Recent Advances in Pulmonary Rehabilitation for Patients with COPD

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ABSTRACT

Pulmonary rehabilitation (PR) is a non-pharmacologic therapy that has emerged as a standard of care for patients with chronic obstructive pulmonary disease (COPD). It is a comprehensive, multidisciplinary, patient-centered intervention that includes patient assessment, exercise training, self-management education, and psychosocial support. PR is usually given in inpatient, outpatient, community-based or home-based setting lasting 8-12 weeks. Positive outcomes from PR include increased exercise tolerance, reduced dyspnea and anxiety, increased self-efficacy, and improvement in health-related quality of life (QoL). Hospital admissions after exacerbations of COPD are also reduced with this intervention. The positive outcomes associated with PR are realized without demonstrable improvements in lung function. This paradox is explained by the fact that PR identifies and treats the systemic effects of the disease. This intervention should be considered in patients who remain symptomatic or have decreased functional status despite optimal medical management. Physical activity in patients with COPD is dependent on many factors, including physiologic, behavioral, social, environmental, and cultural factors. A strong inverse association between daily physical activity and dynamic hyperinflation, which correlates strongly with exertional dyspnea in COPD. Changing physical activity behavior inpatients with COPD needs an interdisciplinary approach, bringing together respiratory medicine, rehabilitation sciences, social sciences, and behavioral sciences. There is a need for more education and learning opportunities for primary care physicians, nurse practitioners, and all allied health care professionals about the process and benefits of PR. There is also a need for the sustainability and the safety of PR in the future study.

KEY WORDS: Pulmonary rehabilitation; Chronic obstructive pulmonary disease (COPD); Home-based low-intensity rehabilitation; Nutritional therapy; Inspiratory muscle training; Physical activity.

ABBREVIATIONS: PR: Pulmonary Rehabilitation; COPD: Chronic Obstructive Pulmonary Disease; ATS: American Thoracic Society; ERS: European Respiratory Society.
The European Respiratory Society (ERS) have adopted the following new definition of PR: “PR is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.” Since the previous statement, we understand the complex nature of COPD, its multisystem manifestations, and frequent comorbidities. Therefore, integrated care principles are being adopted to optimize the management of these complex patients with COPD. PR is now recognized as a core component of this process (Figure 1).3

Health behavior change is vital for optimization and maintenance of benefits from any intervention in chronic care, and PR has taken a lead in implementing strategies to achieve this goal.4 This model might offer further clarification on the content and processes by which various levels of support are achieved. It aids definition of terms and may help practitioners identify individual’s needs and the level of care which is required. Healthcare professionals interested in the field might use this tool to help construct interventions, identify appropriate outcome measures and define the intervention in a standardized way. As suggested by Effing and colleagues,5 for the most severe patients the most comprehensive PR program which includes self-management should be of importance, that is ‘Integrated Care’. For less complicated patients which have basic needs, the minimal ‘action plan’ intervention may be sufficient.5 In the face of a progressive disease, long-term maintenance of health status is challenging. Effing and colleagues6 have commended change in behavior as the only way health status improvements can be sustained. Cognitive behavioral techniques have been proposed as therapies which may be fundamental to facilitating behavior change. Self-efficacy has been acknowledged in the article as an important aspect of behavior change.5,6 By identifying deficits in self-efficacy and manipulating it, behavior change might be more successful.6

Rationale and Outcomes

Recent evidence-based reviews have confirmed the effect of PR on COPD outcomes, including improved exercise capacity, reduced dyspnea and leg discomfort, improved quality of life (QoL), enhanced self-efficacy, improved activities of daily living (Table 1).2–4 The beneficial effects of PR are realized without a demonstrable effect on traditional lung function measurements, such as forced expiratory volume in one second (FEV1).2,3 This discrepancy is well explained by the fact that PR ameliorates the systemic effects of COPD and its common comorbidities.2,4 Prominent systemic effects of COPD include peripheral muscle dysfunction resulting from physical inactivity or systemic
inflammation; muscle wasting, inadequate self-management skills, and anxiety and depression. Systemic effects and co-morbid conditions contribute to the disease burden and might be amenable to therapy. For example, physical conditioning of leg muscles through exercise training reduces lactate production and decreases ventilator load. A lower ventilatory load allows the COPD patients to breathe more slowly during exercise, thereby reducing dynamic hyperinflation. These effects usually reduce exertional dyspnea, even without a change in FEV1.

Maintaining Benefits and Integrating Care

The positive outcomes from PR tend to decrease year by year after discontinuation of the PR program. The reasons for this decline are multifactorial and include decreasing adherence to the exercise program, exacerbations of COPD, development of comorbidities, and longitudinal deterioration from the disease itself. Although, many programs provide post-PR maintenance, the effects on long-term PR outcomes have not been established. Self-management education may promote long-term adherence to the exercise program, but this has not been proven yet. For many years, PR has used an interdisciplinary and integrated process in the long-term management of chronic respiratory diseases, such as COPD. Integration of services is necessary to provide a seamless transition of care across settings (hospital, rehabilitation center, and community) and disciplines (primary care, subspecialty, home services). Although, patient selection along with assessment, exercise training, self-management education, and psychosocial support make up an interdisciplinary PR program, these components should be ideally integrated into lifelong COPD management for all patients, even if PR is not available.

Essential Components of Pulmonary Rehabilitation

Essential components of PR include patient selection and assessment, psychosocial support, self-management education, nutritional support, and exercise training (including inspiratory muscle training (IMT) (Figure 2).

| Table 1: Benefits of Pulmonary Rehabilitation. |
|-----------------------------------------------|
| ● Reduced hospitalization                     |
| ● Reduced unscheduled healthcare visits       |
| ● Improved exercise capacity                   |
| ● Reduced dyspnea and leg discomfort           |
| ● Improved limb muscle strength and endurance  |
| ● Improved health-related quality of life      |
| ● Improved activities of daily living          |
| ● Improved emotional function                   |
| ● Enhanced self-efficacy and knowledge         |
| ● Enhanced collaborative self-management       |
| ● Potential for increased daily physical activity levels |

Figure 2: Basic Construction of Pulmonary Rehabilitation.
One of the actual PR program is a multidisciplinary home-based program (Figure 3). In this program, breathing retraining consists of pursed-lip breathing and diaphragmatic breathing performed in the supine or sitting positions. Exercise training includes upper- and lower-extremity exercise, respiratory muscle stretching calisthenics, level walking, and IMT (Figure 4, 5). Patients with COPD takes education program including lectures about respiratory disease, control of dyspnea, medication, equipment use, nutrition, stress management, relaxation techniques, home exercise, and the concept and benefit of PR. A registered nurse practitioner periodically visits each patient at home and provides information on the role of PR. This PR program differs from the recent home-based PR programs in the point of low-intensity exercise program including such as respiratory muscle stretching calisthenics and low intensity IMT.

**Patient Selection and Assessment**

PR is patient centered; therefore, an initial assessment and goal setting are very important. The initial assessment determines the stage for subsequent optional therapy. Indications for PR include persistent respiratory symptoms (especially exertional dyspnea) or dysfunction in activities of daily living despite appropriate medical treatment. Contraindications include conditions that substantially increase risk during rehabilitation (e.g., severe valvular or ischemic heart disease) or conditions that interfere with the PR procedure. In many cases, the underlying contraindication can be treated or PR can be adapted so that all patients can participate in PR program.
Traditional PR guidelines state that the degree of airflow limitation is not a major selection criterion for PR, but that symptom burden and functional status limitation are the major indications. However, a recent evidence-based practice guideline from the American College of Physicians recommends that physicians consider PR for patients with an FEV1 less than 50% of that predicted. It states that the evidence is not clear whether PR is beneficial in patients whose FEV1 is greater than 50% of that predicted. The recommendation was based on moderate-quality evidence in the randomized clinical trials that were reviewed. The recommendation contradicts the prevailing expert opinion that symptomatic patients may benefit from PR, regardless of their FEV1 and the severity of COPD is clearly influenced by more than the limitation of airflow alone.

Self-Management Education

Self-management education is a central and integral component of PR. It promotes self-efficacy and encourages active participation in healthcare. Self-management education has been shown to be highly effective in improving health status and reducing healthcare utilization. It is usually provided in small group or in a one-on-one setting. An initial assessment helps determine individual educational needs, which are reassessed during the course of PR program. Discussions about advance directives are an important part of the self-management education, as is counseling about early recognition and treatment of COPD exacerbations.

Psychosocial Support

Anxiety, depression, coping problems, and decreased self-efficacy contribute to the burden of advanced respiratory disease. Although, there is minimal evidence to support psychosocial interventions as a single therapeutic modality in patients with COPD, benefits are derived from comprehensive PR programs that include these types of interventions.

A systematic review and meta-analysis comparing comprehensive PR when was compared with standard care shows that PR leads to small to moderate scale improvements in anxiety and dyspnea. Psychosocial and behavioral interventions vary among PR programs, but often involve educational sessions or support groups that focus on coping strategies and stress management. Patients’ family members and friends are also encouraged to participate in these support groups. Patients with substantial psychiatric disease should be referred for appropriate care.

Exercise Training

Exercise training for upper- and lower-extremities: Comprehensive exercise training, including upper- and lower-extremity endurance training and strength training, is an essential component of PR. COPD can be considered a disease of the peripheral muscles with decreased mass, alterations in fiber-type distribution, and decreased metabolic capacity contributing to exercise intolerance. These abnormalities may be amenable to exercise training. Higher levels of exercise training are associated with a greater physiologic training effect, dose-dependent improvements in oxidative enzymes in limb muscles, and larger improvement in exercise capacity.

Exercise training is based on general principles of intensity (higher intensity produces greater results), specificity (only those muscles trained show an effect), and reversibility (cessation of regular exercise training results in a decrease in training effect). Although patients with COPD often have ventilatory limitations to maximal exercise, a physiologic training effect can be achieved if high training targets are used.
intensity of 60 to 80% of the patient’s peak work rate is often feasible.18,19

Strength training is also an important component of exercise training and may yield additional benefits.20 Patients who cannot tolerate high levels of exercise training can also benefit from strength training. Maximizing bronchodilatation, interval training (i.e., alternating high and low intensities), and oxygen supplementation may allow for higher intensity exercise training in some patients.21-23 The optimal duration of training has not been established but depends on the progress of the individual patient. GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines state that eight weeks (with three to four sessions per week) is the minimum duration of a successful PR program, but longer duration awards greater benefits.2-4

Although, high-intensity exercise training is effective and ideal, the rate of implementation and continuation is low especially in home-based PR setting.9,10,24 Therefore, low-intensity exercise training is a realistic choice in home-based PR setting (Figures 3 and 4).9,10

**Inspiratory muscle training (IMT):** Respiratory muscle weakness is observed in COPD patients and contributes to hypercapnia, dyspnea, nocturnal oxygen desaturation and reduced walking distance.25,26 During exercise it has been shown that diaphragm work is increased in COPD and COPD patients use a larger proportion of the maximal inspiratory pressure (PI max) than healthy subjects. This pattern of breathing is closely related to the dyspnea sensation during exercise and might potentially induce respiratory muscle fatigue.4,25,26

In an experiment, a meta-analysis including 32 random controlled trials on the effects of inspiratory muscle training (IMT) in COPD patients were performed.27 In this study the effect size of each individual study was calculated by the difference between the means of the experimental and the control groups before and after the intervention divided by the average population standard deviation.27 Overall the subgroup analyses with respect to training modality (strength or endurance training, added to general exercise training) and patient characteristics were performed. Significant improvements were found in maximal inspiratory muscle strength, endurance time 6 or 12 minutes walking distance and QoL (Table 2).27 Dyspnea was significantly reduced (Borg score and Transitional Dyspnea Index). Endurance exercise capacity was observed to improve, while no effects on maximal exercise capacity were found. Respiratory muscle endurance training revealed no significant effect on PI max, functional exercise capacity and dyspnea. IMT added to a general exercise program improved PI max significantly, while functional exercise capacity tends to increase in patients with inspiratory muscle weakness (PI max <60 cm H2O).27 IMT improves inspiratory muscle strength and endurance, functional exercise capacity, dyspnea and QoL. Inspiratory muscle endurance training was shown to be less effective than respiratory muscle strength training. In patients with inspiratory muscle weakness, the addition of IMT to a general exercise training program improved PI max and tends to improve exercise performance.27-29

Recently, an electronic tapered flow resistive loading (TFRL) device was introduced that has a different loading profile and stores training data during IMT sessions (Figure 6).30 Inspiratory muscle training (IMT) interventions in patients with COPD have been implemented as 2 daily home-based IMT sessions of 30 breaths (3-5 minutes per session) using mechanical threshold loading (MTL) devices.29-31 PI max and 6-minute walking distance (6MWD) increased significantly after IMT using the new protocol with TFRL device (Table 3).30 Randomized
control study (RCT) of IMT using this new type of device has also been implemented recently.32

New advances in the exercise training: As an essential component of PR, there are many new advances in the exercise training in recent years. Water-based exercise training has been shown to be significantly more effective than land-based exercise training and control in increasing peak and endurance exercise capacity and improving health-related quality of life (HRQoL) in patients with COPD and physical comorbidities.33,34 Patients with COPD develop more quadriceps low-frequency fatigue during downhill walking compared to level walking and have lower cardiorespiratory costs.33,34 The effectiveness of downhill walking has been suggested to be effective as part of a comprehensive rehabilitation program.35 The eccentric exercise therapy in the form of downhill walking has been also shown to have positive effects on functions and HRQoL and that had an augmenting effect on the thigh muscles size.36 Whole-body vibration has been shown to be an effective muscle training and also an option in diminishing weakness and muscle wasting.37 Patients with COPD who are immobilized and not available for active physiotherapy may benefit.38 The application of whole-body vibration was safe and feasible and the technique leads to increased energy expenditure.38,39

Nutritional Support

Patients with lower body weight in COPD have impaired pulmonary condition, reduced diaphragmatic mass, lower exercise capacity and higher mortality than those who are sufficiently nourished.40,41 Nutritional support may be useful for their comprehensive care. To assess the impact of nutritional support on anthropometric measures, pulmonary function, respiratory and peripheral muscles strength, endurance, functional exercise capacity and HRQoL in COPD. If benefit is demonstrated, to perform subgroup analysis to identify treatment regimens and subpopulations that demonstrate the greatest benefits.

Recently, randomized controlled trials (RCTs)42 from the Cochrane Airways Review Group Trials Register, a hand search of abstracts presented at international meetings and consultation with experts have been identified. It has been shown that nutritional supplementation facilitates significant weight gain in COPD patients, especially in malnourished COPD.42

Concomitant use of an anti-inflammatory nutritional

| Table 3: Effect of IMT Using TFRL Device.38 |
|-----------------|-----------------|-----------------|
|                | Baseline        | 12-weeks        | Changes         |
| PImax (cmH2O)  | 83.7±24.1       | 105.9±24.8      | 22.3 (16.4-28.1)** |
| PEmax (cmH2O)  | 116.5±31.4      | 139.2±38.0      | 22.7 (11.5-33.9)** |
| QF (kgf)       | 47.2±11.8       | 49.4±10.9       | 2.21 (0.05-4.35)* |
| WBI (kgf/kg)   | 0.78±0.18       | 0.82±0.17       | 0.04 (0.01-0.07)* |
| 6MWD (m)       | 486.6±114.4     | 519.4±111.2     | 32.7 (17.9-47.6)** |
| Borg Dyspnea*  | 4.0 (1.0-4.0)   | 2.5 (1.0-3.3)   | -0.73 (-1.40-(-0.05)) |
| Borg Leg Fatigue* | 2.0 (1.0-3.3) | 2.0 (0.5-2.3)   | -0.20 (-0.72-0.32) |

Paired t-test or Wilcoxon signed-rank test: *p<0.05 vs. Baseline, **p<0.01 vs. Baseline
The values are presented as mean±standard deviation or median (interquartile range).

The change values are presented as mean (95% Confidence Interval).
supplement containing whey peptide, which exhibits an anti-inflammatory effect, with exercise therapy in stable elderly COPD patients with %IBW <110% and % FEV1 <80% may not only increase body weight but may also inhibit systemic inflammation and thus improve exercise tolerance and HRQOL (Figure 7).43,44

Physical activity in COPD: Daily physical activity can be expressed as an overall measure of active energy expenditure, using indirect calorimetry techniques such as doubly labelled water or metabolic carts. Although, doubly labelled water is regarded as a criterion method, this technique does not quantify the duration, frequency and intensity of physical activity performed. Metabolic cart systems which measure expired O2 and CO2; however, cannot be used over extended periods of time.45-47 Physical activity can also be monitored directly using physical activity monitors.

In general, three classes of activity monitors are being used increasingly in chronic disease populations (e.g., COPD); pedometers, accelerometers and integrated multi-sensor systems. Pedometers are devices which estimate the number of steps taken through mechanical or digital measurements in only the vertical plane.45-47 This is a limited measure of physical activity. Accelerometers detect acceleration in one, two or three directions (uni-, bi- or triaxial accelerometers). These devices allow determination of the quality, quantity and intensity of movements. Integrated multisensory systems combine accelerometry with other sensors that capture body responses to exercise (e.g. heart rate or skin temperature) in an attempt to optimize physical activity assessments.45-47 With the advancement of technology, many activity monitors are available recently to measure physical activity (Figure 8).46,47

Physical activity in patients with COPD is dependent on many factors, including physiological, behavioral, social, environmental, and cultural factors.51,52 Watz and colleagues53 have shown that daily physical activity is only weakly associated with post-bronchodilator FEV1. There is, however, a strong inverse association between daily physical activity and dynamic hyperinflation, which correlates strongly with exertional dyspnea in COPD.54,55 In contrast to resting lung function testing, performance on lower-limb muscle function tests and field exercise tests correlates better with physical activity in COPD. Daily symptoms (e.g., dyspnea and fatigue) are associated with lower physical activity levels in patients with COPD.54,55 Impaired health status is weakly-to-moderately related to physical activity in patients with COPD.56,57 Interestingly, this association was confirmed in a 5-year longitudinal observational study, showing that a decline in physical activity is associated with a decline in health status in patients with COPD.58

Physical activity levels predict important outcomes in COPD. Lower physical activity levels are associated with a higher risk of an exacerbation-related hospitalization.59 In addition to baseline levels of physical activity predicting COPD-related hospitalization, a decline in physical activity over time also predicts this outcome, also after adjustment for age, FEV1, and prior hospitalizations.59 Lower physical activity levels also increase the risk of all-cause mortality in patients with COPD.
after controlling or relevant confounding factors. Decline in physical activity over time also predicts mortality. Reflecting these strong associations, physical activity has been included as a factor in multidimensional prognostic scores for all-cause and respiratory mortality or exacerbations and COPD-related hospitalization in stable COPD patients. These outcome studies underscore the importance of promoting physical activity in the earliest stages of COPD, with a goal of more than 2 hours per week.

The effects of pulmonary rehabilitation on physical activity in COPD: The cornerstones of PR are exercise training and education, aimed at behavior change through promoting self-efficacy. For PR to have its greatest long-term impact, the increases in exercise capacity demonstrated in the rehabilitation center would ideally translate into increases in physical activity in the home and community settings. Both increase in the exercise capacities and changes in the adaptive behavioral are necessary to achieve significant and long lasting increase in daily physical activity in the patients suffering from COPD (Figures 9 and 10). This clinical review will cover the definition of physical activity (which is a different component than exercise capacity); its prevalence in COPD, its objective measurement, risk factors for physical inactivity, and potential ways to improve or maintain the components of physical strength. PR has arguably the strongest positive effect of any current therapy on exercise capacity in stable patients with COPD.

Changing physical activity behavior in patients with COPD needs an interdisciplinary approach, bringing together re-
spiratory medicine, rehabilitation sciences, social sciences, and behavioral Sciences. This concise clinical review has presented data that patients with COPD are generally very inactive, and that this physical inactivity is detrimental to both quality and quantity of the life. Therefore, increased efforts to better understand the determinants of physical activity, as well as effective strategies to improve this variable, must be a prominent goal in PR. Physical activity is now listed as one of the main outcome measures of PR programs by the ATS/ERS Official Statement on PR.

Low-intensity and home-based PR with the feedback from using pedometer was effective in improving physical activity, and the improvements of physiological factors were correlated with increased walking time in stable elderly patients with COPD (Figures 9 and 10).

CONCLUSION

PR is a non-pharmacologic therapy that has emerged as a standard of care for patients with COPD. It is a comprehensive, multidisciplinary, patient-centered intervention that includes patient assessment, exercise training, self-management education, and psychosocial support. Positive outcomes from PR include increased exercise tolerance, reduced dyspnea and anxiety, increased self-efficacy, and improvement in HRQoL. Changing physical activity behavior in patients with COPD needs an interdisciplinary approach, bringing together respiratory medicine, rehabilitation sciences, social sciences, and behavioral sciences. There is a need for more education and learning opportunities for primary care physicians, nurse practitioners, and all allied healthcare professionals about the process and benefits of PR. There is also a need for the sustainability and the safety of PR in the future study. Key processes central to achieving these objectives include increasing healthcare professionals, patient awareness and knowledge of PR, increasing patient access to PR, and promoting quality of this program.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

Consent has been taken from the patient’s for purpose of using patient’s photographs for publication in print or on the internet.

REFERENCES

1. Celli BR, MacNee W. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004; 23(6): 932-946. doi: 10.1183/09031936.04.00014304

2. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. NHLB/WHO workshop report. Bethesda, National Heart, Lung and Blood Institute, April 2001; Update of the Management Sections, GOLD web site. www.goldcopd.com. Updated December 2016. Accessed April 4, 2017.
3. Spruit MA, Singh SJ, Garvey C, 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-e64. doi: 10.1164/rccm.201309-1634ST

4. Nici L, Lareau S, ZuWallack R. Pulmonary rehabilitation in the treatment of chronic obstructive pulmonary disease. *Am Fam Physician.* 2010; 82(6): 655-660.

5. Effling TW, Bourbeau J, Verfoulken J, et al. Self-management programmes for COPD: Moving forward. *Chron Respir Dis.* 2012; 9(1): 27-35. doi: 10.1177/1479972311433574

6. Wagg K. Unravelling self-management for COPD: What next? *Chron Respir Dis.* 2012; 9(1): 7-7. doi: 10.1177/1479972311435910

7. O’Donnell DE, Bertley JC, Chau LK, et al. Qualitative aspects of exertional breathlessness in chronic airflow limitation: Pathophysiologic mechanism. *Am J Respir Crit Care Med.* 1997; 155(1): 109-115. doi: 10.1164/ajrccm.155.1.9001298

8. Japanese Respiratory Society (JRS). *JRS Guideline for Chronic Obstructive Pulmonary Disease. 4th ed.* Tokyo, Japan: 2013.

9. Kagaya H, Takahashi H, Sugawara K, et al. Effective home-based pulmonary rehabilitation in patients with restrictive lung disease. *Tohoku J Exp Med.* 2009; 218: 215-219. doi: 10.1620/tjem.218.215

10. Takahashi, H, Sugawara, K, Satake, M, et al. Effects of low intensity exercise training (chronic obstructive pulmonary disease sitting calisthenics) in patients with stable chronic obstructive pulmonary disease. *Jpn J Compr Rehabil Sci.* 2011; 2: 5-12. doi: 10.11336/jjcrs.2.5

11. Pradella C, Belmonte GM, Maria MN, et al. Home-based pulmonary rehabilitation for subjects with COPD: A randomized study. *Respir Care.* 2015; 60: 526-532. doi: 10.4187/respcare.02994

12. Holland AE, Mahal A, Hill CJ, et al. Home-based rehabilitation for COPD using minimal resources: A randomized, controlled equivalence trial. *Thorax.* 2017; 5: 437-444. doi: 10.1136/thoraxjnl-2016-208514

13. Ries AL, Bauldoff Carlin BW, et al. Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practical guidelines. *Chest.* 2007; 131: 4S-42S. doi: 10.1378/chest.06-2418

14. Coventry PA, Hind D. Comprehensive pulmonary rehabilitation for anxiety and depression in adults with chronic obstructive pulmonary disease: Systematic review and meta-analysis. *J Psychosom Res.* 2007; 63(5): 551-565. doi: 10.1016/j.jpsy-chores.2007.08.002

15. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness in patients with chronic obstructive disease. *Am J Respir Crit Care Med.* 1996; 155(3): 976-980.

16. Bernard S, LeBlanc P, Whittom F, et al. Peripheral muscle weakness in patients with chronic obstructive disease. *Am J Respir Crit Care Med.* 1997; 155(1): 109-115. doi: 10.1164/ajrccm.158.2.9711023

17. Sala E, Roca J, Marrades RM, et al. Effects of endurance training on skeletal bioenergetics in patients with chronic obstructive disease. *Am J Respir Crit Care Med.* 1999; 159(6): 1726-1734. doi: 10.1164/ajrccm.159.6.9804136

18. Casaburi R, Patessio A, Ioli F, et al. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients obstructive disease. *Am Rev Respir Dis.* 1991; 143(1): 8-18. doi: 10.1164/ajrccm/143.1.9

19. Troosters T, Casaburi R, Gosselink et al. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2005; 172(1): 19-38. doi: 10.1164/rccm.200408-1109SO

20. Bernard S, Whittom F, Leblanc P, et al. Aerobic and strength training in patients with chronic pulmonary disease. *Am J Respir Crit Care Med.* 1999; 159(3): 896-901. doi: 10.1164/ajrccm.159.3.9807034

21. Vogiazis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J.* 2012; 20(1): 12-29. doi: 10.1183/09031936.02.01152001

22. O’Donnell DE, D’Arsigny C, Webb KA. Effects of hyperoxia on ventilation limitation during exercise during exercise in advanced chronic obstructive pulmonary pulmonary disease. *Am J Respir Crit Care Med.* 2001; 163(4): 892-898. doi: 10.1164/ajrccm.163.4.2007026

23. Somfay A, Porzasz J, Lee SM, et al. Dose-response effect of oxygen on hyperinflation and exercise endurance in non-hypoxemic COPD patients. *Eur Respir J.* 2001; 18(1): 77-84.

24. Normandin EA, McCusker C, Connors M, et al. An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. *Chest.* 2002; 121(4): 1085-1091. doi: 10.1378/chest.121.4.1085

25. Decramer M, Demedics M, Rochette F, et al. Maximal transrespiratory pressures in obstructive lung disease. *Bull Eur Physiopathol Respir.* 1980; 16: 479-490.
26. Polkey MI, Kyr dummy D, Hamnegard CH, et al. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1996; 154: 1310-1317. doi: 10.1164/ajrccm.154.5.8912741

27. Gosselink R, De Vos J, van den Heuvel SP, et al. Impact of inspiratory muscle training in patients with COPD: What is the evidence? *Eur Respir J.* 2011; 37(2): 416-425. doi: 10.1183/09031936.00031810

28. Langer D, Jacome C, Charususin N, et al. Measurement validity of an electronic inspiratory loading device during a loaded breathing task in patients with COPD. *Respir Med.* 2013; 107: 633-635. doi: 10.1016/j.rmed.2013.01.020

29. Langer D, Charususin N, Jacome C, et al. Efficacy of a novel method for inspiratory muscle training in people with chronic obstructive pulmonary disease. *Phy Ther.* 2015; 95(9): 1264-1273.

30. Okura K, Kawagoshi A, Shibata K, et al. The efficacy of moderate-intensity and short duration inspiratory muscle training for elderly patients with COPD. *Eur Respir J.* 2016; 48(Supp 60): PA703. doi: 10.1183/13993003.congress-2016.PA703

31. Charususin N, Gosselink R, McConnel A, et al. Inspiratory muscle training improves breathing pattern during exercise in COPD patients. *Eur Respir J.* 2016; 47: 1261-1264. doi: 10.1183/13993003.01574-2015

32. Charususin N, Gosselink R, Decramer M, et al. Inspiratory muscle training protocol for patients with chronic obstructive pulmonary disease (IMTCO study): A multicentre randomized controlled trial. *BMJ Open.* 2013; 3: e003101. doi: 10.1136/bmjopen-2013-003101

33. McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Water-based exercise in COPD with physical comorbidities: A randomized controlled trial. *Eur Respir J.* 2013; 41: 1284-1291. doi: 10.1183/09031936.00034312

34. McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Acceptability of the aquatic environment for exercise training by people with chronic obstructive pulmonary disease with physical comorbidities: Additional results from a randomised controlled trial. *Physiotherapy.* 2015; 101: 187-192. doi: 10.1016/j.physio.2014.09.002

35. Camillo CA, Burtin C, Hornikx M, et al. Physiological responses during downhill walking: A new exercise modality for subjects with chronic obstructive pulmonary disease? *Chron Respir Dis.* 2015; 12: 155-164. doi: 10.1177/1479972315575717

36. Erfani A, Moezy A, Mazaherinezhad A, et al. Does downhill-walking on treadmill improve physical status and quality of life of patient with COPD? *Asian J Sport Med.* 2016; 6(4): e25821. doi: 10.5812/asjsm.25821

37. Boeselt T, Christoph N, Kehr K, et al. Whole-body vibration therapy in intensive care patients. A feasibility and safety study. *J Rehabil Med.* 2016; 48: 316-321. doi: 10.2340/16501977-2052

38. Wollersheim, T, Haas, K, Wolf, S, et al. Whole body vibration to prevent intensive care unit-acquired weakness: safety, feasibility, and metabolic response. *Critical Care.* 2017; 21: 9. doi: 10.1186/s13054-016-1576-y

39. Gloeckl R, Richter R, Winterkamp S, et al. Cardiopulmonary response during whole-body vibration training in patients with severe COPD. *ERJ Open Res.* 2017; 3: 00101-2016. doi: 10.1183/23120541.00101-2016

40. Wilson Do, Rogers RM, Wright EC, et al. Body weight in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1989; 139: 1435-1436. doi: 10.1164/ajrccm/139.6.1435

41. Schols AMWJ, Buurman WA, del Brekel AJJS, et al. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in subgroup of patients with chronic obstructive pulmonary disease. *Thorax.* 1996; 51: 819-824. doi: 10.1136/thx.51.8.819

42. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Sys Rev.* 2012; 12: CD000998. doi: 10.1002/14651858.CD000998.pub3

43. Sugawara K, Takahashi H, Kasai C, et al. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir Med.* 2010; 104: 1883-1889. doi: 10.1164/j.rmed.2010.05.008

44. Sugawara K, Takahashi H, Kashiwakura T, et al. Effect of anti-inflammatory supplementation with whey peptide and exercise therapy in patients with COPD. *Respir Med.* 2012; 106: 1526-1534. doi: 10.1016/j.rmed.2012.07.001

45. Caspersen C, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep.* 1985; 100(2): 126-131.

46. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. *Eur Respir J.* 2014; 44(6): 1521-1537. doi: 10.1183/09031936.00046814

47. Spruit MA, Pitta F, McAuley E, et al. Pulmonary rehabilita-
tion and physical activity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015; 192(8): 924-933. doi: 10.1164/rcrm.201505-029CI

48. Miura S, Satake M, Tamura Y, et al. Evaluation of walking time according to walking speed using a triaxial accelerometer system. Jpn J Compr Rehabil Sci. 2013; 4: 73-79. doi: 10.11336/jjcrs.4.73

49. Kawagoshi A, Kiyokawa N, Sugawara K, et al. Quantitative assessment of walking time and postural change in patients with COPD using a new triaxial accelerometer system. Int J Chron Obstruct Pulmon Dis. 8: 397-404, 2013. doi: 10.2147/COPD.S49491

50. Kawagoshi A, Kiyokawa N, Sugawara K, et al. Effects of low-intensity exercise and home-based pulmonary rehabilitation with pedometer feedback on physical activity in elderly patients with chronic obstructive pulmonary disease. Respir Med. 2015; 109(3): 364-371. doi: 10.1016/j.rmed.2015.01.008

51. Pitta F, Troosters T, Spruit MJ, et al. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005; 171: 972-977. doi: 10.1164/rcrm.200407-855OC

52. Van Remoortel H, Hornikx M, Demeyer H, et al. Daily physical activity in subjects with newly diagnosed COPD. Thorax. 2013; 68: 962-963. doi: 10.1136/thoraxjnl-2013-203534

53. Watz H, Pitta F, Rochester CL, et al. An official European Respiratory Society statement on physical activity in COPD. Eur Respir J. 2014; 44(6): 1521-1537. doi: 10.1183/09031936.00046814

54. Satake M, Shioya T, Uemura S, et al. Dynamic hyperinflation and dyspnea during the 6-minute walk test in stable chronic obstructive pulmonary disease patients. Int J COPD. 2015; 10: 153-158. doi: 10.2147/COPD.S73717

55. Iwakura M, Okura K, Shibata K, et al. Relationship between balance and physical activity measured by an activity monitor in elderly COPD patients. Int J Chron Obstruct Pulmon Dis. 2016; 1: 1504-1514. doi: 10.2147/COPD.S107936

56. Waschki B, Spruit MA, Watz H, et al. Physical activity monitoring in COPD: compliance and associations with clinical characteristics in a multi-center study. Respir Med. 2012; 106: 522-530. doi: 10.1016/j.rmed.2011.10.022

57. Esteban C, Quitana JM, Abruto M, et al. An impact of changes in physical activity on health-related quality of life among patients with COPD. Eur Respir J. 2010; 36: 292-300. doi: 10.1183/09031936.00021409

58. Hartman JA, Boezen HM, de Greef MH, et al. Physical and psychosocial factors associated with physical activity in patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 2013; 94: 2396-2402. doi: 10.1016/j.apmr.2013.06.029

59. Miravitlilles M, Cantoni J, Naberan K. Factors associated with a low level of physical activity in patients with chronic obstructive pulmonary disease. Lung. 2014; 192: 259-265. doi: 10.1007/s00408-014-9557-x

60. Esteban C, Quitana JM, Abruto M, et al. Influence of changes in physical activity on frequency of hospitalization in chronic obstructive pulmonary disease. Respir Care. 2014; 19: 330-338. doi: 10.1111/resp.12239

61. Garcia-Aymerich, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: A population based cohort study. Thorax. 2006; 61: 772-778. doi: 10.1136/thx.2006.060145

62. Garcia-Rio F, Rojo B, Casitas R, et al. Prognostic value of the objective measurement of daily physical activity in patients with COPD. Chest. 2012; 142(2): 338-346. doi: 10.1378/chest.11-2014

63. Vaes AW, Garcia-Aymerich J, Mariott JL, et al. Changes in physical activity and all-cause mortality in COPD. Eur Respir J. 2014; 44: 1199-1209. doi: 10.1378/chest.11-2014

64. Moy ML, Teylan M, Danilack VA, Gagnon DR, Garshick E. An index of daily step count and systemic inflammation predicts clinical outcomes in chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2014; 11: 149-157. doi: 10.1513/AnnalsATS.201307-243OC

65. Bourbeau J, Nault D, Dang-Tan T. Self-management and behavior changes modification in COPD. Patient Educ Couns. 2004; 52: 271-277. doi: 10.1016/S0738-3991(03)00102-2