บทความวิชาการ

Systemic effects and anemia in chronic obstructive pulmonary disease
ผลกระทบที่เกิดกับร่างกายทั้งระบบและภาวะโลหิตจางในโรคปอดอุดกั้นเรื้อรัง

Sarayoot Mongkol*

สรายุธ มงคล*

Faculty of Physical Therapy, Saint Louis College

คณะกายภาพบำบัด วิทยาลัยเซนต์หลุยส์

Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation and effects to the lung function. COPD also has significant effects on the body system which called systemic effects for example; weight loss, nutritional abnormalities, cardiovascular effects, nervous system effects, and skeletal muscle dysfunction. The prevalence of anemia in COPD is increased and showed a similar to other chronic disease such as chronic heart failure, cancer, and renal failure. The anemic COPD is effect to decrease the exercise capacity and the quality of life. The mechanisms underlying the systemic effects and anemia in COPD are imprecise, but they are correlation with inactivity, systemic inflammation, tissue hypoxia and oxidative stress. Therefore, the clinical assessment and the treatment of COPD which focused on the procedure for decrease the systemic effect and anemia can be the effective approach for treating COPD patients.

Keywords; Chronic obstructive pulmonary disease (COPD), Systemic effect, Anemia

บทคัดย่อ

โรคปอดอุดกั้นเรื้อรังเป็นโรคที่มีการจำกัดของทางเดินหายใจและส่งผลกระทบต่อการทำหน้าที่ของปอด โรคปอดอุดกั้นเรื้อรังส่งผลกระทบต่อการทำหน้าที่ของทุกระบบในร่างกายหรือที่เรียกว่า systemic effect ภาวะดังกล่าวส่งผลให้ผู้ป่วยโรคปอดอุดกั้นเรื้อรังมีภาวะน้ำหนักลด ภาวะความผิดปกติทางโภชนาการ ผลกระทบทางระบบหายใจและไหลเวียนโลหิต ผลกระทบทางระบบประสาท และผลกระทบต่อระบบโครงร่างและกล้ามเนื้อ ความชุกของภาวะโลหิตจางในผู้ป่วยโรคปอดอุดกั้นเรื้อรังมีเพิ่มมากขึ้นเหมือนกับผู้ป่วยโรคหัวใจ โรคมะเร็งและโรคไต นอกจากนี้ภาวะโลหิตจางในผู้ป่วยโรคปอดอุดกั้นเรื้อรังส่งผลทำให้ความสามารถในการออกกำลังกายและคุณภาพชีวิตลดลง กลไกที่ทำให้เกิด systemic effect และภาวะโลหิตจางในผู้ป่วยยังไม่สามารถสรุปได้แน่ชัด แต่จะพบว่าภาวะดังกล่าวมีความสัมพันธ์กับการทำกิจวัตรประจำวันที่ลดลง การอักเสบในระบบร่างกาย ภาวะพร่องออกซิเจนในเนื้อเยื่อ และสภาวะความเครียดออกซิเดชัน (oxidative stress) ดังนั้นการประเมินและการรักษาในผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่ช่วยทำให้ภาวะ systemic effect และภาวะโลหิตจางดีขึ้นน่าจะเป็นแนวทางที่ช่วยทำให้การรักษาในผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีประสิทธิภาพอีกวิธีหนึ่ง

Introduction

Chronic obstructive pulmonary disease (COPD) is a major problem that increases mortality and morbidity worldwide. The World Health Organization (WHO) projects that COPD will be the third leading cause of death, behind coronary artery disease and stroke, by 2020[1]. The regional COPD working group studied the prevalence of COPD in 12 Asia-Pacific countries, and reported the prevalence of moderate to severe COPD in Thailand to be approximately 5%[2]. The previous study had shown that both

* Corresponding author: Faculty of Physical Therapy, Saint Louis College Tel. 085-0406342

E-mail; grn_pt15@hotmail.com

prevalence and incidence of COPD in the Bangkok metropolitan area were increased with increasing age and the disease occurred predominantly among male smokers [3].

COPD is characterized by irreversible airway obstruction, caused by the inflammation of both airways and lungs. It includes chronic bronchitis and emphysema. Chronic bronchitis has a mucus-producing cough present for at least three months in two successive years, and which includes inflammation or irritation of the airways in the lungs. Emphysema is a condition which the walls between alveoli loss the ability to stretch and recoil[1,4]. Spirometry is generally used to confirm the diagnosis[1]. The disease severity can be classified based on the value of force expiratory volume in one second (FEV_1)[1].

There are four factors related to COPD pathology. Firstly, noxious inhalants from tobacco smoking, poison gas, and outdoor air pollution, are the major risk factors in COPD[4]. Tobacco smoking may be the most important factor leading to respiratory inflammation and permanent damage to the airways in COPD patients[5]. Secondly, previous study have found that genetics are another risk factor in COPD[1,4]. Thirdly, studies with animal models have demonstrated that the imbalance between protease and antiprotease enzymes, such as in alpha-1 antitrypsin deficiency, is related to the pathology in COPD[1,6]. Lastly, mediator imbalance may contribute to the pathology. Many studies were found an imbalance of histone acetylase and deacetylase, which then affects gene transcription and expression of DNA in ways similar to the effects of tobacco smoking[1,6].

The pathological changes in COPD are characterized by thickening of the airways such as bronchi and bronchioles, inflammation of the airways with increased secretion and destruction of the alveoli. Increased air trapping in the lung results in hyperinflation, leading to mechanical disadvantage of the ventilatory pump. These condition cause an increased work of breathing (WOB), minute ventilation ($\dot{V}_E$), and a decreased exercise tolerance in COPD[1,5-6]. The inflammatory changes can also be detected in the systemic circulation in COPD patients, including evidence of oxidative stress, the presence of activated inflammatory cells and increased plasma levels of inflammatory cytokine. The concentrations of the cytokines such as Tumor necrosis alpha (TNF-α), Interleukin 6 (IL-6), Interleukin 6 (IL-8), and C-reactive protein (CRP) are increased in patients' sputum. Previous studies have suggested that the inflammatory markers inhibited exercise tolerance and used to predict prognosis in COPD[6,7].

Systemic effects in COPD

There has been an increased evidence of systemic effects associated with COPD, which may negatively have an impact on Quality of life (QOL). Many reports have presented that COPD is associated with significant extra pulmonary abnormalities, such as nutritional abnormalities and weight loss, skeletal muscle dysfunction, and other potential systemic effects[5-6]. The following literature reviews will focus on the characteristics of these systemic effects.

Nutritional abnormalities and weight loss

Nutritional abnormalities and weight loss are common problems found in COPD patients and are associated with increased mortality[5-6]. Loss of lean body mass is the main cause of weight loss in COPD[8-9]. Karadag and colleagues demonstrated that patients with COPD had a significantly lower body mass index (BMI) than normal subjects[9]. Several observations suggest that those with COPD may suffer from cachaxia rather than malnutrition. However, there is no consensus on the pathology of nutrition abnormalities and weight loss in such patients. The energy expenditure of food into the body in COPD induces the abnormal elevated in malnourished COPD patients and contributes to their increased basal metabolic rate. The increased metabolic requirements in COPD patients are the result of the increased oxygen costs of augmented ventilation[1,6]. Previous studies have found that the increase in metabolic rate associated with medications commonly used in the treatment of COPD, and the increase of inflammatory cytokines such as TNF-α and CRP, were the cause of nutrition abnormalities and weight loss[1,5-6]. Other study has found that tissue hypoxia possibly causes an elevated basal metabolic rate in COPD patients[6]. Also, decreased food intake and elevated resting energy requirements are two hypotheses of progressive weight loss in COPD.

Skeletal muscle dysfunction

The skeletal muscle dysfunction is common in patients with COPD. It is described by specific anatomical changes such as fiber-type composition and atrophy. The strength, endurance, and enzyme activities are functional changes in COPD. It is contribute significantly to limited exercise capacity and reduced quality of life[6,8]. This may be a vicious circle involving exercise intolerance, dyspnea, and fatigue in COPD patients. Previous studies have suggested that patients with COPD may stop exercising because of leg fatigue, rather than the dyspnea[5,6,8]. These studies also found abnormalities in skeletal muscles[5,6,8]. Oca and colleagues evaluated the peripheral muscles characteristic in 29 COPD patients. There was a reduced proportion of type I fibers and an increased proportion of type II fibers in COPD. Thus, skeletal muscle dysfunction seems to be found in COPD patients[10]. The diaphragm muscles appear to behave quite differently from skeletal muscles in patients with COPD, from both the structural and functional points of view. The skeletal muscles are generally underused, whereas the diaphragm is constantly working against an increased load[11]. The low physical activity, tissue hypoxia, and systemic inflammation are likely to be relevant pathogenic factors in skeletal muscle dysfunction. Also, the pathological condition of COPD can contribute to physical disability[6]. Thus, skeletal muscle dysfunction seems to be common in COPD patients.

Cardiovascular effects

Curkendall and colleagues studied the prevalence, incidence, and mortality of cardiovascular disease in patients with COPD.

They reported a higher prevalence of all cardiovascular diseases in COPD patients than in the comparison group. In addition, the risks of hospitalization and death from the cardiovascular diseases were increased in these patients[12]. The presence of airflow limitation decrease of lung function was correlated with the presence of cardiovascular diseases. The endothelial function in COPD is abnormal in both pulmonary and systemic circulations and tobacco smoking is a shared risk factor for both COPD and cardiovascular disease[1]. The inflammatory process seen in patients with COPD might be the mechanism responsible for this combination[5]. This may be due to high pulmonary arterial pressure at rest and during exercise, which contributes to heart failure[6,11-12]. Huiart and colleagues also reported that cardiovascular diseases were more often found in COPD patients than in the general population, and that cardiovascular diseases were the major cause of death rather than COPD[13].

Nervous system effects

Previous studies have suggested that abnormalities of the nervous system are frequently found in COPD patients[5-6]. Chronic hypoxia leads to the development of autonomic dysfunction and peripheral neuropathy in COPD patients and have evidence of a sub clinical parasympathetic autonomic neuropathy with apparent preservation of sympathetic function[14]. The characterized may show in stimulus reception, afferent nerve conduction, central processing, efferent nerve conduction, motor end-plate or end-organ response. Measurement of heart rate variability (HRV) can effectively assess the cardiac autonomic nervous activity[15-16] and the level of physical fitness in patients with COPD[6]. Stein and colleagues found that HRV was a good indicator of disease severity affecting the autonomic nervous system and that the index of HRV may have prognostic value in COPD patients[15].

Osteoskeletal effects

Osteoporosis is often found in COPD patients[6,17]. Fractures of the hip, wrist, and spine are frequently found and contribute to increases in morbidity such as severe pain, disability, impaired respiratory function, and mortality[6,17]. Jorgenson and colleagues reported the high prevalence of osteoporosis and it related to loss of bone mass in COPD patients[18]. Osteoporosis can have multiple causes, singly or in combination, including malnutrition, physical inactivity, smoking, steroid treatment and systemic inflammation. Also, these cause are considered to potential contribute to osteoporosis.

Anemia

Anemia is one of the most common public health problems in clinical practice. An estimated 3.4 million persons in USA per year are diagnosed with anemia, and it is increasing in elderly and people with chronic diseases[19-20]. Studies have suggested that anemia is associated with increased mortality and hospitalization[21]. Previous study has suggested that anemia was related to disability, exercise performance, and muscle strength. In Khonkaen, Thailand, studies have suggested a relationship between anemia and chronic diseases[22]. Therefore, anemia is an important public health problem in Thailand.

Anemia is the decrease of red blood cell volume and the decrease of the hemoglobin concentration to carry oxygen from the lungs to the body[23]. According to the WHO, the criterion for anemia is defined as a hemoglobin concentration below 12 grams per deciliter (g/dL) in women and 13 g/dL in men[23]. In normal hemoglobin the concentration ranges between 13-18 g/dL in men and 12-16 g/dL in women. The severity of anemia is classified as severe, moderate, and mild, based on the hemoglobin concentration in red blood cell (RBC). Severe and moderate anemia is defined as hemoglobin concentrations below 8 g/dL and 8-9.9 g/dL, respectively. Mild anemia is defined as a hemoglobin concentration of 10-12.9 g/dL in men and 10-11.9 g/dL in women. A blood test is the standard method for assessing the level of hemoglobin in RBCs. A complete blood count (CBC) may indicate that there are fewer RBCs than normal. The anemia diagnostic tests may include blood smear examination, iron test, hemoglobin electrophoresis, bone marrow biopsy, and reticulocyte count[23-24]. There are many types of anemia, such as iron deficiency, megaloblastic or vitamin deficiency, inherited blood disease, apastic anemia, thalassemia, anemia caused by defective hemoglobin, idiopathic anemia, and anemia of chronic diseases[23].

The chronic diseases such as CHF, CKD, cancer, and COPD are also associated with anemia[23] and anemia of chronic diseases is a common cause of anemia in the elderly[24]. These diseases can inhibit the production of RBCs and decrease RBC lifespan. There are three mechanisms of developing anemia of chronic diseases. Firstly, the increase in levels of interleukin 1 (IL-1) and TNF-α in chronic diseases may inhibit the erythropoietin (EPO) responses. It is contributes to the decrease of RBC lifespan. Secondly, impaired iron utilization may cause anemia of chronic diseases. Lastly, the impaired bone marrow erythropoietic response may also cause anemia of chronic diseases. This decreases RBC production in chronic diseases[5,23]

The effects of anemia in COPD

Previous reports have shown a high prevalence of anemia associated with chronic diseases such as CHF, CRF, cancer, and COPD[15,25-26]. John and colleagues found a high prevalence of anemia in COPD (23.1%), similar to CHF (23.3%)[19]. Other studies have found high hospital admission rates, increased hospital stays, and decreased survival in patients with anemic COPD[25,27].

John and colleagues evaluated the relationship between inflammatory cytokines, hemoglobin concentration in anemic and non anemic COPD patients. They found increased levels of EPO and inflammatory cytokines in the anemic COPD patients. Also, there were no differences in the distribution of anemia at each stage of disease severity. However, this result could not conclusive, because there were only 13 anemic COPD in all 101 COPD subjects. Another study divided the COPD patients into three groups: group 1 (at risk), group 2 (mild to moderate airway obstruction), and group 3 (severe to very severe airway obstruction). The patients in group 3 (the most severe group) had

the highest hemoglobin level, followed by group 2 and group 1. In addition, they found a high prevalence of anemia in group 1, about 27.2% (at risk group) and low prevalence of anemia in group 3, about 13.8%. This study suggested that hypoxia was inversely related to anemia in severe COPD patients. The authors' explanation was that the hypoxia stimulates the kidney for EPO production and consequently the bone marrow to increase RBC production, resulting in elevated hemoglobin concentration in severe COPD patients[19]. In contrast, other studies have suggested that hematocrit decreases with age and level of airway obstruction[28-29]. Therefore, the relationship between the hemoglobin concentration and the level of airway obstruction remains unclear.

The results of anemia are weakness, fatigue, cachexia, impaired cognitive function, and eventually decrease QOL. Kalra and colleagues have studied the effects of anemia on exercise tolerance in patients with CHF. Exercise tolerance in the anemic patients was lower than in the non anemic counterparts. In addition, they found that the exercise capacity or peak VO_2 was significantly decreased in CHF patients with lower hemoglobin levels. Finally, they reported that the hemoglobin below 13 g/dl was an independent predictor of exercise performance in CHF patients[30]. Previous studies have reported that the EPO significantly increased hemoglobin concentration, improved VO_2, and increased exercise tolerance in CHF patients[31-32]. Additionally, COPD was the chronic and systemic disease that was similar to CHF. Therefore, anemia seems to limit exercise capacity in COPD patients.

Schonhofer et al. studied blood cell transfusion in anemic and non anemic subjects with COPD. In the anemic group, the mean of $\dot{V}_E$, and WOB were decreased after receiving RBC transfusion. In the non anemic subjects, ventilation and gas exchange were not significantly different before and after transfusion, but there was an improvement in hemoglobin concentration after blood transfusion[33]. Therefore, anemia contributes to increase $\dot{V}_E$, WOB, and abnormal breathing pattern in patients with COPD. The anemia in COPD is related to skeletal muscle dysfunction[6,8]. An anemic condition limits exercise performance by reducing oxygen carrying capacity during exercise[30]. Thus, it has been suggested that the improvements in hemodynamics and gas exchange were positively associated with the hemoglobin level, and the increase in hemoglobin could improve exercise capacity[26,28]. Therefore, anemia in COPD contributed to reduction in gas exchange, hemodynamic, and oxygen availability in exercising muscles.

The review article has suggested that exercise training can increase EPO production via bone marrow stimulation. This mechanism can increase exercise performance in athletes[34] and decrease mortality from chronic diseases[30]. Therefore, regardless of the types of intervention (medication and non medication), any treatment resulting in an increased hemoglobin level in anemic COPD patients can improve the exercise capacity and may decrease mortality, morbidity, the cost of treatments, and increase QOL.

Conclusion

The systemic effect and anemia in COPD are the factors that limited exercise capacity, decrease the quality of life, and increase the mortality rate in COPD patients. The mechanisms underlying the systemic effects and anemia are unclear, but they are relating with physical inactivity, systemic inflammation, tissue hypoxia and oxidative stress. Therefore, the clinical assessment and the treatment of COPD which focused on the treatment for corrected the systemic effect and anemia could be an effective approach for treating COPD patients.

References

1. National Heart Lung Blood Institute. Global Initiative for chronic obstructive lung disease; Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Workshop 2009.

2. Regional COPD work group. COPD prevalence in 12 Asia–Pacific countries and regions: Projections based on the COPD prevalence estimation model. Respirology 2003; 8: 192–8.

3. Maranetra KN, Chuaychoo B, Dejsomritrutai W, et.al. The prevalence and incidence of COPD among urban older persons of Bangkok Metropolis. J Med Assoc Thai. 2002; 85(11): 1147-55.

4. Singh S. Chronic obstructive pulmonary disease. Cur Anaes & Cri Care 2003; 14: 74-80.

5. Wouters E, Creutzberg E. Systemic effects in COPD. Chest 2002; 121: 127-30.

6. Agusti AGN, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 347-60.

7. Barnes PJ, Chowdhury B, Kharitonov SA, et al. Pulmonary biomarkers in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 174(1):6-14.

8. Casaburi R. Skeletal muscle function in COPD. Chest 2000; 117: 267S-71S

9. Karadag F, Karul AB, Cildag O, Altun C, Gurgey O. Determinants of BMI in patients with COPD. Respirology 2004; 9: 70-5.

10. Montes de Oca M, Torres SH, Gonzalez Y, et al. Peripheral muscle composition and health status in patients with COPD. Respir Med 2006; 100(10): 1800-6.

11. Sauleda J, Gea J, Orozco-Levi M. Structure and function relationships of the respiratory muscles. Eur Respir J 1998;11:906-11

12. Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Ann Epidemiol 2006; 16: 63-70.

13. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest 2005; 28: 2640-6.

14. Stewart AG, Waterhouse JC, Howard P. Cardiovascular autonomic nerve function in patients with hypoxaemic COPD. Eur Respir J 1991; 4: 1207-14.

15. Stein PK, Nelson P, Rottman JN, et al. Heart rate variability reflects severity of COPD in PiZ alpha1- antitrypsin deficiency. Chest 1998; 113: 327-33.

16. Yildiz P, Tükek T, Akkaya V, et al. Ventricular arrhythmias in patients With COPD are associated with QT dispersion. Chest 2002; 122: 2055-61.

17. Ionescu AA, Schoon E. Osteoporosis in chronic obstructive pulmonary disease. Eur Respir J 2003; 22: 64s–75s

18. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease—A cross sectional study. Respir Med 2007; 101(1): 177-85.

19. John M, Lange A, Hoernig S, Witt C, Anker SD. Prevalence of anemia in chronic obstructive pulmonary disease: Comparison to other chronic diseases. Inter J Cardio 2006; 111: 365-70

20. Gabrilove J. Anemia and the elderly: clinical considerations. Best Prac & Research Clin Haem 2005; 18: 417-22.

21. Penninx BW, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. J Gerontol A Biol Sci Med Sci 2006; 61(5): 474-9.

22. Issaragrisil S, Kaufman DW, Anderson T, et.al. The epidemiology of apastic anemia in Thailand. Blood 2006; 107: 1299-307.

23. World Health Organization. Nutritional anemia: report of a WHO Scientific Group. Geneva: Switzerland 1968.

24. Mayhew M. Anemia of chronic disease in the elderly. J Nurse Pract 2006: 261-7.

25. Erschler WB, Chen K, Reyee EB, Dubois R. Economic burden of patients with anemia in selected disease. Value Health 2005; 8(6): 629-38.

26. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and Inflammation in COPD. Chest 2005; 127: 825-9.

27. 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: 1005-12.

28. Similowski T, Agusti A, MacNee W, Schonhofer B. The potential impact of anemia of chronic disease in COPD. Eur Respir J 2006; 27: 390-6.

29. Chambellan A, Challeux E, Similowski T. Prognostic value of the hematocrit in patients with severe COPD receiving long term oxygen therapy. Chest 2005; 128: 1201-8.

30. Kalra PR, Bolger AP, Francis DP, et al. Effect of anemia on exercise tolerance in chronic heart failure in men. Am J Cardio 2003; 91: 888-91.

31. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003; 107: 294-9.

32. Tassiopoulos ST, Kontos A, Konstantopoulos K, et al. Erythropoietic response to hypoxiamia in diffuse idiopathic pulmonary fibrosis, as pooosed to chronic obstructive pulmonary disease. Respir Med 2001; 95: 471-5.

33. Schonhofer B, Wenzel M, Geibel M, Kohler D. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. Crit Care Med 1998; 26: 1824-38.

34. Scoppetta C, Grassi F. Erythropoietin: a new tool for muscle disorders? Med Hypotheses 2004; 63: 73-5.