Clinical and Physiological Effects of Exercise Training in Dyspneic Mild COPD Patients: Design of the Study

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Authors’ contributions

This work was carried out in collaboration between all authors. Authors OD, GL, IN, JL, AB, FR and FS designed the study. Authors GL, GV and OD performed the statistical analysis. Authors OD, AB, GL, FS, PMN and AH wrote the protocol, the first draft of the manuscript. Authors OD, GV, AB, GL managed the analyses of the study. Authors OD, GL and AB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Mild chronic obstructive pulmonary disease (COPD) may be associated with physical inactivity, exercise limitation, and impaired health related quality of life, because of a combination of deconditioning, dyspnea, and reduced peripheral muscle mass. Although the benefits of exercise training (ET) in counteracting these consequences are well established in moderate-to-very-severe COPD, it is unclear if they are also effective in mild disease. The aim of this paper is to describe the design of a randomized controlled trial (RCT) to assess the efficacy of ET in patients with mild COPD and dyspnea, defined by a modified Medical Research Council dyspnea score ≥1. We hypothesize that their effectiveness will be similar to that observed in more advanced disease because of the presence of breathlessness. Consequently, ET will improve exercise limitation and health-related quality of life (HRQoL) in dyspneic mild COPD patients in comparison to usual care.

Methods and Analysis: In this RCT, 60 mild dyspneic COPD patients (post-bronchodilator forced expiratory volume in 1 s [FEV₁] ≥80% of predicted value and post-bronchodilator FEV₁/forced vital capacity [FVC] ≤70%) will be randomized to an intervention or usual care group. The intervention group will receive a 2-month ET program, which will include cycle exercise and muscle resistance training, whereas the control group will receive usual care. Primary outcome will be the change on the six-min walk test after ET. Secondary outcomes will include changes in HRQoL, assessed with the St. George’s Respiratory Questionnaire, and changes in exercise time during a constant load cycle exercise.

Discussion: This will be the first RCT evaluating the efficacy of an ET program in patients with mild COPD. These results could be of relevance to clinical practice and develop new recommendation in mild disease.

Clinical Trials.gov: NCT02930421.

Keywords: COPD; dyspnea; pulmonary rehabilitation.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with low levels of physical activity in daily life, starting early in the course of the disease [1].

In patients with COPD, regardless of disease severity, exercise-induced dynamic hyperinflation and breathlessness may preclude physical activity, thereby causing muscle deconditioning which further worsen exercise capacity, and promote a sedentary lifestyle [2].

In patients with mild COPD, exercise-induced dynamic hyperinflation is similarly present [3,4], but exercise tolerance also depends from reduced peripheral muscle mass and impaired muscle function. Quadriceps cross-sectional area is reduced in patients with mild COPD compared to controls [5], particularly if dyspnea is also present [4]. Reduced quadriceps mass is strongly associated to quadriceps weakness [6,7] and a substantial proportion of patients with mild COPD (28%) had quadriceps weakness [8]. Skeletal muscle impairment may, thus, lead to reduced exercise capacity [4], physical activity limitation [5] and a downward disease spiral in which exercise-induced anaerobic metabolism and quadriceps fatigue promote further immobility [2]. In summary, exercise intolerance and physical activity restriction can already be present in mild COPD because of a combination of dynamic hyperinflation and dyspnea, and skeletal muscle dysfunction and leg discomfort, which preclude physical activity and encourage additional muscle deconditioning.

The exercise training component of pulmonary rehabilitation has been shown to be very effective in improving exercise capacity, dyspnea and quality of life[9]. As a result, in patients with COPD exercise training (ET) is recommended as part of pulmonary rehabilitation in international guidelines [10,11]. In fact, ET is widely regarded as the cornerstone of pulmonary rehabilitation [9,11,12] and the best available means of improving muscle function in COPD, in line with a recent meta-analysis [13] where no differences were found between basic ET programs and more complex interventions that fulfill the current definition of pulmonary rehabilitation [11].
ET has been shown to positively affect dyspnea and exercise intolerance by enhancing skeletal muscle function and decreasing concomitant dynamic hyperinflation, which result in an improvement of exercise tolerance and health related quality of life [11,14-16]. Accordingly, ET may interrupt the cycle of decline leading to inactivity in mild COPD patients. The current guidelines recommend that ET should be considered for patients who have persistent symptoms and activity limitations, and for those who are unable to cope with their illness despite optimal medical management [11]. Even when these conditions may be present in patients with mild COPD, the effects of ET in these patients are currently unclear. A recent systematic review indicated there were significant and beneficial effects of ET with or without any form of education and/or psychological support, on exercise capacity and quality of life in patients with mild COPD [17]. However, their conclusions were based on low-quality studies with heterogeneous ET programs. Thus, although these findings suggest that patients with mild COPD may benefit from ET programs as a part of their disease management, further prospective studies are required.

The purpose of the present article is to describe the design of a randomized controlled trial (RCT), registered on ClinicalTrials.gov with identifier NCT02930421. The overall objective is to evaluate the effects of ET in patients with mild COPD and dyspnea, defined by a modified Medical Research Council (mMRC) dyspnea score ≥1 [18].

1.1 Aims

The study will examine the effects of high-intensity exercise training during 2-months, in a monocentric, randomized controlled design, in dyspneic patients with mild COPD. Outcomes will be the change in exercise performance during the 6 MWT, the change in exercise duration during a constant load cycle exercise, and the change in HRQoL.

1.2 Hypotheses

Since peripheral muscle mass and function improve with ET [11], we hypothesize that this statement is correct and consequently ET will increase exercise capacity in dyspneic mild COPD patients in comparison to usual care.

2. METHODOLOGY

2.1 Study Design

This study is a parallel-group, randomized clinical trial. Patients will be randomly allocated into an intervention (ET) or usual care (UC) group. Study subjects will be recruited from the outpatient clinics and the pulmonary function labs at the Pontifical Catholic University of Chile Health Network by means of physician referral, advertisement in clinical areas, or self-referral at the study center. The Institutional Ethics Committee approved the study protocol and signed informed consent will be obtained from all participants prior to randomization and baseline measurements.

2.2 Randomization and Blinding

Before baseline evaluation, subjects will be randomly assigned to one of the two groups (ET or UC), achieved by stratified randomization using sealed opaque envelopes in equal random block size with order unknown to investigators [19]. Stratified randomization will use mMRC dyspnea as stratum, because dyspnea is related to both physical activity [20] and peripheral muscle mass [21], and may potentially influence the effects of ET. The case manager will subsequently inform patients of their group allocation at the end of the baseline visit. The baseline visit will be scheduled when enough patients could be recruited to begin an ET group. Health staff members involved in outcome measurements (physicians, laboratory technicians, and nurses) will be fully blinded to the randomization list, until the clinical database is unlocked at the end of the trial. Evidently, full blinding procedures are not applicable in this study, since the participating kinesiologists and also the patients could not be blinded to the allocation group.

2.3 Inclusion and Exclusion Criteria

Patients should meet the recruitment criteria, as follows: a) male or female subjects, aged 45-80 years; b) baseline (post-bronchodilator) forced expiratory volume in 1 s (FEV₁) ≥80% of predicted normal and baseline (post-bronchodilator) FEV₁ forced vital capacity (FVC) ≥70%; c) current or ex-smokers with a smoking history of at least 10 pack-years; d) dyspnea during activities of daily life, defined as mMRC dyspnea score ≥1; e) absence of an acute exacerbation in the previous month; f) no history of asthma or other chronic lung disease identified
at screening visit (e.g.: Interstitial lung disease; sarcoidosis; Tuberculosis; Cystic fibrosis; Bronchiectasis; Previous lung resection) and g) absence of comorbidities that would prevent the patient from performing an exercise test, including psychological or cognitive disorders, chronic congestive heart failure; recent myocardial infarction (6 months or less); Cardiac arrhythmia requiring drug therapy; Neuromuscular and peripheral vascular diseases. The presence of usual co-morbidities, such as essential hypertension, diabetes, osteoporosis, hypothyroidism, under proper medical control, and obesity, excluding morbid and super obesity (BMI ≥40 kg/m²), will not be considered an exclusion criterion.

2.4 Study Population

A demographic form will capture age, gender, history of smoking and body mass index (BMI). Assessment of comorbidities will rest on subject’s self-report data, chart review, and objective measurements. Dyspnea will be scored using the mMRC Dyspnea score (range: 0 to 4 points) [18]. Lung function assessment will include spirometry before and after the administration of 400 μg albuterol, static lung volumes, and single-breath diffusion capacity of the lung for carbon monoxide (DLCO). All lung function tests will be performed according to international guidelines [22-24] and standardized as percentages of predicted values [25-27].

2.5 Outcome Measures

Assessment visits will be scheduled at baseline, i.e., the week before ET, and at 2 months, the week after finishing ET. During ET, the kinesiologist will record patient attendance and the reasons for not attending sessions will be also collected. During these evaluation visits, the outcome measures will be performed. Outcome measures will include functional exercise performance, quality of life, and endurance exercise capacity. All outcome measures will be performed by members of the staff not involved in the study.

2.6 Six-min Walk Test

Functional exercise performance will be measured using the 6-min walk test (6 MWT) in a 30-m corridor. The 6MWT will be carried out according to current standards [28,29]. Subjects will perform two tests separated by recovery time of at least 30 min [29]. They will be requested to walk as far as possible, and will be verbally encouraged every 1 min using standardized sentences [30]. For each subject the best of the two test will be selected for analysis. Oxygen saturation, heart rate and symptoms of leg effort and dyspnea will be recorded before and after the test.

2.7 Health-related Quality of Life

HRQoL will be assessed with the St. George’s Respiratory Questionnaire (SGRQ). The SGRQ [31] is a self-administered questionnaire that measures health status in patients with chronic airflow limitation. Their total score as well as its 3 domain sub-scores (symptoms, activities and impacts) will be included in analyses.

2.8 Maximal Exercise Capacity (Incremental Exercise Test)

A symptom-limited incremental cycle exercise test will be conducted to measure the maximal workload (WRmax) [32]. The incremental exercise test will be performed on a ER 800® cycle ergometer (Erich Jaeger, GmbH, Hoechberg, Germany). It will consist of a steady-state resting period (3 minutes of quiet breathing through a mouthpiece) and a 3-minute warm-up of unloaded pedaling at 60-70 revolutions per minute, followed by a stepwise protocol in which the work rate will be increased by 20 watts every 1-minute intervals in order to achieve an exercise duration between 8-12 min [33]. Standardized and continuous verbal encouragement to subjects will be provided by a member of the study team, who will be blinded to patient allocation. All exercise tests will end at the point of symptom-limitation, i.e., peak exercise. The maximum tolerated load will be that sustained for more than 30 seconds.

2.9 Endurance Exercise Capacity (Constant Work Rate Test)

A constant work rate (CWR) cycle endurance test will be performed at 80% of the maximum work rate achieved during the incremental cycle exercise test [32]. Exercise testing will be conducted according to recommended guidelines [34]. Pedaling rates will be maintained between 60-70 revolutions per minute. Standardized and continuous verbal encouragement to subjects will be provided by a member of the study team, who will be blinded to patient allocation. Breath-by-breath measurements [minute ventilation (VE),...
tidal volume (VT), breathing frequency (FR), inspiratory and expiratory time (TI and TE, respectively), duty cycle (TI/TTOT), and mean inspiratory and expiratory flow (VT/TI and VT/TE, respectively), oxygen consumption (VO₂), carbon dioxide production (VCO₂), and end-tidal carbon dioxide partial pressure (PETCO₂) will be collected (Vmax Encore, BD, New Jersey, USA). Pulse oximetry and electrocardiographic monitoring will be carried out throughout exercise, while blood pressure will be determined by sphygmomanometer before, every 2 minutes during exercise, at the end of exercise, and 5 min post-exercise. At rest, every minute during exercise, and at the end of exercise, subjects will rate the intensity of their breathing and leg discomfort using the modified 10-point Borg category-ratio scale [35]. The development of dynamic hyperinflation during the exercise test will be assessed by recording changes in end-expiratory lung volumes. Patients will be instructed to perform inspiratory capacity (IC) maneuvers, which will be performed after Borg ratings pre-exercise, every 2 minutes during exercise, and at end-exercise. Assuming a constant total lung capacity throughout the test, a decrease in IC will indicate an increase in the end-expiratory lung volume, i.e., greater dynamic hyperinflation. Exercise parameters will be reported as absolute values or as percent predicted values [36]. Ventilation will be compared with the maximal ventilatory capacity (MVC), estimated by multiplying the measured FEV₁ by 35 [37].

2.10 Interventions

2.10.1 Exercise training

Patients in the intervention group will follow a 2-month exercise training program. Each participant will be prescribed an exercise plan according to standard guidelines [38]. Participants will undergo 3 sessions per week resulting in a total of 24 training sessions over eight weeks. Exercise training will consist of high-intensity whole-body exercise training, as well as lower and upper limb resistance training according to international standards [11]. Duration of the training session will be 45-60 min from the beginning of the program. Patients will perform endurance training at high intensity (>60% of maximal workload) [11]. The overall training intensity will be increased during the course of the program according to the patient’s symptoms on the Borg scale with a rating of 4–6 on perceived dyspnea sensation or leg effort being an indicator of adequate training intensity [39]. Resistance training of major upper and lower limb muscle groups will comprise 3 sets of 8 repetitions at 60% one-repetition maximum (1 RM) using free weights and ankle weights. Training load will be progressively increased when the previous load could be tolerated during 2 consecutive sessions, to 3 sets of 8 repetitions at 80% of 1 RM as a means of maintaining training overload [11,40]. The intervention will be carried out by kinesiologists with broad expertise in exercise training in patients with COPD.

2.11 Statistical Analysis

2.11.1 Outcomes

The primary outcome measure will be the change after 8 weeks of ET in the walking distance using the 6 MWT. Secondary outcomes will be the change in HRQoL assessed with the SGRQ and change in endurance time to symptom limitation during the CWR cycle endurance test. All these measurements will be performed by blinded observers.

2.11.2 Analysis

To analyze changes from baseline in the walking distance after 8 weeks of ET, we will use analysis of covariance model, including treatment as a fixed categorical variable and baseline walking distance as a continuous covariate [41]. Similar analyzes will be employed for changes in SGRQ and endurance time during the CWR cycle exercise.

2.11.3 Sample size

Using 6MWT data from the study of Riario-Sforza et al. [17,42] (effect size =0.88), a sample size estimation with 80% power at the 5% significance level was performed. This power analysis determined that a statistically significant difference in the 6 MWT after a ET program would be detected with 22 subjects per arm. As ET programs may achieve dropout rates of about 30% [43], 30 patients per arm will be recruited.

3. RESULTS AND DISCUSSION

This will be the first RCT evaluating the efficacy of an ET program in patients with mild COPD.

Recent evidence has shown that dyspnea, reduced quadriceps strength, exercise intolerance, physical activity restriction, and poor
HRQoL can be already apparent in patients with mild COPD [4,5,8,44,45], and may worsen over time [44,46]. There is strong evidence indicating that ET could improve all these impairments [11]; Consequently, current guidelines recommend that rehabilitation should be considered for all patients who have persistent symptoms and activity limitations, regardless of disease severity [11,47,48]. Despite these recommendations, studies evaluating the benefits of ET in patients with mild COPD are scarce. The findings of a systematic review suggested that physical activity promotion can significantly improve physical fitness in patients with mild-to-moderate COPD [49]. However, most patients included in these analyses had moderate COPD and no improvements in HRQoL or dyspnea were found. A more recent systematic review identified three low-quality studies with different designs (retrospective, one-group pre-post-test, and randomized controlled trial) [17]. The authors found significant improvements in exercise capacity (effect size 0.87–1.82) and HRQoL (effect size 0.24–0.86) after comparing pre-post-test data and ET with usual care, respectively. These results are inconclusive and indicate that additional and more robust studies should be conducted in order to properly include exercise training or rehabilitation programs in patients with mild COPD [17]. Consequently, if the present study show that the training program is effective these results could be of relevance to clinical practice and directly incorporated into evidence-based recommendations for treatment strategies in mild disease. It should be stressed, however, that these recommendations will be limited to a selected group of patients with mild COPD, recruited from a single institution, who have dyspnea and relatively irrelevant comorbidities.

The present study has some potential sources of uncertainty. Regarding participation rates, most patients with mild COPD do not experience cumbersome symptoms and might do not feel the need to take part in a physical training program simply because of poor motivation. Moreover, many of these patients will probably have work commitments and lack of time to attend rehabilitation sessions regularly [50]. For these reasons, we have estimated a study dropout of 30%, which seems reasonable since in a recent systematic review less than a third (29%) of clinical trials of ET had a dropout rate >20% [43].

Other potential concern is the true effect size provided by ET in mild disease. The effect size of published trials for the SMWT is high (effect size 0.87–1.82) [17], but the poor quality of these studies does not guarantee similar results in the present study. Actually, it could be argued that since dyspnea and exercise limitation are barely present in most of these patients, the benefits will be marginal. Although other studies have shown that ET may benefit patients with COPD irrespective of their baseline dyspnea, spirometric disease severity, and exercise capacity [51-54], the number of patients with mild COPD in these studies has been small or not reported.

ET program duration is another potential source of uncertainty. It is currently not known what is the ideal length of a rehabilitation program [13]. It is also unknown if the duration of ET programs results in equal benefits in patients with relatively preserved exercise capacity and low dyspnea rates compared with those with more severe disease. Nevertheless, a meta-analysis suggested that patients with more severe disease benefit from a longer duration of therapy (>6 months) [55], whereas patients with mild/moderate COPD benefit from both short- and long-term rehabilitation (<3 and >6 months, respectively).

Lastly, the study is not blinded for participants and kinesiologists, since they will be aware of the treatment procedures. To overcome this constraint all outcome measurements will be assessed by personal unaware of the patient allocation.

Finally, this will be the first RCT evaluating the efficacy of an ET program in patients with mild COPD. If the study shows that the training program improves exercise capacity and quality of life, these results could be of relevance to clinical practice and directly incorporated into evidence-based recommendations for treatment strategies in mild disease.

4. CONCLUSION

This protocol evaluating the efficacy of ET in mild COPD patients. Results could change the therapeutic approach in these group of patients.

CONSENT AND ETHICAL APPROVAL

The Institutional Ethics Committee from Pontificia Universidad Católica de Chile has approved the study protocol and signed informed consent will be obtained from all participants.
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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Van Remoortel H, Hornikx M, Demeyer H, Langer D, Burint C, Decramer M, Gosselink R, Janssens W, Troosters T: Daily physical activity in subjects with newly diagnosed COPD. Thorax. 2013; 68(10):962-963.
2. Polkey MI, Moxham J: Attacking the disease spiral in chronic obstructive pulmonary disease. Clin Med (Lond). 2006;6(2):190-196.
3. Ofir D, Lavenziana P, Webb KA, Lam Y-M, O’Donnell DE: Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177(6):622-629.
4. Diaz AA, Morales A, Diaz JC, Ramos C, Klaassen J, Saldivas F, Aravena C, Diaz R, Lisboa C, Washko GR, et al. CT and physiologic determinants of dyspnea and exercise capacity during the six-minute walk test in mild COPD. Respir Med. 2013;107(4):570-579.
5. Shrikrishna D, Patel M, Tanner RJ, Seymour JM, Connolly BA, Puthucheary ZA, Walsh SL, Bloch SA, Sidhu PS, Hart N et al. Quadriceps wasting and physical inactivity in patients with COPD. Eur Respir J. 2012;40(5):1115-1122.
6. Bernard S, Le Blanc P, Whittom F, Carrier G, Jobin J, Belleau R, Maltais F: Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;158(2):629-634.
7. Seymour JM, Ward K, Sidhu PS, Puthucheary Z, Steier J, Jolley CJ, Rafferty G, Polkey MI, Moxham J. Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. Thorax. 2009;64(5):418-423.
8. Seymour JM, Spruit MA, Hopkinson NS, Natanek SA, Man WD-C, Jackson A, Gosker HR, Schols AMWJ, Moxham J, Polkey MI, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. Eur Respir J. 2010;36(1):81-88.
9. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, et al. American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation. Am J Respir Crit Care Med 2006;173(12):1390-1413.
10. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, Greening NJ, Heslop K, Hull JH, Man WD et al. British thoracic society guideline on pulmonary rehabilitation in adults. Thorax. 2013;68(Suppl 2):i1-30.
11. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.
12. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, ZuWallack R, Herreras C. Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest. 2007;131(5 suppl):4S-42S.
13. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2015(2):CD003793.
14. Vogiatzis I, Zakynthinos S. The physiological basis of rehabilitation in chronic heart and lung disease. J Appl Physiol. 2013;115(1):16-21.
15. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debiare E, Dekhuijzen PN, Fransen F, Gayan-Ramirez G, Gea J, et al. An official American Thoracic Society/European Respiratory Society statement: Update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15-62.
16. Pepin V, Saey D, Laviolette L, Maltais F: Exercise capacity in chronic obstructive pulmonary disease: Mechanisms of limitation. COPD. 2007;4(3):195-204.
17. Jacome C, Marques A: Pulmonary rehabilitation for mild COPD: A systematic review. Respir Care. 2014;59(4):588-594.
18. Mahler DA, Wells CK: Evaluation of clinical methods for rating dyspnea. Chest. 1988;93(3):580-586.
19. Doig GS, Simpson F. Randomization and allocation concealment: A practical guide for researchers. J Crit Care. 2005;20(2):187-191. (Discussion 191-183)
20. Watz H, Waschki B, Meyer T, Magnusen H. Physical activity in patients with COPD. Eur Respir J 2009;33(2):262-272.
21. Kelly JL, Elkin SL, Fluxman J, Polkey MI, Sojjak MA, Hopkinson NS: Breathlessness and skeletal muscle weakness in patients undergoing lung health screening in primary care. COPD. 2013;10(1):40-54.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.
23. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, Burgos F, Casaburi R, Coates, A, Enright P, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-735.
24. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511-522.
25. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. The American Review of Respiratory Disease. 1983;127(6):725-734.
26. Crapo RO, Morris AH: Standardized single breath normal values for carbon monoxide diffusing capacity. The American Review of Respiratory Disease. 1981;123(2):185-189.
27. Quanjer P, Tammeling G, Cotes J, Pedersen O, Peslin R, Yernault J. Lung volumes and forced ventilatory flows. Report work party: Standardization of lung function testing. Eur Respir J. 1993;6 (Suppl.16):5s-40s.
28. Guyatt G, Pugsley S, Sullivan M, Thompson P, Berman L, Jones N, Fallen E, Taylor D. Effect of encouragement on walking test performance. Thorax. 1984; 39(11):818-822.
29. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciruba FC, Pitta F, et al. An official European Respiratory Society/American Thoracic Society technical standard. Field walking tests in chronic respiratory disease. Eur Respir J 2014;44(6):1428-1446.
30. Laboratories ATS/CoPS/CPF. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-117.
31. Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A complete-measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-1327.
32. 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.
33. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ: Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol. 1983;55(5):1558-1564.
34. ERS. Task force, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Goodfellow R, O'Donnell DE, Puente-Maestu L, Schols AM, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J. 2007;29(1):185-209.
35. Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-381.
36. Jones NL, Makrides L, Hitchcock C, Chyphar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. Am Rev Respir Dis. 1985;131(5):700-708.
37. Gandevia B, Hugh-Jones P. Terminology for measurements of ventilatory capacity; A report to the thoracic society. Thorax. 1957;12(4):290-293.
38. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, Spruit MA, Masefield S, Casaburi R, Olin EM, et al. An official American Thoracic Society/European Respiratory Society policy statement: Enhancing implementation, use, and delivery of
pulmonary rehabilitation. Am J Respir Crit Care Med. 2015;192(11):1373-1386.

39. Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. Chest. 1996;109(5):1169-1175.

40. American college of sports medicine. American college of sports medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41(3):687-708.

41. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323(7321):1123-1124.

42. Riarco-Sforza GG, Incorvaia C, Paterniti F, Pessina L, Caliguri R, Pravettoni C, Di Marco F, Centanni S. Effects of pulmonary rehabilitation on exercise capacity in patients with COPD: A number needed to treat study. Int J Chron Obstruct Pulmon Dis. 2009;4:315-319.

43. Sohanpal R, Hooper R, Hames R, Prieb S, Taylor S. Reporting participation rates in studies of non-pharmacological interventions for patients with chronic obstructive pulmonary disease. A systematic review. Systematic Reviews. 2012;1:66.

44. Maltais F, Dennis N, Chan CK. Rationale for earlier treatment in COPD. A systematic review of published literature in mild-to-moderate COPD. COPD. 2013;10(1):79-103.

45. O'Donnell DE, Gebke KB. Activity restriction in mild COPD. A challenging clinical problem. Int J Chron Obstruct Pulmon Dis. 2014;9:577-588.

46. Bridevaux PO, Gerbase MW, Probst-Hensch NM, Schindler C, Gaspoz JM, Rochat T. Long-term decline in lung function, utilisation of care and quality of life in modified GOLD stage 1 COPD. Thorax. 2008;63(9):768-774.

47. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, Ford G, Gervais A, Goldstein R, Hodder R, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J. 2007;14 (Suppl B):5B-32B.

48. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347-365.

49. Chavannes N, Vollenberg JJ, van Schayck CP, Wouters EF. Effects of physical activity in mild to moderate COPD. A systematic review. Br J Gen Pract. 2002;52(480):574-578.

50. Faulkner J, Walshaw E, Campbell J, Jones R, Taylor R, Price D, Taylor AH. The feasibility of recruiting patients with early COPD to a pilot trial assessing the effects of a physical activity intervention. Prim Care Respir J. 2010;19(2):124-130.

51. Evans RA, Singh SJ, Collier R, Williams JE, Morgan MD. Pulmonary rehabilitation is successful for COPD irrespective of MRC dyspnoea grade. Respir Med. 2009;103(7):1070-1075.

52. Garrod R, Marshall J, Barley E, Jones PW: Predictors of success and failure in pulmonary rehabilitation. Eur Respir J. 2006;27(4):788-794.

53. Schroff P, Hitchcock J, Schumann C, Wells JM, Dransfield MT, Bhatt SP. Pulmonary rehabilitation improves outcomes in chronic obstructive pulmonary disease independent of disease burden. Annals of the American Thoracic Society. 2017;14(1):26-32.

54. Lan CC, Chu WH, Yang MC, Lee CH, Wu YK, Wu CP. Benefits of pulmonary rehabilitation in patients with COPD and normal exercise capacity. Respir Care. 2013;58(9):1482-1488.

55. Salaman GF, Mosier MC, Beasley BW, Calkins DR. Rehabilitation for patients with chronic obstructive pulmonary disease. meta-analysis of randomized controlled trials. J Gen Intern Med. 2003;18(3):213-221.