CHAPTER II
LITERATURE REVIEW

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 found the prevalence of COPD in Thailand to be approximately 5% (15). A previous study had shown a relatively high prevalence of COPD in the Bangkok metropolitan area (16).

COPD is characterized by irreversible airway obstruction, caused by the inflammation of both airways and lungs. It includes chronic bronchitis and emphysema. Chronic bronchitis is any chronic cough or mucous reproduction 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 in which the walls between alveoli lose the ability to stretch and recoil (1).

A diagnosis of COPD should be considered in patients who have chronic cough, sputum production, dyspnea, and exercise intolerance. Spirometry is generally used to confirm the diagnosis (1). The disease severity can be classified into five stages by using force expiratory volume in one second (FEV_1) (1).

There are four factors related to COPD pathology. Firstly, noxious inhalants associated with tobacco smoking, poison gas, and outdoor air pollution are the major

risk factors in COPD (17). Tobacco smoking may be the most important factor leading to respiratory inflammation and eventually permanent damage in COPD patients (2). Secondly, previous studies have found that COPD may develop by inducing gene MMP1, MMP9, and MMP12 (1). Therefore, genetics are another risk factor in COPD (1, 17). Thirdly, studies with animal models have demonstrated that the imbalance between protease and antiprotease enzymes, such as in alpha-1 antitrypsin deficiency, are related to the pathology in COPD (1, 3). Lastly, mediator imbalance may contribute to the pathology. Many studies have 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, 3).

The pathological changes in COPD are characterized by thickening of the airways such as bronchi and bronchioles, inflammation of the airways with increased hypersecretion 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 ($V^{\bullet}_{E}$), and a decreased exercise tolerance in COPD (1-3). The concentrations of the cytokines such as TNF-α, IL-6, IL-8, and CRP are increased in patients' sputum. Previous studies have suggested that the inflammatory markers inhibited exercise tolerance. These markers were used to predict prognosis in COPD (3, 18).

Systemic effects in COPD

There is increased evidence of systemic effects associated with COPD, which may negatively impact on QOL. Many studies have suggested that COPD is associated with significant extra pulmonary abnormalities, such as nutritional abnormalities and weight loss, skeletal muscle dysfunction, and other potential systemic effects (2, 3). The following literature review will focus on the characteristics of these systemic effects.

Nutritional abnormalities and weight loss

Nutritional abnormalities and weight loss are common problems in COPD patients and are associated with increased mortality (2, 3). Loss of lean body mass is the main cause of weight loss in COPD (19, 20). Karadag and colleagues demonstrated that patients with COPD had a significantly lower body mass index (BMI) than normal subjects, and also found a decrease in lean body mass in COPD patients (20). 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. 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 (1-3). In addition, other studies have found that tissue hypoxia possibly causes an elevated basal metabolic rate in COPD patients (3, 19, 20).

Skeletal muscle dysfunction

The pathological condition of COPD can contribute to physical disability. There may be a vicious circle involving exercise intolerance, dyspnea, and fatigue in COPD patients (3, 19). Previous studies have suggested that patients with COPD may stop exercising because of leg fatigue, rather than the dyspnea (2, 3, 19). These studies also found abnormalities in skeletal muscles (2, 3, 19). Oca and colleagues evaluated the peripheral muscles in COPD patients compared with normal subjects. There was a reduced proportion of type I fibers and an increased proportion of type II fibers in COPD patients compared to the normal subjects. On cross sectional analysis, decreased muscular strength in COPD patient was strongly related to the loss of muscle mass measured by mean of fat free mass. Thus, skeletal muscle dysfunction seem to be common in COPD patients (21).

Cardiovascular effects

Curkendall and colleagues studied the prevalence, incidence, and mortality rate of cardiovascular disease in patients with COPD. They reported a higher prevalence of all cardiovascular diseases in COPD patients than in the control group. In addition, risk of hospitalization and death from the cardiovascular diseases were increased in these patients (22). The presence of airflow limitation was correlated with the presence of cardiovascular diseases. This may be due to high pulmonary arterial pressure at rest and during exercise, which contributes to heart failure (3, 22, 23). 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 itself (23).

Nervous system effects

Previous studies have suggested that abnormalities of the nervous system are frequently found in COPD patients (2, 3). Chronic hypoxia leads to the development of autonomic dysfunction and peripheral neuropathy in COPD patients. Measurement of heart rate variability (HRV) can effectively assess the cardiac autonomic nervous activity and the level of physical fitness in patients with COPD (3, 24, 25). 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 (24).

Osteoskeletal effects

Osteoporosis is often found in COPD patients (3, 26). Jorgenson and colleagues reported a high prevalence of osteoporosis and related loss of bone mass in COPD patients (27). Fractures of the hip, wrist, and spine are frequently found. Such fractures contributed to increases in morbidity such as severe pain, disability, impaired respiratory function, and mortality (3, 26).

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 women and people with chronic diseases (5, 8). Studies have suggested that anemia is associated with increased mortality and hospitalization (28). Other studies have suggested that anemia was related to disability, exercise performance, and muscle strength. In Thailand, studies have suggested a relationship

between anemia and chronic diseases (29). 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 (30). According to the WHO, the criteria for anemia is defined as a hemoglobin concentration below 12 grams per deciliter (g/dL) in women and 13 g/dL in men (30). 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 are 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. Other diagnostic tests may include blood smear examination, iron test, hemoglobin electrophoresis, bone marrow biopsy, and reticulocyte count (8, 30). 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 (30).

Anemia of chronic diseases (ACD) is a common cause of anemia in the elderly. Chronic diseases such as CHF, CKD, cancer, and COPD are also associated with anemia. These diseases can inhibit the production of RBCs and decrease RBC lifespan. There are three mechanisms of developing ACD. Firstly, the increase in

levels of interleukin 1 (IL-1) and TNF-α in chronic diseases may inhibit the erythropoietin (EPO) responses. This then contributes to the decrease of RBC lifespan. Secondly, impaired iron utilization may cause ACD. The increase in the level of cytokines such as IL-1 and TNF-α inhibits iron utilization in EPO production. Lastly, the impaired bone marrow erythropoietic response may also cause ACD. The increase in IL-1, TNF-α, and transforming growth factor-β (TGF- β) inhibit the EPO production in kidney. This decreases RBC production in chronic diseases.

The effects of anemia in COPD

Previous studies have shown a high prevalence of anemia associated with chronic diseases such as CHF, CRF, cancer, and COPD (5, 31). John and colleagues found a high prevalence of anemia in COPD, about 23.1%, similar to CHF (5). Other studies have found high hospital admission rates, increased hospital stays, and decreased survival in patients with anemic COPD (4, 32).

John and colleagues (31) evaluated the relationship between inflammatory cytokines, hemoglobin concentration in anemic and non anemic COPD patients. They found increased levels of EPO and proinflammatory 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 was not conclusive, because there were only 13 anemic COPD subjects in this study. 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 (5). In contrast, other studies have suggested that hematocrit decreases with age and level of airway obstruction (9, 33). 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 decreased 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 hemoglobin below 13 g/dl was an independent predictor of exercise performance in CHF patients (34). Previous studies have reported that EPO significantly increased hemoglobin concentration, improved VO_2, and increased exercise tolerance in CHF patients (35, 36). 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. (37) 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 control group, ventilation and gas exchange were not significantly different before and after transfusion, but there was

an improvement in hemoglobin concentration after blood transfusion. 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 (3, 19). An anemic condition limits exercise performance by reducing oxygen carrying capacity during exercise (34). 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 (9, 31). Therefore, anemia in COPD contributed to reduction in gas exchange, hemodynamic, and oxygen availability in exercising muscles.

Other studies have shown that exercise training can increase EPO production via bone marrow stimulation. This mechanism can increase exercise performance in athletes (38) and decrease mortality from chronic diseases (36). 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.

Six minute walk test

The 6MWT is a field test which is commonly used to assess exercise and functional capacity in patients with cardiovascular and pulmonary diseases (10, 39). The 6MWT was developed from the 12 minute walk test. The American Thoracic Society (ATS) suggested that the 6MWT was a simple, easy, and safe test (10). It simultaneously assesses the cardiovascular, pulmonary, and musculoskeletal systems during exercise. The 6MWT requires the subject to walk as fast as possible in 6

minutes but does not allow running. Several studies have found the 6MWT to be a valid and reliable test for functional and exercise capacity evaluation in normal persons and those suffering from diseases (10, 40, 41). In regard to COPD, Robinnovich and colleagues introduced the 6MWT as a valid and reliable tool to evaluate exercise tolerance in patients with COPD (42).

The ATS suggests that there are many factors that can cause 6MWD reduction, such as shorter height, older age, body weight, impaired cognitive function, shorter corridor, cardiovascular disease, pulmonary disease, and musculoskeletal disease. In addition, many factors can improve 6MWD such as taller height, male sex, high motivation, taking medication before the test, and oxygen supplementation (10). Books and colleagues evaluated the effect of being indoors and the outdoors on several variables during 6MWT in COPD patients. This study showed that there was no statistically significant difference in the walking distance, the heart rate, oxygen saturation, dyspnea, and leg fatigue between indoors and outdoors. This was because the outdoor climatic factors such as temperature, humidity, and wind speed were similar to those indoors (10).

Comparisons between the 6MWT and the incremental exercise test on the pulmonary and cardiovascular responses have been done (10, 11, 43). Troosters and colleagues suggested that the VO_2 showed a steady state profile from the 3^{rd} to the 6^{th} minutes during 6 MWT. A similar finding was also reported for the incremental cycling exercise test (43). The responses of cardiovascular and pulmonary systems among the 6MWT, incremental shuttle walk test, and incremental cycle ergometer test in moderate to severe COPD were compared. This study demonstrated a positive

linear relationship between the walking distance and VO_2 during 6MWT and incremental shuttle walk test. In addition, peak heart rate and dyspnea were not significantly different among the three tests. Comparable cardiovascular and pulmonary responses during the standardized 6MWT and incremental exercise test were found in moderate to severe COPD (11).

Morante and colleagues (44) investigated oxygen desaturation during the 6MWT in moderate to severe COPD patients. The study suggested that the 6MWT was an effective method for detecting oxygen desaturation during activities of daily living (ADL) in COPD patients. Poulain and colleagues (45) used the 6MWT and the incremental exercise test to evaluate the exercise induced oxygen desaturation associated with moderate COPD. The study found that 28% of total COPD patients showed desaturation in 6MWT, but not in the incremental exercise test. In addition, Turner and colleagues have suggested that the 6MWT is more sensitive than the incremental exercise test for detecting exercise induced hypoxia (11).

Various physiological parameters such as heart rate and oxygen saturation are the variables measured in the 6MWT. These variables can be used to predict mortality, morbidity, and survival rate in many diseases (14, 46, 47). Roul and colleagues investigated the potential of 6MWT to predict the prognosis in CHF patients with New York Heart Association (NYHA) class II and III. This study showed that the patients with 6MWD $\geq$ 300 meters had higher survival rates (14). Previous studies had suggested that the 6MWT could predict mortality and morbidity in COPD patients. There were significant correlations between the total walking distance and survival rate in COPD patients before and after lung volume reduction

surgery (LVRS). The results suggested that walking distance and resting $PaCO_2$ level were the best predictors of mortality and morbidity associated with severe COPD (48). In addition, Solwal and Honeyman indicated that the walking distance could be used to evaluate the level of disability in moderate to severe COPD patients (12, 13).

In conclusion, COPD is a systemic inflammatory disease affecting the whole body. Proinflammatory markers are increased in COPD patients, and this is related to the mechanisms of anemia in COPD. The anemia in COPD contributes to increased mortality, decreased gas exchange, hemodynamics, abnormal breathing patterns, and skeletal muscle dysfunction. Similar systemic effects are found in CHF and CKD. Several studies have suggested that anemia was a factor in further reduction of exercise capacity in CHF and CKD as measured by the 6MWT (7, 14). As yet, there are no data on exercise capacity indicated by 6MWT in anemic COPD patients. Therefore, this study is aimed to evaluate the exercise capacity in anemic COPD patients by using the 6MWT.