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Cardiopulmonary Exercise Testing in the Early Diagnosis of COPD

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Abstract

Objective: Tobacco smoke is the most important factor in the etiology of chronic obstructive pulmonary disease (COPD). Even in developed countries, COPD is among the leading causes of death. Early diagnosis of COPD is crucial to decrease rates of morbidity and mortality. Can COPD be recognized by exercise testing before air flow limitation is diagnosed by pulmonary function tests (PFTs)? This study sought to evaluate the role of cardiopulmonary exercise testing in ex-smokers as an early parameter for diagnosing COPD.

Methodology: Fourteen healthy nonsmokers with normal PFTs (group 1) and 30 ex-smoker GOLD stage 0 COPD patients (group 2) were included in our study. The patients' FEV1 values and FEV1/FVC ratios were normal. The subjects in group 2 had smoked cigarettes for more than 10 pack-years. All subjects underwent PFTs and symptom-limited cardiopulmonary exercise testing (CPET) using a treadmill.

Results: Analyses were performed to determine whether there was a significant difference between groups 1 and 2 with regard to maximum oxygen uptake, breathing reserve, oxygen saturation, maximum minute ventilation, maximum voluntary volume, metabolic equivalent, inspiratory capacity, end expiratory lung volume and heart rate. There was a statistically significant difference in maximum oxygen uptake between groups ($p<0.05$).

Conclusion: Our results demonstrated a mild decrease in maximum oxygen uptake in GOLD stage 0 COPD patients. In high-risk populations, CPET may prove to be an important test in the early identification of COPD.

Keywords: smoking, diagnosis, COPD, CPET.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease that is rising in prevalence and mortality [1]. Cigarette smoking is a major risk factor for developing COPD [2]. Even in developed countries, COPD is among the leading causes of death [3,4].

Spirometric methods have been used in the early diagnosis of COPD; however, results of these methods remain controversial [5]. Several authors have reported high rates of false-positive results when spirometric evaluation is used in healthy populations; however, it can be used as a screening test in high-risk populations [1,4]. The disease is usually not diagnosed until it is clinically apparent and moderately advanced, although early diagnosis and treatment of COPD offer improved outcomes. Thus, early diagnosis of COPD has a critical importance.

This study sought to reveal the ventilatory changes due to maximal exercise in GOLD stage 0 COPD patients who had smoked cigarettes for more than 10 pack-years. We also sought to evaluate the value of cardiopulmonary exercise testing (CPET) in the early diagnosis of GOLD stage 0 COPD in ex-smokers.

MATERIALS AND METHODS

Subjects

Fourteen healthy subjects (group 1) and 30 ex-smoker GOLD stage 0 COPD patients (group 2) were included in this study. All ex-smokers had smoked cigarettes for more than 10 pack-years. Ex-smokers who had coughing and sputum were selected at random from our smoking cessation program prospectively. Subjects with concomitant disease, such as vascular, neuromuscular, or cardiac disease, were excluded from the study. The groups were formed according to the GOLD 2003 consensus report [4]. All subjects had normal forced expiratory volume in one second (FEV1) values (>80%) and FEV1/forced vital capacity (FVC) ratios (>70%). Pulmonary function tests (PFTs) were evaluated for each subject, and maximal heart rate on limited CPET was recorded. Data were analyzed to determine whether there were any between-group differences in terms of maximum oxygen uptake (VO2 max), breathing reserve (BR), maximum voluntary ventilation (MVV), maximum minute ventilation (VE max), inspiratory capacity (IC), end expiratory lung volume (EELV), oxygen saturation (SaO2) and heart rate (HR). IC and EELV were compared between baseline (EELVB, ICB) and peak (EELVP, ICP) exercise to reveal hyperinflation in group 2.

Pulmonary function testing

Subjects' age, height (cm), weight (kg), and body mass index were recorded. Spirometry was performed prior to exercise testing according to the European Respiratory Society (ERS) recommendations [6]. FEV1, FVC, and MVV were measured with a clinical spirometer (SensorMedics

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Table 1. Subject characteristics

	Group I (n:14)	Group II (n:30)	p value
Age (year)	56.71 ± 9.08	48.42 ± 9.24	p >0.05
Gender M	6	12	p >0.05
F	8	18	
BMI kg/m^2	26.14 ± 4.08	48.42 ± 9.24	p >0.05
FEV_1 %	96.42 ± 4.58	92.20 ± 7.16	p >0.05
FEV_1/FVC %	78.14 ± 3.54	78.81 ± 3.66	p >0.05
FEF_{25-75} %	86.86 ± 16.58	71.36 ± 21.98	p >0.05
FEF_{50} %	98.85 ± 22.15	84.09 ± 26.42	p >0.05
MVV L/min	56.71 ± 9.08	87.46 ± 28.77	p >0.05

BMI: Body mass index.
FEV_1%: Forced expiratory volume in 1 second.
FEV_1/FVC%: FEV_1/ Forced vital capacity.
FEF25-75%: Forced expiratory flow.
FEF50%: Forced expiratory flow.
MVV: Maximal voluntary ventilation.

Table 2. Exercise test parameters of the subjects

	Group I (n:14)	Group II (n:30)	P value
VO_2 L/min ± SD	92.00 ± 11.12	82.86 ± 14.03	p <0.05
SaO_2 % ± SD	110.78 ± 16.56	99.60 ± 18.72	p >0.05
Vmax L/min ± SD	79.19 ± 14.20	77.97 ± 12.73	p >0.05
BR ± SD	19.35 ± 7.38	14.13 ± 20.79	p >0.05
METS ± SD	8.44 ± 1.47	8.94 ± 2.02	p >0.05
EELVP ± SD	0.99 ± 0.44	1.06 ± 0.55	p >0.05
EELVB ± SD	0.86 ± 0.59	1.09 ± 0.52	p >0.05
ICB ± SD	2.59 ± 0.75	2.20 ± 0.49	p >0.05
ICP ± SD	2.41 ± 0.64	2.25 ± 0.47	p >0.05

EELVB: Baseline end expiratory lung volume.
EELVP: Peak end expiratory lung volume.
ICB: Baseline inspiratory capacity.
ICP: Peak inspiratory capacity.
BR: Breathing reserve.
METS: Metabolic equivalents.
VO_2: Peak oxygen uptake.
SaO_2: Oxygen saturation with pulse oximetry

Vmax spectra 229, Bilthoven, The Netherlands). A laboratory technician demonstrated each respiratory maneuver to the subject before the test. All subjects performed a maximal expiratory flow maneuver in the sitting position with a nasal clip. At least three reproducible tests were carried out for each measurement, and the best result was recorded. MVV values were calculated in L/minute.

Exercise testing

Symptom- or maximal-heart-rate-limited CPET was performed using a treadmill (Jaeger LE200CE, Nussdorf-Traunstein, Germany) and spirometer (SensorMedics Vmax spectra 229, Bilthoven, The Netherlands). All subjects were told not to eat or drink during the two hours preceding the exercise test. The CPET system was calibrated before each test. Instead of cycle ergometry, the Bruce protocol was chosen using a treadmill because of better subject compliance [7]. ECG, arterial pressure, and SaO_2 were monitored continuously in each subject during the tests. Tests were terminated at the point of maximal heart rate or symptom limitation [8]. Reasons for terminating the test were recorded (i.e., fatigue, chest pain, leg pain, dyspnea). Physiologic data [oxygen consumption (VO_2) and carbon dioxide output (VCO_2)] were measured with breath by breath technique [9]. Oxygen uptake, peak CO2 output (PCO_2), gas exchange ratio (VCO_2/VO_2), minute ventilation [VE(BTPS)], IC, EELV, tidal volume (VT), and SaO_2 were recorded at baseline and peak exercise.

Statistical Analyses

All analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 9.05, SSPS Inc, Chicago, IL, USA). Nonparametric Mann-Whitney test was used to test for significance between groups. Chi-square test was used to evaluate nominally structured data. Results were considered statistically significant at a value of $p<0.05$. Unless indicated otherwise, data are expressed as mean ± SD. Ranges also are given.

RESULTS

General characteristics

Forty-four subjects were included in the study. The control group was composed of healthy non-smokers; subjects in group 2 were ex-smokers who had smoked more than 10 packet-years. Table 1 gives the characteristics of all subjects. Distributions of age, gender, and body mass index in each group were similar.

Pulmonary function

PFT results are shown in Table 1. According to GOLD 2003, all subjects showed normal FEV_1 values and FEV_1/FVC ratios as selection criteria. Fourteen patients in group 2 had lower-than-predicted (≤65%) forced expiratory flow $(FEF)_{25-75}$ and FEF_{50} values (47.50%±7.20% and 57.18%±11.42%).

Exercise tests

Subjects terminated the exercise test owing to general fatigue (n = 35, 76%) or leg fatigue (n = 9, 14%); dyspnea was not observed as a cause of test termination. Table 2 shows the exercise test parameters of all subjects. There was no significant difference in terms of MVV, VE max, or BR between groups; however, there was a mild decrease in VO_2 max (L/min) between groups (p=0.028).

Hyperinflation parameters are shown in Figure 1. In group 2, EELV was increased and IC was decreased slightly at peak exercise, although these changes were not statistically significant.

There were 14 GOLD stage 0 patients in group 2 who had small airway narrowing. When we compared exercise test parameters of these patients in means of peak oxygen uptake (80.93 ± 15.88), metabolic equivalents (METS)

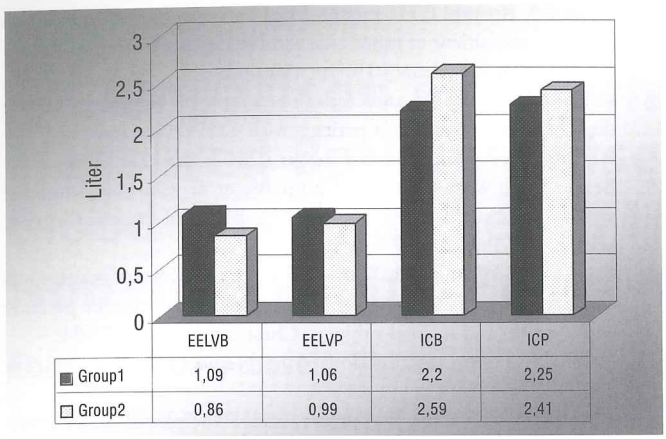

Figure 1: Changes in hyperinflation parameters in groups.
EELVB: Baseline end expiratory lung volume, **EELVP:** Peak end expiratory lung volume, **ICB:** Baseline inspiratory capacity, **ICP:** Peak inspiratory capacity.

(8.60 ± 2.23), BR (14.37 ± 21.58), and VE max (76.23 ± 12.60) with control subjects, there were no significant differences ($p>0.05$). Similarly, there were no significant differences in terms of baseline and peak IC and EELV values in patients with small airway narrowing ($p>0.05$).

DISCUSSION

Smoking is the most important factor in the development of COPD [3,10,8]. Early diagnosis of COPD is important to decrease rates of morbidity and mortality [5]. Spirometric methods are the most extensively used techniques for early diagnosis of COPD [11]. CPETs are used to evaluate treatment response and determine preoperative risk; however, to date, they have not been used to diagnose COPD because they are expensive, time-consuming to perform, and follow-up of patients is difficult [12-14]. To our knowledge, there have been no studies assessing CPETs in the early diagnosis of COPD.

This study was undertaken to evaluate the use of CPETs in the early diagnosis of COPD in ex-smokers who displayed GOLD stage 0 with symptoms in terms of coughing and sputum. When we compared the patients with healthy controls we found that the maximum oxygen uptake in GOLD stage 0 COPD patients was significantly decreased.

We compared healthy nonsmokers who had normal PFTs with GOLD stage 0 COPD patients in terms of VO_2 max, SaO_2, IC, EELV and BR. We found that although there was no difference in nonsmokers in terms of BR and SaO_2, the VO_2 max decreased slightly. It is known that decreases in VO_2 max occur due to ventilation-perfusion mismatch as a response to exercise in COPD patients [15,16]. There have been no studies assessing the metabolic and ventilatory response to exercise in GOLD stage 0 COPD patients. In a recent study, Hogg et al. assessed the small airways of 159 patients according to global criteria for COPD [17]. They pointed out that there was acute and chronic airway inflammation in stage 0 subjects. On the other hand, it was revealed that hyperinflation was increased with maximal exercise in COPD patients [18]. In our study, there was a minimal increase in EELV and decrease in IC at peak exercise in GOLD stage 0 COPD patients. Although these changes were not statistically significant, we thought that minimal hyperinflation could be the cause of decreased VO_2 max at peak exercise. In the light of this data, the authors speculated that the decrease in VO_2 max during exercise can also be attributed to a trigger of airway inflammation in addition to ventilation-perfusion mismatch and minimal hyperinflation in GOLD stage 0 patients.

In smoker subjects, parenchymal changes may develop in addition to airways disease due to smoking or other factors [17]. Thus, we are planning a new study in this regard to evaluate exercise performances and oxygen uptakes with CPET and parenchymal changes via high resolution computerized tomography in GOLD stage 0 subjects.

Heijdra and coworkers reported no significant difference in exercise performance results between smokers and nonsmokers on a 6-minute walk test, but they did not compare oxygen uptake [19]. Similarly, we found no significant difference in mean exercise performance in our study populations. We also did not find a significant difference in mean BR between groups, and the decrease in oxygen uptake was mild in GOLD stage 0 subjects. Thus, we believe that the mild decrease in oxygen uptake does not influence exercise performance in the early stage of COPD.

The ventilatory limitation during exercise can be evaluated by the relationship between VE max and MVV. When VE max nears MVV, the respiratory reserve decreases [12-14,20]. It has been reported that during exercise, VE max nears MVV in patients with COPD; with severe COPD, VE max can be equal to or higher than MVV. Negative values for the respiratory reserve are seen mostly in patients with COPD [15]. In our study, when GOLD stage 0 COPD patients were compared with subjects in the control group, there was no statistically significant difference in terms of respiratory reserve ($p>0.05$). We can explain this as being related to normal MVV and VE max values in the groups.

Vestbo and coworkers followed-up patients with GOLD stage 0 COPD in their 5th and 15th year with regard to symptoms such as coughing and sputum. In that study, 24.3% of the patients were still classified as stage 0 or had progressed to stage 1 and most patients no longer complained of coughing and sputum at the end of the follow-up period. Thus, these authors suggest that GOLD stage 1 is not a practical stage for identifying subjects at risk for

COPD [21]. We also believe that although the decrease in oxygen uptake and increase in hyperinflation at peak exercise may be useful parameters for early diagnosis of COPD in GOLD stage 0 ex-smokers, long-term follow-up with spirometry and exercise tests is necessary.

Another study has reported that lung function is related to pack-years of cigarette smoking [22]. We also believe that the relationship between pack-years of cigarette smoking and CPET parameters should be investigated in more ex-smokers to evaluate the relationship between these two entities.

FEF_{25-75} and FEF_{50} values can be used to confirm airway narrowing in patients whose FEV_1/FVC ratios are inconclusive, as FEF_{25-75} and FEF_{50} are known to decrease in early COPD [13,23]. Some studies have reported a relationship between narrowing of the small airways, inflammation, and fibrosis, and a subsequent decrease in FEV_1 [24,25]. However, Stanescu and colleagues have demonstrated no significant FEV_1 decrease in 13 years of follow-up in smokers with small airway narrowing [26]. Because of these conflicting results, we compared 14 subjects with normal FEV_1 values, FEV_1/ FVC ratios, and low FEF_{25-75} and FEF_{50} values with the control group. VO_2 max and BR did not differ significantly during exercise between these subjects and the control group. Thus, we conclude that small airway obstruction does not influence VO_2 max in GOLD stage 0 subjects.

In conclusion, there is a significant decrease in VO_2 max in high-risk populations, suggesting that this may be an important parameter for the diagnosis of COPD at an early stage. We suggest that to support the results of our study, long-term follow-up with spirometry and exercise test is necessary.

REFERENCES

1. Ferguson GT. For the National Lung Health Education Program (NLHEP): Office Spirometry for Lung Health Assessment in Adults: A Consensus Statement from the National Lung Health Education Program. Chest 2000;117:1146-61.
2. Mannino DM, Gagnon RC, Petty TL, et al. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2000;160:1683-9.
3. Abramson M, Matheson M, Wharton C, Sim M, Walters EH. Prevalence of respiratory symptoms related to COPD and asthma among middle-aged and older adults. Respirology 2002;7:325-31.
4. Global strategy for the diagnosis, management and prevention of COPD NHLBI/WHO Workshop Report. Global initiative for COPD. National Institutes of Health, 2001.
5. Enright P, McBurnie MA, Bittner V, et al. Controversies in the use of spirometry for early recognition and diagnosis of COPD in cigarette smokers. Clin Chest Med 2000; 21(4):645-51.
6. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398-420.
7. Bruce RA, Kusumi F, Hasmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
8. Celli BR, MacNee W, and committee members. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
9. Beaver WL, Wasserman K, Whipp BJ, et al. On-line computer analysis and breath-by-breath graphical display of exercise function tests. J Appl Physiol 1973;34:128-32.
10. Carrion GF, Mahler DA, Ward J, et al. Comparison of continuous and discrete measurement of dyspnea during exercise in patients with COPD and normal subjects. Chest 2004;125(1):77-84.
11. Crapo OC. Pulmonary function testing. N Engl J Med 1994;331:25-30.
12. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation. 2nd Ed. Philadelphia. A Waverly Comp; 1994, pp. 80-94.
13. Ruppel G. Manual of pulmonary function testing. 5th Ed. Missouri. Mosby Year Book; 1991, pp. 122-55.
14. Hughes JMB Lung function tests: physiological principles and clinical applications. 1st Ed. London. WB Saunders; 1999, pp. 133-51.
15. Gallagher CG. Exercise limitation and clinical exercise testing in COPD. Clin Chest Med 1994;15:305-26.
16. Bauerle O, Chrusch CA, Younes M. Mechanisms by which COPD affects exercise tolerance. Am J Respir Crit Care Med 1998;157(1):57-68.
17. Hogg JC, Chu F, Utokaparch S, et al. The nature of small airway obstruction in COPD. N Engl J Med 2004;350:2645-53.
18. O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 2004;23:832-40.
19. Heijdra Y, Pinto-Plata VM, Kenney LA, et al. Cough and phlegm are important predictors of health status in smokers without COPD. Chest 2002;121:1427-33.
20. O'Donnell DE. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. In: Weissman IM, Zeballos RJ, Eds. Clinical Exercise Testing. Basel. Karger AG; 2002, pp. 138-59.
21. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2002;166(3):329-32.
22. Higgins MW, Enright PL, Kronmal RA, et al. Smoking and lung function in elderly men and women. JAMA 1993;269:No:21.
23. Pineda H, Haas F, Axen K, Haas A. Accuracy of pulmonary function tests in predicting exercise tolerance in COPD. Chest 1984;86:564-7.
24. Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. Eur Respir J 2002;19(4):632-8.
25. Cosio M, Ghezzo H, Hogg JC, et al. The relations between structural changes in small airways and pulmonary function tests. N Engl J Med 1978;298:1277.
26. Stanescu D, Sanna A, Veriter C, et al. Identification of smokers susceptible to development of chronic airflow limitation. Chest 1998;114:416-25.

Abbreviations: COPD: chronic obstructive pulmonary disease; HR: heart rate; CPET: cardiopulmonary exercise testing; VE max: maximum minute ventilation; PFT: pulmonary function tests; BR: breathing reserve, VO2 max: maximum oxygen uptake, METS: metabolic equivalents; IC: inspiratory capacity; EELV: end expiratory lung volume; EELVB: baseline end expiratory lung volume; EELVP: peak end expiratory lung volume; ICB: baseline inspiratory capacity; ICP: peak inspiratory capacity.