RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

IMPACT OF BRONCHODILATOR RESPONSIVENESS ON QUALITY OF LIFE AND EXERCISE CAPACITY IN PATIENTS WITH COPD

Francisco Ortega [a,b,c], Eduardo Márquez-Martín[a,b], Borja Valencia[a,b], Pilar Cejudo[a,b], Ana Rodriguez[a], Jose Luis López-Campos[a,b,c], Emilia Barrot[a,b,c].

a. Medical-Surgical Unit of Respiratory Diseases. University Hospital Virgen del Rocío, Seville, Spain.

b. Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain.

c. CIBER de Enfermedades Respiratorias (CIBERES).

Correspondence: Francisco Ortega,MD. Medical-Surgical Unit of Respiratory Diseases. University Hospital Virgen del Rocío, Avd. Manuel Siurot s/n 41013, Seville, Spain.

Email: francisco.ortega.sspa@juntadeandalucia.es

Tel. 955013163; Fax 955013168.

Running head: bronchodilator responsiveness and exercise capacity in COPD.

Keywords: chronic obstructive pulmonary disease; bronchodilator effects; quality of life; exercise; rehabilitation.

Author disclosure: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

ABSTRACT

Background: Bronchial variability in COPD patients may be a phenotypic feature associated with clinical characteristics and differential treatment response.

Objectives: We analysed whether symptoms, quality of life and exercise capacity varied in COPD patients as a function of bronchodilator test results. Further, we compared response to an exercise programme in the groups.

Methods: A positive bronchodilator test result was defined as FVC and/or FEV_1>12% plus >200 ml improvement after 400 µg salbutamol. We studied 198 COPD patients, 94 with positive reversibility and 104 with negative reversibility. Training sessions were carried out on three non-consecutive days each week for 12 weeks, and consisted of a combination of resistance and strength training. Subjects were evaluated on two consecutive days at baseline, and at the end of the 12-week training programme.

Results: Those with positive reversibility had shorter time–to-exhaustion on the endurance test (19.1±12.6 min versus 24.5±14.5 min in negative reversibility patients; p<0.031), shorter distances in the shuttle walking test (380.6 ± 158.2 m versus 438.5±149.1 m in negative reversibility patients; p<0.029) and lower scores on the Chronic Respiratory Disease Questionnaire (18.7±4.6 versus 19.8±4.3 in negative reversibility patients; p<0.015), while we found no significant differences in peak exercise, peripheral muscle strength or dyspnoea. Further, differences between groups in improvements after exercise training were not significant.

Conclusions: Compared to COPD patients with negative reversibility, those with positive reversibility walk for shorter distances, and have shorter endurance times and a worse quality of life, but improvements after exercise training are similar.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by airway obstruction that is not fully reversible. Forced spirometry with a bronchodilator test is essential for the diagnosis and classification of COPD[1]. The diagnosis should be confirmed by post-bronchodilator spirometry, which attenuates the effect of reversibility, making it easier to distinguish between asthma which is completely reversible and COPD which is not. This approach reduces the risk of misclassification [1].

The airway obstruction in COPD, unlike that in asthma, is usually considered permanent or at most partially reversible; that is, usually little change is seen in spirometry after the administration of a bronchodilator. On the other hand, one of the main reasons for excluding patients with COPD from studies and clinical trials of drugs has been that they do show a positive response to bronchodilators or present certain clinical characteristics that, traditionally, have been associated with asthma [2].

There is a need to re-evaluate the concept of asthma and COPD as separate conditions, and to considerer situations when they may coexist, or when one condition may evolve into the other. The so-called overlap syndrome is recognized as the coexistence of increased variability of airflow in a patient with incompletely reversible airway obstruction. Bronchial variability as a phenotypic feature may be present in more than half of patients with COPD [3]. This subgroup showing reversibility with bronchodilators was found to have elevated eosinophil levels in induced sputum and higher concentrations of exhaled NO [4]. Some studies have found airway obstruction reversibility to be an independent positive predictor of survival and a slower decrease in FEV_1 among patients with COPD [5]. Nevertheless, individuals with bronchial hyper-responsiveness (BHR) have a higher risk of developing respiratory symptoms and

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

COPD, the annual decrease in FEV_1 being higher among active smokers with BHR [6]. Indeed, BHR has been found to be significantly associated with mortality due to COPD, this being directly related to the degree of histamine hyper-responsiveness [7].

Patients with COPD who have a positive bronchodilator response seem to respond most often and most strongly to inhaled corticosteroids [8], the effect being longer lasting when these are combined with a long-acting beta-agonists [9,10]. The effect of other types of treatment in this subgroup of patients is unknown. Exercise training has been shown to increase exercise capacity, reduce dyspnoea and improve quality of life among patients with COPD [11]. However, the response to such a programme varies between patients. It is largely unknown what factors determine these results, but phenotypic differences could explain some of theses variations [12].

In particular, it is not known whether, among COPD patients, having a positive bronchodilator response influences important clinical outcomes and, accordingly, could be used to classify patients into different groups in terms of prognosis and appropriate treatments. Our objective was to analyse whether there were differences in symptoms, quality of life and/or exercise capacity among patients with COPD as a function of their bronchodilator responsiveness and whether this was related to their degree of airway obstruction. In addition, we assessed response to an exercise training programme as a function of whether or not patients responded to bronchodilators. Our hypothesis was that qualify of life and exercise capacity would be worse among COPD patients who respond positively to bronchodilators, as would response to an exercise programme.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

METHODS

Study participants

This was an uncontrolled, prospective clinical trial with a cohort of patients with COPD recruited when they attended the hospital for routine appointments for the evaluation of a pulmonary rehabilitation program. Inclusion criteria were: being an adult patient with a diagnosis of COPD according to the international guidelines [1], and a history of smoking of at least 20 pack years, as well as having been clinically stable for at least the previous three months. Exclusion criteria were: the unwillingness to participate in the study, a history of recent exacerbation (< 3 months) requiring systemic corticosteroids or antibiotics, and any contraindication or inability to perform the study tests (including a history of uncontrolled heart disease or the presence of acute respiratory conditions) [1]. A history of asthma was defined as an affirmative answer to both question "Have you ever had asthma?" and "Was this confirmed by a doctor?". The study was approved by the Clinical Research Ethics Committee of the Hospital Virgen del Rocío, and written informed consent was obtained from each subject prior to inclusion in the study. The regular medication of patients remained unchanged and in line with guideline recommendations [1].

Spirometry tests were performed at baseline and 15 min after the administration of 400 µg salbutamol, in accordance with the acceptability and reproducibility criteria of the American Thoracic Society [13]. Acute bronchodilator responsiveness (positive reversibility) was defined using the following criteria: forced vital capacity (FVC) and/or forced expiratory volume in 1 s (FEV_1) ≥ 12% plus ≥ 200 mL improvement [1,14,15]. We included in the analysis all participants with two or more valid spirometry measurements, taken at least three months apart (bronchodilator responsiveness was required to be consistent between measurements). We used the definition and severity

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

stratification of COPD proposed by the Global Iniciative for Chronic Obstructive Lung Disease (GOLD): a ratio of the post-bronchodilator (BD) $FEV_1/FVC < 0.70$ [1].

Training program

Training sessions were carried out on three nonconsecutive days each week for 12 weeks. The duration of sessions was 40-min plus a 10-min warm-up and 10-min cool down. The training program was structured as reported previously [12], and consisted of a combination of resistance and strength training. The endurance training consisted of leg exercise on a calibrated ergocycle (Ergometer ZX1; Kettler Sport, Ense-Parsit, Germany) at a fixed pedaling speed (60 rpm) according to which it was possible to measure the actual work rate (W) achieved by the patient during each session. The physiotherapist was aware of the training intensity prescribed for each patient and encouraged him/her to reach it. The work rate corresponding to 70% of the peak work rate achieved during the baseline incremental exercise test was selected as the target training intensity [6,7]. The strength training included different exercises, which were performed with the following weight lifting procedures: (*1*) 'chest pull' (mainly for strengthening of the latissimus dorsi); (*2*) 'butterfly' (mainly for the pectoralis major muscle); (*3*) 'neck press' (mainly for the triceps brachii and deltoid); (*4*) 'leg flexion' (mainly for the biceps femoris and grastrocnemius); and (*5*) 'leg extension' (mainly for the quadriceps femoris). The weight lifting exercises were performed with gymnastic apparatus (Fitness-Center Classic; Kettler Sport, Ense-Parsit, Germany). The patients performed four series of six to eight repetitions for each of the exercises at a workload of 70 to 85% of the one repetition maximum (1 RM). This test was repeated every 2 weeks for new adjustments of the workload.

Measurement tools

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Subjects were evaluated on two consecutive days at baseline, and at the end of the 12-week training programme. Pre- and posttraining tests were performed under similar conditions. The Shuttle Walking Test (SWT) and the submaximal endurance cycle test were primary outcome measures for this study. Secondary outcome measures were the pulmonary function studies, maximal cycle exercise test, peripheral muscle strength, quality of life, and dyspnoea.

Pulmonary function tests. Spirographic studies were carried out on a Masterlab pneumotachograph spirograph (Erich Jaeger GMBH, Wuerzburg. Germany), following the Spanish Society (SEPAR) [8] and ATS recommendations [13]. Lung volumes (functional residual capacity, residual volume, total lung capacity) were determined plethysmographically, measured by the interruption technique [19]. Carbon monoxide diffusion constant *(Kco)* was measured by using the single–breath method on a Masterlab device (Erich Jaeger GMBH, Wuerzburg. Germany). We measured arterial blood gases at rest (pH, PaO_2, $PaCO_2$) using an ABL 500 device (Radiometer; Copenhagen, Denmark), and maximum respiratory pressures using a Manometer 163 (SibelMed). Patients' nutritional status was evaluated by calculating the body mass index (BMI, weight kg/height m^2). People with a BMI below 21 kg/m^2 were considered to be underweight [20].

Maximal cardiopulmonary exercise test. Maximal cardiopulmonary exercise testing was performed on a cycle ergometer (Collins Respiratory Ergomed, USA) as previously described [21] and according to the international standards [16]. Maximal exercise tolerance was measured by a symptom-limited graded exercise test performed while the patient was breathing room air. Breathing was continuously monitored and inhaled and exhaled gases were collected and analyzed for oxygen consumption and carbon dioxide production. The level of resistance was then increased by 10–15 watts every minute

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

until the maximal exercise level was reached [22]. The exercise was performed on electrocardiographic, heart rate and pulsioxymetric monitoring. All measurements were integrated into the cycle ergometer device and evaluated simultaneously during test. After the exercise, heart rate, blood pressure, and leg fatigue and dyspnoea were assessed using the modified Borg's scale [23].

Submaximal cycle test. The submaximal endurance test was performed with an ergometric cycle set at 70% of the maximum power reached by each patient in the previous maximal test. The endurance time, saturation and heart rate reached were monitored.

Shuttle walking test. The SWT was conducted as described by Singh et al. [24] requiring patients to walk up and down a 10 m course marked out by two cones inset 0.5 m from either end to avoid abrupt changes in direction. There were a maximum of 12 progressive levels (or speeds) lasting for 1 min each. The subject should aim to be at the opposite end to the start by the time the bleep sounds. Maximum level reached, distance covered in meters, blood pressure, heart rate, and dyspnoea, using the modified Borg's scale [23] were measured at the end of exercise.

Peripheral muscle strength. 1RM tests were used for measuring PMS [25]. This 1RM test measures the maximum amount of weight (in kilos) that could be lifted in a single movement using a multigym station (Fitness Classic Centre, Kettler, Postfach, Germany). Five simple exercises involving upper and lower limb large muscle groups were performed (chest pull, butterfly, shoulder press, leg extension and leg curls) as described above.

Dyspnoea scales. Basal dyspnoea was evaluated using the Mahler's Basal and Transitional Dyspnoea Indexes (BDI/TDI) [26], and the modified Medical Research Council scale (MRC) [27]. BDI and TDI have three domains as follows: 1) functional

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

impairment (FI), which determines the impact of breathlessness on the ability to carry out activities; 2) magnitude of task (MT), which determines the type of task that causes breathlessness; and 3) magnitude of effort (ME), which establishes the level of effort that results in breathlessness. A change of at least 1 unit in TDI was used as the criterion for a minimal important meaningful difference (a change of 1 unit in focal score to clinically meaningful effects).

The MRC is a five-point scale (from 0 to 4) based on degrees of various physical activities that precipitate dyspnoea.

Quality of Life. Quality of life was evaluated by means of the Chronic Respiratory Disease Questionnaire (CRDQ), which is a disease specific quality of life questionnaire and is translated and validated in Spanish [28,29]. The questionnaire is made up of 20 items divided into four categories or domains: dyspnoea or breathing difficulty, fatigue, emotional function and mastery. A change of 0,5 U has been identified as the minimum clinically significant change.

Statistical analysis

Statistical analysis was performed using Predictive Analytics SoftWare (PASW, version 18.0; IBM Corporation, Somers, NY). Qualitative and quantitative variables are presented as n (%) and mean ± SD, respectively. Differences between groups (positive reversibility versus negative reversibility in the complete groups and subgroups by degree of obstruction) were assessed using the Student's t-test for quantitative variables and Mann-Whitney U test for ordinal variables, while the pre- to post-training differences were assessed using the paired Student's t-test for quantitative variables and Wilcoxon test for ordinal variables. The results of the different tests before and after training were calculated as the increase (Δ) in every parameter. All results were considered to be statistically significant at a level of $p<0.05$.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

RESULTS

A total of 198 patients, all former smokers, enrolled on the study. Of these, 94 had airflow obstruction with positive reversibility (92 by changes in FEV_1) and 104 with negative reversibility on spirometry. All the patients had moderate-to-severe obstruction, with no significant differences between the two groups. The features of the patients at baseline are summarized in Table 1. Overall 47 patients had a history of asthma, 33 of these showing positive reversibility ($p< 0.001$).

We found no significant differences in peak exercise capacity or muscle strength between patients with positive reversibility and negative reversibility (Table 2). On the other hand, those with positive reversibility had a significantly shorter time-to-exhaustion in the endurance test (19.1 ± 12.6 min in positive reversibility patients versus 24.5 ± 14.5 min in negative reversibility patients; $p<0.031$), and walked a shorter distance in the SWT (380.6 ± 158.2 m versus 438.5 ± 149.1 m in negative reversibility patients; $p<0.029$) (Table 2). There were no significant differences in the degree of dyspnoea (MRC scale and BDI) between the groups. Nevertheless, positive reversibility patients obtained a lower total score on the CRDQ (18.7 ± 4.6 in positive reversibility patients versus 19.8 ± 4.3 in negative reversibility patients; $p<0.015$), mainly due to significantly lower fatigue and emotional function scores (Table 3).

Considering patients by degree of obstruction, 71 were stage II on the GOLD classification (33 with positive reversibility), 65 were stage III (31 with positive reversibility) and 62 were stage IV (30 with positive reversibility). Among those at stage II, there were significant differences between positive reversibility and negative reversibility groups in time to exhaustion in the endurance test (24.5 ± 9.9 min in

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

positive reversibility patients versus 33.3 ± 8.6 min in negative reversibility patients; p<0.001), distance walked in the SWT (474.2 ± 120 m in positive reversibility patients versus 557.6 ± 126 m in negative reversibility patients; p<0.001) and total score on the CRDQ (22.2 ± 3.8 in positive reversibility patients versus 24.1 ± 2.1 in negative reversibility patients; p<0.001). We also found significant differences among those at stage III in these same variables, namely, time to exhaustion in the endurance test (18.3 ± 7.2 min in positive reversibility patients versus 23.7 ± 6.5 min in negative reversibility patients; p<0.005), distance walked (398.3 ± 94 m in positive reversibility patients versus 459.8 ± 105 m in negative reversibility patients; p<0.015) and total CRDQ score (18.5 ± 3.4 in positive reversibility patients versus 19.7 ± 3.2 in negative reversibility patients; p<0.001). On the other hand, we found no significant differences between positive reversibility and negative reversibility patients at stage IV and none (at any of the stages) in the other variables, including peak exercise capacity, peripheral muscle strength or dyspnoea (MRC scale and BDI) (Table 4).

Of all the patients enrolled, 169 completed the exercise training programme (81 with positive reversibility). After the training, all participants had improved in dyspnoea, exercise and strength parameters (table 5). Mean post-training changes are summarized in Table 6. All the post-training improvements were similar for positive reversibility and negative reversibility patients, there being no significant differences in the improvements achieved in any of the variables analysed.

DISCUSSION

Our findings indicate that COPD patients with positive reversibility have a shorter time to exhaustion in endurance exercise testing and walk a shorter distance in the SWT.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

These differences, with respect to those with negative reversibility, were statistically significant among those at stages II and III on the GOLD classification. As for symptoms, degree of dyspnoea was not significantly different but CRDQ score was significantly lower among positive reversibility patients. The improvements achieved after an exercise training programme, in exercise capacity and muscle strength, as well as scores on the questionnaires (BDI/TDI, MRC and CRDQ), were similar in the two groups of patients.

Given the heterogeneity of the disease, the evaluation of individuals with COPD is changing, moving towards the idea of classifying patients into subgroups. It is possible that the current concept of COPD embraces patients with common clinical and/or biological characteristics but who have different prognoses or require different types of treatment. The definition of clinical phenotype should include any characteristic(s) of the illness in which there may be differences between individuals with COPD and which may be associated with different clinical outcomes [30]. To meet this requirement, these characteristics should not be present in all patients, in order that they can be used as a basis for distinguishing subgroups. For some time, it has been known that there is a subgroup of COPD patients showing bronchodilator reversibility and that such individuals usually have elevated eosinophil levels in induced sputum and higher concentrations of exhaled NO [4], as well as responding better to treatment with corticosteroids [8,9], all characteristics of asthma. On the other hand, there are patients diagnosed with severe asthma, many being smokers, who respond less well to corticosteroids than other patients with asthma, and who share other characteristics with COPD patients, such as a high neutrophil count and increased oxidative stress [31].

It is well known that 70-90% of patients with asthma have exercise-induced bronchospasm. These “attacks” are more severe with continuous, prolonged exercise

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

and have been blamed on increased inflammation with heat and water loss on the surface of the respiratory tract [14,32]. On the other hand, in a subgroup of patients with COPD it is possible to obtain an increase in their exercise capacity by administration of a bronchodilator before exercise [33]. The SWT seems to be more sensitive to changes in exercise tolerance, after acute bronchodilation, than cycling performance [34] or the 6-minute test [35].

Our COPD patients with positive reversibility had lower exercise capacity (than the negative reversibility patients) and this was manifested in both the endurance time to exhaustion and the distance walked in the SWT, above all among those in moderate to severe stages of the disease. The difference in the SWT exceeded the threshold for clinical significance established for the test [36]. In relation to this, we could speculate that there was more severe airway inflammation in this subgroup of patients. Exercise capacity is an important parameter given its independent association with mortality [37], the association being stronger that with peak VO_2 measured at maximal exercise [38].

The bronchodilator test (BDT) is not considered to have prognostic value in COPD as results are not sufficiently stable over time. Calverley et al. [39], analysing data from the ISOLDE study, concluded that classifying patients as a function of positive or negative results in the BDT was not reliable as in moderate to severe COPD bronchodilator responsiveness is a continuous variable. However, in that study, patients with more than 10% reversibility in the first BDT were excluded, meaning that the most reversible were omitted and, therefore, results cannot be extrapolated to all COPD patients. Moreover, most patients had reversibility close to the threshold (+12%), and so were more vulnerable to the influence of biological variation. Last, the three BDTs were carried out following different protocols and, consequently, it not surprising that the

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

results differed. On the other hand, the fact that a characteristic or phenotype changes over time does not mean that it is not interesting. Hurst et al. [40], analysing the "exacerbation" phenotype in COPD patients, confirmed that 30-40% initially classed as having this phenotype did not to the necessary changed characteristics during the second year of follow-up.

Subjects with the most severe bronchial hyper-reactivity are predisposed to developing more respiratory symptoms [6]. Our COPD patients with PR were not found to have more dyspnoea than those with negative reversibility but did obtain a worse score on the quality of life questionnaire, indicating worse control of the disease, probably influenced by their lower exercise capacity. The results differed by more than the 0.5 U that has been identified as the minimum clinically significant change [41]. The finding that these differences disappeared among patients at stage IV may indicate that reversibility has less effect with increasing degree of obstruction and age [42]. Further, in this group of patients corticosteroids are more commonly used, which may mean that the disease is better controlled. In relation to this, COPD patients with positive reversibility seem to respond better to inhaled corticosteroids [8]. The influence of other types of treatments is unknown. It has been demonstrated that exercise training improves COPD symptoms and exercise capacity, though the effect varies between patients [11,12]. According to our results, this type of treatment has a positive effect, namely an ability to obtain improvements in a range of clinical and functional parameters, in patients with COPD regardless of their bronchodilator responsiveness.

Some limitations of our study must be considered in evaluating our results. Probably the patient profile with bronchial hyper-responsiveness may be completed with other tests such as methacholine or exhaled nitric oxide. Similarly, although it was not the aim of our study, having no inflammatory markers allows us to relate having a worse exercise

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

capacity and increased inflammation in the airways. Furthermore, although our training program is widely used in patients with COPD, we cannot ensure that other programs can find differences in response in patients with and without reversibility. Further studies could clarify these points.

In conclusion, COPD patients with positive bronchodilator reversibility results could be a subgroup of patients with different characteristics. They have a lower exercise capacity and are able to walk a shorter distance (in the SWT). Moreover, they obtain worse scores on a quality of life questionnaire. Nevertheless, with exercise training, they achieve a similar degree of improvement in a range of parameters to those with negative bronchodilator reversibility results. This does not, however, rule out differences in their response to other types of treatment.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

REFERENCES

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist AS, Calverley P, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for chronic obstructive pulmonary disease (GOLD). Workshop summary. Am J Respir Crit Care Med 2007;176(6):532-555.

2. Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, Kesten S. Bronchodilator responsiveness in patients with COPD. Eu Respir J 2008;31(4):742-750.

3. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it?. Thorax 2009;64(8):728-735.

4. Papi A, Romagnoli M, Baraldo S, Braccioni F, Guzzinati I, Saetta M, et al. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chornic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162(5):1773-1777.

5. Halpin D, Peterson S, Larsson T, Calverly P. Identifying COPD patients at increased risk of mortality: Predictive value of clinical study baseline data. Respir Med 2008;102(11):1615-1624.

6. Brutsche MH, Downs SH, Schindler C, Gerbase MW, Schwartz J, Frey M, et al. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA Cohort Study. Thorax 2006;61(8):671-677.

7. Hospers J, Postma D, Rijcken B, Weiss ST, Schouten J. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. Lancet 2000;356(9238):1313-1317.

8. Leigh R, Pizzichini MMM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J 2006;27(5):964-971.

9. Mahler DA, Wire P, Horstman D, Chang Ch, Yates J, Fischer T, Shah T. Effectiveness of fluticasone propionate and salmeterol combination delivered via the diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166(8):1084-1091.

10. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, Kessler R. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180(8):741-750.

11. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary Rehabilitation. Joint ACCR/AACVPR evidence-based clinical practice guidelines. Chest 2007;131(5 suppl):S4-S42.

12. Ortega F, Toral J, Cejudo P, Villagomez R, Sánchez H, Castillo J, Montemayor T. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166(5):669-674.

13. American Thoracic Society. Lung function testing; selection of reference values and interpretative strategies. Am Rev Respir Dis 1991;144(5):1202-1218.

14. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report 2010. In: http:// ginasthma.org.

15. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948-968.

16. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167(2):211-277.

17. Maltais F, Leblanc P, Jobin J, Berube C, Bruneau J, Carrier L, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155(2):555–561.

18. Recomendaciones de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Normativa para la espirometría forzada. Barcelona: Ed. Doyma; 1985.

19. Goldman HI, Becklake MR. Respiratory function test. Normal values at median attitudes and the prediction on normal results. Am Rev Tub 1959;79(4):457-467.

20. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350(10):1005-1012.

21. Ortega F, Montemayor T, Sanchez A, Cabello F, Castillo J. Role of cardiopulmonary exercise testing and the criteria used to determine disability in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;150(3):747–751.

22. Ward SA, Palange P. Clinical exercise testing. European respiratory monograph. E.R.S. Latimer Trend and Co. Ltd, Plymouth, UK, 2007.

23. Altose MD. Assessment and management of breathlessness. Chest 1985;88(2 Suppl):S77-S83.

24. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 1992;47(12):1019–1024.

25. Lillegard WA, Terrio JD. Appropriate strength training. Med Clin North Am 1994;78(2):457-477.

26. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;85(6):751–758.

27. Sweer L, Zwillich CW. Dyspnea in the patient with chronic obstructive pulmonary: etiology and management. Clin Chest Med 1990;11(3):417-445.

28. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42(10):733-778.

29. Guell R, Casan P, Sangenis M, Sentís J, Morante F, Borras JM, Guyatt G. The Spanish translation and evaluation of a quality-of-life questionnaire in patients with chronic obstructive pulmonary disease. Arch Bronconeumol 1995;31(5):202-210.

30. Han MK, Agustí A, Calverley PM, Celli BR, Criner G, Curits JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182(5):598-604.

31. Shaw DE, Berry MA, Hargadon B, McKenna S, Shelley Mj, Green RH, et al. Association between neutrophilic airway inflammation and airflow limitation in adults with asthma. Chest 2007;132(6):1871-1875.

32. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. Am J Respir Crit Care Med 2000;161(1):309-329.

33. Brouillard C, Pepin V, Milot J, Lacasse Y, Maltais F. Endurance shuttle walking test: responsiveness to salmeterol in COPD. Eur Respir J 2008:31(3):579-584.

34. Pepin V, Saey D, Whittom F, LeBlanc P, Maltais F. Walking versus cycling. Sensitivity to bronchodilation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172(12):1517-1522.

35. Pepin V, Brodeur J, Lacasse Y, Milot J, LeBlanc P, Whittom F, Maltais F. Six-minute walking versus shuttle walking: responsiveness to bronchodilation in chronic obstructive pulmonary disease. Thorax 2007;62(4):291-298.

36. Singh SJ, Jones PW, Evans R, Morgan MDL. Minimum clinically important improvement for the incremental shuttle walking test. Thorax 2008:63(9):775-7.

37. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 2003;167(4):544-549.

38. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. Chest 2007;132(6):1778-1785.

39. Calverley PMA, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 2003;58(8):659-664.

40. Hurst JR, Vestbo J, Anzueto A. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363(12):1128-1138.

41. de Torres JP, Pinto-Plata V, Ingenito E, Bagley P, Gray A, Berger R, Celli B. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest 2002;121(4):1092-8.

42. Johannessen A, Lehmann S, Omenaas ER, Eide GE, Bakke PS, Gulsvik A. Post-bronchodilator spirometry reference values in adults and implications for disease management. Am J Respir Crit Care Med 2006;173(12):1316-1325.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Table 1.Clinical and functional characteristics of the patients at baseline.

Variable	Total (n=198)	positive reversibility (n=94)	negative reversibility (n=104)	p value*
Age (years)	65 ± 7.6	66 ± 6.1	64 ± 7.2	NS
BMI (kg/m^2)	29.5 ± 4.8	28.9 ± 5.2	29.9 ± 3.9	NS
FVC (%)	84.5 ± 14.9	83.2 ± 13.2	85.1 ± 15.1	NS
FEV_1 (%)	42.7 ± 13.5	41.5 ± 15.6	44.1 ± 14.2	NS
RV (%)	162 ± 32.7	155.2 ± 28.2	169.1 ± 40.1	NS
TLC (%)	114 ± 13.8	113.8 ± 12.9	114.7 ± 15.1	NS
K_{CO} % pred	70.6 ± 25.1	71.4 ± 26.1	69.8 ± 24.2	NS
PaO_2 (mmHg)	71 ± 9	70 ± 10	71 ± 10	NS
$PaCO_2$ (mmHg)	41.9 ± 5.4	42.2 ± 5.3	40 ± 4.9	NS

BMI: body mass index. FVC: forced vital capacity. FEV_1: volume expired in one second. RV: residual volume. TLC: total lung capacity. K_{CO} % pred: carbon monoxide diffusion constant. PaO_2: arterial oxygen partial pressure. $PaCO_2$: arterial carbon dioxide partial pressure.
.*Comparing positive reversibility vs. negative reversibility patients. NS: not significant.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Table 2. Exercise capacity and strength of the patients studied at baseline.

Variable	Total (n=198)	positive reversibility (n=94)	negative reversibility (n=104)	p value*
Load (watts)	63.5 ± 23	65.1 ± 21.9	61.9 ± 22.2	NS
Load (%)	45.8 ± 15.4	47.2 ± 16.2	44.8 ± 15.6	NS
VO_2peak (%)	56.5 ± 14.8	54.8 ± 15.4	57.9 ± 16.5	NS
VO_2peak (ml/min/kg)	16.2 ± 6.8	15.8 ± 7.2	16.7 ± 7.6	NS
SWT distance (m)	410 ± 152	380.6 ± 158.2	438.5 ± 149.1	0.029
Endurance (min)	21.8 ± 13.5	19.1 ± 12.6	24.5 ± 14.5	0.031
Chest-pull (kg)	44.5 ± 9.8	45.1 ± 9	43.7 ± 10.2	NS
Butterfly (kg)	20 ± 7	19.4 ± 8.1	21 ± 9.2	NS
Neck-press (kg)	23 ± 6.2	23.4 ± 7.2	22.4 ± 5.2	NS
Leg extension (kg)	38,5 ± 11.4	36.8 ± 10.4	40.2 ± 11.6	NS
Leg flexion (kg)	17.6 ± 5.2	18.2 ± 5.6	17.1 ± 4.2	NS

VO2peak: peak oxygen uptake. SWT: shuttle walking test. *Comparing positive reversibility vs. negative reversibility patients. NS: not significant.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Table 3.Baseline dyspnoea and health status scores.

Variable	Total (n=198)	positive reversibility (n=94)	negative reversibility (n=104)	p value*
Dyspnoea (MRC)	2.2 ± 0.9	2.2 ± 0.8	2.1 ± 1	NS
CRDQ: Dyspnoea	3.9±0.8	3.8±0.8	4.1±0.7	NS
CRDQ: Fatigue	5.4±0.9	5.2±1	5.6±0.8	0.039
CRDQ: Emotional function	4.8±0.9	4.7±0.9	5±0.8	0.030
CRDQ: Mastery	5.1±1	5±1	5.1±0.9	NS
CRDQ Total	19.2±4	18.7±4.6	19.8±4.3	0.015
BDI: Magnitude of task	2.3±0.8	2.2±0.9	2.3±1	NS
BDI: Functional impairment	2.1±0.9	2.1±1	2±0.8	NS
BDI: Magnitude of effort	2.2±0.9	2.1±0.7	2.3±1	NS
BDI Focal score	6.5±2.5	6.4±2.7	6.6±2.8	NS

MRC: Medical research council scale. CRDQ: Chronic Respiratory Disease Questionnaire. BDI: Basal Dyspnoea Index. *Comparing positive reversibility vs. negative reversibility patients. NS: not significant.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Table 4.Exercise capacity, strength, dyspnoea and health status, by severity of obstruction (GOLD classification) and functional reversibility.

Variable	GOLD II (n=71)			GOLD III (n=65)			GOLD IV (n=62)		
	positive reversibility (n=33)	negative reversibility (n=38)	p value*	positive reversibility (n=31)	negative reversibility (n=34)	p value*	positive reversibility (n=30)	negative reversibility (n=32)	p value*
Load (watts)	86.4±17.2	84±18.1	NS	62.5±15	58.7±16.2	NS	46.5±11.7	42.9±13.2	NS
VO_2peak (ml/min/kg)	21.1±6.1	22.9±5.4	NS	15.1±5.2	16.2±4.8	NS	10.7±4.6	11±3.8	NS
SWT distance (m)	474.2±120	557.6±126	<0.001	398.3±94	459.8±105	0.015	270±86	298±92	NS
Endurance (min)	24.5±9.9	33.3±8.6	<0.001	18.3±7.2	23.7±6.5	0.005	14.4±7.6	16.5±9.4	NS
Chest-pull (kg)	52.9±6.5	53.4±7.2	NS	46.4±6.6	44.5±8.1	NS	35.7±5.9	33.8±7.1	NS
Butterfly (kg)	27.3±4.2	26.5±4.8	NS	18.5±4.6	21.9±5.1	NS	12.4±4.3	14.4±4.2	NS
Neck-press (kg)	30.4±4.5	28.15±6.2	NS	21.9±4.8	22.1±4.1	NS	17.6±3.5	16.5±3.8	NS
Leg extension (kg)	48.2±5.4	51.5±4.9	NS	35.1±5.1	38.6±4.2	NS	27.3±5.1	29.9±3.2	NS
Leg flexion (kg)	24.9±3.1	22.6±3.9	NS	17.2±4.2	16.±3.9	NS	12.4±3.8	12.8±4.1	NS
CRDQ total	22.2±3.8	24.1±2.1	<0.001	18.5±3.2	19.7±3.2	<0.001	15.1±3.1	15.4±3.2	NS
BDI focal score	9.2±1.8	9.3±1.7	NS	6.1±2.1	6.2±1.9	NS	3.9±0.8	4.1±1.1	NS

VO2peak: peak oxygen uptake. SWT: shuttle walking test. CRDQ: Chronic Respiratory Disease Questionnaire. BDI: Basal Dyspnoea Index. *Comparing positive reversibility vs. negative reversibility patients. NS: not significant.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Table 5. Response to training program (TP).

Variable	Before TP	After TP	p value*
FVC (%)	84.5 ± 14.9	84.1 ± 15.2	NS
FEV_1 (%)	42.7 ± 13.5	42.9 ± 14.1	NS
Load (watts)	63.5 ± 23	79.2 ± 19.5	< 0.05
VO_2peak (ml/min/kg)	16.2 ± 6.8	18.9 ± 5.1	< 0.05
SWT distance (m)	410 ± 152	501.4 ± 108	<0.001
Endurance (min)	21.8 ± 13.5	43.3 ± 15.4	<0.001
Chest-pull (kg)	44.5 ± 9.8	55.2 ± 7.8	0.005
Butterfly (kg)	20 ± 7	26.7 ± 5.5	0.015
Neck-press (kg)	23 ± 6.2	30.3 ± 5.1	0.015
Leg extension (kg)	38,5 ± 11.4	51.9 ± 9.5	0.005
Leg flexion (kg)	17.6 ± 5.2	26.9 ± 5.6	0.005
CRDQ Total	19.2±4	22.9 ± 3.2	< 0.05

FVC: forced vital capacity. FEV_1: volume expired in one second. VO2peak: peak oxygen uptake. SWT: shuttle walking test. CRDQ: Chronic Respiratory Disease Questionnaire. *Comparing before and after TP. NS: not significant.

RESPIRATORY CARE Paper in Press. Published on June 04, 2013 as DOI: 10.4187/respcare.02399

Table 6. Mean post-training increments in exercise capacity, strength parameters, dyspnoea and health-related quality of life scores, according to the reversibility functional.

Variable	Total (n=169)	positive reversibility (n=81)	negative reversibility (n=88)	p value*
ΔLoad (watts)	15.7±16.1	15.4±16.6	15.9±15.7	NS
ΔLoad (%)	10.6±11.6	9.8±10.4	11.3±12.5	NS
ΔVO_2peak (%)	8.5±10.6	9.2±10.1	7.9±8.3	NS
ΔVO_2peak (ml/min/kg)	2.7±3.4	2.9±3.1	2.5±3.5	NS
ΔSWT distance (m)	91.4±64.7	87.4±68.3	95.5±66.6	NS
ΔEndurance (min)	21.5±17.4	21.2±18.7	21.8±16.5	NS
ΔChest-pull (kg)	10.7±5.9	11.5±5.6	9.9±6.4	NS
ΔButterfly (kg)	6.75±4.1	6.9±4.1	6.6±4.3	NS
ΔNeck-press (kg)	7.3±4.1	7.1±4.6	7.4±3.9	NS
ΔLeg extension (kg)	13.4±7.6	13.6±8.6	13.2±7.1	NS
ΔLeg flexion (kg)	9.3±6.1	9.5±5.9	9.1±6.3	NS
ΔDyspnoea (MRC)	–0.8±0.7	–0.9±0.6	–0.7±0.8	NS
TDI	4.7±1.9	4.6±1.8	4.8±1.7	NS
ΔCRDQ total	3.7±2.5	3.8±2.4	3.5±2.5	NS

VO2peak: peak oxygen uptake. SWT: shuttle walking test. MRC: Medical research council scale. TDI: Transitional Dyspnoea Index. CRDQ: Chronic Respiratory Disease Questionnaire. *Comparing positive reversibility vs. negative reversibility patients. NS: not significant.