Test-Re-Test Reproducibility of Constant Rate Step and Shuttle Walking Tests for the Assessment of Exertional Dyspnea in Patients with Chronic Obstructive Pulmonary Disease (COPD)

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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ABSTRACT

Purpose: Exercise testing modalities to assess the effects of a given intervention should prove to be reliable and reproducible. This study reports on test-retest reproducibility of the 3-min shuttle walking and step testing exercise protocols to assess exertional dyspnea and exercise physiology in COPD patients.

Methods: Stable COPD patients (N=43; 65 ± 6.5 years; FEV_1= 49 ± 16% pred.) equipped with a portable Jaeger Oxycon Mobile® metabolic system repeated the walking or stepping tests on two occasions separated by 7 to 14 days. At each visit, participants performed, in a randomized order, four externally paced 3-min bouts of shuttle walking at speeds of 1.5, 2.5, 4.0 and 6.0 $km \cdot h^{-1}$ or of stepping at a constant rate of 18, 22, 26 and 32 $steps \cdot min^{-1}$, respectively. Each exercise bout was separated by a 10-min rest period. Ventilation, heart rate, gas exchange parameters and Borg dyspnea score were obtained for each bout during the last 30-seconds of exercise.

Results: The majority of patients completed stepping or walking at the slowest cadence but only 33% completed walking at 6.0 $km \cdot h^{-1}$ and 40% completed stepping at 32 $steps \cdot min^{-1}$. Test-retest Pearson correlation coefficients for ventilation, heart rate, gas exchange parameters and dyspnea scores over the four exercise bouts, all exceeded 0.80 with the highest coefficient found for ventilation ($r \geq 0.95$). Intra-class correlation coefficients were similar to Pearson. Bland & Altman representation showed that a similar proportion of dyspnea data points (92 vs. 96%) lied within 2 SD of the mean difference between test-retest values for dyspnea Borg scores during walking and stepping.

Conclusion: Results show very good reproducibility for both 3-min shuttle walking and stepping exercise protocols in patients with COPD.

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RÉSUMÉ

Rationnel. Des alternatives aux tests à l'effort faits en laboratoire sont nécessaires afin de mieux refléter les symptômes ressentis lors des activités de la vie quotidienne chez les patients atteints de maladies chroniques. Un tel outil devrait définir l'intensité de l'exercice avec précision et démontrer une bonne reproductibilité. Cette étude a examiné la reproductibilité d'un test de marche à rythme constant (MRC) et d'un test d'escaliers (ES) pour évaluer la dyspnée à l'effort chez les patients atteints de MPOC.

Méthode. Des patients MPOC stables (N=43; 65 ± 6.5 ans; VEMS= 49 ± 16% prédit) équipés d'un système métabolique Jaeger Oxycon Mobile® ont complété les tests de MRC et d'ES répétés à un intervalle de 7 à 14 jours. Chaque test était composé de quatre niveaux de 3 minutes d'exercice à intensité constante (MRC : 1,5, 2,5, 4,0 et 6,0 $km \cdot h^{-1}$; ES : 18, 22, 26 et 32 $marches \cdot min^{-1}$) séparées par des périodes de 10 minutes de repos. La ventilation (V_E) le rythme cardiaque, les paramètres d'échange gazeux et les scores de dyspnée (échelle Borg modifiée) ont tous été mesurés durant la dernière 30 secondes à la fin de chaque période d'exercice.

Résultats. Presque tous les patients ont complété le MRC et l'ES aux cadences plus lentes, toutefois, aux cadences plus élevées seulement 33% ont complété le MRC à une vitesse de marche de 6,0 $km \cdot h^{-1}$ et 40% ont complété l'ES à une cadence de 32 $marches \cdot min^{-1}$. Les coefficients de corrélations entre le test 1 et le test 2 pour la ventilation, rythme cardiaque, les paramètres d'échange gazeux et les scores de dyspnée pour les niveaux 1 à 4 étaient tous supérieurs à 0,80 avec le coefficient le plus élevé ($r \geq 0,95$) trouvé avec la ventilation. Les graphiques de Bland et Altman démontrent une dispersion semblable des scores de Borg pour la dyspnée (92 vs. 96%) qui sont tous situé à deux écarts-types de la valeur moyenne de la différence entre les valeurs du test 1 et du test 2 durant la MRC et l'ES.

Conclusion. Les résultats démontrent une très bonne reproductibilité pour les deux tests (MRC et ES) chez les personnes atteintes de MPOC.

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PART I: REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is one of the only global diseases that is increasing in prevalence. In Canada, over 714,000 people (2.3% of the population) have been diagnosed with COPD (O'Donnell 2004a). There is still no definite answer as to the exact mechanisms of the disease. Similarly, there is no cure and current medicine allows only for retardation of disease progression.

1 Review of Chronic Obstructive Pulmonary Disease

Although there are several leading research bodies across the world, currently no clear definition of COPD has been agreed upon globally. In response to lack of attention brought to COPD, the US National Heart, Lung, and Blood Institute has come together with the World Health Organization to create the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2005). The objectives of GOLD are to raise awareness about COPD and to improve prevention and treatment of the disease. The most accepted definition of COPD is that published by GOLD. In 2006, GOLD published a new statement describing COPD as a preventable and treatable disease with some systemic effects that may contribute to the severity in individual patients. The pulmonary aspect is characterized by airflow limitation that is progressive and not fully reversible. Exposure of the lungs to noxious particles or gases produces an abnormal inflammatory response that further contributes to the airflow limitation. Overall, a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) that is unique to each individual are the causal factors to the chronic airflow limitation characteristic of COPD. Inasmuch as both the American and European Thoracic Societies play major roles in GOLD, they themselves have published their own position paper on COPD. The sole variation from the most recent GOLD definition is the direct implication

of cigarette smoking as a causal factor in the development of the disease. Another slight variation to the definition of COPD is that published by the Canadian Thoracic Society where they describe shortness of breath and activity limitation as cardinal symptoms of the disease. It is therefore evident that there is no clear definition of COPD that is agreed upon globally. The major point of variation is the topic of etiology. The exact cause and mechanism by which COPD develops currently eludes scientists. Despite disagreement on the causal factors, airflow limitation is the accepted defining characteristic of the disease.

As the defining factor of COPD, airflow limitation is at the fore-front of current investigations. The degree of airflow limitation characteristic of COPD is quantified by changes in the fraction of expired air in one second (FEV_1) and its ratio with the functional residual capacity (FRC). Standard spirometry is used to measure a variety of lung volumes and capacities. Spirometry is the most widely used noninvasive test of pulmonary function and mechanics (Pierce 2005). In conjunction with pulmonary gas exchange measurements, spirometry provides a complete objective assessment of lung function (Evans 2003; Pierce 2005). More specifically, spirometry is the measurement of dynamic lung volumes and capacities with respect to time (Evans 2003; Pierce 2005). Data collection occurs during forced maneuvers of expiration and inspiration to establish the timely effectiveness of lung emptying and filling (Pierce 2005). Maximal flow-volume curves reflect the complex interactions between dynamic airway function, lung recoil and the forces applied to the lung surface by the respiratory muscles (Calverley 1995).

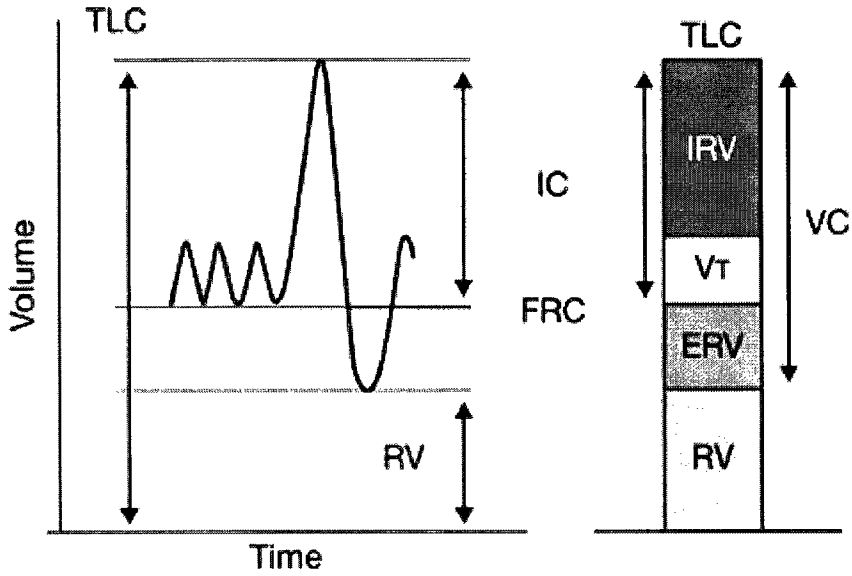

Figure 1. Lung volumes and capacities (From (Ferguson 2006)

As COPD progresses various changes occur to the lung volumes. Figure 1 depicts a typical spirometric tracing including total lung capacity (TLC), inspiratory capacity (IC), tidal volume (V_T), functional residual capacity (FRC), and residual volume (RV). Although not apparent until the late stages of COPD, tidal volume can be seen to decrease slightly. Residual volume, on the other hand, is increased in the COPD population (4.20L) as compared with healthy aged individuals (2.10L) (Fishman 1998). Residual volume of the lung is the volume that remains in the lung after complete expiration (Forster II 1986). The increase in residual volume indicates lung hyperinflation during quiet breathing (Forster II 1986). As COPD progresses the closing volumes in the lungs decrease and air trapping ensues. With more air being contained within the lung the residual volume increases. Structural changes that cause a reduction in lung elasticity are also attributable to the increase in RV (Forster II 1986).

The lung capacities are also greatly affected by the expiratory flow limitation characteristic of COPD. The normal approximate value for total lung capacity is 5.8L

(Guyton 2000); in COPD, volumes above 8L can be seen. Vital capacity (VC) is the volume of gas that can be expelled forcefully from the lungs after a maximal inspiration (Forster II 1986). In a healthy individual, VC is approximately 4.60L whereas a volume of 3.80L is characteristic of COPD patients (Fishman 1998; Guyton 2000). The decrease in vital capacity found in COPD can be attributed to the increase in residual volume discussed above (Forster II 1986). The inspiratory capacity is the maximal volume of inspired air from functional residual capacity to total lung capacity. In COPD, hyperinflation of the lung causes a decrease in the IC of the patient as seen in Figure 2.

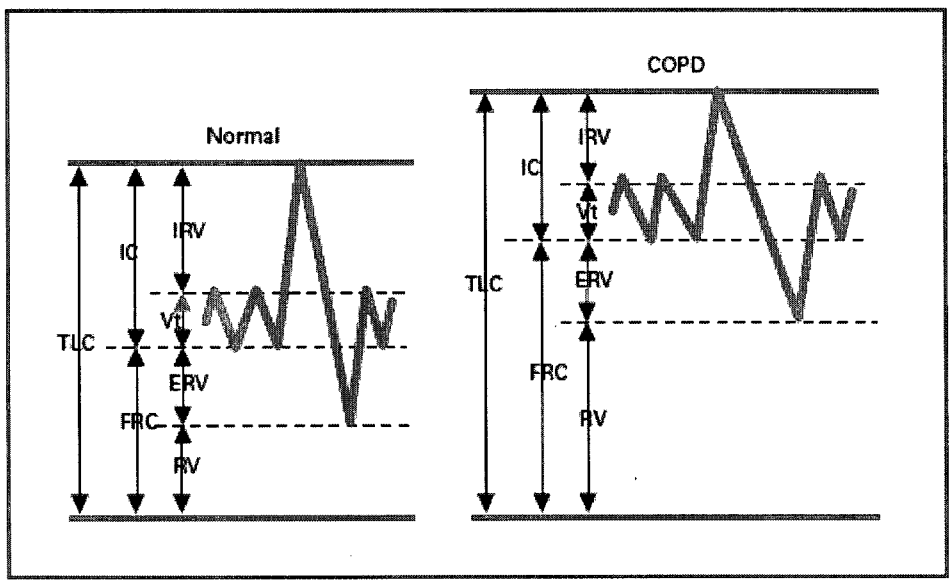

Figure 2. Lung volumes and capacities in healthy normals and patients with COPD. (Pierce 2005)

Figure 2 is a spirometric tracing showing lung capacities and volumes as compared from healthy normals to COPD patients. The functional residual capacity of the lung is increased in the COPD population as depicted in Figure 2. Parallel to the changes in RV, the increases in FRC represent hyperinflation of the lung mainly due to

reduction in lung elasticity (Forster II 1986). Partial airway obstruction, characteristic of COPD, also contributes to changes in FRC (Forster II 1986).

The gradual modifications of the lung associated with COPD create minor changes in the spirometric measurements. With disease progression, lung volumes and capacities display greater variation from the healthy aged.

Another major component of lung function assessment is the fraction of expired air in one second (FEV_1). The significance of measuring FEV_1 is its ability to demonstrate expiratory flow capacity. Reductions in FEV_1, as seen in COPD, demonstrate airflow obstruction within the lung. The effects of smoking and smoking cessation on FEV_1 can be seen in Figure 3.

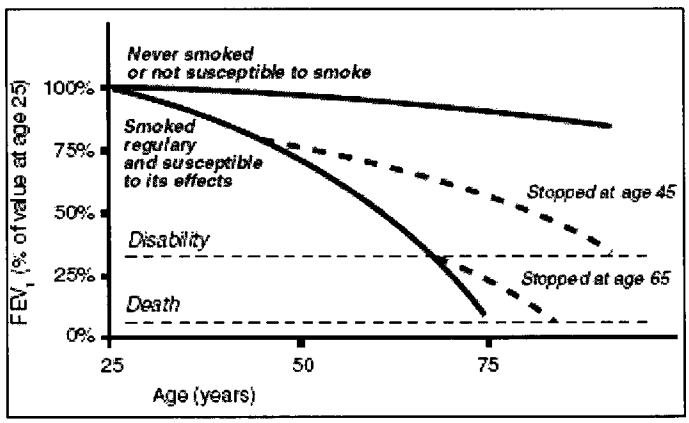

Figure 3. Progressive decline in FEV_1 in patients with COPD (O'Donnell 2004a)

As can be seen in this figure, there is a natural decrease in FEV_1 associated with ageing, the natural rate of decline of FEV_1 after the age of 25 ranges from 25 to 30mL/year, which is further exacerbated by cigarette smoking (Cooper 2005). It should be noted that smoking cessation can attenuate the accelerated decline in FEV_1 caused by smoking. If cigarette smoking continues, a state of disability will be reached at approximately 70 years of age, followed by premature death near 75 years.

Although there are discrepancies between the various groups, the most common standard for classification of disease severity has been based upon the measured FEV_1 and the ratio of FEV_1 to FVC. The FEV_1/FVC ratio is the most accurate index of airflow obstruction (Pierce 2005). Ratios below 70% are considered to be at risk although it should be noted that a natural decline of the ratio with age does exist (Pierce 2005). The spirometric classifications of COPD as published by GOLD, American Thoracic Society/European Respiratory Society and Canadian Thoracic Society are shown in Tables 1-3.

Table 1. GOLD spirometric classification of COPD based upon FEV_1 and FEV_1/FVC ratio

Severity	FEV_1 (% predicted)	FEV_1/FVC
Mild COPD	≥80	<70%
Moderate COPD	50≤ FEV_1 <80	<70%
Severe COPD	30≤ FEV_1 <50	<70%
Very Severe COPD	<30	<70%

Classification based upon postbronchodilator FEV_1
FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity

Table 2. ATS/ERS spirometric classification of COPD based upon FEV_1 and FEV_1/FVC ratio

Severity	FEV_1 (% predicted)	Postbronchodilator FEV_1/FVC
Mild COPD	≥80	≤0.7
Moderate COPD	50-80	≤0.7
Severe COPD	30-50	≤0.7
Very Severe COPD	<30	≤0.7

FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity

Table 3. CTS spirometric classification of COPD based upon FEV_1 and FEV_1/FVC ratio

Severity	FEV_1 (% predicted)	FEV_1/FVC
Mild COPD	60-79	<0.7
Moderate COPD	40-59	<0.7
Severe COPD	<40	<0.7

FEV_1: Forced expiratory volume in one second; FVC: Forced expiratory vital capacity

All three classification tables outline 80% of FEV_1 and a FVC/FEV_1 ratio of 0.7 to be the initial cutoff for the diagnosis of COPD. Although each group uses a slight variation of the values, they all acknowledge that both FEV_1 and the ratio of FVC/FEV_1 are the crucial indicators of disease severity. The discrepancy in the characterization of disease severity amongst the various groups causes difficulty in comparing research from various areas. Similarly, it becomes very difficult to ascertain the true burden of the disease on a global platform.

The incidence, prevalence, morbidity and mortality associated with COPD fluctuate between countries and within countries. The one commonality amongst countries is that the population characteristics of COPD are all directly related to the pervasiveness of smoking (GOLD 2006). The incidence of COPD is constantly increasing with the aging population. The WHO estimates 1.1 billion smokers worldwide, increasing to 1.6 billion by 2025. Lindberg et al (2006) conducted a 7-year cumulative study in northern Sweden in which the estimated incidence of COPD was 4.9% and 11.0% according to the spirometric criteria of GOLD II and GOLD, respectively. The pulmonary damage caused by cigarette smoking depends on the length and intensity of exposure and baseline lung function. Abnormalities in lung function, respiratory symptoms and a greater decline in FEV_1 annually have all been shown to be more prevalent in cigarette smokers when compared to non-smokers (GOLD 2005). Tobacco smoking accounts for an estimated 80 to 90% of the risk of developing COPD (ATS 1995). In Canada, approximately 90 percent of COPD cases are caused by cigarette smoking (O'Donnell 2004a). Overall, tobacco kills about 45,000 Canadians a year (O'Donnell 2004a).Even though smoking is the leading cause of COPD, the disease

develops in only about 20% of smokers. In a study by Peloken et al. (2006) over 40% of smokers developed chronic bronchitis and half of those cases progressed to COPD. The World Health Organization estimates 80 million cases of moderate to severe COPD currently exist globally. Countries in which cigarette smoking is still very common represent the countries with the highest prevalence of COPD worldwide. In 2000, there were approximately 14 million cases of COPD in the United States. According to the World Health Organization, COPD is predicted to rise from the 12^{th} to the 5^{th} most prevalent disease and from 6^{th} to 3^{rd} most common cause of death by 2020 (Barnes 2000). Therefore, COPD has become one of the most prominent causes of death in the majority of countries (GOLD 2006). In 2005, an estimated 3 million deaths were caused by COPD worldwide, of which 90% of these deaths occurred in low- and middle-income countries. Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless immediate action is taken to reduce the underlying risk factors, namely tobacco use.

1.1 Aetiology of Chronic Obstructive Pulmonary Disease

Of much concern is the incomplete understanding of the causes of COPD, especially in developing countries. With rising incidence, the need for a more accurate definition of the mechanistic cause of COPD is needed. Although various factors have been attributed to the development of COPD there is no definite answer as to what specifically causes COPD. There are several factors that are regarded to be more influential towards the disease pathology. Cigarette smoking is considered the leading contributor to the development of COPD. Alpha-1 Antitrypsin deficiency and occupational dusts and chemicals have also been listed as confounding factors towards

the genesis of COPD (Becklake 1989; Whittemore 1995; Sethi 2000; Matheson 2005; Ranes 2005; Richmond 2005).

By definition, Alpha-1 Antitrypsin deficiency is a genetic disorder that results from a gene mutation. Only 1-2% of COPD patients suffer from Alpha-1 Antitrypsin deficiency (Sethi 2000). Ranes and Stoller (2005) have estimated 0.003% of Americans have severe Alpha-1 Antitrypsin deficiency. Alpha-1 antitrypsin is a potent protein inhibitor that targets neutrophil elastase, a protease enzyme. Neutrophil elastase in the lung functions to break down and remove bacteria. Alpha-1 Antitrypsin has a protective function over the normal lung cells, preventing their degradation by neutrophil elastase (Richmond 2005). The tissue destruction that ensues therefore produces a similar clinical presentation to emphysema and chronic bronchitis (Richmond 2005).

Although smoking is considered to be the prominent cause of COPD, occupational exposures to various dusts and chemicals have been shown to play a role in the development of airflow obstruction associated with COPD (Becklake 1989). Increased bronchial response to environmental exposures is the underlying mechanism of COPD as outlined by the Dutch hypothesis. The Dutch hypothesis suggests that although pathologically different, asthma, chronic bronchitis, and emphysema are variations of the same basic disease. The distinction between the three occurs when confounding environmental and genetic factors produce variations in pathology. Airway hyperresponsiveness is therefore the basis of the general disease state (Kasper 2006).

Various countries in Europe have now classified COPD in miners to be an occupational disease in which compensation can be paid (Cooper 2006). Trupin's population-based study estimates one in five cases of COPD may be attributable to

occupational exposure. Comparably, using the data from the US population-based Third National Health and Nutrition Examination Survey (NHANES), Hnizdo et al (2002) have estimated 19.2% overall and 31.1% of never smokers diagnosed with COPD can attribute their disease state to occupational exposure.

Unequivocal evidence for the association of several occupations with COPD has been published by Tuchsen and Hannerz (2000). Similarly, Matheson et al (2005) found occupational exposure to biological dust increased the risk of respiratory symptoms and COPD. According to the study published by Soutar and Hurley (1986) approximately 0.76mL of FEV_1 is lost per ghm^{-3} of dust exposure. A dose-response relationship has been demonstrated between the risk of COPD and coke oven emission exposure (Hu 2006). Workers exposed to cadmium showed reductions in FEV_1, FEV_1/FVC, and DLCO which suggests airflow obstruction (Kasper 2006). Similarly, there is strong evidence that a relationship between coal mine dust and reductions in lung function exists. It should be understood that the aforementioned risk factors are all considered to be confounding factors with cigarette smoke.

There is a myriad of effects attributed to smoking cigarettes but there is only a handful that contributes directly to the pathogenesis of COPD. Initial damage can be seen in the cilia and mucous glands. Injury and loss of cilia leads to the improper clearing of airways (GOLD 2005). Supplemental to cilia damage is the hypertrophy and hyperplasia of the mucous glands (GOLD 2005). Maestrelli et al. (2001) suggest that cigarette smoke is a direct cause of goblet cell hyperplasia. With increased production of mucous, changes in the airway surface liquid may influence the ability to effectively remove particulates from the airways. A thicker layer of mucous would encroach on the low

viscosity sol layer where the cilia are able to beat. Any inhibition of this movement will diminish the effectiveness of the mucociliary clearance mechanism. A secondary effect of increased mucous production is the possibility of mucous plug development. Mucous plugs can create major points of airflow obstruction (Hogg 2004). Mucous gland hypertrophy and hyperplasia have been outlined as the anatomical basis for chronic cough and sputum associated with COPD (O'Donnell 2004a).

After long-time exposure, destruction of the lung parenchyma caused by inflammation leads to decreased alveolar attachments and decreased lung elastic recoil (GOLD 2005). One of the most detrimental aspects of the abnormal inflammatory response is the repetitive cycles of injury and repair of the peripheral airway walls (GOLD 2005). This continual process leads to structural remodeling that incorporates larger amounts of collagen and scar tissue producing irreversible airway obstruction (GOLD 2005).

As no specific cause has been pinpointed, it is likely that COPD is a culmination of several factors working in conjunction. Despite this lack of a specific origin, many of the mechanisms behind the presentation of COPD have been explored.

1.2 Pathophysiology of Chronic Obstructive Pulmonary Disease

The term COPD encompasses various different and frequently concomitant conditions including chronic bronchitis and emphysema (Trupin 2003). The disease is rarely found in a pure state, it is normally found as a mixture of these two distinct pathologies (Trupin 2003). Chronic bronchitis and emphysema both originate from a similar source, but the pathologies differentiate in their histology. Although distinct, their symptoms, including airflow limitation, link the two pathologies together.

1.2.1 Chronic Bronchitis

The Canadian Thoracic Society has defined chronic bronchitis as having cough and sputum for three months in a minimum of two consecutive years (O'Donnell 2004a). Vestbo and Hogg (2006) explain chronic bronchitis to be a benign disease that occurs early in COPD, while the innate immune response is still fully functional. To understand the ramifications of this benign disease it is critical to examine its histological characteristics, namely goblet cell hyperplasia and metaplasia as well as mucus hypersecretion.

The lungs' first line of defense against toxic inhalants is the epithelial surface of the airways (Maestrelli 2001). Cigarette smoke is considered a major determinant of goblet cell hyperplasia in the peripheral airway epithelium (Maestrelli 2001). In the peripheral airways, the submucosal glands are shown to increase in size (Snider 1989). Although the epithelium is intact, squamous cell metaplasia and hyperplasia of goblet cells are characteristic traits of chronic bronchitis (Turato 2001). More specifically, mucus gland hypertrophy has been considered to be the hallmark histological characteristic of chronic bronchitis (Reid 1960). Goblet cell hyperplasia is a causal factor for the excess production of mucus within the lung (Maestrelli 2001; Turato 2001).

Obstructive chronic bronchitis is associated with increased permeability of the airway mucosal microvasculature and epithelium (Bresser 2000). The inflammation of the mucus-secreting glands in the airway epithelium is thought to be the cause of increased mucus production, reduced mucociliary clearance and increased permeability of the epithelium (MacNee 2005). Results have shown that potent mucus secretagogues are secreted by the neutrophils circulating within the lung (MacNee 2005). Similarly,

inflammation has been implicated in mucus hypersecretion through the overproduction of mucin by inflammatory leukocytes (MacNee 2005). The main site of mucus hypersecretion is found in the central airways (Turato 2001). The excess production of mucus associated with goblet cell hyperplasia may alter the surface tension of the airway lining fluid thereby creating instability within the peripheral airways which facilitates their closure (Maestrelli 2001; Turato 2001).

Through increased permeability of the airway epithelium and inflammation, goblet cell hyperplasia and metaplasia ensue. These physical changes cause increases in mucus production that further exacerbate the disease state. These histological features of chronic bronchitis create the critical distinction from emphysema.

1.2.2 Emphysema

Emphysema has been acknowledged as a major part of COPD but neither GOLD nor the American Thoracic Society/European Respiratory Society have published a clear definition of the pathology. Emphysema is defined by the Canadian Thoracic Society as permanent abnormal enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls (O'Donnell 2004a).

Structural changes and chronic inflammation are the characteristic pathological changes of COPD (GOLD 2006). These pathological changes can be found throughout the lung; in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature (GOLD 2006). Airway narrowing is the most defining change that occurs in the peripheral airways of COPD patients (GOLD 2005). Emphysema patients exhibit characteristic alveolar septa destruction resulting in irreversible enlargement of the air spaces (Birell 2005). A distinction according to the manner of tissue destruction has

created two sub-divisions of emphysema: centrilobular and panlobular emphysema (Turato 2001). Centrilobular emphysema is primarily caused by cigarette smoke (MacNee 2005). It is characterized by dilation and destruction of the respiratory bronchioles along with the associated pulmonary capillary bed (O'Donnell 2004a). The upper zones of the lung experience more severe and more frequent lesions as compared to the lower areas (Turato 2001). A higher degree of hyper-reactivity and airway inflammation is also characteristic of centrilobular emphysema (Turato 2001).

Contrarily, panlobular emphysema is more widespread in that there is even destruction throughout the ascinus (MacNee 2005). This even distribution of destruction is explained by the association of panlobular emphysema with the genetic Alpha-1 Antitrypsin deficiency (MacNee 2005). In contrast to centrilobular emphysema, panlobular emphysema is associated with higher lung compliance (Turato 2001). This can be explained by the association of the airflow limitation in panlobular emphysema to loss of elastic recoil as opposed to airway inflammation (Turato 2001).

Cigarette smoking and other risk factors activate the inflammatory response that is the basis for the repeated cycles of injury and repair of the walls of the peripheral airways that ensues (GOLD 2005). The injury itself originates both directly from inhaled toxic particles and gases, and indirectly by the action of inflammatory mediators. Acutely, airway epithelial cells activate CD8+ T-lymphocytes that cause alveolar wall destruction (Calverley 2003). Chronic airway, parenchymal and pulmonary vasculature inflammation is distinctive of COPD. The intensity and characteristics of the inflammation vary with disease progression. With increasing disease severity, inflammation damages the lungs and leads to the pathologic changes characteristic of

COPD (GOLD 2005). The specific mechanisms by which pulmonary inflammation occurs in response to tobacco exposure are beyond the scope of this paper. Generally, the inflammation related injury initiates the pulmonary repair processes; this injury-and-repair process causes structural remodeling of the airway wall. Increased collagen content and scar tissue formation narrows the lumen and produces fixed airway obstruction. In COPD, structural changes in the airway walls are the most important cause of the increase in peripheral airways resistance (GOLD 2005). Further airway narrowing can be caused by supplemental inflammatory changes such as airway edema and mucus hypersecretion (GOLD 2005).

Another aspect of emphysema is tissue destruction without repair. Cigarette smoking causes an imbalance in the protease-anti-protease equilibrium within the lung (Snider 1989; Hogg 2002). The increase in proteases, most specifically elastase, circulating in the lung disrupts the natural injury-repair process (Snider 1989). Elastase targets the elastin component of the parenchymal walls for degradation. The imbalance between the digestion of elastin and its formation readily produces lung tissue destruction. Emphysema patients exhibit characteristic alveolar septa destruction resulting in irreversible enlargement of the air spaces (Birell 2005). Elastic tissue within the lung is one of the major sites of emphysematous lung tissue destruction (Hogg 1994). Supplemental to the loss of elastic tissue is the reduction of gas exchanging surface area. The alveolar walls containing the pulmonary capillaries are the basis for the human gas exchange mechanism. The destruction of the alveolar walls and associated capillaries greatly reduces the ability of the lung to oxygenate the blood. The severity of pulmonary

emphysema seems to be a reflection of the overall inefficiency of the lung as a gas exchanger (GOLD 2005).

1.2.3 Symptoms of Chronic Obstructive Pulmonary Disease

Although the histological characteristics of chronic bronchitis and emphysema are quite different, they combine to produce the symptoms characteristic of COPD. By definition, chronic bronchitis is characterized by chronic cough and sputum production (O'Donnell 2004a). MacNee (2005) describes the chronic cough and sputum production associated with chronic bronchitis to be the result of an innate immune response triggered by the toxic particles in cigarette smoke. According to the Canadian Thoracic Society, it is the hypertrophy and hyperplasia of mucus glands which form the anatomical basis of chronic cough and sputum (O'Donnell 2004a). In contrast to emphysema, chronic bronchitis presents with prominent cough and sputum production with initially minimal dyspnea (Robins 1983). Typically, cough is the initial symptom of COPD to develop (Georgopoulos 1991). The importance of coughing is its function in clearing the airways from excess mucus (Cherniack 1991). Excess mucus production decreases the efficiency of the mucociliary mechanism and therefore coughing is necessary to ameliorate airway clearing (Cherniack 1991).

Chronic sputum production is the defining characteristic of chronic bronchitis (Saetta 1997). A normal healthy individual produces approximately 10mL of sputum each day which can be cleared and swallowed easily (Georgopoulos 1991). It is the inability to properly clear the excess sputum that becomes a primary symptom of chronic bronchitis. The quality of the sputum is also very important; in stable COPD sputum appears white in color, whereas in the circumstance of infection colors ranging from

yellow to green can appear (Georgopoulos 1991). The culmination of the histological ramifications of chronic bronchitis causes the characteristic symptoms of chronic cough and sputum production present in patients. These clinical symptoms become some of the defining factors in the diagnosis of COPD.

The foremost repercussion is the trademark expiratory airflow limitation that leads to the obstructive nature of the disease. This limitation affects the ability of these individuals to respond to challenges and constraints such as demands for increased energy requirements requiring adjustments in ventilatory requirements such as exercise.

2 Physiological Repercussions of Chronic Obstructive Pulmonary Disease

Physiological repercussions of COPD are primarily an expiratory flow limitation, leading to lung hyperinflation and pulmonary gas exchange anomalies. It is now well established that repercussions of the disease are also seen on peripheral muscular function due in part to the ensuing physical deconditioning but also potentially as a result of a chronic inflammatory process (O'Donnell 2001b). Similarly, it has been suggested that pulmonary hyperinflation and/or pulmonary hypertension may limit potential adjustments in exercise cardiac output (O'Donnell 2001b). A full discussion of these systemic repercussions of COPD is however beyond the scope of this review. Therefore in the interests of discussing the pulmonary repercussions of COPD, it is imperative to examine two essential aspects of the respiratory system: the mechanics of breathing and gas exchange.

2.1 Expiratory Flow Limitation

COPD is characterized by airflow limitation specifically during the expiratory phase of ventilation. Essentially, expiratory flow limitation refers to a functional

condition in which expiratory flow cannot increase (Tantucci 1999). Generally, in healthy normals the peripheral airways contribute to approximately 25% of the total airway resistance (Calverley 1995). In moderately severe COPD, the peripheral airways can contribute up to 80% of the increased resistance (Calverley 1995). Measurements of expiratory flow velocity such as forced expiratory volume in one second (FEV_1), the ratio of FEV_1/FVC, forced expiratory flows at fractions of FVC (FEF_{50} and FEF_{75}), and peak expiratory flow (PEF) are used to assess the degree of expiratory airflow limitation (Cherniack 1991). FEV_1 reflects the reduction in cross-sectional area due to COPD that causes flow limitation (Calverley 2003). The GOLD definition for airflow limitation is described in terms of the ratio of FEV_1/FVC (GOLD). Both FEV_1 and FVC are shown to decrease but it is the greater decrease in FEV_1 relative to FVC that depicts the increasing airflow limitation. Currently there are no established norms for FEF_{50}, FEF_{75} and PEF values for COPD classification. Although, predicted equations based upon race, age and height do exist and are in common use (Hankinson 1999).

The most significant consequence of limited expiratory flow is improper emptying of the lung and resulting air trapping. This in turn may have significant repercussions on the ability to increase tidal volume (V_T) and respond to demands for greater ventilation. Indeed, tidal volume may be seen as the difference between the end-inspiratory lung volume (EILV) and the end-expiratory lung volume (EELV). These operating lung volumes may be positioned within the total lung capacity of an individual.

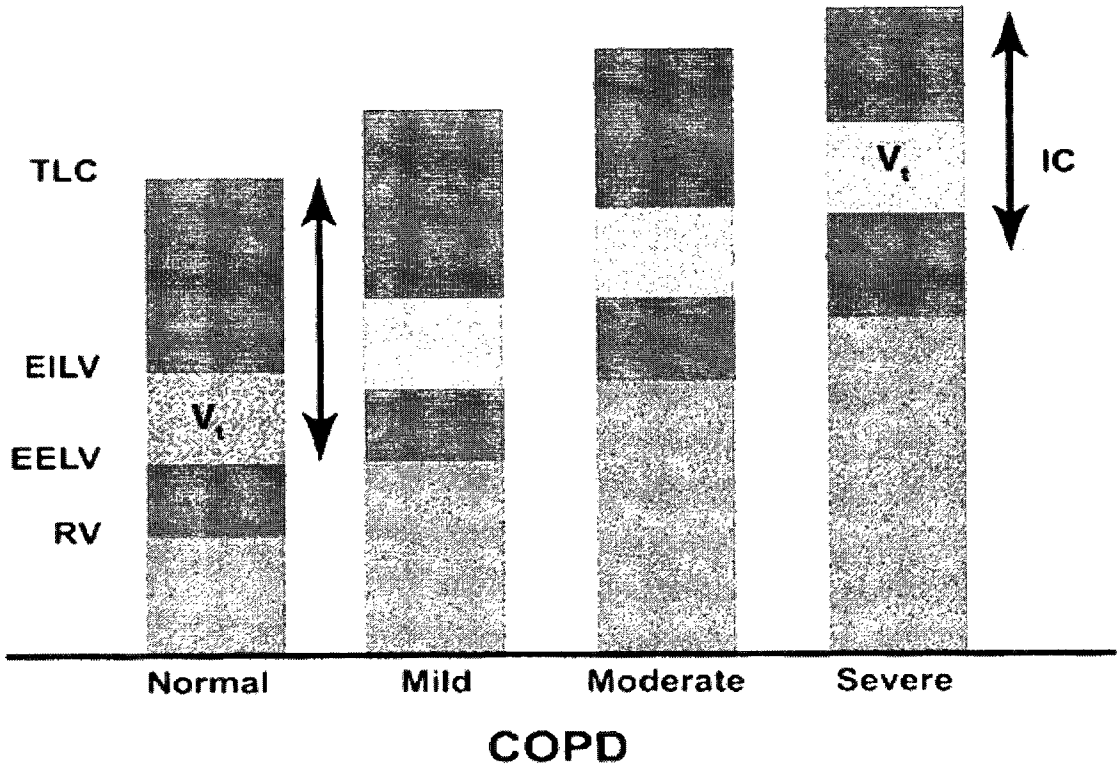

Figure 4. Operating lung volumes in healthy normals and patients with COPD (modified from Cooper, 2006)

Figure 4 depicts the typical changes to operating lung volumes as compared to healthy control individuals as well as that occurring as a result of increasing disease severity. Firstly, it is evident that COPD patients exhibit large increases in residual volume. Residual volume has been shown to increase more than two-fold in emphysematous COPD as compared to healthy aged controls (Cherniack 1991). Secondly, it can be seen from Figure 4 that tidal volume seems to remain unchanged. The changes occur mostly as the increase in residual volume causes an upward shift in the end-expiratory lung volume and thus in the end-inspiratory lung volume. This phenomenon of higher operational lung volumes at rest is referred to as static lung hyperinflation. Lung hyperinflation is defined as an increase in functional residual capacity above predicted normal (Calverley 1995). By convention, an individual's lungs

are hyperinflated when total lung capacity is greater than 120% of the predicted value (O'Donnell 2006a). Although this cutoff remains slightly arbitrary as no standardized system of classification has been developed for the assessment of hyperinflation severity (O'Donnell 2006a). Static hyperinflation is an outcome of decreased elasticity in the lung parenchyma (Ferguson 2006). In healthy individuals, the elasticity of the alveoli and airways help to keep the airways open during expiration as well as provides recoil pressure to counteract the chest wall recoil pressure (Ferguson 2006). Contrarily, in COPD the emphysematous destruction of elastic tissue alters the lung's recoil, impairing the lung volume to distending pressure relationship (Ferguson 2006). Therefore, a greater lung volume is required to sustain the same distension pressure, increasing the functional residual capacity and decreasing the inspiratory capacity (Ferguson 2006).

Over the last 30 years, inspiratory capacity measurements have been used to quantify the degree of dynamic hyperinflation during exercise (Calverley 2003). Inspiratory capacity maneuvers are used to assess the degree of lung inflation which is calculated as the difference between the TLC and the EELV. As can be seen in Figure 4, IC values for COPD patients are significantly reduced. Thus it is evident that there is a significant difference in the inspiratory capacity of a COPD patient versus their healthy counterparts.

These effects of COPD on static lung volumes are further exacerbated when exercise is introduced. Exercise-induced hyperinflation, or dynamic hyperinflation, can occur independently or in addition to static hyperinflation. In a study by O'Donnell et al. (2001) the extent of dynamic hyperinflation during exercise was shown to be inversely related to the amount of resting static hyperinflation. The increase in hyperinflation

appears to be a direct consequence of the patient's existing expiratory flow limitation (Gibson 1996). From the perspective of operational lung volumes, the already apparent increases in end-expiratory and end-inspiratory lung volumes due to static hyperinflation are exaggerated by exercise. End-expiratory lung volume has been shown to increase up to 75% of total lung capacity, an average of 0.3 to 0.6L, in COPD patients during heavy exercise (Babb 1991; Gibson 1996; Koulouris 1997; O'Donnell 1997; O'Donnell 1998; Johnson 1999; O'Donnell 2001b; Ferguson 2006). This is contrary to healthy normals who during heavy exercise reduce their end-expiratory lung volume an average of 0.7L or 44% of total lung capacity (Henke 1988; O'Donnell 1997). In the 2000 paper by Nici et al, along with increases in end-expiratory lung volume, results show end-inspiratory lung volume to attain levels as high as 95% of total lung capacity at maximal exercise in COPD patients as compared to 75 to 90% of total lung capacity in healthy aged-matched controls (Younes 1984; Johnson 1992). These findings by Nici et al. (2000) of increased end-inspiratory lung volume have also been demonstrated by several other groups (Younes 1990; O'Donnell 1993; Belman 1996; Koulouris 1997).

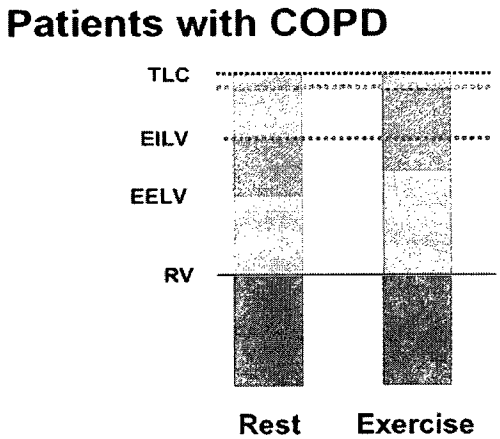

Figure 5. Relative operational lung volumes at rest and during exercise in COPD patients (modified from Cooper, 2006)

More specifically, during exercise there is a severe mechanical constraint limiting tidal volume expansion as can be seen in Figure 5 (Calverley 2003). The above figure demonstrates the adjustments in operational lung volumes that occur in COPD patients when transitioning from rest to exercise. It should be noted that the above figure is a representation of the typical adjustment of a patient with COPD to exercise. This reaction will vary based upon disease severity, as seen in Figure 4, and by predominant disease pathology. Increases in minute ventilation with exercise cause tidal volume to expand higher into the inspiratory capacity (Ferguson 2006). With increases in end-expiratory lung volume, the maneuverability of the tidal volume is greatly decreased. It follows that end-inspiratory lung volumes are increased at this point to maintain an adequate tidal volume as seen in the figure (Calverley 2003). When the end-inspiratory lung volume encroaches upon the total lung capacity envelope, further expansion of the lung is impossible (Calverley 2003). O'Donnell et al. (2001) have shown a clear statistical relationship between tidal volume restriction and maximal exercise performance.

During exercise, the aforementioned inspiratory capacity technique is used assuming that total lung capacity does not change appreciably with increased intensity (Stubbing 1980; Yan 1997). Therefore, reductions in the inspiratory capacity must be a result of increased end-expiratory lung volume as opposed to the inability to generate maximal effort due to fatigue or weakness (O'Donnell 2001a; Calverley 2003). Furthermore, Nici has shown dynamic hyperinflation to be between 10-40% of inspiratory capacity at end-exercise (Nici 2000). Lung inflation status becomes a dynamic system that changes constantly depending predominantly on tidal volume and expiratory time (Calverley 2003).

Lung hyperinflation is determined by the breathing frequency and the amount of flow limitation (Ferguson 2006). As inspiratory capacity is limited even at rest, increases in minute ventilation needed for exercise can only occur as a result of increased respiratory rate (Ferguson 2006).

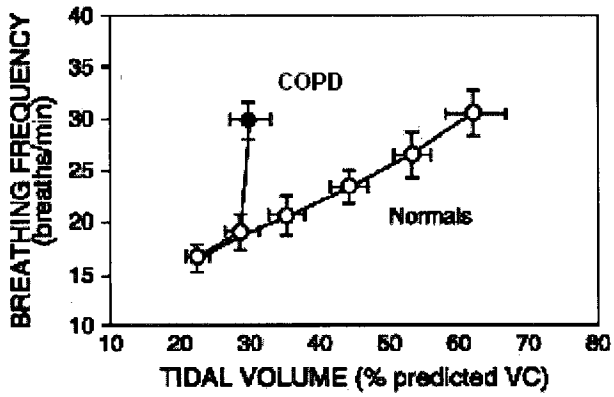

Figure 6. Relationship between breathing frequency and tidal volume during exercise in healthy normals and patients with COPD (modified from O'Donnell et al., 2006)

As depicted in Figure 6, the breathing frequency response to exercise shows a drastic increase in comparison to the response by healthy normals. Inspiratory time is reduced in COPD patients with the introduction of exercise, as demonstrated by the dramatic increase in breathing frequency shown in Figure 6. In this instance, as breathing frequency increases, the time for both inspiration and expiration are reduced. In response to this, COPD patients have developed a mechanism whereby inspiratory time (T_I/T_{TOT}) is decreased during exercise to help increase time for expiration (Barbera 1991; O'Donnell 1993). This adaptation is converse to the normal healthy reaction to exercise whereby individuals increase their inspiratory time with increasing workload (O'Donnell 1993). The decrease in inspiratory time by COPD patients has been described not as a contributor, but as a response that attempts to moderate dynamic hyperinflation (Bauerle

1998). The inspiratory time becomes insufficient to moderate the increases in the end-expiratory lung volume and thus dynamic hyperinflation is exacerbated (Nici 2000). It follows that, any situation that increases breathing rate will induce further decreases in expiratory time contributing to a continuous cycle of air trapping and therefore hyperinflation. Daily activities can trigger such increases in breathing frequency in the COPD population but it is much more pronounced during exercise. This is the basis of the major limitation that COPD imposes on its patients' daily lives.

2.2 Pulmonary Gas Exchange

The detrimental effects of lung hyperinflation on respiratory function can be further compounded when disturbances in gas exchange are present. Essential to proper gas exchange is alveolar ventilation (V_A), the partial pressure of oxygen in the alveoli (P_AO_2) and perfusion of the alveolar capillaries. The follow in g is a summary of the effects of COPD on the aforementioned factors that determine gas exchange with in the lung.

The effects of tissue destruction can be enhanced by insufficient alveolar ventilation. Mechanically, the restriction on tidal volume expansion limits pulmonary ventilation. In more distal areas of the lung, this leads to reduced alveolar ventilation. Alveolar ventilation can be determined by the difference between tidal volume and dead space volume multiplied by breathing frequency. As dead space volume does not change appreciably, changes in tidal volume and breathing frequency are the crucial factors controlling alveolar ventilation. As mentioned above, hyperinflation confines the capacity of patients to increase their total lung volume thereby limiting their ability to increase tidal volume. Therefore, with minimal increases in tidal volume, breathing frequency is

the primary controller of alveolar ventilation. As described above, increases in respiratory rate do occur with exercise (Figure 7) but do reach a ceiling with respect to inspiratory and expiratory time. To a degree, this coping mechanism is effective in maintaining alveolar ventilation. Although, in a similar fashion, increases in respiratory rate to meet demands for enhanced alveolar ventilation can also be limited.

In addition to limited alveolar ventilation, the reduced alveolar-capillary surface area consecutive to alveolo-capillary structures may result in a significant reduction in the gas exchange efficiency. In the parenchyma, emphysematous surface area destruction reduces diffusion capacity, increasing gas exchange impairment (GOLD 2005). Furthermore, due to disruptions in alveolar-capillary membrane integrity and/or diffusion limitations caused by chronic inflammation, arterial oxygen tension (PaO_2) levels may be seen to be lower in COPD than in normal healthy individual (Sandek 2001). Barbera et al (1990) have shown that even in mild COPD an alveolar-arterial oxygen difference (A-a O_2) of greater than 15mmHg can occur as compared to normal values under resting conditions of approximately 10mmHg in healthy individuals (Jones 1997). Arterial oxygen tension is a measure of the partial pressure of oxygen dissolved in the arterial blood (Guyton 2000). Arterial oxygen tension levels are an accurate measure of the efficiency of the lung as a gas exchanger as it is the final product of the system. The only precise method of measuring arterial oxygen tension is to analyze arterial blood samples using an arterial line. During the progression of COPD, it has been shown that a gradual decrease in arterial oxygen content occurs (Sandek 2001). Oxygen tension within the arteries has been found to range from 58 to 85mmHg in the COPD population (O'Donnell 2002; Tojo 2005) as compared to healthy normals who exhibit levels of 95 to 100mmHg.

The implications of this decreased arterial oxygen content are increased areas of alveolar ventilation to perfusion ratio mismatching (Jones 1997).

A major consequence of COPD pathophysiology is the phenomenon of the mismatching of ventilation and blood perfusion within the lung (Kasper 2006). An imbalance in the ventilation to perfusion ratio is the principal determinant of pulmonary gas exchange under both acute and chronic conditions (Calverley 2003). Barbera et al. (1990) concluded that emphysema and the inflammatory infiltrate of the bronchiolar wall (chronic bronchitis) act in conjunction in the impairment of the ventilation-perfusion ratio in mild COPD. The assessment of the pulmonary ventilation-perfusion ratio is performed using the multiple inert gas elimination technique which involves the integration of arterial, pulmonary arterial and mixed expired inert gas measurements with and without arterial sampling (Wagner 1977; Wagner 1985). Wagner et al (1977) published a study that laid the framework for characterizing ventilation-perfusion variations. They utilized the multiple inert gas elimination technique to examine the mechanism of impaired gas exchange in advanced COPD (Wagner 1977). Three patterns of ventilation-perfusion inequality found in advanced COPD patients were described: 1) a pattern with considerable areas with a high ventilation-perfusion ratio and none of low; 2) a pattern characterized by several regions of low and almost none of high ventilation-perfusion ratio; and 3) a combined pattern of both high and low ventilation-perfusion ratios. Patients that demonstrated areas of high V_A/Q also displayed, for the most part, large increases in compliance which may be a reflection of decreased blood flow due to the destruction of alveoli and their associated vasculature (Wagner 1977; GOLD 2005). Furthermore, pathological narrowing of the lumen in the pulmonary arteries, due to

bronchial inflammation causing vascular lesions, would decrease regional alveolar perfusion leading to high V_A/Q (Barbera 1990). Wagner et al. (1977) elaborated that the redistribution of perfusion was insufficient to explain all gas exchange abnormalities and therefore concluded that the majority of high V_A/Q ratio is a reflection of both ventilatory inequality and reduced perfusion. Conversely, the low ventilation-perfusion ratio is consistent with airway obstruction such as mucus, edema, and/or airway remodeling (Wagner 1977). Barbera et al. (1990) hypothesized two mechanisms to describe areas of low ventilation-perfusion ratio. First, distortion and narrowing of the airway lumen may be a supplemental effect of emphysematous destruction of the bronchiolar walls (Barbera 1990). The narrowing of the lumen could potentially cause reduced ventilation to the subsequent alveoli (Barbera 1990). Secondly, characteristic of centrilobular emphysema, certain alveoli exhibit increased residual volume with reduced compliance leading to a reduction in the ventilation-to-volume ratio (Barbera 1990). Consequently, the associated alveolar ventilation would therefore be reduced producing areas of low ventilation-perfusion ratio (Barbera 1990). Wagner et al. (1977) stated that in the case of very low V_A/Q, the reduction of ventilation is the predominant contributing factor. This situation would most likely be the product of airway obstruction due to mucus, edema, and airway distortion characteristic of chronic bronchitis (Wagner 1977). Moreover, reductions in ventilation of well-perfused areas within the lung have been shown to be the prominent cause of an increased alveolar-arterial oxygen tension difference at rest creating a cyclical dwindling of gas exchange mechanics (Jones 1997).

It can therefore be said that the physiological repercussions of COPD are vast but can be grouped for the most part into two main categories: the mechanics of breathing

and gas exchange abnormalities. It is the interaction between these two affected areas that produce the debilitating repercussions characterizing COPD. It is clear that further research is needed to more comprehensively understand the exact mechanisms that are at work. Currently, much research has been focused on the performance effects of COPD. The following section will discuss the use of exercise testing to examine the repercussions of COPD on activities of daily living.

3 Exercise Testing in Chronic Obstructive Pulmonary Disease

Exercise testing has long existed for use in the assessment of maximal exercise capacity in healthy individuals and functional exercise tolerance in patients with chronic diseases (ATS 2002). Its value in the clinical setting is particularly important as many diseases may not present with clinical manifestations until significant reductions in the functional capacity of the affected organ(s) occurs (Marciniuk 1996). Exercise testing usually proceeds either in the laboratory environment or using field tests.

3.1 Laboratory Exercise Testing

Exercise testing in the laboratory setting requires several decisions to be determined in order to conduct an appropriate test for the desired outcomes. Firstly, the measurement approach must be determined; either the direct or indirect method. The direct approach implies obtaining direct measures of the targeted outcome measure. For example, recording of an ECG allows a direct assessment of cardiac rhythm adaptation. Similarly, the assessment of the maximal energy output is best obtained through measurement of external power and oxygen uptake. On the other hand, indirect assessment implies the use of calculations and/or predictions to estimate the desired outcome measure, such as maximal or peak exercise capacity or other estimates of

exercise tolerance. The approach is typically chosen depending on the importance of obtaining precise assessment of a specific determinant of the exercise response.

Within both the direct and indirect approaches there exists two types of exercise testing; maximal exercise testing and submaximal exercise testing. As inferred from the name, maximal exercise testing involves working individuals to their maximal exercise capacity. This is of great importance as the true maximal values are measured. Submaximal exercise testing, on the other hand, can be implemented for estimation of peak values through the use of prediction equations. Submaximal exercise testing is also useful when measurements of physiological responses to exercise at metabolic steady state are desired.

Three exercise modalities are predominantly used in the laboratory setting: cycle ergometry, treadmill walking/running and arm cranking. The common inherent characteristic of these three testing modalities is their ability to elicit large muscle groups, an essential characteristic of a good testing modality. Cycle ergometry, treadmill walking/running and arm cranking have also been utilized in various disease populations, including COPD, for quantification of factors limiting exercise and defining the underlying pathophysiological mechanisms (ATS 2002).

There are several important advantages to using laboratory methods for exercise testing. First, laboratory testing provides the opportunity to obtain direct measurements of various physiological parameters during exercise such as heart rate, blood pressure, ventilation, gas exchange and oxygen consumption as well as derive more indirect measurements such as cost of physiological or mechanical work or mechanical efficiency which also requires that the mechanical work or power output be precisely quantified.

Second, the standardized approach generally used in laboratory testing allows for the monitoring of the evolution of disease or comparison of post-intervention responses which contribute greatly to the understanding of the disease or its clinical management.

On the other hand, the required equipment is often quite costly and complex requiring the assistance of skilled technical personnel for its utilization and maintenance. Such funds and technical know how may however not be readily available in all primary care facilities. In the absence of laboratory testing, validated and standardized field tests may be seen as valuable alternatives. Field testing does present the challenge of examining the physiological responses to exercise in a less structured environment (i.e. on a playing field, in a clinic or at home). For example, tests using exercising modalities requiring the involvement of the oxygen transport system while soliciting a large muscle mass component have been developed to reproduce the physiological challenges of treadmill or cycle ergometry testing. Similarly, step testing has been used in large regional or national wide studies to characterize the physical fitness of healthy children or adult populations (Bailey 1976; Shephard 1976; Weller 1992). Because the outcomes of such studies are necessarily simple and accessible measures, most of these studies focused only on the measurement of exercise heart rate or the speed of walking or stepping allowing for computation of work capacity. Such an approach would therefore preclude the use of field testing for specific screening or diagnosis of disease states such as coronary heart disease, asthma or myopathies. However, given that a simple outcome measure reflecting the exercise-induced symptom associated with a disease may be obtained, such tests could present the advantage of being used in the primary care setting to monitor disease evolution and disease intervention strategies.

3.2 Field Testing Modalities

Field tests have been implemented to predict maximal oxygen uptake when limited equipment is available or when assessing large groups of individuals at one time (ACSM 2006). As with laboratory testing, the approach, type and modality of the field test are essential decisions, based upon the basic principles of exercise testing, that must be made prior to conducting the exercise. Currently there are two predominant modalities being used in the clinical setting; stepping and walking tests. Both stepping and walking tests have been created on the basis of a standardized speed of movement. Simply put, for any given body mass, the cost of walking at a given speed is well known and similarly the cost of vertical displacement of the center of gravity over the step height is known. The standardization of the movement cadence allows the acknowledgement of the mechanical work achieved and the associated whole body predicted oxygen cost. Furthermore, the peak working capacity is generally defined by the participant's inability to maintain the set movement cadence. Alternately, participants may be asked to continue walking for a set period of time, after which the distance traveled is acknowledged (ATS 1995).

3.2.1 Step Tests

Step testing is one of the oldest basic exercise modalities that is still used, albeit several variations of step height, number of steps and stepping rate do exist (Weisman 2002). Historically, symptom-limited stair climbing has been vastly used in pulmonary medicine for fitness and functional evaluation (Shephard 1976) as well as pre-operative screening (Holden et al., 1992; Brunelli et al., 2002). In 1976, Shepard and colleagues published an article examining the validity and safety of the Canadian Home Fitness Test

(CHFT) in healthy individuals aged 15 to 69 years (Shephard 1976). This test was designed with two stages of stepping for which a recording sets the age- and sex-specific rhythm for ascending and descending two stairs (20.3cm in height to conform to a normal domestic step according to the Canadian building code) and time signals for counting immediate recovery heart rate (Shephard 1976; Shephard 1980a). If the specified heart rate value was not reached at the end of the stage the participant continued to the subsequent level. Due to difficulty of attaining and maintaining the pre-recorded pace, the test was adjusted to a count of the ascents and descents during the 3-minute work bout.

In 1993, Shephard and Bouchard revisited the approach to interpreting the heart rate values from the Canadian Home Fitness Test. They applied a modified version of the Åstrand nomogram procedure to create an empirical five-level categorization of aerobic fitness based upon the rate of stepping and the five to fifteen-second recovery heart rate count (Shephard 1993).

The validity portion of the 1976 study by Shephard et al. found that when the predictions of maximal oxygen consumption from the heart rate measurements at the end of the 3 minute exercise bout during the Canadian Home Fitness Test were correlated to those predicted from a submaximal cycle ergometry test (Astrand 1960) the correlation coefficient was r=0.72 for the 1152 subjects studied. The authors described the test to be valid as a simple tool for the assessment of aerobic power in healthy individuals aged 15 to 69 (Shephard 1976). This is surprising as the correlation that they presented (r=0.72) indicates that 48% of the variance is left unexplained.

The data collected by Bailey et al. (1976) on 1544 healthy individuals residing in Saskatoon, evaluated the maximal oxygen consumption prediction equation for the

Canadian Home Fitness Test by comparing it with cycle ergometry. The means of predicted maximal oxygen uptake from the Canadian Home Fitness Test and cycle ergometry were compared. The difference between the two means was 0.6 $mL \cdot kg^{-1} \cdot min^{-1}$ STPD for men and women 15 to 69 years of age. The day-to-day test-re-test reproducibility of recovery heart rates for the Canadian Home Fitness Test was shown to have a correlation coefficient of 0.79 (Bailey 1976). Again, this correlation has 37% of its variance that is unexplained. The above studies lead to the conclusion that as related to a submaximal or maximal cycle ergometer test, the Canadian Home Fitness Test needs further testing to establish its validity for prediction of maximal oxygen consumption. However, it was deemed of interest as a discriminator of physical fitness and was used on a large scale study of the Canadian population.

Within this pan-Canadian study by Shephard et al. (1976) the evaluation of safety of the Canadian Home Fitness test was also determined by examining the number of negative occurrences during the test. Of the 14,000 adults who were tested by Recreation Canada no major problems occurred, leading Shephard et al (1976) to the conclusion that the Canadian Home Fitness Test is also a safe method of assessing aerobic power.

Shortly after the creation of the Canadian Home Fitness Test, Cumming and Glenn (1977) examined the use of the BORG scale of perceived exertion (Borg 1982), in terms of intensity of exercise, instead of post-exercise heart rates for the prediction of maximal oxygen consumption. The self-measured heart rate and BORG scale ratings were correlated with the estimated maximal oxygen consumption using the Bruce, Kusumi and Hosmer method (Bruce 1973) during the treadmill test in 230 healthy men 45 to 69 years of age. The highest correlation value for the comparison of self-measured

heart rate with treadmill oxygen consumption was r=0.62 (Cumming 1977) obtained on 230 participants across all ages. Whereas, the correlation between the BORG scale ratings and the oxygen consumption from the treadmill exercise was r=0.81 (Cumming 1977), thus prompting the authors to suggest that the BORG scale assessment of exercise intensity to be a better predictor of maximum oxygen uptake than the self-measured heart rate.

In 1975, Jette et al conducted a preliminary study revisiting the topic of the validity of the Canadian Home Fitness Test. They determined that the predicted oxygen cost of stepping during the Canadian Home Fitness Test corresponded well with the measured oxygen consumption from the treadmill with Pearson correlations of 0.92 being reported in healthy individuals (15 to 69 years of age) (Jette 1975). In a similar fashion, Weller and associates (1992) correlated the estimated oxygen consumption during the Canadian Aerobic Fitness Test (CAFT) with the measured maximal oxygen consumption during a maximal treadmill protocol in 129 healthy subjects aged 15 to 69 years of age. The comparison of the two measures of oxygen consumption yielded a Pearson r of 0.83 and an intraclass correlation coefficient (ICC) of 0.81 (Weller 1992). These values indicate that 31% of the variance between tests is unexplained whereas some 70% of the total variance can be accounted for by within subject variation.

In 1992, Cox et al. reexamined the reliability of the Canadian Home Fitness Test. In a test-re-test repeatability study of the CAFT on thirty healthy subjects (18 to 65 years of age), no significant difference between the mean values of oxygen consumption for the three trails on consecutive days was found (Cox 1992).

As with all tests, there are some limitations associated with the Canadian Home Fitness Test. The principle limitation of the Canadian Home Fitness Test occurred in the home version where individuals counted their own heart rate at end exercise (Shephard 1981). As previously described above, the Canadian Home Fitness Test does require further investigation into the validity of the estimation of maximal oxygen consumption as the current data is inconclusive.

In 2001, a Canadian group developed a self-paced stepping test to predict aerobic fitness in healthy elderly adults (≥65 years of age); the first step test to be used in the healthy aged population (Petrella 2001). The test consists of stepping up and down two steps (20cm in height) twenty times at three different paces: self selected to be "slow", "normal" and "fast" with 5-minute rest periods between each stage. Post-exercise heart rate and time to complete were the two outcome measures recorded during the Self-Paced Step Test. The objective of this study was to examine the potential usefulness of a submaximal self-paced step test as a predictor of maximal oxygen consumption in older adults in the primary care setting (Petrella 2001).

The 'normal' step-pace correlation with maximal oxygen consumption, as measured by maximal treadmill testing, was no different (women 0.93; men 0.91) from fast pace (0.95; 0.90) (Petrella 2001). Furthermore, no difference was found between laboratory and clinic measurements from baseline to 52 weeks (Petrella 2001). This data indicates that the 'normal' step-pace of Petrella's step test is not sex-specific and is reproducible over a period of 52 weeks in the healthy aged population. The predicted maximal oxygen consumption values were compared with measured values taken during the maximal treadmill test; the correlation between the predicted and measured values

was determined to be r=0.92 (Petrella 2001). This study demonstrated that indeed the Self-Paced Step Test can be used as a reliable predictor of maximal oxygen consumption in healthy elderly adults (>65 years of age). Currently, there is no data to support the validity or reproducibility of the Self-Paced Step Test in other populations.

The simplicity in conducting the Self-Paced Step Test was assessed by comparing results taken by trained and untrained examiners (Petrella 1998). In this study, a similar healthy aged population was divided into two groups to perform the Self-Paced Step Test for either a trained or an untrained examiner. Results indicate that the experience of the examiner did not affect the test's ability to predict maximum oxygen consumption (Petrella 1998). As such, the Self-Paced Step Test is a simple test that does not require a trained examiner and could be easily implemented into the primary care setting.

The Self-Paced Step Test also exhibits an important limitation; as a self-paced test the amount of work being done is not quantified and therefore it is difficult to make comparisons between individuals.

As of yet no stepping test has been developed specifically to assess the COPD population. Currently, the predominant field testing modality used for testing COPD patients is walking.

3.2.2 Walk Tests

In lung disease, corridor walking tests have been one of the most widely used forms of testing for the purpose of repeated measures of maximal exercise capacity estimation (Stevens 1999). Within the modality of walking there are two distinct types of tests: timed walk and externally paced walk tests. The advantage of using walking tests as a measure of exercise tolerance are: (1) it is an activity of daily living and thus there is no

need for practice learning; (2) some walk tests have been shown to induce almost maximal oxygen consumption (Swinburn 1985); (3) they are cost efficient in that minimal equipment is required (Swerts 1990); and (4) with their simplicity, patients can perform the tests independently, enabling them to monitor their own progress (Swerts 1990).

3.2.2.1. Timed Walk Tests

Timed walk tests are self-paced tests where the outcome measure is distance covered during the allotted time. These tests have predominantly been developed over times ranging between 2 and 12 minutes, and are better known as the 12-, 6- and 2-Minute Walk Tests. In each of these tests individuals are asked to walk along a course of a set distance at their desired pace for the specified duration of the test. Individuals are allowed to take breaks during the test but are encouraged to maintain a steady pace throughout the test. Maximal exercise capacity can be estimated using the distance walked during these timed walk tests and their associated prediction equations that can incorporate a combination of the following parameters: age, weight, FVC, FEV_1, and DLCO (Cahalin 1995; Ambrosino 1999).

In 1968, Cooper created the 12-minute running test to assess maximal oxygen uptake as a measure of fitness in 115 healthy young men in the US Air Force (17 to 52 years of age). The objective of the test was to cover the greatest possible distance in twelve minutes at a relatively steady pace. In the original study by Cooper (1968), the validity and reliability of the 12-Minute Cooper test were examined. A Pearson correlation coefficient of 0.89 was determined between the oxygen consumption measured during the 12-Minute Cooper Test and the values obtained during a treadmill

maximal oxygen consumption test (Cooper 1968). Furthermore, the four day test-re-test coefficient of reliability was 0.97 for the 12-Minute Cooper Test (Cooper 1968). From this study, the Cooper Test was established as being both valid and reliable for use in healthy young men.

This test was then adapted to estimate exercise tolerance in COPD patients by converting the test to a walking test by McGavin et al. (1976). Due to the length of time and exhausting nature of the 12-Minute Walk Test, Butland et al. (1982) explored the use of 2- and 6-minute walking tests for patient populations.

Between the 12-, 6- and 2-Minute Walk Tests a total of 37 studies were found outlining the measurement characteristics of each test; they are summarized below. The 12-Minute Walk Test has been examined by several groups for its use in a variety of populations. Eight studies were found (Tables 4 & 5), of which five describe the validity (McGavin 1976; Alison 1981; Swinburn 1985; Bernstein 1994; Kosak 2005) and three examine the reliability (Mungall 1979; O'Reilly 1982; Larson 1996) of the 12-Minute Walk Test. Twenty-five studies on the 6-Minute Walk Test were found (Tables 4 & 5). Eighteen of these studies examined the validity (Table 4) and sixteen assessed the reliability (Table 5). Seven studies were found on the 2-Minute Walk Test (Tables 4 & 5). Of these, four studies examined the validity (Butland 1982; Bernstein 1994; Kosak 2005; Leung 2006)and four evaluated the reliability (Guyatt 1984; Eiser 2003; Leung 2006; Stolwijk-Swuste 2008) of the 2-Minute Walk Test. The studies on all three tests were conducted using several different populations including healthy older adults (n=1), COPD (n=17), chronic heart failure (n=9), children with cystic fibrosis or end-stage cardiac or pulmonary disease (n=2), stroke patients (n=2), patients with end-stage lung

disease (n=1), patients with pacemakers (n=2), peripheral artery disease (n=1), late-onset sequelae of poliomyelitis (n=1), and idiopathic interstitial pneumonia (n=1).

Table 4. Studies of Validity of the 12-, 6- and 2-Minute Walk Tests

Study	N/ Subject Status[1]	Age (years)	Other	Comparison Test	Correlation Coefficient
12MWT					
(Bernstein 1994)	9 COPD	67±4	male only; FEV_1=1.32±0.28L	6MWT / 2MWT	0.94[e] , 0.97[d]
(McGavin 1976)	35 COPD	40-70	male only; FEV_1=1.05±0.58L	Cycle Ergometry	0.52
(Alison 1981)	25 COPD	38-75	FEV_1=45.1±4.8% pred	Cycle Ergometry	0.68
(Swinburn 1985)	17 COPD	49-73	FEV_1=0.8±0.3L	Cycle Ergometry	0.51
(Kosak 2005)	18 S	77±11		6MWT / 2MWT	0.99
6MWT					
(Butland 1982)	10 COPD	61±11	FEV_1=1.28±0.66L	12MWT / 2MWT	0.96[f] , 0.89[d]
(Wijkstra 1994)	40 COPD	62.4±5.0	FEV_1= 1.2±0.3L	Cycle Ergometry	0.81[c]
(Rejeski 2000)	209 COPD	67.2±6.0	FEV_1=1.57±0.58L	Treadmill	0.64
(Turner 2004)	20 COPD	64.0±7.5	FEV_1= 0.8±0.3L	Cycle Ergometry	0.73
(Bernstein 1994)	9 COPD	67±4	men only; FEV_1=1.32±0.28L	Cycle Ergometry / 12MWT / 2MWT	0.51 , 0.97[f] , 0.95[d]
(Guyatt 1985a)	25 COPD / 18 CHF	64.7±8.3	FEV_1=0.97±0.25L	Cycle Ergometry	0.58[b]
(Guyatt 1985b)	25 COPD / 18 CHF	64.7±8.3	FEV_1=0.97±0.25L	Cycle Ergometry	0.58[b]
(Riley 1992)	16 CHF	48-76		Treadmill	0.88
(Cahalin 1996)	45 CHF	49±8		Cycle Ergometry	0.64
(Lucas 1999)	307 CHF	52±13		Cycle Ergometry	0.57
(Roul 1998)	121 CHF	59±11		Cycle Ergometry	0.65

(Zugck 2000)	113 CHF	54±12		Cycle Ergometry	0.68
(Cahalin 1995)	60 ESLD	44±11		Cycle Ergometry	0.73
(Eaton 2005)	30 IIP	73±8.5		Cycle Ergometry	0.78[a]
(Nixon 1996)	17 CESCPD	9-19		Cycle Ergometry	0.7
(Gulmans 1996)	23 CCF	11.1±2.2		Cycle Ergometry	0.76 , 0.76[c]
(Langenfeld 1990)	97 P	67±13		Cycle Ergometry	0.74[c]
(Pereira de Sousa 2008)	24 P	48±14.4		Treadmill	0.71[a]
2MWT					
(Butland 1982)	10 COPD	61±11	FEV_1=1.28±0.66L	12MWT / 6MWT	0.89[e] , 0.96[d]
(Bernstein 1994)	9 COPD	67±4	men only; FEV_1=1.32±0.28L	Cycle Ergometry / 12MWT / 6MWT	0.45 , 0.94[f] , 0.95[e]
(Leung 2006)	47 COPD	71.8±8.3	FEV_1=0.94±0.28L	6MWT	0.94[e]
(Kosak 2005)	18 S	77±11		12MWT / 6MWT	0.99[f] , 0.99[e]

Correlation coefficients are given for comparison with peak VO_2 unless stated otherwise.
a: refers to estimated peak VO_2; b: refers to time to exhaustion; c: refers to Wmax; d: refers to 2-Minute Walk Distance (2MWD); e: refers to 6-Minute Walk Distance (6MWD); f: refers to 12-Minute Walk Distance (12MWD)
[1] COPD: Chronic Obstructive Pulmonary Disease; S: Stroke; CHF: Chronic Heart Failure; ESLD: End-Stage Lung Disease; IIP: Idiopathic Interstitial Pneumonia; CESCPD: Children with End-Stage Cardiac or Pulmonary Disease; CCF: Children with Cystic Fibrosis; P: Pacemaker

The studies examining the validity of the three self-paced walking tests will be presented in two groupings: those examining intrinsic validity and those focusing on concurrent validity. In all there is not an overwhelming amount of information on any of the tests, although predominantly the information is pertaining to the 6-Minute Walk Test. The primary reasoning for the lack of information is the incomplete data collection or presentation that exists in the articles that have been published on the topic. The studies that have more complete data will be discussed.

Studies that have examined the intrinsic validity of the 12- and 6-Minute Walk Tests have utilized either the treadmill or cycle ergometry. The validity of the 12-Minute Walk Test as a predictor of maximal oxygen consumption was assessed as a correlation with maximal oxygen consumption during cycle ergometry, maximal work, as well as treadmill time to fatigue. The 12-Minute Walk Test was validated using cycle ergometry for the prediction of peak exercise capacity in COPD patients (n=3). The three validation studies that examined the ability of the 12-Minute Walk Test to predict peak exercise capacity by correlating with peak work rate or peak oxygen consumption during cycle ergometry presented Pearson r-values ranging from 0.51 to 0.68 (McGavin 1976; Alison 1981; Swinburn 1985). The assessment of validity from these studies left unexplained variation in the range of 54 to 74%.

Most studies have validated the 6-Minute Walk Test by correlating the distance walked to maximal oxygen consumption, time to exhaustion, and maximal work during either cycle ergometry or treadmill exercise (Table 4). In the seventeen studies that examined the intrinsic validity of the distance walked in 6-minutes the Pearson correlations ranged from 0.51 to 0.88 (Table 4).

From Table 4 we can see that 80% of the reported correlations between the 6-minute walking distance and maximal oxygen uptake have more than 26% unexplained variation. There are a number of factors that could have contributed to the lower correlations being reported, the most prominent being a discrepancy between studies in the instructions relative to the speed of walking that participants should be attempting to maintain. Indeed, the effects of encouragement on the results of the 6-Minute Walk Test have been examined (Guyatt 1984). In the study by Guyatt et al. (1984), the 6-Minute

Walk Test was shown to be significantly influenced by encouragement (mean improvement of 30.5m). Thus it is likely that depending on the nature of the instructions given to participants or the encouragements provided throughout the test, subjects perform at a higher or lower percent of their peak aerobic capacity leading to higher or lower correlations with measured peak oxygen uptake. In response to this potential confounder the American Thoracic Society has published specific guidelines on encouragement during the 6-Minute Walk Test (ATS 2002). Several of the aforementioned studies were conducted prior to the ATS publication and therefore some studies offered no encouragement whereas others had varying degrees of verbal support for the participants. Thus, variations in the level of encouragement given to participants could be a major contributing factor to the variations in correlations that is seen in Table 4. Overall, the amount of unexplained variation from the correlations between the 6-minute walk distance and maximal oxygen consumption does not lend great support to the validation of the 6-Minute Walk Test.

There were no studies found examining the intrinsic validity, with respect to maximal oxygen uptake, of the 2-Minute Walk Test. The lack of data for any of the three tests can be attributed to the fact that there is much uncertainty whether any of these self-paced walking tests are indeed maximal exercise tests. The first indication that the tests are of a submaximal nature is the results presented by Butland et al. (1982). They evaluated the 12-, 6- and 2-Minute Walk Tests for concurrent validity and found very high correlation coefficients between the 12- and 6-Minute Walk Tests (r=0.95), the 12- and 2-Minute Walk Tests (r=0.86) as well as between the 6- and 2-Minute Walk Tests (r=0.89) (Butland 1982). These results indicate that all three self-paced tests are similar

measures of exercise tolerance. However, this does not provide evidence for appropriate correlation with peak oxygen uptake. Given the high degree of correlation between distance walked over a 12 minute time frame and a 6 minute time frame, it is difficult to imagine that both of these tests were completed at a maximal intensity, unless it is also associated with a selection bias to eliminate subjects who could not sustain a maximal or near maximal pace for 12 minutes. The authors believed that the greater variation during the 12-Minute Walk Test was not due to increased random variation; rather it indicated the test was more discriminating (Butland 1982). Alternatively, the wide discrepancy of correlation coefficients, as seen in later work, may be a reflection of variability in the implementation of the tests as described above (ie. encouragement).

As not all facilities are equipped with treadmills, cycle ergometers and more specifically metabolic carts, some researchers are unable to obtain direct measurements of maximal oxygen uptake and therefore must turn to alternatives. In these instances, similar tests are used for comparison so as to validate the desired test. In addition to the studies above who examined the intrinsic validity, the 12-, 6- and 2-Minute Walk Test have all been examined in terms if concurrent validity.

The validity of the distance walked during the 12-Minute Walk Test has also been assessed as a correlation with the distances walked during the 2- and 6-Minute Walk Tests. The highest overall correlations of the validity of the 12-Minute Walk Test were found between the distance walked during 12-Minute Walk Test and the distances walked during the 2- (r=0.94) and 6-Minute Walk Tests (r=0.97) in elderly men with COPD (Bernstein 1994). Furthermore, the study by Bernstein et al. (1994) also demonstrated

high correlations between the distance walked during the 6-Minute Walk Test and the distance walked during the 2-Minute Walk Test (r=0.89).

As the 2-Minute Walk Test had no data to support intrinsic validity, there were more studies examining the concurrent validity as compared to those found for the 12- and 6-Minute Walk Tests. Four studies validated the distance walked during the 2-Minute Walk Test with respect to the distance walked during the 6-Minute Walk Test (Butland 1982; Bernstein 1994; Kosak 2005; Leung 2006) and three with respect to the distance walked during the 12-Minute Walk Test (Butland 1982; Bernstein 1994; Kosak 2005) in patients with COPD. Butland et al. (1982), Bernstein et al. (1994) as well as Leung et al. (2006) all found correlations with distances walked in the 2- and 6-Minute Walk Tests that ranged between 0.89 and 0.99. The correlations between the 2- and 12-Minute Walk Test were similar with a range of 0.94-0.99 (Butland 1982; Bernstein 1994; Kosak 2005).

Although, all three self-paced walk tests demonstrate high concurrent validity, the conclusion that they are all valid tests is based upon the premise that at least one has been shown to have high intrinsic validity. Therefore, to solidify the 12-, 6- and 2-Minute Walk Tests as valid tests, further testing is required.

Walking Test Reliability

The second measurement property of the self-paced walking tests that will be examined is the reliability of the tests. In the six studies that examined the reliability of the 12- and 6-Minute Walk Tests, it was determined that two practice walks were necessary to eliminate any learning effects (Mungall 1979; Guyatt 1984; Guyatt 1985b; Langenfeld 1990; Riley 1992; Larson 1996). After two practice walks, the one week test-re-test reproducibility of the 12-Minute Walk Test was shown to be 0.98 in patients with

COPD (Larson 1996). Furthermore, there was less than 10% variation in the mean distance walked between tests if performed on the same day or two weeks later (O'Reilly 1982). The two studies that examined the test-re-test reproducibility demonstrated an acceptable variation in mean distance walked of 4 to 10% may occur between repeat testing one to two weeks apart (O'Reilly 1982; Larson 1996).

Similarly, the one-to-two week test-re-test reproducibility of the 6-Minute Walk Test was assessed in older adults, COPD patients, children with cystic fibrosis, peripheral artery disease, and idiopathic interstitial pneumonia patients (Table 5). The Pearson coefficients of the test-re-test reproducibility studies range from 0.90 to 0.98 (Gulmans 1996; Montgomery 1998; Harada 1999; Rejeski 2000; Eaton 2005). In addition, Opasich et al. (1998) determined that in adults with chronic heart failure, two tests performed half an hour apart were equivalent to two tests performed on consecutive days, based upon mean comparison.

In addition, the test-re-test reproducibility of the 6-Minute Walk Test has been assessed through intraclass correlations for heart failure, stroke and chronic lung disease patients with values ranging from 0.82 to 0.99 (Guyatt 1985a; Cahalin 1996; O'Keeffe 1998; Roul 1998; Eng 2004). Thus results show good repeatability of the test in various populations.

Of the five studies that evaluated the reproducibility of the 2-Minute Walk Test three found intraclass correlations of the repeated measures ranging from 0.88 to 0.99 for the distance walked during the test in COPD and late-onset sequelae of poliomyelitis patients (Leung et al., 2006; Stolwijk-Swuste et al., 2008). The above data support the

finding that the 12-, 6- and 2-Minute Walk Tests are indeed reproducible tests after 2 practice walks have been performed.

Table 5. Studies of Reliability of the 12-, 6- and 2-Minute Walk Tests

Study	N/ Subject Status[1]	Age (years)	Other	Timing	Test-re-test
12MWT					
(Mungall 1979)	13 COPD	47-64	male only; FEV1=1.54±0.06L	Same day	NSD
(O'Reilly 1982)	10 COPD	52-70	male only; FEV1=0.81±0.21L	Same day , 2 weeks later	r=98 , r=0.95
(Larson 1996)	108 COPD	64±8	FEV1=38±13 % pred	One week	r=0.98
6MWT					
(Harada 1999)	86 OA	75±6		One week	r=0.95
(Rejeski 2000)	209 COPD	67.2±6.0	FEV1=1.57±0.58L	Two week	r=0.91
(Roomi 1996)	15 COPD	70-89	FEV1=49±5% pred	2-10 days	NSD
(Guyatt 1984)	25 COPD / 18 CHF	64.7±8.3	FEV1=0.97±0.25L	One week	NSD
(Guyatt 1985a)	25 COPD / 18 CHF	64.7±8.3	FEV1=0.97±0.25L	Two week	ICC: 0.91-0.92
(Guyatt 1985b)	25 COPD / 18 CHF	64.7±8.3	FEV1=0.97±0.25L	Two week	NSD
(Cahalin 1996)	45 CHF	49±8		Same day	ICC: 0.96
(Roul 1998)	121 CHF	59±11		Same day	ICC: 0.82
(Riley 1992)	16 CHF	48-76		One week	NSD
(Opasich 1998)	233 CHF	54±9		30 min apart : 2 consecutive days	NSD
(O'Keeffe 1998)	60 CHF	74-92		3-8 weeks	ICC:0.91
(Montgomery 1998)	64 PAOD	68±7		One week	r=0.94
(Langenfeld 1990)	97 P	67±13		Same day	NSD
(Gulmans 1996)	23 CCF	11.1±2.2		One week	r=0.90
(Eng 2004)	12 S	62.5±8.6		NCD	ICC: 0.99

(Eaton 2005)	30 IIP	73±8.5		One week	r=0.98
2MWT					
(Guyatt 1984)	25 COPD / 18 CHF	64.7±8.3	FEV1=0.97±0.25L	One week	NSD
(Eiser 2003)	57 COPD	69±8	FEV1=35±12 % pred	One week	NSD
(Leung 2006)	47 COPD	71.8±8.3	FEV1=0.94±0.28L	Within 2 days	ICC:0.99
(Stolwijk-Swuste 2008)	57 LOSP	57.3±7.2		Three week	ICC: 0.88-0.96

[1] *COPD: Chronic Obstructive Pulmonary Disease; OA: Older Adults; S: Stroke; CHF: Chronic Heart Failure; PAOD: Peripheral Artery Occlusive Disease; IIP: Idiopathic Interstitial Pneumonia; CCF: Children with Cystic Fibrosis; P: Pacemaker; LOSP: Late-onset Sequelae of Poliomyelitis*
NCD: Not clearly defined; NSD: No significant difference

As a group, the self-paced walking tests may therefore be seen to be quite reproducible. These tests may be used with some success to discriminate between subjects on their general exercise tolerance or functional ability but have not been shown to be highly valid for determining peak aerobic power or capacity. In addition, these tests exhibit some limitations in terms of test duration, encouragement and set-up. Firstly, during the 2-Minute Walk Test, patients with minimal limitation may not achieve their maximal capacity. Another consideration for the 2-minute walk test is that in such a short period of time, the cardiorespiratory system may not be adequately stressed in patients with mild disease severity (Leung 2006). On the other hand, using the 6- and 12-minute walk tests may be too exhausting for more severe patients (Leung 2006). The above two situations are extremely dependent on the instructions and encouragement given to the participants. A significant limitation to self-paced walk tests is the effect of encouragement on performance as demonstrated by the study by Guyatt et al. (1984) (described above). From a practical perspective, as with the 6-Minute Walk Test, the 2- and 12-Minute Walk Tests should be performed in a 30m corridor with a hard surface with low traffic flow (ATS 2002). There are not very many readily available corridors of

this size that are seldom traveled in the primary care setting. The use of a shorter or busier hallway could potentially affect the performance of the participant. In response to these disadvantages, some scientists have turned towards externally paced walking tests. In the group of externally paced walking tests there is one predominant test that has emerged, the Incremental Shuttle Walk Test.

3.2.2.2 Externally Paced Walk Test

In comparison to the timed walk test, externally paced walking tests are designed such that the work rate is dictated to the participants through auditory or visual cues providing a walking pace to be followed.

In 1992, Singh and colleagues created a shuttle walking test for use in the COPD population. The Incremental Shuttle Walk Test (ISWT) is a standardized externally paced submaximal walking test used to assess endurance (Singh 1992). The Incremental Shuttle Walk Test is also used in the COPD population to measure the maximal capacity of the individual to perform exercise by applying a progressive incremental protocol (Singh 1992; Ambrosino 1999). Pace is externally controlled through the use of a pre-recorded compact disc, an accepted method of standardizing walking speed (Revill 1999). An incremental exercise test is advantageous for comparisons using equivalent exercise intensities, for example pre- and post-training (Turner 2004). Unlike the self-paced tests, the Incremental Shuttle Walk Test is progressive, therefore eliminating motivation and encouragement as confounding factors (Singh 1994; Campo 2006). Due to its standardization, the maximal speed achieved during the Incremental Shuttle Walk Test is more representative of the patient's maximal capacity than the 6- and 12-minute walk tests (Campo 2006).

Thirteen studies were found outlining the validity and reliability of the Incremental Shuttle Walk Test (Tables 6 & 7). Of these, seven examined the validity in patients with COPD, chronic heart failure and post-coronary artery bypass surgery (Singh 1992; Singh 1994; Green 2001; Turner 2004; Fowler 2005; Rosa 2006; Pulz 2008). In turn, nine studies have examined indices of reproducibility of the Incremental Shuttle Walk Test (Payne 1996; Green 2001; Lewis 2001; Dyer 2002; Eiser 2003; Zwierska 2004; Fowler 2005; Campo 2006; Pulz 2008).

Table 6. Studies of Validity of the Incremental Shuttle Walk Test

Study	N/ Subject Status[1]	Age (years)	Other	Comparison Test	Correlation Coefficient
(Singh 1992)	30 COPD	45-74	FEV_1=0.36-2.85L	6MWT	ρ=0.68*
(Singh 1994)	19 COPD	64±7	FEV_1=1.02±0.38L	Treadmill	0.88
(Turner 2004)	20 COPD	64.0±7.5	FEV_1=0.8±0.3L	Cycle Ergometry	0.73
(Rosa 2006)	24 COPD	67.8±7.5	FEV_1=48.6±021.0% pred	6MWT	0.80*
(Green 2001)	7 CHF	56.7±1.5		Treadmill	0.83
(Pulz 2008)	63 CHF	51.3±10.2		Treadmill	0.79
(Fowler 2005)	39 P-CAB	61.2±8.5		Treadmill	0.79 - 0.87

Correlation coefficients are given for comparison with peak VO_2 unless stated otherwise.
** refers to 6-Minute Walk Distance (6MWD)*
[1] COPD: Chronic Obstructive Pulmonary Disease; CHF: Chronic Heart Failure; P-CAB: Pre-Coronary Artery Bypass

The validity of the Incremental Shuttle Walk Test was assessed by comparing it with the 6-Minute Walk Test, maximal cycle ergometry and a maximal treadmill test (Singh 1992; Singh 1994; Turner 2004; Rosa 2006; Pulz 2008). As such, both the concurrent and intrinsic validity of the test were examined. In the initial study by Singh et al. (1992) examining the concurrent validity, the relationship between the distance walked in 6 minutes with the distance walked during the Incremental Shuttle Walk Test

was ρ=0.68. In support of this, Rosa et al. (2006) also examined the relationship between the Incremental Shuttle Walk performance and the 6-minute walk distance to find an r of 0.80 ($p<0.001$) in patients with COPD.

Subsequently, 19 stable COPD patients were used to compare the Incremental Shuttle Walk Test with the maximal oxygen consumption measured during a maximal treadmill test for the purpose of determining the intrinsic validity of the test (Singh 1994). Results showed a correlation of r=0.88 between the performance during the Incremental Shuttle walk Test and the peak oxygen consumption measured using an incremental RAMP treadmill test (Singh 1994). In addition, the Incremental Shuttle Walk Test was also compared to a cardiopulmonary exercise test on the bicycle in patients with COPD (Turner 2004). The correlation between the performance on the Incremental Shuttle Walk Test and the cycle ergometry was r=0.73 ($p<0.001$) (Turner 2004). Similarly, Fowler et al. (2005) compared the peak oxygen consumption during treadmill exercise with three Incremental Shuttle Walk Test performances and found Pearson correlations of 0.79 to 0.87 in patients post-coronary artery bypass. In two studies of chronic heart failure patients, the correlation between peak oxygen consumption during an incremental treadmill exercise test and the distance walked during the Incremental Shuttle Walk Test produced a range of Pearson correlations of 0.79 to 0.83 (Green 2001; Pulz 2008). The three populations (COPD, coronary artery bypass and chronic heart failure), have all been shown to have similar Pearson correlations between the oxygen consumption during the Incremental Shuttle Walk Test and either cycle ergometry of treadmill exercise in the range of 0.73 to 0.88. In general, results from validation of the Incremental Shuttle Walk Test establish this test to be more valid for the assessment of peak aerobic power than the

timed-walk tests, probably on account of the better standardization of walking speeds. The interpretation of the correlative data however still leave 23 to 37% unexplained variation which may be related to ergometer used since the lowest correlation was found when comparing the walking test to direct peak cycle ergometry testing. The consistency between populations is however of value since it indicates a similar response irrespective of the underlying pathophysiological impairment in the oxygen transport system.

Table 7. Studies of the Reliability of the Incremental Shuttle Walk Test

Study	N/ Subject Status[1]	Age (years)	Other	Findings	Test-re-test
(Dyer 2002)	50 COPD / 32 C	70-85	FEV_1=1.2±0.1L	Two week	NSD
(Eiser 2003)	57 COPD	69±8	FEV_1=35±12 % pred	One week	NSD
(Campo 2006)	30 COPD	68.6±7.2	FEV_1=1.0±0.5L	One week	ICC: 0.88
(Payne 1996)	30 DCP	27-76		Same day	NSD
(Lewis 2001)	25 HT	53±8		One day	r=0.90
(Pulz 2008)	63 CHF	51.3±10.2		Same day	NSD
(Green 2001)	7 CHF	52.4±3.2	male only	One week	r=0.98
(Fowler 2005)	39 P-CAB	61.2±8.5		One week	NSD
(Zwierska 2004)	55 IC	52-85		NCD	ICC: 0.87

[1] *COPD: Chronic Obstructive Pulmonary Disease; C: Control; DCP: Dual Chamber Pacemaker; P-CAB: Pre-Coronary Artery Bypass; HT: Heart Transplant; CHF: Chronic Heart Failure; IC: Intermittent Claudication*
NCD: Not clearly defined; NSD: No significant difference

The Incremental Shuttle Walk Test has been shown to have a test-re-test correlation coefficient of 0.90 ($p<0.0001$) after one practice walk for patients with heart transplantation (Lewis 2001). In patients with chronic heart failure, Green et al. (2001) found one week test-re-test reproducibility of distance walked during the Incremental Shuttle Walk Test to be r=0.98. Similarly, there was no difference in the mean test results found between repeated tests in dual chamber pacemaker patients, post-coronary artery bypass surgery patients or chronic heart failure patients (Payne 1996; Fowler 2005; Pulz

2008). Also, the one week test-re-test reproducibility was found to have an intraclass correlation of 0.88 in clinically stable COPD patients and 0.87 in intermittent claudication patients (Zwierska 2004; Campo 2006). Overall, the Incremental Shuttle Walk Test has been shown to exhibit reasonable intrinsic validity as well as good reproducibility. It is important to note that to date, there has not been any validation or reliability studies performed on healthy or aged populations for this test.

From the above section we can see that while there may be good field tests for the prediction of peak oxygen consumption in the general healthy population, what has been developed in the chronic disease population is more valuable as a discriminating tool to provide some understanding of the patient's functional status. Given the good reproducibility of the walking tests, they are most likely also appropriate to assess the evolution of disease, although the sensitivity of the tests, i.e. the minimal change in primary outcome that can be detected has not been clearly established. To date, there is however very little related to the stepping modality in the chronic disease population that would lead us to make a similar assessment of the value of this modality for the assessment of peak work capacity in patients. The question at hand, may however, be to what extent are stepping tests of interest in the primary care setting to target the assessment of peak aerobic power or peak work capacity when the object is to intervene to improve the patient's quality of life i.e. enhancing the patients ability to partake in activities of daily living. Given that participation is often curtailed on account of symptoms, it is of interest that few tests have focused on symptoms as the primary testing outcome. Further developments are therefore warranted to advance our ability to monitor and intervene on exercise tolerance of patients with chronic disease.

4. Statement of the Problem

As can be seen from the above literature review, COPD disease processes lead to significant reductions in pulmonary function resulting in patients experiencing significant at times debilitating dyspnea upon even the slightest increase in energy demands. Exercise testing is therefore vastly used in the COPD population to assess the severity of disease and its evolution and to monitor the efficacy of treatment. In the majority of cases, patients are seen in a primary care setting where exercise testing may be difficult to achieve as the sophisticated equipment necessary for laboratory testing maybe be unavailable. An appropriate substitute for laboratory testing would be a simple and cost efficient field test that is applicable to activities of everyday life. To obtain objective exercise measurements, the test needs to be reproducible over time yet be sensitive enough to detect changes in performance due to disease progression, rehabilitation or pharmacological intervention.

Step testing as well as walking are exercise modalities that adequately reproduce activities of daily living that employ large muscle masses and thus bear the advantage of reproducing symptoms commonly experienced by patients. These modalities have been integrated in field tests to characterize exercise tolerance or capacity in various subgroups of the population healthy and diseased, young and old (ATS 2002). However, the outcome measure for the timed-walked tests focuses on the distance walked while that of step testing uses a heart rate response to characterize the individual's exercise capacity. Exertional dyspnea has traditionally been assessed in the laboratory setting using a BORG visual scale. This measurement has also been incorporated in the application of the 6-Minute Walk Test for measurement of exertional dyspnea in COPD patients

(Cumming 1977) however, lack of standardization of the 6-Minute Walk Test protocol limits its ability for monitoring patient responses to treatment or the evolution of disease. Therefore, there is much need for a standardized test that focuses on the main outcome of exertional dyspnea in the COPD population that does not require sophisticated equipment or an extraordinary amount of space and is easy to use.

Our research group has recently elaborated two new field test protocols using exercise modalities commonly used in activities of daily living, namely, walking and stair stepping for the assessment of exertional dyspnea in the COPD population. In both tests, standardization is ensured by imposing a constant movement cadence for a period of 3-minutes at the end of which a BORG dyspnea score is recorded. The shuttle walk test involves walking over a 10m distance at a given walking speed provided through an auditory signal while the step test involves going up and down a one-step stair apparatus with an audio signal indicating the footwork cadence.

4.1 Main Objective

The general framework for this thesis work was to examine the feasibility and applicability of whole body exercise field tests which could be used in the clinical setting to assess the effects of pharmacological, educational or exercise rehabilitation interventions on exertional dyspnea. More specifically, to develop a tool that could be used to a) effectively assess the degree of exertional dyspnea of patients with COPD resulting from exercise that is of a similar energy expenditure to that of physical activities of daily living b) that can establish a relationship between the extent of dyspnea and quantifiable exercise-related energy expenditure of patients with COPD c) that can be used in a clinical setting with minimum space and/or technical equipment d) that will

have the sensitivity to be used in a within-subject design to detect the changes in dyspnea that can occur in response to a therapeutic intervention. However, in order to confirm the value of these tests in the clinical setting, good measurement properties are needed. An essential requirement of a measure to be meaningful is that it is valid and reproducible or reliable.

The primary goal of this master's thesis was to examine the reproducibility of the two newly designed externally paced field tests (step and shuttle walking) for the assessment of exertional dyspnea in patients with moderately severe COPD. This work therefore reports on two parameters of reproducibility, reliability and agreement, in a within-subject design to detect the day-to-day changes in dyspnea one-week apart in patients with stable moderate to severe COPD. In this development phase, the tests were administered as a set of four discontinuous bouts of three-minutes of stepping or walking, each of which being performed at a set movement pace from very slow to fast. It is hoped that through data collected in this study will allow to eliminate those speed of movements which are either too slow to induce a significant level of dyspnea or too high to high to be realistically completed in these patients.

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PART II: EXPERIMETAL ARTICLE

INTRODUCTION

The diagnosis of chronic obstructive pulmonary disease (COPD) is generally based on the spirometric measurement of the one second forced expiratory volume (FEV_1). Although necessary for diagnostic purposes and useful for follow-up of the disease, FEV_1 correlates poorly with symptom intensity, exercise capacity and health-related quality of life (9, 20, 44, 58). Moreover, physicians rarely rely only on FEV_1 thresholds to make therapeutic decisions. Rather, the general recommendation is that treatment effectiveness should be based on the assessment of patient-perceived outcomes such as symptoms, exercise capacity and perceived health (9).

Timed-walking tests are commonly carried out in patients with chronic diseases to provide a general assessment of exercise tolerance and physical capabilities on the basis of the distance walked in a pre-determined time frame, usually between 6 and 12 minutes (51). However, the lack of standardization of walking speed during these tests may compromise the evaluation of treatment effect upon repeated tests. Indeed, results from a recent study of COPD patients showed the 6-minute walking test to be less responsive to bronchodilation than the endurance shuttle walk, during which the walking speed is externally imposed (58). Moreover, the fact that the primary outcome of these tests is the distance covered rather than dyspnea reduces their ability to assess the impact of therapeutic interventions on exertional dyspnea, especially given the lack of standardization in walking speed when achieving these tests.

Stair climbing may also contribute to dyspnea during activities of daily living in patients with COPD. Step testing has been used for many years to predict maximal

exercise capacity in the general healthy adult population (48) and more recently to assess physical fitness and to provide appropriate exercise prescription for older adults in the primary care setting on the basis of exertional heart rate (41, 42). This testing methodology which is based on a standardized movement cadence to move up and down on one or two steps has however not been applied for the assessment of exertional dyspnea.

With a view to capture the extent of exertional dyspnea experienced by patients with COPD during activities of daily living, our group has recently developed paced stepping (40) and walking tests that could be carried out in the primary care setting as they require minimum equipment and are easy to administer. A novel aspect of these field tests is that the primary outcome measure is directly related to the exercise-induced symptom i.e. exertional dyspnea. However, in order to confirm the value of these tests in the clinical setting, good measurement properties are needed. An essential requirement of a measure to be meaningful is that it is valid and reproducible or reliable.

The primary aim of this article is to demonstrate the reproducibility of two newly designed externally paced field tests (step and shuttle walking) for the assessment of exertional dyspnea in patients with moderately severe COPD, i.e. the degree to which repeated measurements provide similar results (52).

We report on two parameters of reproducibility, reliability and agreement (10). Reliability concerns the degree to which subjects can be distinguished from each other, despite measurement error (53) and this property is required for discriminative purpose. The agreement concerns the absolute measurement error (3), e.g., how close the repeated measures are from each other. Small measurement error is required for evaluative

purposes in which one wants to distinguish clinically important changes from measurement error.

METHODS

Patient Population

Forty-three stable patients with COPD (36M / 7F) participated in the study. Subjects were recruited from the Montreal Chest Institute and Hôpital Laval. Patients were over the age of 50, had a smoking history of $\geq$ 10 pack-years, a $FEV_1 \leq 80\%$ predicted, a FEV_1/FVC ratio $\leq 70\%$, and had no change in treatment regimen over the preceding four weeks or during the course of the study. Patients were excluded if they had a history of asthma, if they used oxygen therapy, had a $SpO_2 < 80\%$ upon exertion, musculoskeletal problems or any other contraindication to exercise. The study protocol was approved by our respective institutional research ethics boards and written informed consent was given by all patients.

Experimental Protocol

Each patient visited the laboratory on five separate occasions over a 2-3 week period. On their first visit, patients completed pulmonary function testing according to the ATS/ERS standards (26, 28, 46, 57) (Medisoft body box 5500 ®) and received medical clearance to participate in the study. Dyspnea was graded using the Medical Research Council (MRC) dyspnea scale (14). Patients were then asked to perform the Incremental Shuttle Walk Test (50) to assess peak exercise capacity. After a short rest period, patients were then familiarized with the stepping and shuttle walking procedures at paces of 18

steps·min^{-1} and 1.5 km·h^{-1}, respectively. During Visit 2, the patient performed either the Step Test or the Shuttle Walk test, in a randomized order. The second exercise test that was not performed during Visit 2 was performed at Visit 3, two to four days after Visit 2. Within 1-2 weeks the tests were repeated in the same order during Visits 4 and 5.

Step Test

The Step Test protocol consisted of four bouts of 3 minutes each, at constant stepping rates of 18, 22, 26 and 32 steps·min^{-1} (40). The patient was instructed to start stepping upon hearing the audio instructions for "step-up" indicating to place both feet up onto the first stair, with the rate being targeted to the movement of each foot, and "step-down" indicating to step back down to the floor, one foot after the other.

Shuttle Walk Test

The Shuttle Walk Test protocol consisted of four bouts of 3 minutes each at constant shuttle walking speeds of 1.5, 2.5, 4.0 and 6.0 km·h^{-1}. The test was performed on a 10m shuttle walk course in the hospital corridor with cones placed at 0.5 and 9.5m to allow for a 0.5m turning radius at either end. The patient started walking upon the start of the audio track and was to arrive at the other cone by the next auditory signal.

The protocol was conducted in the same manner for the walking and the stepping tests in that patients were instructed to maintain the imposed cadence for the entire 3-minute exercise bout or until they became symptom limited and felt unable to maintain the cadence. They were asked to stop if they fell behind the imposed pace. A 10-minute rest period was given between each walking or stepping bout to allow for breathing and

heart rate to return to baseline. The test was terminated once the patient was unable to complete a given bout or after having completed all four bouts. Prior to, and at the end of each exercise bout, patients were asked to rate their level of breathlessness on the 10-point modified Borg scale (4). At baseline and throughout all exercise tests, patients were equipped with a compact portable telemetric system (Jaeger Oxycon Mobile®) for monitoring of ECG and ventilatory and gas exchange parameters as well as a finger oxymeter for measurement of transcutaneous oxygen saturation (SpO_2).

Treatment of Data

Outcome measures taken at the end of each bout of stepping or shuttle walking were: exertional dyspnea Borg score, heart rate (HR), oxygen consumption (VO_2), ventilation (VE), breathing frequency (F_b), tidal volume (V_T). Baseline values were taken from the last 30 seconds of a continuous 3-minute quiet sitting rest prior to beginning the test. Average values were calculated from the last 30 seconds of each 3-minute bout recording.

Statistical Analysis

Mean comparison of dependent variables obtained at each stepping or shuttle walking cadence for trials 1 and 2 was carried out using an ANOVA for repeated measures on trial and cadence.

The overall test-re-test reproducibility of each test was assessed by calculating a Pearson correlation coefficient between trials 1 and 2 for each dependent outcome measure. Test-re-test reliability was evaluated using Intraclass Correlation Coefficient

(ICC) as it reflects both systematic and random differences in test measures (24). An ICC, if higher than 0.75, was judged to be excellent (13). To assess the homogeneity and the consistency of each separate bout of shuttle walking or stepping, test-re-test Intraclass Correlation Coefficients (ICC) were calculated. In addition, in order to test for the homogeneity of the relationship given the potential discriminative effects of the various movement cadences or disease severities, specific test-re-test correlation coefficients were calculated for each cadence and each class of disease severity and compared to the overall correlation using Fisher-Z-transformations and Chi square analyses.

All analyses were carried out using Statistica 6.0 (StatSoft®). Statistical significance was set at $p<0.05$.

Finally, the limits of agreement between trials of dyspnea scores were established using a Bland and Altman representation for both walking and stepping. The limits of agreement were calculated as ± 2 standard deviations and the percentage of scores within the corresponding values was taken as a parameter of agreement.

RESULTS

DESCRIPTION OF PATIENT POPULATION

Patients' characteristics and pulmonary function data are presented in **Table 1**. Results show on average, moderate to severe airflow obstruction, hyperinflation and impaired diffusion capacity. The majority of patients showed moderate to severe disease as attested by their classification into GOLD stages II and III (36 of 43) and MRC dyspnea score of 2 to 3 (30 of 43). Seven of the 43 patients were classified as GOLD stage IV.

Table 1. Patients' characteristics and pulmonary function

	Total (N= 43)
Age (years)	65 ± 7
Gender (M/F)	36/7
BMI (kg/m^2)	27 ± 6
FEV_1 (L)	1.4 ± 0.5
FEV_1 (% predicted†)	49 ± 16
FEV_1/FVC (%)	42 ± 11
TLC (L)	7.5 ± 1.4
TLC (% predicted†)	124 ± 18
FRC (L)	5.2 ± 1.2
FRC (% predicted†)	158 ± 32
IC (L)	2.5 ± 0.7
DLCO (% predicted†)	59 ± 16.0

Abbreviations: BMI: Body Mass Index; FEV1: Forces expiratory volume in one second; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; FRC: Functional Residual Capacity; IC: Inspiratory Capacity; DLCO: Diffusion capacity of carbon dioxide
Values are mean ± standard deviation.
†Predicted values were derived from the ECCS prediction equations (40)

FEASIBILITY OF STEP TEST AND SHUTTLE WALK TEST

Thirty-five of the 43 patients (81%) completed stepping at 18 steps·min^{-1}, 34 (79%) at 22 steps·min^{-1}, 30 (70%) at 26 steps·min^{-1} and only 17 (40%) patients were able to fully complete stepping at 32 steps·min^{-1} during either one of the trials. The totality of patients completed shuttle walking at 1.5km·h^{-1}, 40 (93%) at 2.5km·h^{-1}, 36 (84%) at 4.0km·h^{-1} and only 14 (33%) patients were able to fully complete the shuttle walk at 6.0km·h^{-1} during either one of the trials.

REPEATABILITY OF STEP TEST AND SHUTTLE WALK TEST

Table 2 shows mean VO_2, HR, VE, and Borg dyspnea obtained during trial 1 and trial 2 at each of the four cadences. The mean difference between trials 1 and 2 was less than 5% for all dependent variables and was not statistically significant.

Table 2. Mean VO_2, HR, VE, and Borg dyspnea scores from trials 1 and 2 of the Shuttle Walk and the Step Test

Shuttle Walk	**Trial**	**1.5 km·h^{-1}**	**2.5 km·h^{-1}**	**4.0 km·h^{-1}**	**6.0 km·h^{-1}**
VO_2 (ml·kg·min^{-1})	1	8.7 ± 1.2	10.4 ± 1.5	13.7 ± 2.1	20.8 ± 3.0
	2	8.6 ± 1.4	10.3 ± 1.5	13.7 ± 2.1	20.8 ± 3.1
HR (beats·min^{-1})	1	90 ± 12	93 ± 13*	100 ± 12	122 ± 13
	2	91 ± 14	93 ± 14*	100 ± 12	122 ± 13
VE (L·min^{-1})	1	20.8 ± 4.1	24.7 ± 5.1	30.5 ± 6.9	49.3 ± 12.3
	2	20.6 ± 4.6	24.6 ± 5.5	30.5 ± 6.8	49.7 ± 12.6
Dyspnea Borg score	1	1.4 ± 1.6	1.5 ± 1.6*	2.0 ± 1.5	4.6 ± 1.9
	2	1.4 ± 1.4	1.5 ± 1.9*	2.0 ± 1.5	4.1 ± 1.4
Step Test	**Trial**	**18 steps·min^{-1}**	**22 steps·min^{-1}**	**26 steps·min^{-1}**	**32 steps·min^{-1}**
VO_2 (ml·kg·min^{-1})	1	15.8 ± 1.6	17.9 ± 1.9	20.1 ± 2.0	23.1 ± 2.6
	2	15.4 ± 1.9	17.2 ± 2.1	19.8 ± 2.4	22.9 ± 3.3
HR (beats·min^{-1})	1	108 ± 12	116 ±14	125 ± 15	131 ± 14
	2	107 ± 12	115 ± 12	122 ± 14	129 ± 14
VE (L·min^{-1})	1	35.5 ± 7.4	40.5 ± 7.8	47.1 ± 8.3	58.1 ± 11.7
	2	34.5 ± 7.0	39.3 ± 7.2	44.7 ± 6.9	54.9 ± 11.0
Dyspnea Borg score	1	2.9 ± 1.3	3.7 ± 1.4	5.0 ± 2.0	5.4 ± 2.5
	2	2.4 ± 1.3	3.2 ± 1.5	4.5 ± 2.0	5.6 ± 2.5

VO_2: Oxygen Consumption; HR : Heart Rate; VE: Ventilation
Values are means ± standard deviation. No significant difference was found between trial means.

RELIABILITY OF STEP TEST AND SHUTTLE WALK TEST

Figure 1 shows the individual data for trials 1 and 2 obtained for dyspnea over all cadences. As can be seen from the test-re-test correlation coefficients obtained for the Shuttle Walk test and the Step Test, the correlations between trials 1 and 2 were strong and statistically significant. Test-re-test correlation coefficients for VO_2, VE, V_T, F_b are shown in **Figure 2** for both tests over the four cadences. Overall, the test-re-test correlation coefficients for all variables were equally strong and statistically significant, with values never falling below 0.93 in all cases.

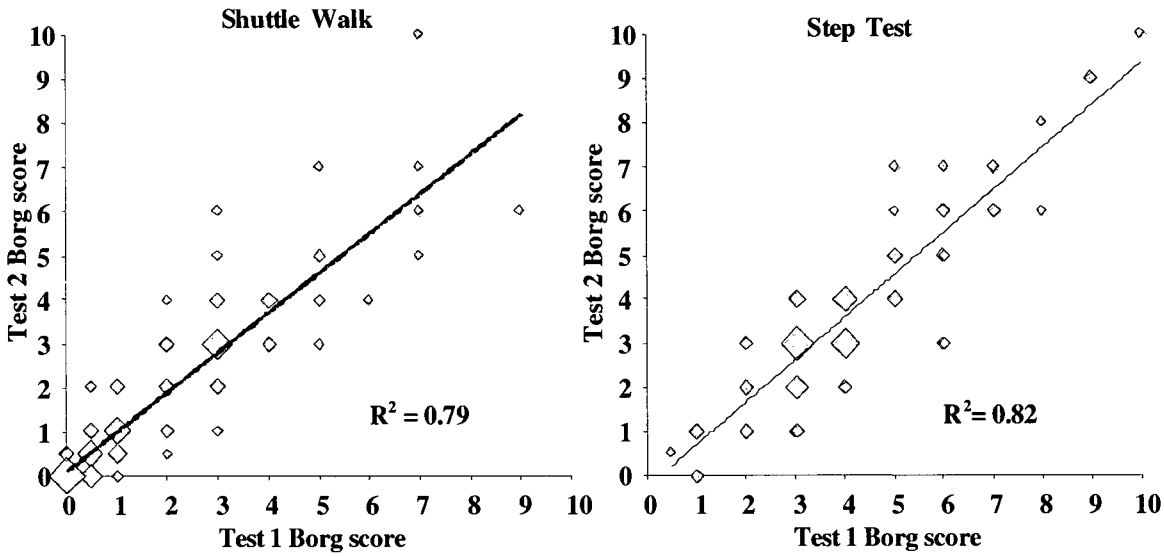

Figure 1. Borg dyspnea scores obtained at trials 1 and 2 for the Shuttle Walk (left) and Step Test (right). Statistical significance was established for all correlations ($p<0.05$). The size of each point is indicative of the number of data points it represents. Thus the larger the point, the more data points being represented.

The test-re-test Pearson and Intraclass Correlation Coefficients (ICC) calculated for all dependent variables over the four cadences are provided in **Table 3**. Results show Pearson coefficients of approximately 0.90 for all physiological responses as well as the BORG score rating. Similar coefficients were found for ICC and Pearson correlation coefficients. The test-re-test ICC coefficients calculated for the Shuttle Walk and the Step Test as a function of movement cadence are shown in **Table 4**. Results indicate good reliability across all movement cadences with no difference between cadences.

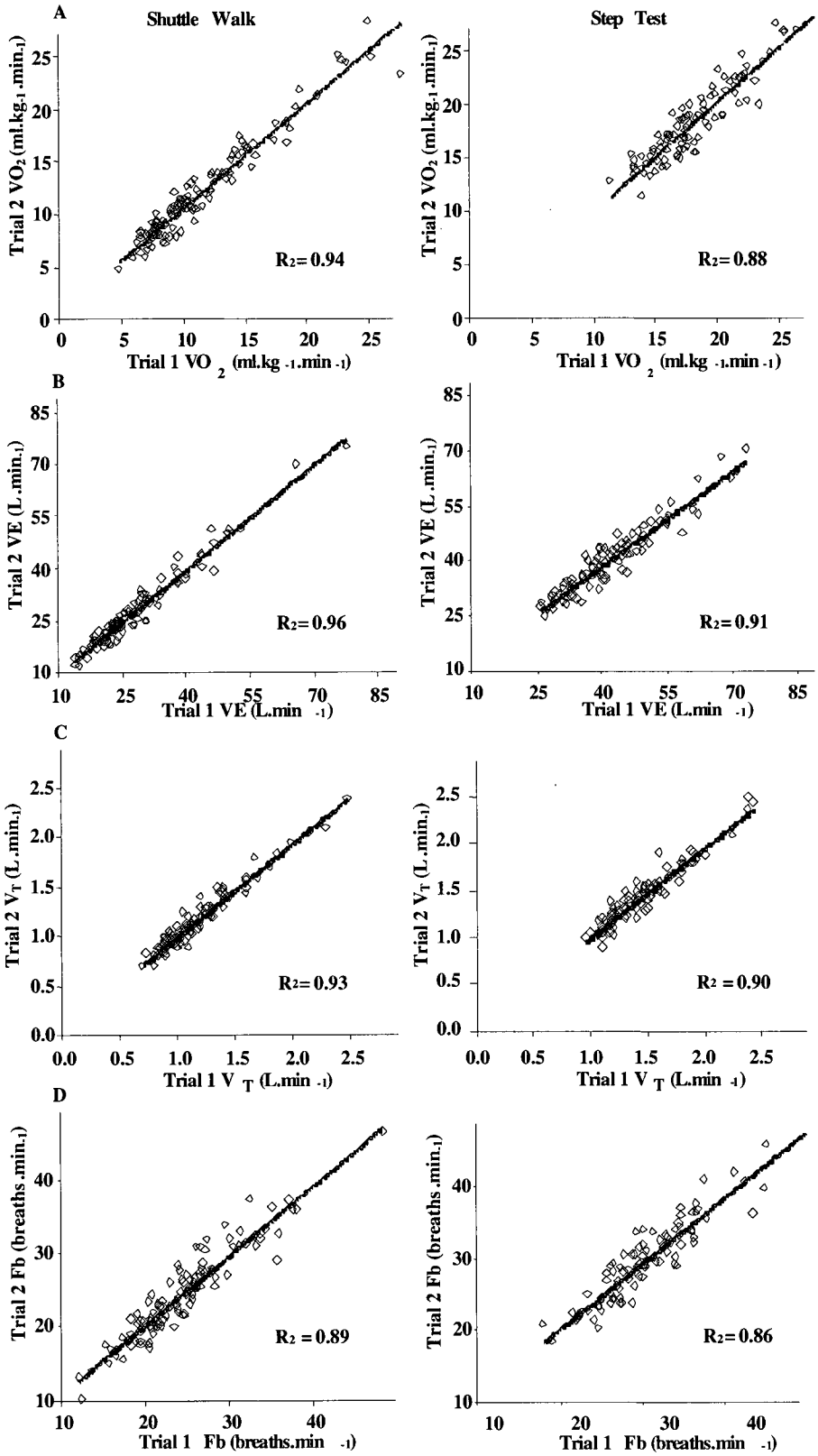

Figure 2. Test-re-test for **(A)** VO_2, **(B)** VE, **(C)** tidal volume (V_T), and **(D)** breathing frequency (F_b) for the Shuttle Walk (left) and the Step Test (right).

Table 3. Overall Pearson and Intraclass Correlation Coefficients for the test-re-test Shuttle Walk and the Step Test.

	Shuttle Walk		Step Test	
	Pearson r	Intraclass r	Pearson r	Intraclass r
VO_2(ml·kg·min^{-1})	0.97	0.98	0.93	0.93
HR (beats·min^{-1})	0.94	0.83	0.83	0.93
VE (L·min^{-1})	0.98	0.99	0.95	0.96
VT (L·breaths)	0.97	0.97	0.95	0.95
Fb (breaths·min^{-1})	0.94	0.92	0.93	0.92
Borg score	0.89	0.91	0.90	0.91

Table 4. Intraclass Correlation Coefficient for the test-re-test on the Shuttle Walk and the Step Test as a function of movement cadence.

	Movement cadence			
Shuttle Walk	**1.5 km·h^{-1}**	**2.5 km·h^{-1}**	**4.0 km·h^{-1}**	**6.0 km·h^{-1}**
VO_2(ml·kg·min^{-1})	.84	.86	.92	.82
HR (beats·min^{-1})	.86	.95	.93	.96
VE (L·min^{-1})	.94	.95	.96	.95
VT (L·breaths)	.94	.98	.96	.98
Fb (breaths·min^{-1})	.88	.92	.95	.91
Borg score	.88	.85	.78	.80
Step Test	**18 steps·min^{-1}**	**22 steps·min^{-1}**	**26 steps·min^{-1}**	**32 steps·min^{-1}**
VO_2(ml·kg·min^{-1})	.78	.83	.88	.87
HR (beats·min^{-1})	.87	.92	.93	.95
VE (L·min^{-1})	.92	.91	.92	.94
VT(L·breaths)	.94	.96	.95	.97
Fb (breaths·min^{-1})	.85	.89	.85	.95
Borg score	.79	.84	.92	.94

* ($p<0.05$) Chi square analysis revealed no statistical significance across movement cadence on the overall study sample correlation coefficients.

Figure 3 shows a Bland & Altman representation of the dyspnea scores obtained on trials 1 and 2 for both field tests. In both cases, more than 90% of data points lie within 2SD of the average values of the two trials, indicating good agreement in dyspnea score between the two trials. The inter-trial agreement in Borg dyspnea score was relatively narrow with a mean difference ± 2SD of 0.05 ± 1.76 for the Shuttle Walk and 0.42 ± 1.71 for the Step Test.

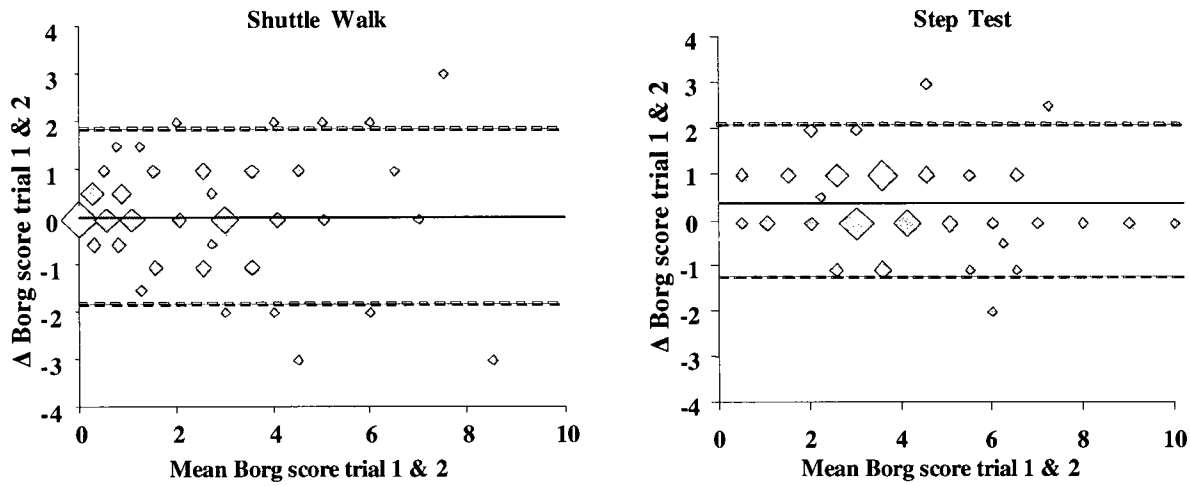

Figure 3. Bland & Altman representation of difference in Borg Dyspnea scores from trial 1 to trial 2 versus mean individual Borg Dyspnea scores for the Shuttle Walk (left) and the Step Test (right). The solid line within the graph represents the bias. The broken lines represent the upper and lower limits of agreement. The size of each point is indicative of the number of data points it represents. Thus the larger the point, the more data points being represented.

DISCUSSION

The popularity in the general clinical practice of self-paced walking tests does not mean that these are the best tests to use for monitoring results of interventions meant to reduce symptoms. The main outcome measure of the self and externally-paced walking

tests is distance (m) completed. The 6- and 12-minute walking distances are generally shown to have good test-re-test repeatability. Their validity to predict peak aerobic power however remains questionable since reported coefficients range between 0.51 and 0.81 in patients with COPD (1, 2, 17, 18, 27, 43, 54, 56, 59). This may potentially be related to the lack of standardization in instructions relative to the speed of walking that participants should be attempting to maintain or to the encouragements provided, as this may be seen to have a significant effect on the distance walked (19).

This study examined the test characteristics of two novel externally paced stepping and walking methodologies aimed at easily monitoring exertional dyspnea in the primary care setting. Results from this study show good compliance with the imposed exercise protocol in most patients except those with severe disease, demonstrating adequate feasibility of these tests. Similarly, results indicate good test-re-test reproducibility for both the stepping and the walking protocols with respect to Borg dyspnea scores, suggesting that these clinical tools may be useful to assess the impact of pharmacological or rehabilitation interventions on the exertional dyspnea of patients with moderately severe COPD. Results also show good reproducibility and agreement for test-re-test measurements of VO_2 and minute ventilation, suggesting that the test is adequate to capture the standard physiological responses to the exercise stimulus.

FEASIBILITY OF THE STEP TEST AND THE SHUTTLE WALK TEST

Self-paced timed walk tests are commonly used to obtain a one-time assessment of functional capacity in patients with chronic disorders because of their simplicity of use. The 6-Minute Walk Test has been, and continues to be extensively used in COPD as

it shows a good prognostic value for disease staging (2, 55). Similarly, step testing is one of the oldest field testing modalities first introduced to characterize the level of physical fitness based on the heart rate response to stepping (48). Because it requires little space and simple equipment to monitor, interest has been growing to use symptom-limited stair climbing in the clinical setting. It has been used successfully for pre-operative screening (5, 22), or to diagnose the presence of ischemic heart disease through the assessment electrocardiogram (48).

In the present study the externally paced walking and stepping tests were designed to focus on the COPD-specific symptom of exertional dyspnea. As can be seen from the present study, values of VO_2 and VE remained in the range of those generally measured in COPD patients of similar disease severity using cycle ergometry or treadmill testing in a laboratory environment (49, 56). Our findings clearly establish the feasibility of both the walking and the stepping tests in patients with MRC stage II to IV disease severity as nearly all patients completed at least three of the four incremental movement cadences. It may be suggested however that the cadences may need to be reduced for COPD patients with GOLD stage IV since only a few successfully completed more than the first lower movement cadences.

REPRODUCIBILITY OF THE STEP TEST AND THE SHUTTLE WALK TEST

Repeatability

Our results indicate no significant mean differences in either dyspnea or ventilatory parameters between trials 1 and 2, suggesting that no significant learning effect has occurred once patients have been familiarized with the procedure. This

observation contrasts with results from studies using self-paced walk tests showing that these may entail a significant learning effect leading to 7-9% improvements in distance walked under test-re-test conditions (2, 18, 19, 25, 27, 30, 37, 50, 51, 54). In the present study, the field tests combined both the externally imposed pacing and a set time duration (for walking), thus standardizing both total distance covered and cadence, and as a result, exercise intensity. Therefore, standardizing movement pace would appear to reduce the potential for a significant learning effect to occur enhancing the observed repeatability.

Reliability

The one-to-two week test-re-test reproducibility of the 6-Minute Walk Test was assessed in older adults, patients suffering from heart failure, COPD, peripheral artery disease, idiopathic interstitial pneumonia, and children with cystic fibrosis. Results generally show good repeatability in various populations with the test-re-test Pearson correlation on distance walked ranging from 0.90 to 0.98 overall with intra-class coefficients ranging between 0.82 and 0.99 (7, 11, 12, 16, 18, 21, 29, 36, 38, 43, 47). Similar test-re-test Pearson and intra-class correlation coefficients have also been reported for the distance walked using the Incremental Shuttle Walk Test (49) with a Pearson coefficient of 0.98 on two trials one week apart in patients with chronic heart failure (15) and intraclass coefficients of 0.88 and 0.87 in clinically stable patients with COPD (8) and intermittent claudication (60).

As mentioned above, step testing is one of the oldest basic exercise modalities that is still used, albeit several variations do exist. Validation of the Canadian Home Fitness Test against directly measured peak oxygen uptake in healthy adult populations

resulted in correlation coefficients ranging from 0.88 to 0.91(23, 48). More recently, an adaptation of the Canadian Home Fitness Test step testing was validated in healthy elderly adults (≥65 years of age) using a self-determined stepping pace (42). There are however only few reports on test-re-test reliability with one study reporting an intra-class correlation coefficient of 0.92 computed from stepping heart rate measured on two tests performed 1-2 weeks apart (45) in healthy older adults while a good inter-trial reliability was found for the prediction of peak VO_2, heart rate and perceived exertion in firefighters (6).

In the present study, the main outcome was not distance walked or climbed but the exercise-related symptom of dyspnea. There is little data if at all, regarding the test-re-test reproducibility of field tests on physiological outcomes such as ventilation or gas exchange parameters. In this study, field tests were not used to predict or estimate peak work capacity but rather to generate for a given imposed movement cadence, a reproducible level of exertional dyspnea. Our findings demonstrate that this is the case. Based on the measured indices of reliability, our results show that the field tests are good discriminatory tools. No significant differences in mean physiological parameters have been observed from one week to the next for any of the stepping cadences or walking speeds. In addition, strong Pearson and intra-class correlation coefficients were found for all physiological responses including the BORG scores (**Table 3**) such that at least 80% of the variance in scores could be accounted for over the population tested within a short time period and across the four movement cadences. Similarly, a more specific examination of test-re-test coefficients across movement cadences indicate equally good relationships for all walking speeds and stepping cadences with no significant difference

between movement cadences. Thus, whatever the cadence selected for use, reproducible physiological responses and resulting exertional dyspnea will be recorded.

Given the equally strong degree of reproducibility found across all movement speeds, it is conceivable that, in the future, the test could be performed using a single or at most two movement cadences, selected on the basis of the patient's FEV_1 related disease severity. Deciding on which one or two of the four movement cadences may be most appropriate may be determined according to both practical and physiological observations. With respect to the former, results show a marked drop in the number of patients completing the highest movement cadence (6 $km \cdot h^{-1}$ and 32 $steps \cdot min^{-1}$) for both the walking and the stepping test. It would therefore follow that a general selection of those movement cadences may be inappropriate. From the physiological response perspective, our results indicate that values of VO_2, HR, VE and BORG scores recorded for the second and third movement cadences are of the same magnitude as those generally reported during standard submaximal cycling tests (31, 33) and reproduce well the demands of movement speed in the spontaneously selected stair climbing (40). Thus it may be suggested that as a general rule for patients with FEV_1 between 30 and 80% predicted and $FEV_1/FVC < 70\%$, the second and third movement cadences i.e. 2.5 and 4.0 $km \cdot h^{-1}$ or 22 and 26 $steps \cdot min^{-1}$ could be targeted. Data on a greater number of patients is however required to enable appropriate identification of targeted levels using a regression analysis from patients' standard characteristics.

Agreement

The agreement concerns the absolute measurement error (3), e.g., how close the repeated measures are from each other. Small measurement error is required for evaluative purposes in which one wants to distinguish clinically important changes from measurement error. Our results show a mean difference in Borg ratings of less than 0.5 units from trial 1 to trial 2 for both the Shuttle Walk and the Step Test with the majority of scores remaining within a 1 point unit of the modified BORG scale. This difference level remains below the minimum clinically important difference of 1 unit on the modified 10-point modified Borg scale (4) indicating good overall agreement.

Walking vs Stepping tests: is one better than the other?

The need to consider the appropriateness of one exercise modality over another when attempting to detect changes in exertional dyspnea has recently been demonstrated. In a study comparing cycling to externally-paced walking it was shown that while cycle endurance testing may be appropriate to detect changes following the administration of a bronchodilator (32, 34, 35), its responsiveness to detect changes in dyspnea may be less than that of a walking-based exercise test (39). In the present study, equally strong reproducibility was found for both externally paced walking and stepping tests. Both tests bear an advantage over cycle endurance testing in that they more closely match the nature of activities of daily living that induce exertional dyspnea in these patients. Thus, while the walking protocol may be better suited than cycling, our results suggest that stepping may be equally appropriate to detect changes in exertional dyspnea in patients with COPD. On the basis of limits of agreements, a somewhat smaller difference was found

for the Shuttle Walk suggesting tighter control on exertional dyspnea. It should be noted that although the Shuttle Walk has slightly better agreement, the Step Test shows less dispersion on the Bland and Altman representations. Similarly, from a practical perspective, the argument could be made that given the less space requirements of step testing; this may be better suited for use in the primary care setting.

CONCLUSION

Our study showed that both field tests using 3-minute bouts of externally paced walking or stepping are highly reproducibile to monitor exercise-induced physiological responses and symptoms in patients with stable COPD. These tests using short bouts of constant load exercise may be used to provide physicians with an accurate, reproducible, and well-tolerated evaluation of the level of exertional dyspnea encountered by their patients in the course of their daily activities. Thus, within a period of 5 or 10 minutes, the clinical management team could monitor the evolution of disease or assess the outcome of pharmacological or exercise training interventions. Follow up studies are however required to determine the sensitivity of the tests to interventions, i.e. pharmacological or fitness training.

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