study by Calverley et al. (2003), patients treated with inhaled long acting β_2 agonists (LABAs) combined with inhaled corticosteroids showed no decrease in potassium levels. In the study by Cazzola et al. (1998) the mean plasma potassium level insignificantly decreased by 0.45 mmol/liter with the use of salmeterol.

The most controversial findings concerning salmeterol have come from the Salmeterol Multicenter Asthma Research Trial (SMART) study (Nelson et al., 2006). One arm of this study utilized salmeterol as mono-therapy for asthmatics, and a negative interim analysis caused the study to be discontinued. In this group, there was a small but statistically significant increase in respiratory-related deaths and the risk was even greater in African Americans (Nelson et al.).

This study was the major reason that the Food and Drug Administration issued a “black box” warning for all long acting β_2 agonists. The SMART study has been quite controversial and has affected the treatment therapies for obstructive lung disease. Although the study only involved individuals with asthma, there has been concern that the risk of respiratory-related death might also apply to patients with COPD. A systematic review of LABAs by Rodrigo, Nannini and

Rodriguez-Roisin (2008) did not find an increased risk for respiratory death in patients with COPD, contrary to the findings of the SMART study performed in patients with asthma. The authors (Rodrigo et al.) support the beneficial effects for the use of LABAs in patients with moderate-to-severe COPD.

Inhaled anticholinergics and β_2-agonists have been shown to improve shortness of breath in patients with COPD (ATS, 1999). Clinical benefits of bronchodilators include decreased breathlessness and improved exercise performance even though these improvements correlate weakly with a positive change in spirometry values (ATS, 1999; Hanania & Donohue, 2007).

Liesker et al. (2002) reviewed thirty-three double blinded, randomized and placebo-controlled studies about the effects of bronchodilators on dyspnea and exercise capacity in patients with COPD. Six minute and twelve minute walk tests were the most frequently utilized tests for steady-state exercise. Cycling, treadmill walking and shuttle walking were employed for incremental testing (Liesker et al.). These researchers found that inhaled anticholinergics and short-acting β_2-agonists improve functional capacity (Liesker et al.). The benefit of long acting β_2-agonists on functional capacity was not clear, and the addition of a second bronchodilator had no proven advantage but this effect has not been sufficiently studied (Liesker et al.).

Evaluating Functional Status

Because COPD has no cure, to achieve the best possible quality of life, patients must be able to maximize their functional status as the disease progresses. Disease severity as assessed by spirometry and dyspnea are central variables for evaluating functional status. Two important components to functional status are functional capacity (the ability to perform physical activity at a standardized level) and functional performance (the ability to perform physical activity required for daily living) (Leidy, 1995).

Functional capacity may be measured by walk tests (Larson & Leidy, 1998), and functional status models have included either a twelve-minute walk test (Weaver et al., 1997) or a six-

minute walk test (Yeh et al., 2004). Several different walk tests have been described in the literature, with one excellent review systematically presenting a qualitative overview of these studies (Solway, Brooks, Lacasse & Thomas, 2001). Clinical trials and observational studies that incorporated walking tests were reviewed, and five different types of walk tests were evaluated (Solway et al.). Included in the review were two, six and twelve minute walks, a self-paced walk and the shuttle walk test. The six-minute walk test (6MWT) was found to be the most thoroughly researched and established measurement, causing Solway et al. to recommend it as the test of choice when using a functional walk test for research or clinical purposes. Similarly, Butland, Pang, Gross, Woodcock and Geddes (1982), compared two, six and twelve minute walk tests to determine which one was the superior test for patients with lung disease. All time duration tests were reproducible, when patients walked at a constant speed throughout each test (Butland et al.). They concluded the twelve minute walk test was more discriminating; despite yielding a wider spread of results, but the differences between all three were not large (Butland et al.). A significant disadvantage was that the twelve-minute walk test was too time consuming and fatiguing for the patients as compared to a six-minute walk (Butland et al.). Thus, the six-minute walk was deemed a “sensible compromise” (Butland et al.)

Stair climbing is another method of testing physical endurance. Approximately 80% of peak oxygen uptake is achieved in the first minute of the climb (Casas et al., 2005). Casas et al. felt this was a major safety concern with using this test. The shuttle walk test uses an audio signal from a tape cassette instructing the patient how fast he or she needs to walk (ATS, 2002). This incremental shuttle walk test utilizes a 10-meter course, and the walking speed is increased every minute (ATS). The test ends when the patient cannot reach the turnaround point within the time allotted (ATS). Both the stair climbing test and the shuttle walk test have not been used as frequently and are less validated than the 6MWT (ATS). Also there is greater potential for cardiovascular problems with both of these methods (ATS), a consideration of special relevance in patients with COPD as the tobacco usage that contributed to their COPD is also a contributor

to the development of coronary artery disease. Casas et al. thus recommends the 6MWT as the most suitable choice for patients with COPD. The limitation in the distance walked may be a combination of ventilatory impairment and physical deconditioning, so the effects of inhaled bronchodilators may enhance both functional capacity and functional performance (Larson & Leidy).

Six-minute Walk Test

When compared to traditional tests of lung function, the six-minute walk test has been found to be more reflective of the activities that patients perform in their daily lives and accurately demonstrates their functional performance level (ATS, 2002). The test is easy to administer and has been standardized by the American Thoracic Society (ATS) (2002) in order to assist researchers and clinicians. This test simply measures the total distance walked by a patient in six minutes.

Comparing a 6MWT standardized hallway walk versus walking on a treadmill demonstrated that the two methods are not interchangeable (Stevens et al., 1999). Walking in a corridor is a skill set that is utilized daily by patients, but this does not easily transfer to walking on a treadmill. One explanation for the varying results on different surfaces is that patients are unable to pace themselves on a treadmill (ATS, 2002). There was wide variability in the results obtained by treadmill walking, with little or no correlation to the results from standardized hallway walking. (Stevens et al.) Therefore, it is not recommended to perform a 6MWT on a treadmill (ATS).

The 6MWT should be performed indoors using a hallway that measures 100 feet or more (ATS). Enright (2003) also suggested that an oval or circular track should not be used for a 6MWT. However, studies by Bansal et al. (2008) and Sciurba et al. (2003) reported that modifying a track layout (such as making the track circular or oval) caused only minimal change in distances walked, but that the track layout should be standardized for comparison. Institutions using circular

tracks showed greater distances than straight tracks, but these results were less variable than a patient's day-to-day variation (Bansal et al.).

Studies on elderly patients with a variety of chronic diseases demonstrated that expected values of the 6MWT should be adjusted according to the patient's age, gender, height and weight (Enright et al., 2003). One study found that height was the most important variable for the distance walked and that if combined with age, weight and gender these variables were responsible for approximately 60% of the variance occurring during the 6MWT (Troosters, Gosselink & Decramer 1999). Another study evaluating elderly individuals without major chronic illnesses found that age and then gender were the most predictive factors for distance walked in the 6MWT (Steffen, Hacker & Mollinger, 2002).

The 6MWT is more than a research tool; it is commonly used to measure the effects of many therapies. For example, it is established practice in formal pulmonary rehabilitation programs to test patients before they start the exercise program and again at the end of the rehabilitation sessions in order to document their progress. Other examples include pre- and post-treatment comparisons following lung transplantation or lung volume reduction surgery; single measurements of functional status of patients with COPD, heart failure, or cystic fibrosis; and to aid in the prediction of mortality in patients with COPD, heart failure and primary pulmonary hypertension (ATS, 2002).

Taking a practice test is not necessary in most clinical settings, but is not prohibited, even though it may result in minor variations in subsequent results (ATS, 2002). If a practice test is incorporated into the protocol, at least a one hour delay should occur between the practice test and the second test, with the highest 6MWT distance being the one that is recorded (ATS). Some studies, such as Steffen et al. (2002) and Sciurba et al. (2003), found that patients were able to walk further on the second day of testing and felt that a practice walk was beneficial.

Since the 6MWT is the fundamental tool used to evaluate the functional status of patients with COPD, an important question to answer is, "How much does the 6MWT need to improve in

order for the patient to perceive a noticeable improvement in walking ability?" A study by Redelmeier, Bayoumi, Goldstein and Guyatt (1997) sought to answer this question. Redelmeier et al. found that there was a poor correlation between the patients' actual and perceived changes in their capacity to walk. However, within limits of the technique of their study, the threshold of clinical importance identifying at what distance a patient would notice a difference in their functional status was found to be 54 meters (Redelmeier et al.). In an updated study by Puhan et al. (2008), patients with moderate-to-severe COPD needed to have a change of 35 meters in order to show an important effect change in the distance walked in six minutes. This corresponded with a 10% change from the baseline distance walked in six minutes. That is, patients would need to increase their total distance achieved in a 6MWT by 35 meters in order to state that they were subjectively improving. This key piece of information, defining the milestone that must be crossed to document *functional* improvement, will be the standard for this research.

Current Studies

Currently there are only fifteen articles dedicated to researching the combination of inhaled bronchodilators in patients with COPD. Most of these articles used spirometric changes as the measured endpoint**.** Only three studies included the use of a six-minute walk test for evaluating the functional change in performance that occurred with inhaled medications. Other measured endpoints include various dyspnea scales as well as diary cards and Saint George's Respiratory Questionnaire (SGRQ). Studies using either salmeterol or formoterol were included, as these medications are both long acting $beta_2$ agonists (identical pharmacologic category) with the same mechanism of action, differing primarily in the time of onset of action.

Cazzola et al., (2008), Fuso et al., (2003) and Celik, Kayacan, Beder and Durmaz (1998) researched the use of formoterol alone for COPD. Additionally the article by Celik et al. studied salmeterol separately from formoterol. Cazzola et al. used formoterol without a placebo control, but found that after the first dose of formoterol the six-minute walk test improved by 35.3 meters,

with further improvement to 53.6 meters after 5 days of use. Additionally, there was a significant improvement in the subjects' Modified Borg Scores (i.e., lessening of dyspnea). Fuso et al. utilized a shuttle walk test and found statistically significant improvements in FEV_1, Modified Borg Scores and the shuttle walk test with the use of formoterol versus placebo. Celik et al. studied the onset and duration of both formoterol and salmeterol and measured the spirometric changes that occurred with each and found these two medications comparable for bronchodilation. All three of these studies involved small numbers of subjects and should be considered pilot studies.

Donohue et al. (2002) and Richter et al. (2006) tested tiotropium and a long acting $beta_2$ agonist (salmeterol and formoterol respectively) separately to see which medication was superior for patients. Richter et al. performed a short term study focusing upon the onset and duration of action of formoterol and tiotropium and found them to be comparable. Donohue et al. studied salmeterol and tiotropium over a six month period and found tiotropium to be superior for bronchodilitation, decreasing dyspnea and producing meaningful changes in health-related quality of life. Tiotropium alone was studied by Tashkin and Kesten (2003) and was found to be effective for long term therapy whether or not the patient responded to this medication in the short term.

When studying the combination of tiotropium and a short acting $beta_2$ agonist named fenoterol (which is not available in the United States but is similar to albuterol) or ipratropium Kerstjens et al. (2007) found that both short acting bronchodilators had additive effects when combined with tiotropium. However, the effect of fenoterol was superior to that of ipratropium. As ipratropium is a short acting anticholinergic bronchodilator (and tiotropium is a long acting anticholinergic bronchodilator), it was not surprising that this medication was not as effective as adding a short acting $beta_2$ agonist to tiotropium. Combining two different classes of inhaled bronchodilators, with different but theoretically additive mechanisms of action, would be expected to provide more benefit than using two medications with duplicative mechanisms of action.

Eight studies involved the combination of tiotropium with a long acting $beta_2$ agonist such as salmeterol or formoterol. Aaron et al. (2007) focused upon hospitalizations and exacerbations of COPD as their primary outcome of interest. This study had significant limitations because more than 40% of the patients receiving tiotropium plus placebo or tiotropium plus salmeterol discontinued therapy prematurely. The seven remaining studies (Cazzola, Centanni et al., 2004, Cazzola, Di Marco et al., 2004, Cazzola, Noschese et al., 2005, Tashkin et al., 2008, van Noord et al., 2005, van Noord et al., 2006 & Vogelmeier et al., 2008) used spirometric changes to assess the response to tiotropium and a long acting $beta_2$ agonist. Only one study by Vogelmeier et al. (2008) evaluated the effect of combined therapy using a six-minute walk test. The test was performed on each subject upon entry and after 24 weeks of therapy. Formoterol and tiotropium were studied separately, combined, and compared to placebo. All treatments were statistically superior to placebo in terms of the primary endpoint, which was the FEV_1 two hours post-dose after 24 weeks of therapy. The improvement in the six-minute walk test was statistically significant when compared to placebo, but this difference was only 17 meters, which may not translate into a functionally meaningful improvement in patient symptoms. This distance is much lower than the distance of 35 meters that was found to be clinically significant in the study by Puhan et al., (2008). With regard to other indices studied, significant differences were not found in frequency of exacerbations or quality of life questionnaires (Vogelmeier et al.).

Summary

This review of the literature confirms our lack of knowledge regarding the effects of combining inhaled bronchodilators on improving the functional status in patients, irrespective of the current GOLD guidelines. To date, studies investigating combined inhaler therapy for COPD have focused almost entirely on spirometric changes, with only one study evaluating functional status by a six-minute walk test. The validity of drug therapy is not established until multiple

investigators have successfully duplicated research. This pilot study may provide supporting data that will encourage the need for additional studies in larger populations.

CHAPTER 3

METHODS AND PROCEDURES

This chapter describes the methods and procedures used for this pilot study. Research design, patient sampling and testing environment (see Protocol, Appendix D) are described, as well as, the procedures for data collection and data analysis. Study delimitations are also addressed.

Research Design & Setting

The purpose of this study was to evaluate the combined effect of tiotropium and formoterol on the functional status of patients with moderate-to-severe COPD. Functional status, for this study, involved the evaluation of the patients' maximum potential to perform physical activity at a standardized level (defined as Functional Capacity, Chapter 1). A double-blind randomized crossover study design was used to determine the additional effect of inhaled formoterol (12 mcg) versus inhaled placebo when added to tiotropium (18 mcg) (See Figure 3.1). Study participants included a non-probability convenience sample of patients who received their medical care in the office of Texas Pulmonary and Critical Care Consultants, P.A. (TPCCC) in Bedford, Texas. Patients are assumed to be representative of the local geographical population. The study was initiated, conducted, and concluded by Catherine Jones, RN, MSN, ANP-C with Gary L. Jones, MD as the designated physician. The pulmonary physicians from the Bedford office of TPCCC were solely responsible for approving the selection of their patients who participated in this study and approving their patients' written consent. All medications were

prescribed by the primary physician for each patient enrolled in the study. (See Physicians Approval Form, Appendix E and TPCCC Board Approval Appendix F.

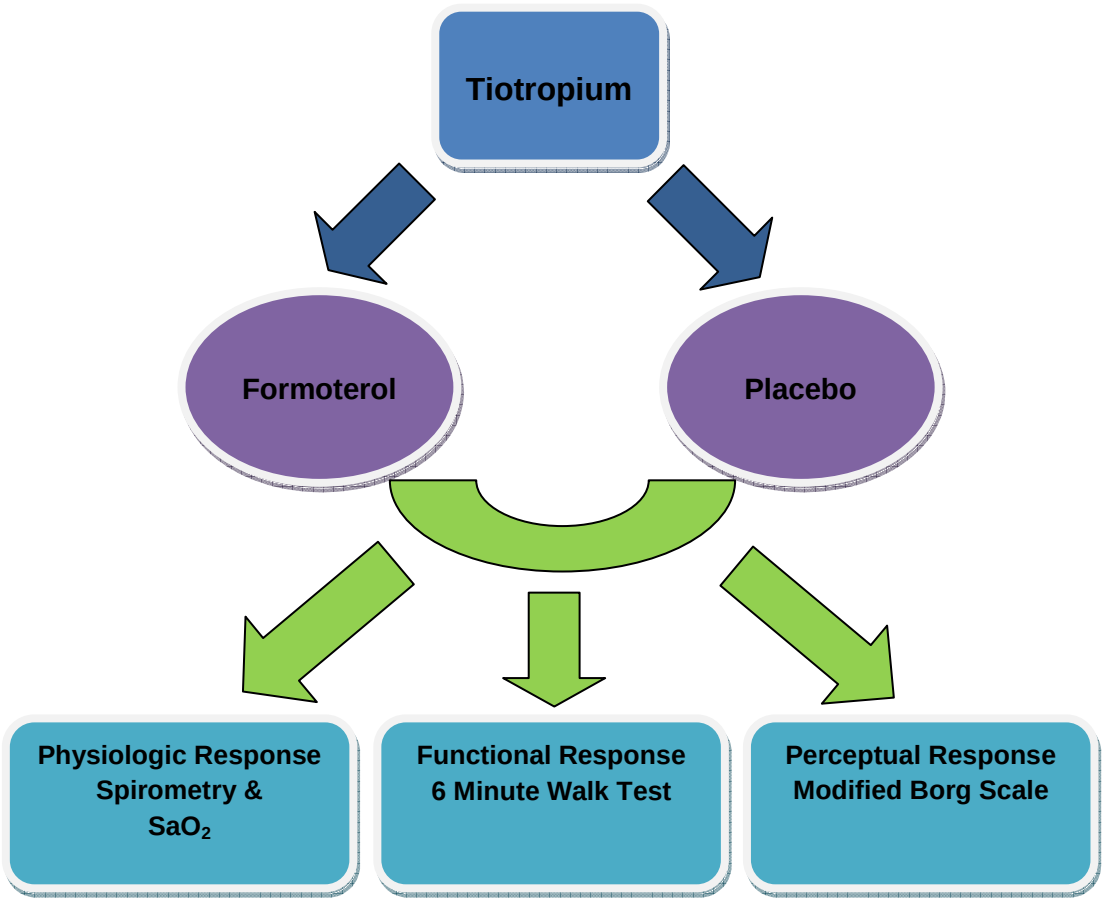

Figure 3.1. Study Design

Subjects

The patients participating in this study were recruited from the medical office of Texas Pulmonary & Critical Care Consultants P.A. in Bedford, Texas. The pulmonologists and clinical office staff were provided with the entry criteria (Appendix G) and, when appropriate, the name of

the patient was provided to the investigator. Additionally, colorful fliers (Appendix H) noting the entry criteria and financial incentive were also prominently displayed in the office waiting room and examination rooms, allowing patients to self-refer themselves to the investigator. The investigator then approached these patients in person or by telephone to determine their level of interest. If the patient exhibited a willingness to participate, an appointment was made for the enrollment process.

Inclusion Criteria

Subjects to be included in this study met the following criteria:

1. The medical diagnosis of moderate-to-severe COPD
2. Use of inhaled tiotropium for a minimum of 45 days
3. Smoking history greater than or equal to 10 pack years
4. Smoking cessation for at least one month prior to the study
5. Age 50-80 years
6. Ability to read and speak English
7. Ability to perform a six-minute walk test
8. Body mass index (BMI) of 21 to 30
9. Concurrent use of inhaled corticosteroids for a minimum of 45 days

Spirometry measurements, as determined by GOLD guidelines (2008) for initially diagnosing and staging COPD, were also used in this study to assess the current level of severity of COPD. Patients were eligible for the study if they had been taking inhaled tiotropium for at least 45 days. Tiotropium reaches a steady state within 48 hours but requires more than a week to obtain further improvements in lung function (van Noord et al., 2002). Patients had a smoking history greater than or equal to 10 pack years or more with a cessation of smoking for at least one month prior to the study. The 10 pack year history eliminated patients who developed COPD

not associated with smoking. Patients were at least 50 years of age to avoid the early onset of COPD associated with non-identified environmental exposures and/or genetic predispositions. Patients were able to read and speak English in order to provide informed consent and comply with the study protocol. A body mass index (BMI) calculated as weight (kg) divided by height^2 (m^2), of 21 to 30 was required to decrease the risk of comorbidities, such as breathlessness, associated with obesity. Patients taking inhaled corticosteroids were allowed to continue the medication to avoid safety problems associated with discontinuing the medication and potentially decreasing lung function. Inhaled corticosteroids have been shown to decrease the frequency of exacerbations, so discontinuing this medication could possibly increase the risk of an exacerbation.

Exclusion Criteria

Patients were excluded from participating in this study for the following reasons:

1. Lung diseases other than COPD (i.e. asthma, tuberculosis, interstitial lung disease, lung cancer)
2. Family history of alpha-one antitrypsin deficiency or early onset of COPD (younger than 50 years of age).
3. Resting heart rate of greater than 120 beats per minute
4. History of congestive heart failure
5. A myocardial infarction within the last 12 months
6. Presence of unstable or stable angina
7. Exacerbation of COPD within the last month
8. Hospitalization within the last three months
9. Change in activities of daily living prior to or during the study
10. Chronic use of oral corticosteroids
11. Use of oral corticosteroids during the last month

12. Use of portable oxygen therapy with exertion and/or an oxygen saturation of < 90%

Patients with lung diseases that did not meet the essential spirometric criteria for COPD were excluded to avoid any potential changes in spirometry associated with other diseases. Examples include asthma, tuberculosis, interstitial lung disease, and lung cancer. Patients with a familial history of alpha-1 antitrypsin deficiency were excluded because of the markedly enhanced tendency for COPD. This disease is manifested in individuals who smoke at a much younger age and does not represent the majority of patients with COPD. Patients with a resting heart rate of greater than 120 beats per minute were excluded because tachycardia increases myocardial work load and oxygen demand thereby posing a safety concern. Likewise, patients with a history of congestive heart failure, recent myocardial infarction or angina were excluded. Patients who had recent hospitalizations, recent illnesses or changes in activities of daily living were excluded. Each of these can temporarily or permanently influence the functional status of patients with COPD and alter spirometric measures. Patients using oral corticosteroids within the last month or requiring the routine use of oral corticosteroids were excluded to reduce the potential to confound study results. Patients requiring portable oxygen or demonstrating significant hypoxemia (an oxygen saturation of < 90%) were also excluded (See Appendix I on pulse oximetry).

Measurement Methods

The combined effect of tiotropium and formoterol on the patient's functional status was evaluated by a six-minute walk test and spirometry, and a change in the patient's perception of dyspnea and perception of fatigue was evaluated using a Modified Borg Scale. As discussed in chapter 2, spirometric values have only limited correlation with symptoms of functional status, as well as dyspnea and fatigue; therefore, the six-minute walk test and spirometry were assessed with a repeated measures cross over design. Because functional status varies significantly among individuals of similar fitness, the repeated measures cross over design allowed patients to

serve as their own control thereby increasing statistical power with less error variance. Also, by changing only one variable (formoterol versus placebo), the design minimized the variability that occurred among patients.

Spirometry

Standardization for the performance of spirometry was established by the American Thoracic Society (ATS) and European Respiratory Society (ERS) task force and published in 2005 (Miller et al.). The Puritan-Bennett Renaissance II spirometer used in this study met these (ATS/ERS) standards for accuracy and precision. Calibration of the spirometer was performed daily with a three liter syringe according to specified directions (see calibration directions in Appendix J) (Miller et al.). The investigator prepared the patient by explaining the procedure combined with a visual demonstration to ensure accurate results. (See spirometry procedure in Appendix K). Demographic data was entered into the spirometer data base with the patient seated. Neutral or a slightly elevated head position was used as well as a proper seated posture (Miller et al.). A disposable mouthpiece was placed into the patient's mouth with lips and teeth completely surrounding the end piece. Nose clips were utilized to eliminate added nasal breathing throughout the maneuver (Miller et al.). The patient was then instructed to inhale completely and rapidly and exhale maximally until no more air can be expelled (Miller et al.). This maneuver is a forced blow that requires a maximum effort, so the investigator coached enthusiastically and loudly. A minimum of three blows and a maximum of eight blows were necessary to provide repeatability and validity of this test (Miller et al.). There were at least two blows with a forced vital capacity and forced expiratory volume in one second variability within 150 milliliters to be considered an acceptable test.

Six Minute Walk Test

The six-minute walk test has been standardized by the American Thoracic Society (2002) and this study followed the published protocol. A straight 30 meter (100 foot) indoor hallway was used with large cone markers indicating the end of each turn around point. One chair was placed at the starting point while other chairs were placed along the entire walk track should the patient experience distress. A prescribed script (see Appendix L) was used during the walk test, and detailed notes were taken on the patients' worksheet (see Appendix M). The final distance walked was recorded both in meters and in feet.

Modified Borg Scale

The Modified Borg Scale (Appendix N) is a subjective measurement of the patient's perception of dyspnea and perception of fatigue as measured independently on a numerical scale from 0 to 10 (0 indicating nothing at all and 10 indicating very, very severe) (Borg, 1982). The use of this scale is widespread throughout the pulmonary literature and as such represents one of several different measurement tools. However to date the Modified Borg Scale has not been rigorously psychometrically tested (Jadad, Rizo, Cubillos & Stahl, 2004). Moderate effect size changes have been shown to occur with bronchodilator therapy and a unit change of 1.0 has been found to be significant in prior studies. It should be noted, however, that the Modified Borg Scale is most appropriately used after a stimulus such as walking exercise (thus its relevance to this study) rather than in reference to a recent historical recollection of dyspnea (Ries, 2005).

Procedure

Patients presenting to the Bedford office of TPCCC for routine appointments were identified by the pulmonologists or nurses as potential subjects for the study using the inclusion/exclusion criteria and referred to the investigator. Flyers of the study were also posted in

the office areas which may have encouraged patients to contact the investigator. During the first visit, the potential subjects were interviewed by the investigator using the Orientation Meeting Script (Appendix O). If patients were interested, a screening assessment was conducted (Appendix P) which included the patient's medical history. Qualified subjects agreeing to participate were then asked to read and sign the IRB consent forms. The patient's height, weight, pulse, and oxygen saturation were measured. The height and weight of the patient was taken using a designated measurement pole and a Health-o-meter balance scale, respectively, with the patient's shoes and jacket removed. Oximetry was performed with a Nonin Model 8500P oximeter (finger clip).

After all informed consent forms were signed, spirometry was performed to ensure that the patient had moderate-to-severe COPD as defined by the GOLD guidelines. The level of severity was determined by the ratio of the forced expiratory volume in one second to the forced vital capacity (FEV_1/FVC), and the forced expiratory volume in one second (FEV_1), with the categories of severity being defined by the GOLD guidelines (2008). The patient then completed one practice walk of 2 minutes on the prescribed course to become familiar with the procedure. Subsequently, the patient was randomly assigned. Randomization was assured by utilizing a table of random numbers obtained from the statistics textbook (Levin & Fox, 2003, p. 452-453). The first medication was randomized into odd and even numbers with formoterol and placebo assigned by a single coin flip. Gary Jones, M.D., used the table of random numbers and assigned participants accordingly without the knowledge of the investigator (Appendix Q). Thus, the study was double-blinded.

Inhaled medication therapy was reviewed by the investigator with the patient and, if the patient was taking a long acting beta-2 agonist, it was discontinued for the duration of the study. If the patient was taking a combination long acting beta-2 agonist/inhaled corticosteroid inhaler (e.g., Advair® or Symbicort®), then the corticosteroid was continued as usual while the long acting beta-2 agonist was discontinued. Patients were provided a replacement inhaled

corticosteroid, as found in their combination inhaler, which was used during the study. Tiotropium was continued as previously prescribed. A short acting beta-2 agonist (albuterol) was provided to replace the long acting beta-2 agonist during the study. The patient was instructed that albuterol may be taken every 4 to 6 hours as needed for shortness of breath. If, however, albuterol was used within 8 hours (minimum time for wash out) of the scheduled appointment, the appointment was rescheduled. Use of inhaled albuterol was documented (Appendix R) throughout the study. Once patients understood the current medication regimen, they were given written instructions to take home (Appendix S). A waiting period of at least 48 hours was required to allow adequate wash-out of formoterol. After 48 hours, the patient presented for the first of two additional visits. To avoid diurnal variation between visits, all patients walked in the morning hours.

The testing procedure for the second and third visit was identical except for the inhaled medication. The allotted time preceding each visit allowed for a 48 hour delay before crossing over into the other arm of the study (i.e., patient receiving placebo if the second visit involved formoterol or patient receiving formoterol if the second visit involved placebo). On arrival to the clinic, the patient was asked to sign the re-consent form (Appendix T). The investigator then assisted the patient with the inhaled placebo or formoterol in a double-blinded manner. Following this, a standardized 60 minute waiting period was required to allow peak effect of the medication (Celik, Kayacan, Beder & Durmaz, 1999). During this time, patients had access to magazines and DVDs, and were provided water to drink. Coffee, tea, or soft drinks were not provided. After the 60 minute waiting period, the patient was assessed using oximetry and a Modified Borg Scale. This was followed by the six-minute walk test and reassessment with oximetry and the Modified Borg Scale. After a rest period of ten minutes, spirometry was performed. The third visit concluded with a debriefing where investigator thanked and compensated the patients for their participation in the study, instructed them on resuming pre-study medications, and answered any questions they had about the study.

Ethical Considerations

Patients meeting the study criteria and agreeing to participate in the study were required to acknowledge their consent by signing an informed consent form approved by the Institutional Review Board (IRB) at The University of Texas Arlington. The Declaration of Helsinki and good clinical practice guidelines directed the study. Only the principal investigator enrolled patients in the study. The study procedures were presented to patients in verbal and written formats, and all questions were answered. Patients were informed that they had the right to withdraw from the study at any time without adverse consequence to their care. Permission from the IRB at The University of Texas Arlington, the executive board of Texas Pulmonary and Critical Care Consultants, P.A. (Appendix F) and the three pulmonologists from the Bedford office of TPCCC was obtained (Appendix E). All study data was kept at the research site in a locked cabinet or in the physical possession of the investigator. The appropriate forms were submitted for approval to the IRB at The University of Texas Arlington and their responses are included in Appendix U:

1. Institutional Review Board Approval of Protocol (# 2010-0028)
2. IRB informed consent in English
3. Minor modification approval letter – 11/6/2009
4. Minor modification approval letter – 12/21/2009

Potential risks

Using a long acting beta-2 agonist (formoterol) as the study medication temporarily changed the patients' current medication regimen. For example, if patients were taking a long-acting beta-2 agonist, it was discontinued for the duration on the study and substituted with a short acting beta-2 agonist (albuterol) that could be taken every 4-6 hours as needed for shortness of breath. Patients were informed that if they experienced significant palpitations and/or tremors from the albuterol, they were to stop the medication and immediately inform the investigator.

There was also a potential minimal risk to the patients' physical well being from walking indoors on a flat surface for one 2 minute walk and two separate 6 minute walks. Consequently, patients were told to stop immediately stop and sit down in a chair if they experienced chest pain, intolerable dyspnea, gait instability, leg cramping, diaphoresis, or if the investigator noticed a pale or ashen appearance (ATS, 2002). Chairs were available along the entire walk track. The investigator was prepared to administer inhaled albuterol via a powered nebulizer should the patient experience dyspnea that did not rapidly return to a routine steady state. Oxygen via nasal cannula was available to be administered if the patient experienced hypoxemia as evidenced by an oxygen saturation of less than 90% via oximetry. If the patient required further assistance, a physician would be notified and/or the patient would be accompanied by wheelchair to the Emergency Department of Harris Methodist H.E.B. Hospital, which is adjacent to the Bedford office of TPCCC.

Benefits

Compensation of fifty dollars (money order) for time and travel expenses was given to all participants who completed this study. Five dollars was given after the first and second visits and forty dollars was given at the end of the study. For patients who started the study but did not complete it, the appropriate compensation was mailed to them.

Power Analysis

A power analysis using SAS 9.2 for Windows was conducted to determine the statistical power for this pilot study sample size. The statistical power yielded from a mixed factorial ANOVA of the primary outcome variable, meters walked, was 28.6%. This power estimate was based upon a moderate effect size (difference between treatments = 35 meters, SD = 111), a study alpha of .05 and a beta of .20. A sample size of 18 patients was computed.

Data Analysis

The primary outcome measurement was the total distance walked in 6-minutes by each patient on 2 separate occasions. The dependent variables were the spirometric results, the six-minute walk test, and the Modified Borg Scale. The independent variables were the formoterol or placebo received on the second and third visits. A mixed factorial analysis of variance (ANOVA) was computed with the order of treatment as the between factor and the treatment as the within factor. If the test for the main effect of "between–subjects" factor (order of treatments) was not significant, then that factor was dropped and a one-way repeated measures ANOVA was employed. A change in the 6-minute walk test of 35 meters was required to demonstrate significant changes in functional status. At baseline, Puhan et al. (2008) reported patients walked distances ranging from 249 to 473 meters. For perspective, the usual distance walked in 6 minutes by marathon runner was 1,500 meters, average person on street 700 meters, and a patient waiting for hip replacement was 200 meters (Redelmeier et al.). SPSS 16.0 was used for these computations. Demographic, Modified Borg Scale and oximetry data was analyzed by employing descriptive statistics.

Delimitations

1. The cohort was a convenience sample of those patients in the Bedford office of Texas Pulmonary and Critical Care Consultants, P.A. Because this was a convenience sample of patients and a small sample size from one pulmonary practice in a suburban area, the ability to apply the findings to the general population of patients with moderate-to-severe COPD is limited.
2. The financial incentive of fifty dollars may have encouraged patients to participate who would otherwise decline. Whether the study results would differ between the two groups are not known.

3. Patients with COPD who are less motivated for walking exercise and/or adhering to their medication may have declined to participate, therefore limiting the ability to generalize findings to a larger population.
4. Only patients with moderate-to-severe COPD were included, so this study cannot represent patients with mild or very severe COPD.

Summary

This is a double blinded and placebo controlled pilot study investigating the combined effect of tiotropium and formoterol on the functional status of patients with moderate-to-severe COPD receiving care in the Bedford office of Texas Pulmonary and Critical Care Consultants, PA. A convenience sample meeting the inclusion and exclusion criteria was recruited. The use of tiotropium and inhaled corticosteroids was kept constant, with the addition of formoterol or placebo used as the study variable. All patients received both a placebo and formoterol in a randomized fashion. Spirometry, a six-minute walk test and the Modified Borg Scale were the measurement tools utilized to assess the functional status of these patients. Statistical analysis was performed using SAS for the power analysis, and SPSS was used to compute all the statistical data.

CHAPTER 4

FINDINGS

This chapter describes the process of patient selection and reports the results of statistical analysis for the measurement methods used to assess “The Combined Effect of Tiotropium and Formoterol on the Functional Status of Patients with Moderate-To-Severe COPD”. Study hypothesis stated that patients with moderate-to-severe COPD will show significant improvements in functional status as measured by spirometry, the six-minute walk test, and the Modified Borg Scale. Interpretations of the study findings are addressed in Chapter 5.

Study Sample

All participants in this study were patients of pulmonary physicians from the Bedford office of Texas Pulmonary & Critical Care Consultants, P.A. Of the total number of patients approached to participate, only two patients declined because of their reluctance to change their current medication therapy. One patient forgot about her enrollment appointment, and then dropped out due to family issues. The major obstacle in soliciting patient participation was the inclusion criteria e.g., Body mass index of 21-30 and the use of inhaled tiotropium for a minimum of 45 days or the exclusion criteria e.g., use of portable oxygen therapy. Another factor limiting potential participants was the season. The study was conducted during the fall and winter months when infectious respiratory illnesses are particularly high often causing exacerbations of COPD and sometimes hospitalization.

Twenty patients were ultimately enrolled in the study. Two patients did not complete the study. The first patient to withdraw from the study was a male with moderate COPD. After the first

visit, he began using his albuterol inhaler more frequently and felt that he was unable to stop using his long acting $beta_2$ agonist (salmeterol) for the duration of the study. He completed the enrollment visit, but did not return. The second patient was a female with severe COPD who experienced the only significant side effect related to the study medication. Prior to entering the study, she was taking Symbicort® (formoterol & budesonide) as one of her maintenance inhalers. This was discontinued for the duration of the study and replaced with only budesonide. On the second visit**,** after inhaling the study medication**,** she suddenly experienced tachycardia with a heart rate of 180 per minute and an oxygen saturation of 95%. The patient was immediately assisted to an exam room where she rested. After ten minutes**,** her heart rate returned to the normal rate of 100 per minute and an oxygen saturation of 90%. Dr. Gary Jones was immediately notified by telephone and instructions were given for her to make an appointment to see her primary physician for a follow up evaluation. The Institutional Review Board was informed of this episode in a timely manner and a written report was submitted. It is presumed that the patient experienced a supraventricular tachycardia unrelated to COPD. The patient may have been pre-disposed to this condition and the medication taken at this particular time triggered the episode. The patient did state that she had experienced similar palpitations previously but failed to communicate these to her physician— nor did she mention these episodes on her screening assessment form or during the interview.

Nine Caucasian women and nine men completed the study. Descriptive statistics are presented in Table 4.1. Patient age ranged from 59 to 78 years, with a mean of 70. Patient height varied between 58 and 72 inches (mean of 67 inches). Patients weighed 109 to 208 pounds (mean of 159). Body mass index ranged from 21 to 30 kg/m^2 (mean of 26). The history of personal tobacco use was calculated in pack years (packages of cigarettes smoked per day multiplied by the number of years smoked). Pack year history ranged from 25 to 120 (mean of 61 pack year history of tobacco use). On entry into the study, enrolled patients had a mean FEV_1 % predicted of 52% (range of 34 to 74% predicted). Ten patients were classified as stage II or

moderate COPD according to GOLD guidelines (Table 2.2, page 24), and eight patients were stage III or severe COPD.

Table 4.1. Descriptive Statistics for Study Patients

	Minimum	**Maximum**	**Mean**	**Std. Deviation**
Years of age	59	78	69.78	5.55
Height in inches	58	72	65.61	3.94
Weight in pounds	109	208	158.72	26.83
BMI (kg/m^2)	21.00	30.00	25.9	2.88
Pack year history	25	120	61	29.83
FEV_1 % Predicted	34	74	51.72	12.99

Spirometry

Spirometry was performed three times on all patients: on the first visit to comply with inclusion criteria, and then on the second and third visits, after patients inhaled placebo or formoterol, waited 60 minutes for the study medication's maximum effect, completed the six-minute walk test and rested 10 minutes. Table 4.2 shows the mean changes in both FEV_1 and FVC following the inhalation of formoterol compared to placebo. The mean FEV_1 increased from 1.33 to 1.41 liters, while the mean FVC increased from 2.66 to 2.81 liters.

Table 4.2. Spirometry Changes

	Minimum	**Maximum**	**Mean**	**Std. Deviation**
FEV_1 Placebo	0.67	2.53	1.33	0.52
FEV_1 Formoterol	0.79	2.51	1.41	0.52
FVC Placebo	1.67	4.27	2.66	0.80
FVC Formoterol	1.85	4.30	2.81	0.75

A mixed factorial analysis of variance (ANOVA) was computed with the order of treatment as the between factor and the treatment as the within factor. The between subjects factor (order of treatments) was not significant for either FEV_1 or FVC. A one-way repeated measures ANOVA comparing the spirometry testing of patients after the inhalation of a placebo and formoterol revealed a significant difference between the two groups for both FEV_1 and FVC. The FEV_1 was computed with $(F1,17) = 126.74$, $p < 0.05$, and the FVC was $(F1,17) = 228.99$, $p < 0.05$. When patients inhaled formoterol they significantly increased both their FEV_1 and FVC.

The American Thoracic Society states that to be clinically significant the FEV_1 or the FVC must change at least 12% and 200 mL. Using this definition, twelve patients had no significant clinical change in either of their spirometry values. Of the six patients who demonstrated an improvement in spirometric values, only one had a change in FEV_1 that met these criteria. Five patients had a clinically significant change in their FVC.

Six-Minute Walk Test

The six-minute walk test was performed on the second and third visits after patients inhaled the placebo or formoterol and waited 60 minutes for the study medication's maximum effect. Table 4.3 shows the mean distance patients walked in six-minutes after the inhaled placebo was 377.5 meters, with a range of 265 to 539 meters (869 to 1768 feet with a mean of 1238). The mean distance patients walked after the inhaled formoterol was 387.28 meters, with a range of 282 to 527 meters (925 to 1729 feet with a mean of 1270). A mixed factorial analysis of variance (ANOVA) was computed**,** using the order of treatment as the between factor and the six-minute walk distance as the within factor. The order of treatments was not found to be significant.

Table 4.3. Six-Minute Walk Tests Expressed in Meters

	Minimum	Maximum	Mean	Std. Deviation
Placebo	265	539	377.5	71.51
Formoterol	282	527	387.28	62.87

A one-way repeated measures ANOVA was used to analyze the distance that patients walked in six minutes after inhaling either a placebo or formoterol. A significant difference was revealed between the two groups ($F_{1,17} = 588.91$, $p < 0.05$). After the patients inhaled formoterol, they walked significantly farther than when they inhaled a placebo medication. Although this change in distance walked was *statistically* significant, a *clinically* significant improvement was not achieved. As previously discussed, Puhan et al. (2008) determined that the six-minute walk distance would need to improve by 35 meters to be considered clinically significant. Individual changes in distance walked ranged from negative 12 meters to positive 43 meters. Only two patients were able to achieve the clinically significant distance change**,** improving 38 and 43 meters respectively.

Modified Borg Scale

The Modified Borg Scale was used on the second and third visit to independently quantify the patients' perception of dyspnea and the perception of fatigue in response to the study medication before and after the six-minute walk test. The scale ranges from zero, indicating "nothing at all", to a ten, indicating a very, very severe or maximal perception of dyspnea or fatigue. Patients received the inhaled placebo or formoterol, waited 60 minutes for the study medication's maximum effect and then rated their pre-walk perception of dyspnea and their perception of fatigue. The post-walk assessment was repeated immediately following the six-

minute walk test. Table 4.4 shows a mean change in dyspnea scores of minus 0.22 from pre- to post-walk after inhaling placebo, and a mean change of minus 0.06 from pre- to post-walk after inhaling formoterol. Table 4.5 shows a mean change of minus 0.92 from pre- to post-walk after inhaling placebo and a mean change of minus 0.64 from pre- to post- walk after inhaling formoterol. The data, therefore, indicate that the patients' perception of dyspnea and perception of fatigue was less with inhaled placebo than with inhaled formoterol and less after the six-minute walk test than before the six-minute walk test.

Table 4.4. Modified Borg Scale for Dyspnea

	Minimum	**Maximum**	**Mean**	**Std. Deviation**
Pre-walk Placebo	0	3	0.64	0.94
Post-walk Placebo	0	4	0.42	1.14
Pre-walk Formoterol	0	2	0.47	0.67
Post-walk Formoterol	0	4	0.53	1.04

Table 4.5. Modified Borg Scale for Fatigue

	Minimum	**Maximum**	**Mean**	**Std. Deviation**
Pre-walk Placebo	0	5	2.92	1.40
Post-walk Placebo	0	7	2.0	2.05
Pre-walk Formoterol	0	4	2.67	1.27
Post-walk Formoterol	0	7	2.03	1.94

Summary

This pilot study of 18 patients with moderate-to-severe COPD measured the effects of inhaled formoterol compared to inhaled placebo on the functional status of patients as determined by FEV_1 and FVC via spirometry, the distance walked during a six-minute walk test, and the patients' perception of dyspnea and fatigue via the Modified Borg Scale. *Statistically* significant improvement was demonstrated in all measures except the Modified Borg Scale. *Statistically* significant spirometric changes of both the FEV_1 and FVC occurred, but were not increased by the 12% and 200 mL change stated as *clinically* significant by the American Thoracic Society. One patient was found to have a clinically significant change in FEV_1, and five patients obtained clinically significant changes in their FVC with formoterol. The distance walked in six-minutes was found to be *statistically* significant, but did not achieve the commonly accepted *clinically* significant change of 35 meters. Only two patients were able to walk a clinically significant distance after inhaling formoterol. No significant subjective improvement in dyspnea or fatigue was reported by patients after inhaling formoterol as compared to placebo. Demographic data was not found to identify discerning characteristics that would be beneficial for distinguishing which patients benefitted most from the combined therapy.

CHAPTER 5

DISCUSSION

The purpose of this study was to evaluate the combined effect of tiotropium and formoterol on the functional status of patients with moderate-to-severe COPD. Methods used to assess functional status were spirometry, the six-minute walk test, and the Modified Borg Scale. This chapter will address the advantage and disadvantage of each method in light of current research and the results of this study, as well as, the direction for future research. Unfortunately, there is no one component of lung function that correlates precisely with functional status.

Major Findings

Model

The model in Chapter 1 (Figure 1.1) reflects the components of functional status identified by Leidy (1995), Weaver et al (1997), and Yeh et al. (2004) that were incorporated in this study. The components include the severity of disease, functional capacity, functional performance, dyspnea and fatigue. Dynamic hyperinflation, which is also relevant to the pathology of COPD, was included in the model but not measured due to present difficulties in obtaining accurate and consistent measurements.

Functional capacity was measured by the six-minute walk test, and disease severity was measured by spirometry. Both dyspnea and fatigue were measured by the Modified Borg Scale. It is presumed that these are valid measurements for determining the functional status of patients

with COPD. Prior studies (described in Chapter 2) have indicated that combining long-acting bronchodilators i.e. tiotropium and formoterol, each with different mechanisms of action, may be more beneficial in relieving symptoms of COPD than one drug alone.

Spirometry

This pilot study comparing tiotropium and formoterol to tiotropium and placebo found spirometric changes of *statistical* significance, but not of *clinical* significance. Guidelines by the American Thoracic Society regarding significant clinical change in spirometry are an increase of 12% and 200 milliliters for either the FEV_1 or the FVC. Only one patient demonstrated a clinical improvement in FEV_1 and five patients achieved a clinically significant increase in FVC.

Frequently, patients with COPD do not obtain significant clinical changes in spirometry but this lack of improvement does not deter the current recommendations for inhaled medication therapy. The results from this study reflect the current literature findings of variable spirometric improvements from inhaled medications. Since these study patients were already using tiotropium and an inhaled corticosteroid, significant clinical spirometric changes by the addition of formoterol may not be achievable. Clearly, additional studies with larger sample sizes are required to confirm or reject any potential benefit.

Although most studies of therapeutic interventions have focused on improvements in spirometric values, information is accumulating that there is poor correlation between patient symptoms and FEV_1. Patients frequently report improved quality of life irrespective of positive changes in FEV_1 or FVC. Still, spirometric testing continues to be the easiest and most reproducible outcome measure to obtain and therefore the one most utilized by investigators. In the most recent study available, Tashkin, Pearle, Iezzoni & Varghese (2009) examined patients for 12 weeks using the combination of formoterol and tiotropium compared to tiotropium alone. Unlike the results of this pilot study, the authors reported clinically significant improvements in FEV_1, FVC, and clinical symptom scores when using combination therapy. Their study is not

directly comparable in that actual data on FEV_1 and FVC were not reported. In addition, the authors used cumulative Area Under the Curve data of sequential measurements for these parameters over time and did not use the Modified Borg Scale to quantitate clinical symptoms.

Six Minute Walk Test

In this pilot study, clinically significant improvements were not demonstrated. To some extent these results are intuitively obvious. If the patient takes the medication for five days rather than one day, and achieves a steady-state level of medication [a medication such as formoterol with a ten hour half-life (UpToDate, n.d.)], it would take roughly fifty hours to achieve a steady-state level to anticipate further benefit (53.6 meters). Therefore, adding a drug such as formoterol to a regimen that already includes potent medications such as inhaled corticosteroids and tiotropium may or may not be of benefit. No clinical benefit using the 35 meter benchmark was derived in this study. This study adds to previous work using six-minute walk testing to evaluate formoterol and tiotropium [Richter et al. (2006); Vogelmeier et al. (2008); & Cazzola et al. (2008)]. Only Cazzola et al. (2008) was able to obtain a clinically significant improvement in distance walked after five days of formoterol therapy. After one dose of formoterol the distance improved by only 35.3 meters as compared to the 53.6 meters obtained after five days of therapy. Patients in the Cazzola et al. study were allowed a short acting beta-2 agonist as the only inhaled medication other than formoterol. This differs from the current pilot study where patients were routinely taking both inhaled tiotropium and an inhaled corticosteroid.

Several studies have indicated that the six-minute walk test may be a reasonably accurate prognostic indicator of functional status. Redelmeier, Bayoumi, Goldstein & Guyatt (1997) concluded that patients would notice a difference in their functional status with a change in 54 meters while performing the six-minute walk test. Recently Puhan et al. (2008) reported that patients with moderate-to-severe COPD needed to improve by only 35 meters in order to note a change in functional status. The study presented here was able to achieve a *statistically*

significant improvement in the six-minute walk test, but not the *clinically* significant distance as determined by Puhan et al. As discussed in Chapters 1 and 2, the literature concerning functional status in patients with COPD is sparse and fairly primitive. Only through validation of the work by Puhan et al. by other investigators, and additional research similar to this pilot study**,** will the distance that is truly reflective of an improvement in functional status be determined.

Modified Borg Scale

The Modified Borg Scale was utilized in this study to assess the patient's subjective level of dyspnea and fatigue. The patients rated their severity of dyspnea and fatigue on a scale of 0 to 10 (0 indicting nothing at all and 10 indicating very, very severe) before the six-minute walk test and immediately after the walk test. It was an unexpected finding that patients frequently reported more dyspnea at rest, prior to the walk test, and less dyspnea immediately after the walk test even though patients appeared to be more short of breath. The reason for the paradox is not clear. The finding does, however, reinforce the dilemma that the determinants of dyspnea are not completely understood and require more investigation. This study did support the lack of correlation between spirometric values and perceived dyspnea. For example, a common statement by patients with COPD engaged in outpatient pulmonary rehabilitation programs is that they often feel better at the end of an exercise session than when they arrived, even though they are tired and tachypneic at the time.

New Directions

As discussed in Chapter 2, dynamic hyperinflation is one of the major changes that occur in patients with COPD, and the ability to accurately quantify the degree of dynamic hyperinflation would add valuable information to the study of functional status. This study did not attempt to measure dynamic hyperinflation due to inherent technical difficulties in testing. Precise measurement of lung volumes requires the use of body plethysmography and cannot be

performed while walking. An indirect measurement of dynamic hyperinflation can be achieved by recording a decline in inspiratory capacity (IC) with exercise, although this too is a difficult test to perform accurately. Recent attempts have been made to quantify dynamic hyperinflation using an easier method of measuring inspiratory capacity. Currently, accurate measurements of IC are obtained using a stationary bicycle or treadmill in a highly controlled laboratory setting with specialized equipment. Callens et al. (2009) utilized a handheld spirometer to measure IC immediately after completing a six-minute walk test. The maneuver was performed with the patient standing and the researcher prompting the patient with a command of "at the end of the next normal breath out, take a deep breath all the way in". Before the walk IC was measured with a mean of 2.30 liters (range of 1.85 to 2.53) and after the walk with a mean of 2.08 liters (range of 1.64 to 2.58). The median change in IC was minus 0.210 liters (range of 0.055 to minus 0.44 liters). The walk-induced dynamic hyperinflation was no longer significant 75 seconds after the end of testing. Given the logistics of applying a nose piece as soon as the patient stops walking, handing the patient the spirometer, placing the mouthpiece appropriately in the mouth, and giving the command, allows enough time for such a rapid decrease in dynamic hyperinflation that reproducibility of test results is questionable (Callens et al.). Hopefully, in the future, newer techniques will be developed that will more easily and accurately measure IC which can be used to assess functional status in patients with COPD

Limitations

This study has limitations since it is a pilot study and is therefore underpowered. Twenty patients were enrolled and 18 patients completed the study. Since a convenience sample was obtained from a single suburban pulmonary medicine office, these findings may not apply to rural or densely populated inner cities. All the patients were Caucasian, so this study would not represent other ethnicities. All patients were currently taking a combination inhaled corticosteroid

and long acting beta-2 agonist (either Advair® or Symbicort®). The role played by the inhaled corticosteroid will need further investigation.

Conclusions

The study did find *statistically* significant increases in the distance walked in six minutes and also *statistically* significant improvements in spirometric testing after the addition of formoterol to tiotropium. Mean *clinically* significant changes were not obtained in either the six-minute walk test or the spirometry testing, albeit two patients (11%) did achieve clinically significant increases in their six-minute walk tests, and six patients (33%) achieved clinically significant increases in their spirometry testing. The findings of this study did show variability in the responses of patients with respect to distance walked and changes in lung function. Current medication guidelines by GOLD are the same for all patients with COPD and vary only with the level of severity. With COPD being such a heterogeneous disease, therapies in the future may need to be patient specific. A potential research question is how will the clinical and therapeutic differences in patients be identified? Presently, these differences are elusive but if better delineated would allow for accurate assessments of functional status in patients with COPD in response to treatment. Pending further research, it is recommended that patients with moderate-to-severe COPD continue to use the currently recommended combination inhaled therapy of formoterol and tiotropium.

Recommendations for Future Research

The most intriguing aspects of this study involve some of the limitations. There is little ability to quantify functional status precisely, and near absent correlation between changes in the six-minute walk test, spirometry, and symptoms. The variability in these findings speaks to the need to identify patients who respond to inhaled medication therapy and those who do not. This process will help refine medication therapy for responsive patients. Additional research is needed

to more accurately identify the components of functional status that will represent this patient population. Perhaps a greater focus on the development of a more practical and reliable method of measuring dynamic hyperinflation would provide the needed information.

Researchers will need to continue to evaluate and maximize the functional status of these patients. The six-minute walk test may be incorporated into practice in order to assess the patients' current functional status. Whether this measurement will ultimately be the best tool to assess functional status will need to be validated by future research.

Implications for Nursing

COPD is a common disease, diagnosed in more than 12 million Americans so nurse practitioners, working in a variety of clinical settings, may encounter symptomatic patients. It is critical, therefore, that the nurse practitioner has a sound knowledge base of the disease process and the clinical manifestations. Patients experiencing dyspnea at rest or on exertion, chronic cough with or without sputum production, and wheezing should be promptly referred for pulmonary function tests. If COPD is diagnosed early, the step-wise approach to medical management can reduce the patient's frequency of exacerbations, improve their quality of life, enhance their functional status, and prolong survival.

The nurse practitioner directly caring for patients with COPD must continuously evaluate the patients' adherence to their medication regimen and the physiologic response. Otherwise, optimal clinical benefit will not be obtained. Inhaler therapy is complex and oftentimes, patients simply get confused. As a result, they may fail to take their medications, or because of poor technique fail to receive the adequate dose. It is quite common for patients to question the need for combination therapy so the purpose and potential benefit must be explained and the patient's understanding assessed.

The goal in prescribing medications is always to relieve symptoms and maximize functional status but this will only occur if patients actually take their medication. In 2007, the

International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), a non-profit association, was founded for this very purpose—to promote patient adherence to prescribed medications. Patient adherence with inhaled medications needs to be defined, and this adherence requires that appropriate evaluative measurement tools be established. Implications for non-adherence should be addressed and these barriers identified and evaluated. Membership includes pharmaceutical representatives, health-care providers, and patients. As a nurse practitioner who cares for patients with COPD, it has been my honor to be selected this year (2010) as a member of this important health care team.

Lastly, the nurse practitioner must be cognizant of the patient's financial status because this too influences their access to prescribed medications. The cost of inhaled medication continues to rise and there are no generic substitutes currently available on the U.S. market. In 2007, one out of seven patients, under age 65, reported being unable to fill a prescription in the previous year because they could not afford it (Congdon & Charneski, 2009). And if they can't afford the medication, they are not going to be taking it. For patients of Medicare age, once their coverage limit is reached then the Coverage Gap or "donut hole" occurs. It is during this period of time, the cost of mediations is not covered, and the patient pays full price. Only when a new calendar year begins or the patient reaches the $5,100 in the prescribed medication cost does the Medicare coverage begin again.

Summary

This study found improvements in both the six-minute walk test and in spirometry that were *statistically* but not *clinically* significant. It is recommended that patients continue to take the combined therapy of formoterol and tiotropium until research contradicts this evidence. More research is needed to ascertain the best measurement of functional status and which patients will benefit from combination therapy.

APPENDIX A

THE GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTUCTIVE LUNG DISEASE (GOLD) GUIDELINES FOR THERAPY

Table A.1. GOLD (2008) Guidelines for Therapy.

I: Mild	II: Moderate	III: Severe	IV: Very Severe
Active reduction of risk factor(s); influenza vaccination			
Short-acting bronchodilator (when needed)			
	Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation.		
		Add inhaled glucocorticosteroids if repeated exacerbations.	
			Add long term oxygen if chronic respiratory failure. Consider surgical treatments.

APPENDIX B

EXPLANATORY MODEL FOR FUNCTIONAL STATUS IN COPD

BY WEAVER, RICHMOND & NARSAVAGE

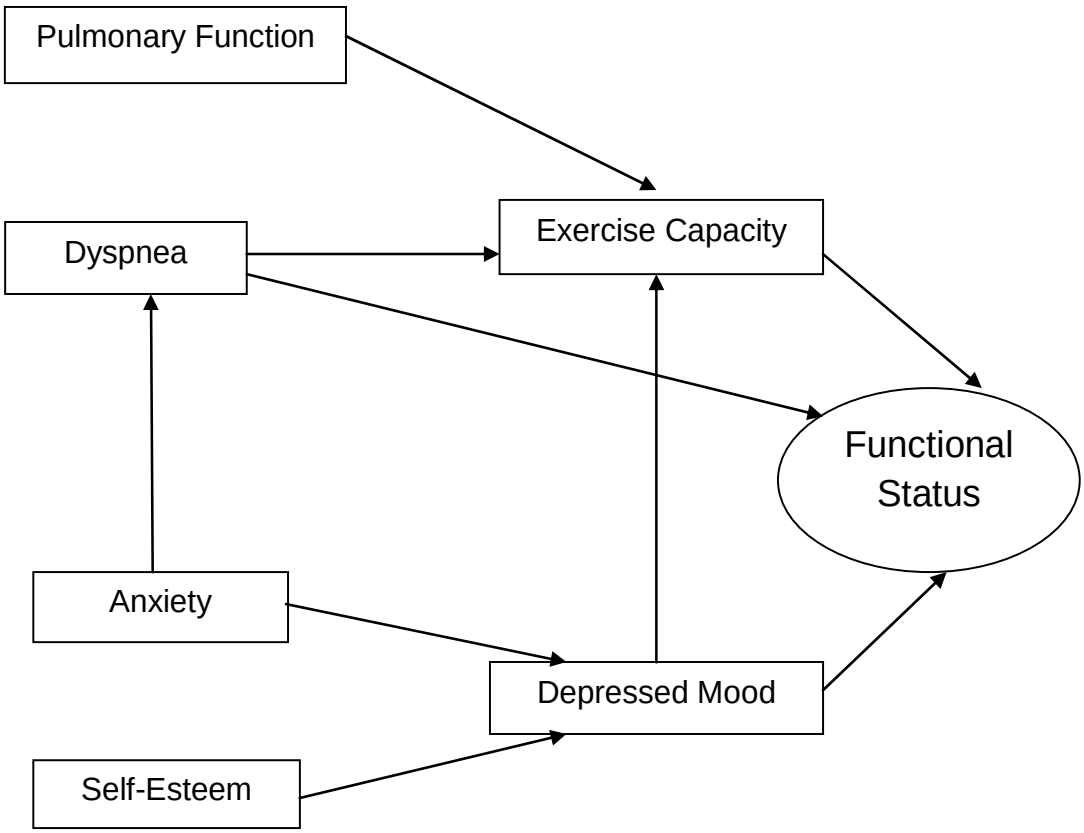

Figure B.1 Explanatory Model for Functional Status in COPD by Weaver, Richmond & Narsavage (1997).

APPENDIX C

FUNCTIONAL STATUS MODEL FOR COPD

BY YEH, CHEN, LIAO & LIAO

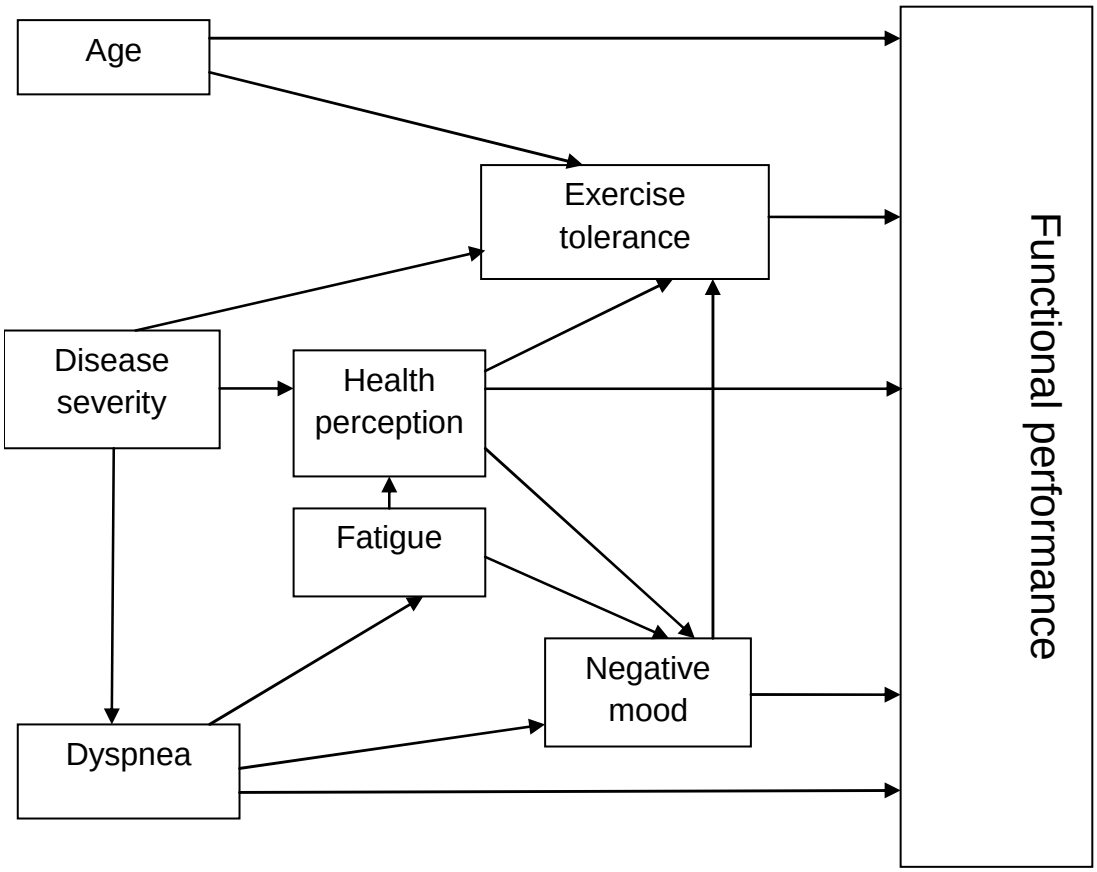

Figure C.1. Functional Status Model for COPD
by Yeh, Chen, Liao & Liao (2004).

APPENDIX D

PROTOCOL

PROTOCOL

Potential subjects will be identified and initially screened by their pulmonary physicians or the office nurses. Once identified they will be referred to:

The investigator, Catherine S. Jones, RN, MSN, ANP-C will initiate, conduct, and conclude this study.

She will:

1. Meet with identified potentially eligible patients in the Bedford office of Texas Pulmonary & Critical Care Consultants, P.A. (TPCCC) for a screening interview using the Orientation Meeting Script (Appendix O).

2. Interview potentially eligible patients outlining eligibility, study requirements, and the process for completing the study. This will involve reviewing all inclusion and exclusion criteria as well as changes in the patients' current medication regimen during the study. (Appendix P)

3. Review the consent document with the eligible patients and answer any questions.

4. Inform the patients they may withdraw from the study at any time but if they elect to do so, they will immediately resume their pre-study medication regimen.

5. Obtain consent of all patients agreeing to participate in the study by having them sign an informed consent form approved by the Institutional Review Board (IRB) at The University of Texas at Arlington.

6. Obtain verbal consent from the primary pulmonologist approving the participation of his patient(s) in the study.

7. Initiate first intervention after consent is signed which will include:

   A. Height and weight of the patient with a designated measurement pole and a Health-o-meter balance scale. Shoes and jacket will be removed.
   B. Screening oximetry with Nonin Model 8500P oximeter to document the study requirement for an O_2 Sat of 90% or greater and a resting pulse rate of less than 120 beats/minute.
   C. Screening spirometry as established by American Thoracic Society (ATS) with a Puritan-Bennett Renaissance II spirometer. (See Appendix J & K).
   D. Inform patients on the need for adjusting their inhaled medications for the duration of the study and provide both prepared verbal and written instructions (Appendix S) on the replacement medications. Assess the patients' understanding of the adjusted medication regimen by having them repeat the instructions and initial the prepared form for the patients to take home to help with the new medication routine. Record the date and time inhaled albuterol is taken (q 4-6 hours for shortness of breath). Instruct the patients to bring the form (Appendix R) to each scheduled appointment.
   E. Instruct the patient as applicable based on pre-study medication regimen to:

1. Discontinue the use of combined long-acting beta-2 agonist/inhaled corticosteroid (either Advair or Symbicort) for duration of the study and take the replacement of the same inhaled corticosteroid _____puffs twice a day for the duration of the study.
2. Continue taking inhaled tiotropium as prescribed (Inhale one 18 mcg capsule of tiotropium via HandiHaler once in the morning).
3. Use the short acting beta-2 agonist (albuterol inhaler) q4-6 hours for shortness of breath. Record date and time used on prepared form.
4. Telephone Catherine Jones at the provided telephone number if experiencing shortness of breath requiring albuterol inhaler the morning of the scheduled appointment. The visit will be rescheduled.
    A. Using a prepared script (Appendix J) explain the procedure for the six minute walk test and have the patient perform a two minute practice walk that will be not scored.
    B. Assess oxygen saturation with the oximeter after the two-minute practice test to rule out exercise induced hypoxemia.
    C. Using a script and a laminated Modified Borg Scale (Appendix L), patients' will rate their level of shortness of breath and fatigue after performing the walk test.
    D. Randomly assign patients into double blinded interventions by Gary Jones MD (designated physician) without knowledge of the investigator. (See appendix Q).

    1. Schedule date and time for second intervention following adequate wash out period from current inhaler medication (48 hours). Give patient the scheduled date and time in writing.

Prior to second intervention have patient sign re-consent form (Appendix T).
Start second intervention which will include:

A. Ask patient to sign re-consent form to participate in the study.
B. Assist with inhalation of placebo or formoterol (18 mcg).
C. Wait for one hour to allow maximum benefit from study medication. Water will be provided but no coffee, tea, or soft drinks. Magazines and DVDs will be available.
D. Assessment of pulse rate, Modified Borg Scale, and oximetry after one hour.
E. First six minute walk test
F. Assessments of Modified Borg Scale and oximetry immediately after the six minute walk after sitting in a chair. Spirometry will be performed after a ten minute rest period.
G. Schedule date and time for third intervention after wash out period of 48 hours

2. Prior to third intervention have patient sign re-consent form (Appendix T).
Start third and final intervention which will include:

A. Ask patient to sign re-consent form to participate in the study.
B. Assist with inhalation of placebo or formoterol (18 mcg).
C. Wait one hour to allow maximum benefit from study medication; water will be provided but no coffee, tea, or soft drinks. Magazines and DVDs will be available.
D. Assessment of pulse rate, Modified Borg Scale and oximetry
E. Second six minute walk test
F. Assessments of Modified Borg Scale and oximetry immediately after the six minute walk after sitting in a chair. Spirometry will be performed after a ten minute rest period.
G. Debriefing and instructions on resuming pre-study medication regimen
H. Compensate patients for study participation.

APPENDIX E

PHYSICIANS APPROVAL FORM

FORM-A-1

Date: 9/30/09

To: Institutional Review Board

University of Texas at Arlington

From: Pulmonary physicians from the Bedford office of Texas Pulmonary & Critical Care Consultants, P.A.

Re: Clinical study performed by Catherine Jones, RN, MSN, ANP-C

Titled: The combined effects of tiotropium and formoterol on the functional status of patients with moderate-to-severe COPD

We have read and approve the proposed study and protocol involving our patients with moderate-to-severe chronic obstructive lung disease. This study will be initiated, conducted and, concluded by Catherine Jones, RN, MSN, ANP-C on the premises of our Bedford office with Gary L. Jones, MD as the designated physician.

Mrs. Jones has provided us with the inclusion/exclusion criteria of patients she seeks for the study. As we see patients who we think meet these criteria, we will tell them about the opportunity to participate in the study. We will be solely responsible for the selection of our patients who will be participating in this study. All medications to be used will be prescribed by the primary physician for each patient enrolled in the study.

We understand the Methods and Procedures of the study and provide authorization for it to be conducted on our office premises.

Gary L. Jones, MD, FCCP

James T. Siminski, MD, FCCP

Donald L. Washington, Jr., MD

APPENDIX F

TEXAS PULMONARY & CRITICAL CARE CONSULTANTS, PA

BOARD APPROVAL FORM

TEXAS PULMONARY & CRITICAL CARE CONSULTANTS, P.A.

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Jack G. Gilbey, Jr., M.D.
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North Richland Hills, Texas 76180
(817) 284-4343
(817) 590-4393 Fax

January 12, 2008

To: Institutional Review Board
University of Texas - Arlington

From: Mr. Tim Pruden, M.B.A.
Business Manager

Re: Research proposal by Catherine Jones, RN, ANP-C

The Executive Board of Texas Pulmonary & Critical Care Consultants, P.A. has reviewed and approved the proposal by Catherine Jones, RN, ANP-C to perform six minute walk tests before and after the administration of inhaled bronchodilators in patients with chronic obstructive pulmonary disease on the premises of our Bedford office.

Sincerely,

Tim Pruden
Business Manager

APPENDIX G

SCREENING CRITERIA

Patient's Name:_____

Screening Criteria for Study

	Inclusion Criteria:
	Moderate-to-severe COPD
	Using tiotropium (Spiriva) for at least 45 days
	Pack year history of at least 10 pack years or more
	50 – 80 years old
	Able to read & speak English
	Able to perform six-minute walk test
	BMI of 21 to 30
	Using inhaled corticosteroid for at least 45 days

	Exclusion Criteria:
	Lung diseases other than COPD (i.e. asthma, TB, interstitial lung disease, lung cancer)
	Family history of Alpha-1 antitrypsin deficiency
	Resting heart rate of > 120 beats/minute
	History of CHF
	MI within last 12 months
	Unstable or stable angina
	Exacerbation of COPD within last 1 month
	Hospitalization within last 3 months
	Changes in activities of daily living prior to the study (i.e. starting pulmonary rehab)
	Chronic use of oral corticosteroids
	Use of oral corticosteroids within last month
	Use of portable oxygen therapy with exertion &/or oxygen saturation of < 90%

APPENDIX H

RECRUITMENT FLYER

Research study in this Bedford office to learn more about

Patients with COPD and their inhaled medications

If you have moderate to severe COPD, 50-80 years of age, currently take Spiriva, and able to walk unaided for 6 minutes inside on flat ground,

please ask Casey the Nurse Practitioner or our office staff for more information

*If you meet the criteria & participate you will receive up to a $ 50.00 money order.

APPENDIX I

PULSE OXIMETRY

PULSE OXIMETRY

Pulse oximetry will be utilized as a screening tool on the first intervention with the patient and will also be used before and after the six minute walk tests to ensure that safety is maximized. Patients with oxygen saturations of less than 90% will be excluded from this study. A sustained oxygen saturation of 88% or less satisfies the requirement to prescribe oxygen therapy by Medicare standards.

The first primitive oximeter was invented by Carl Mattes in 1935 (Mechem, 2008), and this device has dramatically improved over time. Pulse oximeters are excellent non-invasive tools used to assess the saturation of oxygen in arterial hemoglobin (Trumper, 1989). Oximetry will reliably detect hypoxemia well before medical personnel can clinically recognize it (Trumper). Patients with COPD may exhibit hypoxemia especially during exercise or sleep, and an oximeter is often indicated for monitoring their hemoglobin oxygen saturation.

Oximeters estimate the saturation of hemoglobin with oxygen through use of Beer-Lambert's Law (Trumper, 1989). This law states that "if a solute is dissolved in a clear solvent, its concentration can be determined if a light of known wavelength is transmitted through the solution" (Trumper). Two wavelengths of light are utilized for pulse oximeters in order to assess the absorption of oxygenated (saturated) and deoxygenated (unsaturated) hemoglobin. Unsaturated hemoglobin absorbs light in the spectrum of 600 to 750 nm, whereas saturated hemoglobin absorbs light in the band of 850 to 1000 nm (Mechem, 2008). The measurement ratio of these two forms of hemoglobin estimates the percentage of oxygen saturation. Red and infrared light emitting diodes and a photo detector make up the oximeter device (Mechem, 2008). The emitter and the two photo detectors should be opposite one another with the tissue in-between. While this device was first developed utilizing an earlobe clip, currently both the two-sided finger probe and the ear clip are commonly used. While arterial oxygen saturation of

hemoglobin is referred to as S_aO_2, the non-invasive measurement with a pulse oximeter is designated as S_pO_2 (DeMeulenaere, 2007).

Normal arterial oxygen saturation is between 97 and 99%; however, a S_pO_2 of greater than 95% correlates with a normal range of the partial pressure of arterial oxygen (P_aO_2), i.e., 80 to 100 mmHg (DeMeulenaere, 2007). Oximeters in the laboratory are considered to be reliable between 70 to 100% S_pO_2 (DeMeulenaere), but in clinical practice the lower range accuracy is considered to be 80% (Mechem, 2008). The displayed pulse and oxygen saturation values are averaged based upon the prior measured three to six seconds, so this delay needs to be taken into account by the health care provider (Mechem). In clinical practice, a desaturation with exercise of ≥ 5% is considered abnormal (Mechem).

Common sources of inaccurate readings from pulse oximeters include improper probe placement, motion artifact, or ambient light (Mechem, 2008). Cold extremities or poor peripheral perfusion may cause unsatisfactory signal reception (DeMeulenaere, 2007). Black and brown fingernail polish has been found to decrease measured oxygen saturation by approximately 2% (Chan & Chan, 2003). However, if the probe is placed transversely on the finger, rather than in the usual top-to-bottom position, there are no differences in saturations measured with or without the presence of fingernail polish (Chan & Chan). Lastly, in chronic heavy smokers (who inhale significant amounts of carbon monoxide, falsely high oximetry readings may occur. This is due to the replacement of oxygen for carbon monoxide on hemoglobin (carboxyhemoglobin) indicating a higher, but inaccurate, hemoglobin oxygen saturation (Mechem).

APPENDIX J

CALIBRATION OF SPIROMETER

Calibration of Spirometer

1.	Calibration of spirometer should be performed daily.
2.	Use 3 liter syringe to check calibration of spirometer.
3.	Attach calibration syringe to spirometer with plastic adaptor.
4.	Check volume accuracy: 3 varying flow rates between 0.5 and 12 liters/second with injection times between less than 1 second, 6 seconds, and in the middle of these two flow rates.
5.	Volume obtained from syringe should be +/- 3.5% of known volume with a range of 2.90-3.10 liters.
6.	Maintain a notebook log listing date and achievement of calibration.

APPENDIX K

SPIROMETRY PROCEDURE

Spirometry Procedure

1. Calibrate spirometer.
2. Seat patient comfortably in a chair.
3. Input demographic data of patient: age, gender, height in inches, ethnicity and weight in pounds.
4. Describe procedure and demonstrate if needed.
5. Instruct patient to inhale as deeply as possible.
6. Place nose clip on patient's nose.
7. Instruct patient to put mouthpiece in mouth, completely sealing the mouthpiece.
8. Instruct patient to exhale as hard and as long as possible (at least 6 seconds but no more than 15 seconds).
9. Remove nose clip.
10. Patient removes mouthpiece and is allowed to rest.
11. Repeat procedure, when the patient is ready, for at least 2 more times with a maximum of 8 attempts. The machine will indicate if the patient's attempt is not acceptable. The best spirometry effort will be selected by the machine and listed first on the print out. Two efforts (FEV1 & FVC) need to match within 150 mL to be acceptable.

APPENDIX L

SIX MINUTE WALK TEST SCRIPT

Six-Minute Walk Test Script

Before walk: “The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.”

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

“Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog.

Start when you are ready.”

During walk: Speaking in an even tone of voice.

1 minute: “You are doing well. You have 5 minutes to go.”

2 minutes: “Keep up the good work. You have 4 minutes to go.”

3 minutes: “You are doing well. You are halfway done.”

4 minutes: “Keep up the good work. You have only 2 minutes left.”

5 minutes: “You are doing well. You have only 1 minute to go.”

5:45: “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.”

6 minutes: “Stop!” Mark the spot where the patient stopped by placing a piece of tape on the floor. Offer congratulations by recognizing the patient’s effort when the test is over.

American Thoracic Society (2002).

APPENDIX M

SIX MINUTE WALK TEST WORKSHEET

WORKSHEET FOR 6-MINUTE WALK TEST

Date_____ Patient ID Number_____ Age_____

Height_____inches Weight_____pounds Gender_____

Medications taken today: (dose & time)

Tiotropium: _____

Inhaled Corticosteroid: _____

_____

Any change in patient history since last visit?

_____

_____

Vital Signs: BP_____ Respiratory Rate_____

Oxygen Saturation/Pulse: Pre-walk_____ Post-

walk_____

Borg Scale: Dyspnea Pre-walk_____ Post-walk_____

Fatigue Pre-walk_____ Post-walk_____

6MWT results: Walk test number_____

Number of laps_____ x 60 meters + final partial lap (measured with tape measure)

_____ = _____TOTAL METERS (_____feet) walked in 6 minutes

Discomfort, pain or other symptoms during testing:

_____

_____

Notes: _____

_____

Lap counter: _____

APPENDIX N

MODIFIED BORG SCALE

& INSTRUCTIONS

MODIFIED BORG SCALE

This scale is a subjective measurement of dyspnea and fatigue.

SCALE	SEVERITY
0	Nothing at all
0.5	Very, very slight (Just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (Maximal)

American Thoracic Society, 2002.

INSTRUCTIONS FOR MODIFIED BORG SCALE

1. Give laminated Modified Borg Scale to patients.
2. Instruct patients to select the number on the scale from 1 to 10 that indicates their shortness of breath at this precise moment. Zero indicates no shortness of breath, 10 indicates severe shortness of breath.
3. Instruct patients to select the number on the scale from 1 to 10 that indicates their fatigue at this precise moment. Zero indicates no fatigue, 10 indicates severe fatigue.

APPENDIX O

ORIENTATION MEETING SCRIPT

ORIENTATION MEETING SCRIPT

This meeting will usually occur during a routine office appointment.

INTRODUCTION – Hello, I am Catherine Jones or "Casey" the Nurse Practitioner for this office. I am also a PhD nursing student at the University of Texas at Arlington conducting research to investigate the combined effect of using two long-acting inhaled bronchodilators (Spiriva and Foradil) on decreasing the symptoms of COPD like shortness of breath and fatigue. Would you have a few minutes now for me to explain the study to see if you would be interested in participating? I would appreciate your time.

If the patient says yes, I will continue.

PURPOSE OF THE STUDY –

As I said before, I will be testing the effect of adding Foradil to your present medication Spiriva to improve your shortness of breath and fatigue. Your physician will prescribe the Foradil that you will use during the study at no cost to you. The study will involve three visits with each visit taking approximately 1 ½ hours to complete. There are certain criteria for participating in the study therefore you would need to answer a few questions concerning your medical history. If you meet the criteria (and I believe you will), I will ask you to read and sign a consent form indicating your approval. You could then have the first visit today or I will schedule it at another time that would be more convenient. Either way, I want to mention briefly what the three visits involve.

The <u>first visit</u> will involve: Height and weight measurements, screening oximetry to determine % 0_2 saturation, spirometry (a breathing test), and a 2 minute practice walk. The practice walk is to familiarize you with the procedure involved for a 6 minute walk test that you will be asked to perform during the 2^{nd} and 3^{rd} visits.

The <u>second visit</u> will involve you inhaling a placebo or Foradil. After waiting for 60 minutes, the time required for the medication's maximal effect, you will be involved in the following: (1) rating your level of dyspnea and fatigue on a scale of 1 to 10, (2) oximetry, (3) 6 minute walk test, (4) rating your level of dyspnea and fatigue on a scale of 1 to 10, (5) oximetry, (6) and spirometry.

The third visit will involve the same sequence of events as the second visit, except for the medication. You will receive the medication not received on the second visit. To compensate for your time and expense, you will receive a $5.00 money order for the first and second visits and a $40.00 money order for the third visit.

Do you have any questions at this time? Would you be willing to participate in the study?

If the patient says no, “I want to thank you for your time today”. If the patient says yes, “Would you be able to begin the first visit today?”If the patient says yes, then I will have the patient respond to the questions on the screening assessment form (the inclusion and exclusion criteria).

CONSENT TO PARTICIPATE FOR ACCEPTED PATIENTS

This is a copy of the consent form for you to read and sign. There is no hurry. Take your time and please feel free to ask questions that you have about the consent form or the three visits? I do want to emphasize that you may withdraw from the study at any time without any consequences or changes to your medical care from your physician or this office. Whether you withdraw from the study or finish the study, you are to immediately resume your previous inhaled medications—just like you were taking them prior to the study.

APPENDIX P

SCREENING ASSESSMENT FORM

SCREENING ASSESSMENT FORM

Date: _____

Patient Name: _____

Date of Birth: _____

Height: _____ Weight: _____

Telephone Numbers: (Home) _____

(Cellular) _____

Do you use a Spiriva (tiotropium) inhaler routinely for at least the last 45 days?

_____Yes _____ No

Do you have a history of smoking cigarettes for more than 10 years _____Yes _____No

Number of packs/day _____ years of smoking _____

Have you been tobacco free for at least one month? _____Yes _____No

Quit date_____

Are you able to walk for six minutes without help? _____Yes _____No

Are you currently taking one of these inhalers for at least 45 days?

Circle the one you use:

Advair Symbicort Asmanex Pulmicort QVAR

Do you have a history of:

Asthma _____Yes _____No Tuberculosis _____Yes _____No

Lung cancer _____Yes _____No Other forms of lung disease _____Yes _____No

Congestive heart failure _____Yes _____No

Heart attack in the last year _____Yes _____No

Cardiac arrhythmias _____Yes _____No Chest pain _____Yes _____No

If yes, does the chest pain occur at rest ___or with physical activity ___? If at other times, please explain.

_____

_____

Hospitalized in the last 3 months _____Yes _____No

Oxygen therapy during the daytime _____Yes _____No

Oxygen therapy at night _____Yes _____No

Recent change in your exercise routine _____Yes _____No

Family history of Alpha One Antitrypsin Deficiency or diagnosis of COPD at an age younger than 45 years _____Yes _____No

APPENDIX Q

RANDOMIZATION LOG

RANDOMIZATION LOG

Patient Number	Random Number	First Medication	Second Medication
1	2	Placebo	Formoterol
2	7	Formoterol	Placebo
3	8	Placebo	Formoterol
4	4	Placebo	Formoterol
5	7	Formoterol	Placebo
6	0	Placebo	Formoterol
7	3	Formoterol	Placebo
8	3	Formoterol	Placebo
9	1	Formoterol	Placebo
10	5	Formoterol	Placebo
11	8	Placebo	Formoterol
12	2	Placebo	Formoterol
13	7	Formoterol	Placebo
14	3	Formoterol	Placebo
15	9	Formoterol	Placebo
16	0	Placebo	Formoterol
17	5	Formoterol	Placebo
18	1	Formoterol	Placebo
19	3	Formoterol	Placebo
20	6	Placebo	Formoterol

Heads = even = placebo

Tails = odd = formoterol

Row 17 Column 6- 25

APPENDIX R

ALBUTEROL DOCUMENTATION FORM

Albuterol Documentation Form

Patient Number _____

You have been given a short acting albuterol inhaler _____ to use during this study for relief of shortness of breath. Use this inhaler or albuterol in your nebulizer every 4 to 6 hours as needed for shortness of breath. Please record each date and time used in the spaces below and **bring this form with you for your next visit**.

Start Date of Study_____

End Date of Study _____

Date	**Time**

Please call Casey if you have concerns about the increased use of albuterol at XXX-XXX-XXXX.

APPENDIX S

INSTRUCTIONS FOR PATIENTS

Instructions for _____Number_____

1. STOP using combination inhaler _____for the duration of this study.
2. Continue to use Spiriva (tiotropium) inhaler every morning as prescribed and use in the morning before coming to the office for each visit.
3. Use inhaled corticosteroid _____ puffs twice a day for the duration of this study and use in the morning before coming to the office.
4. Use an albuterol inhaler _____ as needed for shortness of breath every 4 to 6 hours and record when you use this inhaler on the albuterol documentation form.
5. If you need to use your albuterol inhaler _____ the morning of testing (within 8 hours), please telephone Catherine Jones at the provided phone number because your testing may need to be rescheduled.
6. Please return to this office at _____AM on _____for the next visit when the study testing will begin.
7. Wear supportive walking shoes and comfortable clothing for the walk test.
8. Please call our **office at (XXX) XXX-XXXX or my cellular phone at (XXX) XXX-XXXX** if you have any questions about this study or experience any problems of concern.

Catherine “Casey” S. Jones, RN, MSN, ANP-C

1604 Hospital Parkway, Suite 403

Bedford, Texas 76022

I have read this form & understand what I need to do for this study: _____
Patient Signature

Physician’s Initials_____

APPENDIX T

RE-CONSENT FORM

Re-Consent Form

Second Visit: I consent to continue with this research study today and will do what is asked by the investigator (Casey). All of the procedures have been discussed and my questions answered at my first visit. If I have any further questions I will ask, and I know that I may stop at any time should I wish not to continue.

Patient:_____

Date:_____

Third Visit: I consent to continue with this research study today and will do what is asked by the investigator (Casey). All of the procedures have been discussed and my questions answered at my first visit. If I have any further questions I will ask, and I know that I may stop at any time should I wish not to continue.

Patient:_____

Date:_____

APPENDIX U

UNIVERSITY OF TEXAS ARLINGTON

INSTITUTIONAL REVIEW BOARD FORMS

October 13, 2009

THE UNIVERSITY
OF TEXAS
AT ARLINGTON

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Catherine Jones
Dr. Nancy Handy
The University of Texas at Arlington
Nursing
Box 19407

RE: Expedited Approval of Protocol

TITLE: *The Combined Effect of Tiotropium & Formoterol on the Functional Status of Patients with Moderate-to-severe COPD*

IRB No.: 2010-0028

The University of Texas Arlington Institutional Review Board (UTA IRB) has determined that this research is eligible for expedited review in accordance with Title 45 CFR 46.110(a)-(b)(1), 63 FR 60364 and 63 FR 60353, category (4)(7).

The IRB Chairman (or designee) approved the protocol effective October 12, 2009. IRB approval for the research shall continue until October 11, 2010. In order for the research to continue beyond the first year, Continuation Review must be completed within the month preceding the date of expiration indicated above. A reminder notice will be forwarded to the attention of the Principal Investigator (PI) at that time.

The approved subject sample size is 20.

Important Note: The IRB approved and stamped informed consent document (ICD), showing the approval and expiration date of the article must be used when prospectively enrolling volunteer participants into the study. The use of a copy of any consent form on which the IRB-stamped approval and expiration dates are not visible, or are replaced by typescript or handwriting is prohibited. The signed consent forms must be securely maintained on the UT Arlington campus for the duration of the study plus three years. The complete study record is subject to inspection and/or audit during this time period by entities including but not limited to the UT Arlington IRB, Regulatory Services staff, OHRP and by study sponsors (if the study is funded).

Please be advised that as the principal investigator, you are required to report local adverse (unanticipated) events to this office within 24 hours. In addition, pursuant to Title 45 CFR 46.103(b)(4)(iii), investigators are required to, "promptly report to the IRB ***any*** proposed changes in the research activity, and to ensure that such changes in approved research, during the period for which IRB approval has already been given, are **not initiated without prior IRB review and approval** except when necessary to eliminate apparent immediate hazards to the subject."

INFORMED CONSENT

PRINCIPAL INVESTIGATOR NAME:
Catherine "Casey" S. Jones

TITLE OF PROJECT:
The combined effect of tiotropium (Spiriva) & formoterol (Foradil) on the functional status of patients with moderate-to-severe COPD.

INTRODUCTION
You are being asked to participate in a research study. Your participation is voluntary. Please ask questions if there is anything you do not understand.

PURPOSE:
Will the combined effect of tiotropium (Spiriva) and formoterol (Foradil) improve the functional status of patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) as evidenced by improvements in the ability to complete a six-minute walk test with less shortness of breath and fatigue, and a positive change in a breathing test (spirometry)?

DURATION:
Three visits (each visit 1 1/2 hours) within a two week period.

PROCEDURES:
First visit: I will measure your height, weight, pulse rate, oximetry (which measures amount of oxygen in your blood), and have you perform a breathing test (spirometry). You will then walk a two-minute practice walk test. After your walk test, you will look at a laminated chart with a Borg Scale (which measures shortness of breath & fatigue) and point out your level of shortness of breath & fatigue that best matches a number on the card.

Your inhaled medications will be adjusted for the duration of the study. You will discontinue your inhaled bronchodilator (long acting beta-2 agonist) - salmeterol (Serevent) or formoterol (Foradil) and will be given a free albuterol inhaler to use instead for the study. All changes in inhaled medications will be reviewed with you.

Second visit: I will help you to inhale either a placebo (a fake capsule) or formoterol (Foradil) by an Aerolizer. I will measure your respiratory rate & blood pressure. You will wait for one hour while the medication takes effect. Before & after you walk, you will point out your level of shortness of breath & fatigue on a Borg Scale. I will also measure your oxygen saturation & pulse rate before & after you walk. You will then walk for six-minutes for the six-minute walk test. After you have rested for 10 minutes, you will perform a breathing test (spirometry).

Third visit: Same procedures as second visit but this time you will inhale the medication not received on the second visit. For example, if you received formoterol on the second visit then you would now inhale a placebo. I will not know which medication you will be inhaling, so I will not be biased.

Patients will be randomized into two groups: all patients will receive both a placebo and formoterol (Foradil), but in a different order. Dr. Gary Jones

will randomize the patients, and this will determine if you will receive the formoterol on the second or third visit.

POSSIBLE BENEFITS:
You may show significant improvements in functional status as measured by the six-minute walk test &/or spirometry after the addition of inhaled formoterol to your current inhaled tiotropium therapy.

COMPENSATION:
To compensate for your time and expense a total of $50.00 money order will be given to you when you complete the study. You will receive a $5.00 money order for the first and second visits & a $40.00 money order for the third visit.

POSSIBLE RISKS/DISCOMFORTS:
Stopping the use of your inhaled long acting beta-2 agonist (bronchodilator) - salmeterol (Serevent) or formoterol (Foradil) which you may take in a combination inhaler (Advair or Symbicort) may make you more short of breath. Therefore, you will be provided a free short acting albuterol inhaler to use every 4 to 6 hours as needed for shortness of breath. You may experience rapid heart rate or shakes with the use of albuterol.

Walking for six-minutes may make you more short of breath.

If you experience significant heart palpitations &/or tremors from the albuterol then you may stop at any time. Minimal physical risk may occur with the six-minute walk tests. If you exhibit chest pain, severe shortness of breath, unstable walk, leg cramping, sweating, or a pale/ashen appearance you will be immediately stopped. Chairs will be available close to the entire walk track, & you will be told to sit down should you experience distress. Inhaled albuterol by a nebulizer will be given should you experience shortness of breath that does not rapidly return to a routine steady state. Oxygen by nasal cannula (a plastic tube in your nose) will be given if you have a low blood oxygen level. If you need further assistance, a physician will be notified. If necessary, you will be accompanied by the investigator in a wheelchair to the Emergency Department of Harris Methodist H.E.B. Hospital, which is adjacent to the Bedford office of TPCCC.

ALTERNATIVE PROCEDURES/TREATMENTS:
If you choose not to participate in the study, your health care at Texas Pulmonary & Critical Care Consultants will not change.

WITHDRAWAL FROM THE STUDY:
You may discontinue participation at any time without penalty or loss of benefits. Your health care in the Bedford office of Texas Pulmonary & Critical Care Consultants will not change.

NUMBER OF PARTICIPANTS: We expect 20 participants to enroll in this study.

CONFIDENTIALITY:
Raw data documents will initially be kept at the office site in a locked cabinet in the investigator's office. Only the investigator will have a key. The documents will then be transferred permanently to UTA to a locked cabinet in Room 508 Pickard Hall. Documents will be maintained at UTA in a locked cabinet for a minimum of 3 years after

the completion of all study procedures. Access to this cabinet may be only by the Associate Dean of the Center of Nursing Scholarship and Technology (CNST) - Dr. Carolyn Cason and the Administrative Services Officer of the CNST - Angelita "Angel" Winter.

If in the unlikely event it becomes necessary for the Institutional Review Board to review your research records, then The University of Texas at Arlington will protect the confidentiality of those records to the extent permitted by law. Your research records will not be released without your consent unless required by law or a court order. The data resulting from your participation may be made available to other researchers in the future for research purposes not detailed within this consent form. In these cases, the data will contain no identifying information that could associate you with it, or with your participation in any study.

CONTACT FOR QUESTIONS:
Questions about this research or your rights as a research subject may be directed to Catherine "Casey" S. Jones at (817) 832-2010 or the Bedford office of Texas Pulmonary & Critical Care Consultants at (817) 354-9545. You may contact Chairperson of UT Arlington Institution Review Board at (817)-272-3723 in the event of a research-related injury to the subject.

CONSENT:
Signatures: *[Please include all of this bolded text:]*
As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

Signature and printed name of principal investigator or person obtaining consent Date

By signing below, you confirm that you have read or had this document read to you.
You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time

You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled, and the you may discontinue participation at any time without penalty or loss of benefits, to which you are otherwise entitled.

SIGNATURE OF VOLUNTEER **DATE**

OCT 1 2 2009
APPROVED
OCT 1 1 2010
Institutional Review Board

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AT ARLINGTON

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November 9, 2009

Catherine Jones
Dr. Nancy Handy
Nursing
The University of Texas at Arlington
Box 19407

IRB No.: **2010-0028**

RE: Minor Modification Approval Letter

Title: *The Combined Effect of Tiotropium & Formoterol on the Functional Status of Patients with Moderate-to-severe COPD*

The UT Arlington Institutional Review Board (UTA IRB) Chair (or designee) reviewed and approved the modification(s) to this protocol on **November 6, 2009** in accordance with Title 45 CFR 46. 110(b)(2). Therefore, you are authorized to conduct your research. The modification(s), indicated below, was deemed minor and appropriate for expedited review.

- **UPDATE the inclusion criteria to include ages 60-75 and BMI of 21-30**
- **UPDATE the recruitment flyer and screening tool to reflect changes**

Pursuant to Title 45 CFR 46.103(b)(4)(iii), investigators are required to, "promptly report to the IRB ***any*** proposed changes in the research activity, and ensure that such changes in approved research, during the period for which IRB approval has already been given, **are not initiated without IRB review and approval** except when necessary to eliminate apparent immediate hazards to the subject."

The modification approval will additionally be presented to the convened board on December 8, 2009 for full IRB acknowledgment [45 CFR 46.110(c)]. All investigators and key personnel identified in the protocol must have documented *Human Subjects Training* or *CITI* Training on file with the UT Arlington Office of Research Administration Regulatory Services.

THE UNIVERSITY
OF TEXAS
AT ARLINGTON

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January 4, 2010

Catherine Jones
Dr. Nancy Handy
Nursing
The University of Texas at Arlington
Box 19407

IRB No.: **2010-0028**

RE: Minor Modification Approval Letter

Title: *The Combined Effect of Tiotropium & Formoterol on the Functional Status of Patients with Moderate-to-severe COPD*

The UT Arlington Institutional Review Board (UTA IRB) Chair (or designee) reviewed and approved the modification(s) to this protocol on **December 21, 2009** in accordance with Title 45 CFR 46. 110(b)(2). Therefore, you are authorized to conduct your research. The modification(s), indicated below, was deemed minor and appropriate for expedited review.

- **UPDATE inclusion criteria to include 50-80 years of age**
- **UPDATE recruitment document and inclusion/exclusion criteria sheet to reflect these changes and a typo**

Pursuant to Title 45 CFR 46.103(b)(4)(iii), investigators are required to, "promptly report to the IRB ***any*** proposed changes in the research activity, and ensure that such changes in approved research, during the period for which IRB approval has already been given, **are not initiated without IRB review and approval** except when necessary to eliminate apparent immediate hazards to the subject."

The modification approval will additionally be presented to the convened board on January 12, 2010 for full IRB acknowledgment [45 CFR 46.110(c)]. All investigators and key personnel identified in the protocol must have documented *Human Subjects Training* or *CITI* Training on file with the UT Arlington Office of Research Administration Regulatory Services.

The UT Arlington Office of Research Administration appreciates your continuing commitment to the protection of human research subjects. Should you have questions or require further assistance, please contact Robin Dickey by calling (817) 272-9329.

Sincerely,

Patricia Turpin, Ph.D., RN, NEA, BC
Clinical Associate Professor
UT Arlington IRB Chair

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