Three minutes walking test in correlation to six minutes walking test in COPD patients

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List of Abbreviations

Abb.	Full term
6MWD	6 min walk distance
ATS	American Thoracic Society
CAP	Community-acquired pneumonia
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
EGFR	Epidermal growth factor receptor
ET-1	Endothelin-1
FEV1	Forced Expiratory Volume in one second
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
ICS	Inhaled corticosteroids
JIA	Juvenile idiopathic arthritis
LABA	Long-acting beta2-agonists
LAMAs	Long-acting antimuscarinics
mMRC	Modified British Medical Research Council
mPAP	Mean pulmonary artery pressure
PH	Pulmonary hypertension
SABA	Short-acting beta2-agonists
SAMAs	Short-acting antimuscarinics
SD	standard deviation
WHO	World health organization

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by progressive airflow limitation and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking ***(Gold, 2017).***

Since it was first introduced the six walking test has been considered the standard test for the functional evaluation of patients with chronic obstructive pulmonary disease (COPD) and is used in diverse clinical situations; evaluation of pulmonary rehabilitation protocols, drug response or preoperative study of patients submitted to lung transplant or volume reduction ***(Bernstein et al., 1994).***

The test is simple, easy and non-incremental it is known that, regardless of the duration, walking tests are influenced by factors which modify the value of the results. Thus, the mood of patients, how the patient is motivated and the learning effect are factors that can some way modify the results ***(Morgan et al., 1983).***

Aim of the Work

To determine the reproducibility of the distance covered in 3 min and its correlation with the 6 min walking test.

Chapter 1

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases ***(GOLD, 2018)***.

However, in many patients, the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnea, reduced health related quality of life and increased mortality ***(Rabe et al., 2007).***

Co-morbidities such as congestive heart failure, pulmonary hypertension, depression, muscle wasting, weight loss, lung cancer and osteoporosis can frequently be found in patients with COPD and are considered to be part of the commonly prevalent non pulmonary sequelae of the disease ***(Barnes et al., 2009; Chatila et al., 2008).***

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also

by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration ***(Vestbo et al., 2013)***.

Epidemiology:

COPD is a leading cause of morbidity and mortality worldwide. In 2001 the global burden of disease project of the world health organization (WHO) identified COPD as the sixth leading cause of mortality in countries of middle or low income, accounting for 4.9% of total deaths ***(Buist et al., 2007).***

In 2011, it ranked as the fourth leading cause of death ***(Lozano et al., 2012)***. The WHO estimates that by 2020 COPD will become the third leading cause of death worldwide ***(GOLD, 2011).***

More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally ***(Lozano et al., 2012).***

The prevalence of COPD varies greatly per country and also within different countries ***(Buist et al., 2008).***

This heterogeneity can be contributed to not only differences in diagnostic methods and classification but also to smoking habits, population, age, environmental exposure such as biomass fuel exposure and air pollution, occupational exposure, prevalence of pulmonary tuberculosis, chronic asthma and socioeconomic status ***(Salvi, 2009)***.

Statistical analysis of COPD prevalence in Egypt showed that 3 million from the Egyptian population have COPD. In different studies prevalence were from 3.3% up to 10%. Prevalence rate in men was ~6.7% while it was ~1.5% in women ***(Khattab et al., 2011).***

A study published in 2014 showed that the prevalence of COPD among high-risk Egyptians by global initiative for chronic obstructive lung disease "GOLD" criteria was 9.6% ***(Said et al., 2014).***

Risk Factors

Exposures to

I- **Tobacco smoke:** Smoking as the cause of COPD has been irrefutably established through several major international reports ***(Jindal et al., 2006)***. Cigarette smoking is by far the most important risk factor for COPD either active or passive exposure to smoke ***(Holt, 1987).***

II- **Occupational dusts and chemicals:** Studies of coal miners have shown an increased mortality due to bronchitis and emphysema especially centrilobular emphysema, A relationship between dust exposure and degree of emphysema has been found in studies of coal and hard-rock miners. Occupational exposure to dust increases mortality due to chronic obstructive pulmonary disease, even in never-smokers ***(Bergdahl et al., 2004).***

III- **Outdoor and indoor air pollution:** Exposure to high levels of outdoor air pollutants is associated with increased

mortality and morbidity due to COPD and related cardiorespiratory diseases also indoor air pollution from biomass combustion has been found to contribute to COPD and other cardiorespiratory diseases ***(Liu et al., 2008).***

IV- **Infections:** whooping cough, bronchiolitis or pneumonia in the first year of life were associated with a significant reduction in forced expiratory volume in one second"FEV1" measured in the first decade ***(Tager et al., 1988).***

Host Factors:

I- **Genes:** The genetic risk factor that is the best documented is a severe hereditary deficiency of alpha-1 antitrypsin followed by others like: microsomal epoxide hydrolase, glutathione S-transferase, alpha-1 anti-chemotrypsin and cytokine TNF ***(Harrison et al., 1997).***

II- **Airway hyper-responsiveness:** Asthma and airway hyper-responsiveness, identified as risk factors that contribute to the development of COPD, are complex disorders related to a number of genetics and environmental factors. Asthmatics as a group, experience a slightly accelerated loss of lung function compared to non-asthmatics, as do smokers with airway hyper-responsiveness compared to normal smokers ***(Tashkin et al., 1996).***

III-* Lung growth:** Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD ***(Tager et al., 1988).

Others

I-* Socioeconomic status:** Risk of developing COPD is inversely related to socioeconomic status ***(Prescott et al., 1999).

II-* Nutrition:** Malnutrition can reduce both respiratory muscle mass and the strength of the remaining muscle fibers developing emphysema that was shown in experimental studies on animals ***(Sahebjami and Vassallo, 1980).

III-* Oxidative stress:** Oxidants generated either endogenously from phagocytes and other cell types or exogenously from air pollutants or cigarette smoke as well as intracellular oxidants, an imbalance between oxidants and antioxidants is considered to play a role in the pathogenesis of COPD ***(MacNee, 2005).

IV-* Asthma:** Asthma patients were found to have a twelve-fold higher risk of acquiring COPD over time than those without asthma ***(Vonk et al., 2003).

Pathology

Pathological changes characteristic of COPD are found in the airways, lung parenchyma, and pulmonary vasculature. The pathological changes include chronic inflammation, with

increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation ***(GOLD, 2017).***

1. Chronic Bronchitis

Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely not all patients with COPD have symptomatic mucus hypersecretion, when present mucus hypersecretion is due to an increased number of goblet cells and enlarged submucosal glands, both because of chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR) ***(GOLD, 2017).***

Inflammation is observed in the mucosa, in the smooth muscle cell layers and submucosal glands. Inflammation is a better pathologic marker of chronic bronchitis than mucous gland hypertrophy. In large airways (>2 mm) mononuclear cell, macrophage, CD8+ T lymphocyte and plasma cell involvement was observed in stable COPD and during exacerbations of chronic bronchitis ***(Satta et al., 1999).***

Submucosal bronchial gland enlargement is a key feature in chronic bronchitis; Mucus hypersecretion is typical in central airways in patients with chronic bronchitis, there is increasing