Chronic obstructive pulmonary disease : new insights in morning symptons and physical activity

Buul, A.R. van

Introduction

GENERAL INTRODUCTION OF COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that is characterised by airway obstruction and chronic inflammation of the airways. According to the latest information of the World Health Organisation (WHO), COPD is the third leading cause of death worldwide.[1] The most common symptoms in COPD are dyspnoea, chronic cough and sputum production. Components of COPD such as emphysema and chronic bronchitis were first described in 17th century.[2] In the 19th century, hyperinflated lungs were discovered in particular families, indicating that there should be familial predispositions or environmental factors that cause long abnormalities. Nowadays, the most important causes of COPD are exposition to noxious gases and tobacco smoking. A diagnosis of COPD should be considered in any patient with symptoms of dyspnoea, chronic cough or sputum production and a history of risk factors for COPD.[3]

Diagnosis

If there is a suspicion of COPD, the diagnosis should be confirmed by pulmonary function testing. Typical for COPD is airway obstruction that is caused by narrowing of the small airways, alveolar damage and loss of elasticity of the lungs.[4] Airway obstruction is defined as a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) lower than 0.7 or FEV_1/FVC below the lower limit of normal (LLN). The severity of airflow limitation is expressed as a percentage of predicted FEV_1. There are four COPD stages: mild (FEV_1 ≥80% predicted), moderate (50% ≤ FEV_1 <80% predicted), severe (30% ≤ FEV_1 <50% predicted) and very severe COPD (FEV_1 <30% predicted).[3] Airflow limitation solely is not enough to stage COPD severity. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement, patients' symptoms, history of exacerbations and thereby risk of future exacerbations should be taken into account as well.[3] Higher symptom burden[5] and a higher number of severe exacerbations are related with higher mortality rates.[6, 7]

Treatment

There are no curative options for COPD. Major treatment goals in COPD are reduction of symptoms and prevention of acute exacerbations. Symptoms can be monitored with questionnaires. The most widely used questionnaires are the modified Medical Research Council (mMRC),[8] COPD Assessment Test (CAT)[9] and Clinical COPD Questionnaire (CCQ).[10] For the risk assessment for future exacerbations, the number of moderate and severe exacerbations should be used as a predictor, since previous exacerbations are the best predictor for future exacerbations.[11] An exacerbation is defined as a sudden worsening of respiratory symptoms that results in additional therapy.[3] A low risk for

future exacerbations is defined as having had 0 or 1 exacerbation during the previous year (not leading to hospital admission); high risk as ≥2 exacerbations or ≥1 leading to hospital admission. Pharmacological and non-pharmacological treatment are developed to reduce symptoms and prevent exacerbations. Most prescribed pharmacological treatment are bronchodilators and inhaled corticosteroids. However, pharmacological treatment has no effect on mortality.[3] Moreover, non-pharmacological interventions are recommended to improve COPD status. These interventions include the reduction of exposure to risk factors and smoking cessation, education and self-management, adequate sleep, a healthy diet, exercise training and sufficient physical activity. Despite the existing treatment options, COPD is still in the top five leading causes of disability-adjusted life-years.[12] Therefore, more research is needed in factors that are related with poor outcomes in COPD to encourage the development of novel treatment options. In this thesis the focus is on morning symptoms and physical activity.

MORNING SYMPTOMS IN COPD

Occurrence

In COPD, symptoms vary over the day.[13] However, for decades, morning symptoms were considered a feature of asthma.[14] In 2009, the first study with focus on morning symptoms in COPD was published.[15] This study showed that the majority of patients with COPD experience morning symptoms. Following this study, more research has been conducted in this field. Depending on the used questionnaire and the study population, 39.8 to 94.4% of all COPD patients experience symptoms in the morning.[15-22] Most frequently occurring morning symptoms are coughing, sputum production and shortness of breath. Morning symptoms are in general mild to moderate.[16, 19, 22] Patients mentioned morning symptoms as a cause of work absenteeism.[23]

Assessment

Nine years after the first publication about morning symptoms in COPD, a morning symptoms questionnaire was validated.[24] Before that, researchers used non-validated morning symptom questionnaires.[18, 25-30] These different questionnaires contained one to nineteen questions about morning symptoms and most of them evaluated the type of symptoms, severity of symptoms and the impact of the symptoms on daily life. Furthermore, some studies used non-COPD specific questionnaires that included one or more questions about morning symptoms.[18, 25, 31-33]

Associated factors

It has been shown that morning symptoms are associated with night time symptoms, [19, 21, 22] poorer health status,[19, 21, 22, 33, 34] current smoking, exacerbations,[19, 21, 22] more depression,[19] more anxiety,[19] more use of oxygen in the previous week,[22] more use of rescue medication and more primary care visits. It is unknown whether morning symptoms could be a target for therapy to improve these outcomes since the causality between morning symptoms and other factors is still unknown.

PHYSICAL ACTIVITY IN GENERAL

Definition and recommendations

Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure."[35] As this definition already suggests, movements vary in intensity. The intensity of physical activity can be expressed in metabolic equivalents (METs). One MET is nearly equivalent to the energy expenditure of sitting quietly.[36] Activities that cost <3.0 MET are categorised as light intense activities, for example hair styling. Activities that cost 3.0 to 6.0 MET are categorised as moderate intense activities, for example walking the dog. Activities that cost >6.0 MET are categorised as (very) vigorous intense activities, for example jogging.[36] According to the physical activity recommendations of American College of Sports and Medicine, adults should be physically active for at least 30 minutes a day in moderate intense physical activity in bouts of at least 10 minutes, for at least five days a week.[37] Another option to reach the activity recommendations is to be physically active 20 minutes a day in vigorous intense physical activity in bouts of at least 10 minutes, for at least three days a week. When physical activity recommendations are not reached, a person is physically inactive. Older adults are less likely to reach the activity recommendations than younger adults.[38] The physical activity domains in which people spent their time have changed during the past decades; less time is spent in work and transport-related physical activity due to the development of new technologies and urbanisation; and more time could be spent in leisure time physical activity. Changing physical activity is challenging, because physical inactivity is associated with several factors including low interest in physical activity, low education level, health related factors and a high body mass index.[39, 40]

Measurements

There are various methods to assess physical activity. One method to assess physical activity is the use of activity questionnaires. Activity questionnaires are easy to use in practice and they are cheap.[41] Disadvantages are recall bias and (gross) overestimation of physical activity.[41] Objective assessments of physical activity can be performed with devices.

Pedometers are most accurate in step counting.[42] However, pedometers do not contain information about movement intensity. (Triaxial) accelerometers are devices that assess acceleration in multiple directions and thereby reflect bodily movement. Several accelerometers have been developed, with different features, designs and measured output.[43, 44] Disadvantages of accelerometry are lack of adherence and the need for technical expertise.[41] In COPD, accelerometers are validated tools to evaluate physical activity.[44]

Chronic diseases

Physical inactivity results in a higher risk of cardiovascular disease, various types of cancer, diabetes, obesity and mortality. [45-48] Physical inactivity is common in chronic diseases such as COPD, cardiovascular diseases, kidney disease and diabetes.[49] In a group of adults without a chronic disease about 50% is physically active, whereas only 30% of patients with a history of COPD reach the recommended physical activity levels.[49]

PHYSICAL ACTIVITY IN COPD

Known activity characteristics

Physical activity is substantially lower in patients with COPD than their healthy peers.[50, 51] Physical inactivity is not specific to severe COPD only; the decline is already present in mild and moderate COPD[52] and pulmonary function is only weakly associated with physical activity.[53] There is an annual decrease in physical activity.[54] Low physical activity in COPD is related to high mortality rates,[55] lower quality of life, more dyspnoea and more previous exacerbations.[56] Thus, physical inactivity seems to be a matter of concern in COPD that needs to be addressed. It is unknown whether COPD causes inactivity due to symptoms, or that it is actually the other way around: that physical activity is a risk factor for the development of COPD symptoms. Previous research has shown that patients with COPD have different activity characteristics when compared to their healthy peers: patients with COPD perform activities slower,[15] at a lower walking speed,[46] and there is an increased duration between steps.[57] Furthermore, they take more breaks[15] and they perform activities in fewer and shorter bouts.[53]

Decrease in physical activity

Patients with COPD experience barriers to be physically active, such as a lack of infrastructure, lack of willpower, other psychological problems, lack of time, invalidating symptoms like dyspnoea and fatigue.[58, 59] Moderate and severe acute exacerbations of COPD drastically decrease physical activity.[60] Frequently, these exacerbations lead to hospitalizations. Following hospitalization, it is difficult for patients to perform physical activities.

It generally takes more than one month to become as active as they were before the exacerbation, if they even return to their pre-exacerbation level.[61]

Physical activity stimulation

Regular physical activity is recommended for all COPD patients.[3] Some level of physical activity results in less decline in pulmonary function when compared to patients who live a sedentary lifestyle.[54] Therefore, (easy) interventions to improve physical activity should be developed. Several interventions are proven to be effective: counselling, direct physical activity feedback and pulmonary medication. Physical activity counseling and real-time feedback were more successful in studies that included stable patients with COPD[62, 63] than studies that included unstable patients. Placebo-controlled medication trials have shown positive effects of long-acting beta2 agonists (LABA)[64, 65] and a long-acting muscarinic antagonist (LAMA)/LABA combination on physical activity parameters.[66] Pulmonary rehabilitation is a multidisciplinary intervention with focus on exercise training, education and behaviour change to improve physical and psychological conditions.[67] The effects of pulmonary rehabilitation are inconsistent; some studies have shown no significant effects on physical activity[68, 69], while others shown significant improvements.[70, 71] Maintenance of the positive effects of pulmonary rehabilitation on the longer term is challenging.[72]

OUTLINE OF THE THESIS

There are no curative options for COPD yet. Nowadays, COPD is still in the top five of diseases that are responsible for disability-adjusted life-years worldwide.[12] Therefore, more research is needed to improve factors that are related with poor outcomes in COPD. The aim of this thesis was to gain more knowledge about morning symptoms and physical activity in COPD in search of novel treatment options. In the studies described in this thesis, morning symptoms were assessed with a questionnaire and physical activity was assessed with a physical activity questionnaire and/or accelerometry.

Chapter 2 is a systematic review on the existing evidence about the association between morning symptoms and physical activity in COPD. Following this systematic review, the MOrning symptoms in-Depth observationAl Study (MODAS) was conducted to investigate the association between morning symptoms and objectively measured physical activity. The results of this study are described in **chapter 3** and **chapter 4.**

In the MODAS, the focus was on moderate to very severe COPD patients. However, physical inactivity is already present in mild and moderate COPD. Therefore, physical activity was

studied in non-severe COPD patients as well. We studied the associations between physical activity and other patient characteristics. The results are presented in **chapter 5**.

This thesis continues with an evaluation of a novel systematic approach for asthma and COPD patients referred to secondary care pulmonology. The novel systematic approach consisted of a predefined diagnostic evaluation combined with an optional internet-based self-management support system. Outcomes of the systematic approach were compared with usual care. The results are shown in **chapter 6**. Finally, in **chapter 7**, a summary of the most important findings, a discussion and suggestions for further research and clinical practice is presented.

LIST OF ABBREVIATIONS

CAT: COPD Assessment Test
CCQ: Clinical COPD Questionnaire
COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
LABA: Long-acting beta2 agonist
LABA: Long-acting muscarinic antagonist
LLN: lower limit of normal
METs: metabolic equivalents
mMRC: Medical Research Council
MODAS: MOrning symptoms in-Depth observationAl Study
WHO: World Health Organisation

REFERENCE LIST

1. World Health Organization. The top 10 causes of death. http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Date accessed: 16 August 2018
2. Petty TL: The history of COPD. *Int J Chron Obstruct Pulmon Dis* 2006, 1:3-14.
3. Global Initiavive for Chronic Obstructive Lung Disease. 2018 Global strategy for prevention, diagnosis and management of COPD. http://goldcopd.org/ Date accessed: 16 August 2018
4. Bohadana A, Teculescu D, Martinet Y: Mechanisms of chronic airway obstruction in smokers. *Respir Med* 2004, 98:139-151.
5. Celli BR, Cote CG, Marin JM, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004, 350:1005-1012.
6. Gedebjerg A, Szepligeti SK, Wackerhausen LH, et al: Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study. *Lancet Respir Med* 2018.
7. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, et al: Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005, 60:925-931.
8. Bestall JC, Paul EA, Garrod R, et al: Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999, 54:581-586.
9. Jones PW, Harding G, Berry P, et al: Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009, 34:648-654.
10. Kon SS, Dilaver D, Mittal M, et al: The Clinical COPD Questionnaire: response to pulmonary rehabilitation and minimal clinically important difference. *Thorax* 2014, 69:793-798.
11. Hurst JR, Vestbo J, Anzueto A, et al: Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010, 363:1128-1138.
12. Murray CJ, Barber RM, Foreman KJ, et al: Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* 2015, 386:2145-2191.
13. Lopez-Campos JL, Calero C, Quintana-Gallego E: Symptom variability in COPD: a narrative review. *Int J Chron Obstruct Pulmon Dis* 2013, 8:231-238.
14. Global Initiative for Asthma. 2018 GINA Report, Global Strategy for Asthma Management and Prevention. http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Date accessed: 16 August 2018
15. Partridge MR, Karlsson N, Small IR: Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. *Curr Med Res Opin* 2009, 25:2043-2048.
16. Bateman ED, Chapman KR, Singh D, et al: Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res* 2015, 16:92.
17. Kessler R, Partridge MR, Miravitlles M, et al: Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J* 2011, 37:264-272.
18. Kim YJ, Lee BK, Jung CY, et al: Patient's perception of symptoms related to morning activity in chronic obstructive pulmonary disease: the SYMBOL Study. *Korean J Intern Med* 2012, 27:426-435.

19. Miravitlles M, Worth H, Soler Cataluna JJ, et al: Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the AS-SESS study. *Respir Res* 2014, 15:122.
20. O'Hagan P, Chavannes NH: The impact of morning symptoms on daily activities in chronic obstructive pulmonary disease. *Curr Med Res Opin* 2014, 30:301-314.
21. Roche N, Small M, Broomfield S, et al: Real world COPD: association of morning symptoms with clinical and patient reported outcomes. *Copd* 2013, 10:679-686.
22. Stephenson JJ, Cai Q, Mocarski M, et al: Impact and factors associated with nighttime and early morning symptoms among patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015, 10:577-586.
23. Roche N, Chavannes NH, Miravitlles M: COPD symptoms in the morning: impact, evaluation and management. *Respir Res* 2013, 14:112.
24. Hareendran A, Make BJ, Zaiser E, et al: Evaluation of the psychometric properties of the Early Morning Symptoms of COPD Instrument (EMSCI). *Int J Chron Obstruct Pulmon Dis* 2018, 13:1633-1645.
25. Partridge MR, Miravitlles M, Stahl E, et al: Development and validation of the Capacity of Daily Living during the Morning questionnaire and the Global Chest Symptoms Questionnaire in COPD. *Eur Respir J* 2010, 36:96-104.
26. Kulich K, Keininger DL, Tiplady B, et al: Symptoms and impact of COPD assessed by an electronic diary in patients with moderate-to-severe COPD: psychometric results from the SHINE study. *Int J Chron Obstruct Pulmon Dis* 2015, 10:79-94.
27. Marin JM, Beeh KM, Clemens A, et al: Early bronchodilator action of glycopyrronium versus tiotropium in moderate-to-severe COPD patients: a cross-over blinded randomized study (Symptoms and Pulmonary function in the moRnING). *Int J Chron Obstruct Pulmon Dis* 2016, 11:1425-1434.
28. Garrow AP, Khan N, Tyson S, et al: The development and first validation of the Manchester Early Morning Symptoms Index (MEMSI) for patients with COPD. *Thorax* 2015, 70:757-763.
29. Palsgrove A, Houghton K, Hareendran A: The development of the early morning symptoms of COPD instrument (EMSCI). vol. 14:A233-A510. PRS51: In Value Health. ; 2011.
30. Globe G, Currie B, Leidy NK, et al: Development of the chronic obstructive pulmonary disease morning symptom diary (COPD-MSD). *Health Qual Life Outcomes* 2016, 14:104.
31. Jones PW, Quirk FH, Baveystock CM: The St George's Respiratory Questionnaire. *Respir Med* 1991, 85 Suppl B:25-31; discussion 33-27.
32. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF: Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *Copd* 2012, 9:90-101.
33. Soler-Cataluna JJ, Sauleda J, Valdes L, et al: Prevalence and Perception of 24-Hour Symptom Patterns in Patients With Stable Chronic Obstructive Pulmonary Disease in Spain. *Arch Bronconeumol* 2016, 52:308-315.
34. Tsiligianni I, Metting E, van der Molen T, et al: Morning and night symptoms in primary care COPD patients: a cross-sectional and longitudinal study. An UNLOCK study from the IPCRG. *NPJ Prim Care Respir Med* 2016, 26:16040.
35. Caspersen CJ, Powell KE, Christenson GM: Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985, 100:126-131.
36. Ainsworth BE, Haskell WL, Whitt MC, et al: Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000, 32:S498-504.

37. Haskell WL, Lee IM, Pate RR, et al: Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007, 39:1423-1434.
38. Hallal PC, Andersen LB, Bull FC, et al: Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* 2012, 380:247-257.
39. Carraca EV, Mackenbach JD, Lakerveld J, et al: Lack of interest in physical activity - individual and environmental attributes in adults across Europe: The SPOTLIGHT project. *Prev Med* 2018, 111:41-48.
40. Lubs L, Peplies J, Drell C, et al: Cross-sectional and longitudinal factors influencing physical activity of 65 to 75-year-olds: a pan European cohort study based on the survey of health, ageing and retirement in Europe (SHARE). *BMC Geriatr* 2018, 18:94.
41. Pitta F, Troosters T, Probst VS, et al: Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. *Eur Respir J* 2006, 27:1040-1055.
42. Schneider PL, Crouter SE, Lukajic O, et al.: Accuracy and reliability of 10 pedometers for measuring steps over a 400-m walk. *Med Sci Sports Exerc* 2003, 35:1779-1784.
43. Rabinovich RA, Louvaris Z, Raste Y, et al: Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J* 2013, 42:1205-1215.
44. Van Remoortel H, Raste Y, Louvaris Z, et al: Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS One* 2012, 7:e39198.
45. Al-Mallah MH, Sakr S, Al-Qunaibet A: Cardiorespiratory Fitness and Cardiovascular Disease Prevention: an Update. *Curr Atheroscler Rep* 2018, 20:1.
46. Watz H, Pitta F, Rochester CL, et al: An official European Respiratory Society statement on physical activity in COPD. *Eur Respir J* 2014, 44:1521-1537.
47. Paffenbarger RS, Jr., Hyde RT, Wing AL, et al: The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993, 328:538-545.
48. Rockhill B, Willett WC, Manson JE, et al: Physical activity and mortality: a prospective study among women. *Am J Public Health* 2001, 91:578-583.
49. Brawner CA, Churilla JR, Keteyian SJ: Prevalence of Physical Activity Is Lower among Individuals with Chronic Disease. *Med Sci Sports Exerc* 2016, 48:1062-1067.
50. Pitta F, Troosters T, Spruit MA, et al: Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005, 171:972-977.
51. Troosters T, Sciurba F, Battaglia S, et al: Physical inactivity in patients with COPD, a controlled multi-center pilot-study. *Respir Med* 2010, 104:1005-1011.
52. Van Remoortel H, Hornikx M, Demeyer H, et al: Daily physical activity in subjects with newly diagnosed COPD. *Thorax* 2013, 68:962-963.
53. Donaire-Gonzalez D, Gimeno-Santos E, Balcells E, et al: Physical activity in COPD patients: patterns and bouts. *Eur Respir J* 2013, 42:993-1002.
54. Waschki B, Kirsten AM, Holz O, et al: Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015, 192:295-306.
55. Garcia-Aymerich J, Lange P, Benet M, et al: Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006, 61:772-778.
56. Gimeno-Santos E, Frei A, Steurer-Stey C, et al: Determinants and outcomes of physical activity in patients with COPD: a systematic review. *Thorax* 2014, 69:731-739.

57. Yentes JM, Rennard SI, Schmid KK, et al: Patients with Chronic Obstructive Pulmonary Disease Walk with Altered Step Time and Step Width Variability as Compared with Healthy Control Subjects. *Ann Am Thorac Soc* 2017, 14:858-866.
58. Amorim PB, Stelmach R, Carvalho CR, et al: Barriers associated with reduced physical activity in COPD patients. *J Bras Pneumol* 2014, 40:504-512.
59. Kosteli MC, Heneghan NR, Roskell C, et al: Barriers and enablers of physical activity engagement for patients with COPD in primary care. *Int J Chron Obstruct Pulmon Dis* 2017, 12:1019-1031.
60. Demeyer H, Costilla-Frias M, Louvaris Z, et al: Both moderate and severe exacerbations accelerate physical activity decline in COPD patients. *Eur Respir J* 2018, 51.
61. Pitta F, Troosters T, Probst VS, et al: Physical activity and hospitalization for exacerbation of COPD. *Chest* 2006, 129:536-544.
62. Hospes G, Bossenbroek L, Ten Hacken NH, et al: Enhancement of daily physical activity increases physical fitness of outclinic COPD patients: results of an exercise counseling program. *Patient Educ Couns* 2009, 75:274-278.
63. Moy ML, Janney AW, Nguyen HQ, et al: Use of pedometer and Internet-mediated walking program in patients with chronic obstructive pulmonary disease. *J Rehabil Res Dev* 2010, 47:485-496.
64. Watz H, Krippner F, Kirsten A, et al: Indacaterol improves lung hyperinflation and physical activity in patients with moderate chronic obstructive pulmonary disease--a randomized, multicenter, double-blind, placebo-controlled study. *BMC Pulm Med* 2014, 14:158.
65. Hataji O, Naito M, Ito K, et al: Indacaterol improves daily physical activity in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2013, 8:1-5.
66. Watz H, Mailander C, Baier M, et al: Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to severe COPD: a randomised, placebo-controlled, crossover study (The MOVE Study). *BMC Pulm Med* 2016, 16:95.
67. 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:e13-64.
68. Coronado M, Janssens JP, de Muralt B, et al: Walking activity measured by accelerometry during respiratory rehabilitation. *J Cardiopulm Rehabil* 2003, 23:357-364.
69. Mador MJ, Patel AN, Nadler J: Effects of pulmonary rehabilitation on activity levels in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev* 2011, 31:52-59.
70. Pitta F, Troosters T, Probst VS, et al: Are patients with COPD more active after pulmonary rehabilitation? *Chest* 2008, 134:273-280.
71. Sewell L, Singh SJ, Williams JE, et al: Can individualized rehabilitation improve functional independence in elderly patients with COPD? *Chest* 2005, 128:1194-1200.
72. Egan C, Deering BM, Blake C, et al: Short term and long term effects of pulmonary rehabilitation on physical activity in COPD. *Respir Med* 2012, 106:1671-1679.