Differences in Cardiopulmonary Exercise Test Results by American Thoracic Society/European Respiratory Society-Global Initiative for Chronic Obstructive Lung Disease Stage Categories and Gender*

Victor M. Pinto-Plata, MD, FCCP; Romulo A. Celli-Cruz, BSc; Carlos Vassaux, MD; Luis Torre-Bouscoulet, MD; Asante Mendes, MD; John Rassulo, BS†; and Bartolome R. Celli, MD, FCCP

Background: **The American Thoracic Society (ATS)/European Respiratory Society (ERS)-Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed a new staging system based on the degree of airflow obstruction. Its validity to predict exercise capacity as an outcome has not been extensively studied. We hypothesized that exercise performance measured by cardiopulmonary exercise test (CPET) results should decline significantly with each disease stage, independent of gender.**

Methods: **We examined 453 consecutive incremental CPET and pulmonary function tests performed in patients who had been referred to a single respiratory physiology laboratory in a tertiary care hospital. They were divided into a control group (normal lung function) and ATS/ERS-GOLD stages 1 to 4. We measured anthropometrics, peak work (in watts), peak oxygen uptake (in liters per kilogram per minute and percent predicted), breathing reserve (in percent predicted), and arterial blood gas response. We compared these results between different stages and genders.**

Results: **The mean (± SD) age for the entire group was 64 ± 11 years, the mean FEV_1 was 66 ± 28%, and the mean body mass index (BMI) was 27.2 ± 5.82 kg/m^2. Patients in stage 4 were significantly younger ($p < 0.001$) and had a lower BMI ($p < 0.02$) compared to those in stages 1 to 3. There was a significant reduction in exercise capacity for patients at every stage except for those in stage 1, who had values similar to those of the control group. Women had better lung function and exercise capacity than men, but the difference disappeared when adjusted by COPD stages.**

Conclusions: **The ATS/ERS-GOLD staging system can be used to indicate differences in exercise capacity in patients with COPD stages 2 to 4 and to normalize apparent gender disparities. The value of differentiating stage 1 patients requires further studies with different outcomes.**

(CHEST 2007; 132:1204–1211)

Key words: arterial blood gas; COPD; dyspnea; exercise test

Abbreviations: ANOVA = analysis of variance; ATS = American Thoracic Society; BMI = body mass index; CPET = cardiopulmonary exercise test; ERS = European Respiratory Society; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = heart rate; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference; $\dot{V}O_2$ = oxygen uptake; $\dot{V}/\dot{Q}$ = ventilation/perfusion

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[1] were introduced in 2001 to set universal standards in the prevention, diagnosis, and management of patients with COPD. Based on the FEV_1 values and following the changes introduced by the American Thoracic Society (ATS)

and European Respiratory Society (ERS),[2] these guidelines modified the physiologic staging on November 2006 and now categorize COPD in four stages (1 to 4). Although practical, this classification is arbitrary in nature. This physiologic staging system has been useful to demonstrate higher mortality risk in patients in stages 3 and 4,[3] and among patients in stages 0 to 2.[4] However, the capacity of the guidelines to identify the development of subsequent airway obstruction in patients previously classified as being in stage 0 is controversial.[5,6]

Some studies[7–9] have shown that other measurable clinical variables other than FEV_1 are excellent predictors of mortality. Among them, exercise capacity has been demonstrated to be an important variable to measure and follow during the course of the disease.[8,9] Implicit in the staging of a disease is that each step confers a prognostic implication. Therefore, exercise capacity should decrease with increasing categories of the staging system. Equally important, each stage should correct for gender differences if the staging system is to be widely applicable. Previous studies with small numbers of patients with mild-to-severe disease using different classifications[10,11] have shown some evidence of worsening exercise capacity as the disease is more severe and limited evidence than exercise capacity is decreased in men compared to women.[12] However, there has been no report that compares exercise performance in patients with different levels of disease severity using the ATS/ERS and GOLD physiologic criteria and by gender. In addition, no study has systematically evaluated the value of any staging system on gas exchange, the primary function of the lung.

We have prospectively collected data to include lung function, cardiopulmonary exercise test (CPET) response including gas exchange in patients with COPD. The aims of this study were to determine the difference in lung function and exercise parameters including gas exchange among patients in the different ATS/ERS-GOLD physiologic stages and in both genders. We also compared the results with those from a control group of similar age.

*From the Division of Pulmonary, Critical Care and Sleep Medicine (Drs. Pinto-Plata, Vassaux, Mendes, and Celli, and Mr. Rassulo), Caritas St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA; School of Science (Mr. Celli-Cruz) Boston College, Boston, MA; and Instituto Nacional de Enfermedades Respiratorias (Dr. Torre-Bouscoulet), México, DF.
†Deceased.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received March 12, 2007; revision accepted June 8, 2007.

Correspondence to: Victor M. Pinto-Plata, MD, FCCP, Caritas St. Elizabeth's Medical Center, 736 Cambridge St, Boston, MA 02135; e-mail: vpinto@copdnet.org
DOI: 10.1378/chest.07-0593

Materials and Methods

We reviewed all of the cardiopulmonary exercise tests and paired pulmonary function tests performed in the Pulmonary Physiology Unit at Caritas St. Elizabeth's Medical Center between January 2002 and December 2005. All of the patients signed an informed consent form. The Institutional Review Board reviewed the protocol and approved the study. Patients were referred by primary care physicians, nurse practitioners, or specialists. All patients were interviewed by a physician, and a list of symptoms, comorbidities, and current medications was obtained. The inclusion criteria were age $\geq$ 40 years; history of or current cigarette smoking; and the presence of cough, sputum production, and/or dyspnea. Exclusion criteria included recent COPD exacerbation (within 2 months), myocardial infarction ($<$ 3 months), uncontrolled hypertension, angina, or neuromuscular conditions that would interfere with the exercise test.

Patients performed pulmonary function test following ATS/ERS guidelines[2] within 1 week of the CPET. Based on ATS/ERS-GOLD criteria, the cohort was divided into the following four stages (FEV_1/FVC ratio $\leq$ 0.7 for all stages): stage 1 (mild disease), $FEV_1 \geq 80\%$ predicted; stage 2 (moderate disease), $FEV_1 < 80\%$ and $\geq 50\%$ predicted; stage 3, $FEV_1 < 50\%$ and $\geq 30\%$ predicted; and stage 4, $FEV_1 < 30\%$ predicted. The control group was defined as patients with respiratory symptoms (*ie*, cough, sputum production, and/or dyspnea) with normal spirometry findings (previously classified as GOLD stage 0 or as *patients at risk* by ATS/ERS). The CPET was performed following ATS/American College of Chest Physician standards.[13] All exercise parameters were calculated using formulas described by Wasserman et al.[14] Patients performed exercise using a cycle ergometer, and gas exchange was measured using a metabolic cart (V Max; SensorMedics; Yorba Linda, CA). The protocol included the following three stages: resting (2-min duration with the subject sitting up, not pedaling); warm up (3-min duration pedaling against no resistance); and symptom-limited exercise was completed by encouraging patients to reach exhaustion. Work was increased at a rate of 15 or 30 W/min. During every stage, while breathing room air, the oxygen uptake ($\dot{V}O_2$), carbon dioxide production, heart rate (HR), respiratory rate, and tidal volume were measured. An arterial blood gas was obtained at rest and at the peak of the exercise, and was measured in the central laboratory of the institution.

Statistical Analysis

All results were expressed as the mean $\pm$ SD. A *t* test for independent groups was used to determine the difference between men and women in different pulmonary function and exercise test parameters. A χ^2 test was used to compare proportions between genders. We used one-way analysis of variance (ANOVA) to determine the differences among the five groups of patients regarding anthropometrics, pulmonary function test (FEV_1, FVC, ratio) and exercise parameters (in watts), peak $\dot{V}O_2$ (in liters and percent predicted), anaerobic threshold, heart reserve, respiratory reserve, oxygen pulse, and arterial blood gas results (pH, PaO_2, and $PaCO_2$). The *post hoc* difference between different stages was analyzed using the Scheffé test.[15] A p value of < 0.05 was considered to be significant.