การเปรียบเทียบระยะทางที่เดินได้ภายใน 6 นาที ระหว่างผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีและไม่มีภาวะโลหิตจาง

A comparison of six-minute walk distance between COPD patients with and without anemia

สรายุธ มงคล[1]* จตุพร วงศ์สาธิตกุล[2]

Sarayoot Mongkol[1]* Jatuporn Wongsathikul[2]

[1]คณะกายภาพบำบัด วิทยาลัยเซนต์หลุยส์

[1]Faculty of Physical Therapy, Saint Louis College

[2]คณะกายภาพบำบัด มหาวิทยาลัยมหิดล

[2]Faculty of Physical Therapy, Mahidol University

*Corresponding author (Email: grn_pt15@hotmail.com)

Received December 2014

Accepted as revised January 2015

Abstract

It is known that exercise capacity in patients with COPD is reduced. Also, anemia can reduce exercise capacity. However, there was no evidence of the reduction of exercise capacity in anemic COPD patients. The aim of this study was to compare the six-minute walk distance (6MWD), the heart rate, and the oxygen saturation immediately after the test (HRim and SpO2im) among the normal subjects and the COPD patients with and without anemia during six-minute walk test (6MWT). Fifty one sedentary elderly subjects were recruited into this study. Thirty four subjects were diagnosed as COPD. According to their hemoglobin level, they were divided into two groups: the anemic group and the non-anemic group (11.58 ± 0.72 g/dL vs. 13.21 ± 1.00 g/dL; $p<0.05$). Thirty five apparently healthy subjects were used as the control group. The spirometry maneuvers and the 6MWT were performed in all subjects. Additionally, blood samples were collected to identify their hemoglobin level. The lowest hemoglobin level was found in the anemic group compared with the non-anemic and the control group (11.58 ± 0.72 g/dL vs. 13.21 ± 1.00 g/dL vs. 13.08 ± 0.32 g/dL). The shortest 6MWD was statistically showed in the anemic group compared with the non-anemic and the control group (300.12 ± 88.55 m. vs. 390.12 ± 50.75 m. vs. 470.35 ± 43.10 m; $p< 0.05$). The SpO2im in the anemic group was statically significant difference among the groups (84.82 ± 6.69% vs. 90.06 ± 7.11% vs. 96.65 ± 2.62%; $p< 0.05$). However, the HRim was not different among the groups. Also, moderate to very severe COPD patients with anemia have reduced 6MWD.

Bull Chiang Mai Assoc Med Sci 2015; 48(1): 67-74. Doi: 10.14456/jams.2015.23

Key word: COPD, Anemia, Six minute walk test

บทคัดย่อ

โรคปอดอุดกั้นเรื้อรัง และภาวะโลหิตจางมีผลทำให้ความสามารถในการออกกำลังกายลดลง แต่ยังไม่มีการศึกษาถึงความสามารถในการออกกำลังกายในผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีภาวะโลหิตจาง การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อเปรียบเทียบระยะทางที่เดินได้ในการทดสอบด้วยการเดิน 6 นาที อัตราการเต้นของหัวใจ และ ความอิ่มตัวของออกซิเจนในเม็ดเลือดแดง ในทันทีที่เสร็จสิ้นการทดสอบ ในกลุ่มคนปกติและผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีและไม่มีภาวะโลหิตจาง วิธีการทดลอง ผู้เข้าร่วมการศึกษาทั้งหมดมีจำนวน 100 คน โดยแบ่งออกเป็นผู้ป่วยโรคปอดอุดกั้นเรื้อรัง ระดับปานกลางถึงรุนแรง จำนวน 75 คน ซึ่งแบ่งออกเป็นสองกลุ่ม คือ กลุ่มที่มีภาวะโลหิตจาง จำนวน 30 คน และไม่มีภาวะโลหิตจางจำนวน 35 คน และมีคนปกติจำนวน 35 คน เป็นกลุ่มควบคุม การทดสอบ ประกอบด้วย การเจาะเลือด การวัดสมรรถภาพปอด และการทดสอบด้วยการเดิน 6 นาที ผลการทดลองพบว่าผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีภาวะโลหิตจาง มีระดับฮีโมโกลบินต่ำกว่ากลุ่มอื่น (11.58 ± 0.72 vs. 13.21 ± 1.00 vs. 13.08 ± 0.32 g/dL) กรัม/เดซิลิตร) พบว่า ผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีภาวะโลหิตจาง มีค่าระยะทางที่เดินได้ภายใน 6 นาที น้อยที่สุดเมื่อเทียบกับกลุ่มอื่น อย่างมีนัยสำคัญทางสถิติ (300.12 ± 88.55 vs. 390.12 ± 50.75 vs. 470.35 ± 43.10 เมตร; $p< 0.05$) และ พบว่าความอิ่มตัวของออกซิเจนในเม็ดเลือดแดง มีค่าต่ำที่สุดในผู้ป่วยโรคปอดอุดกั้นเรื้อรังที่มีภาวะโลหิตจาง อย่างมีนัยสำคัญทางสถิติ (84.82 ± 6.69% vs. 90.06 ± 7.11% vs. 96.65 ± 2.62%; $p< 0.05$) แต่อัตราการเต้นของหัวใจหลังการทดสอบทันที ของทั้งสามกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ สรุปได้ว่าภาวะโลหิตจางในผู้ป่วยโรคปอดอุดกั้นเรื้อรัง เป็นสาเหตุทำให้ผู้ป่วยโรคปอดอุดกั้นเรื้อรัง ระดับปานกลางถึงรุนแรงมีความสามารถในการเดิน 6 นาทีลดลง

วารสารเทคนิคการแพทย์เชียงใหม่ 2558; 48(1): 67-74. Doi: 10.14456/jams.2015.23

คำสำคัญ: โรคปอดอุดกั้นเรื้อรัง ภาวะโลหิตจาง การทดสอบด้วยการเดิน 6 นาที

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation and inflammation of the airways and the lungs.[1] The clinical manifestations in COPD are chronic cough, sputum production, dyspnea, exercise intolerance, deconditioning, and decreased quality of life.[2] COPD has diverse effects, including respiratory and peripheral muscle weakness, weight loss, impaired cardiovascular system, and abnormalities of the autonomic nervous system.[3]

Anemia is a common condition associated with chronic diseases such as chronic heart failure (CHF), chronic kidney disease (CKD), cancer, rheumatoid arthritis (RA), and COPD.[4,5] The clinical symptoms of anemia in chronic diseases are weakness, fatigue, cachexia, impaired nutrition, and exercise intolerance.[6] Previous studies have shown that proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), and C-reactive protein (CRP) are increased in patients with COPD, similar to the mechanisms of anemia.[2,3] Other studies have suggested that anemia contributes to exercise intolerance and dyspnea in chronic diseases.[7,8] Additionally, the anemia in COPD contributes to increased mortality, decreased gas exchange and hemodynamic, abnormal breathing, and skeletal muscle dysfunction.[9] Therefore, the anemia associated with COPD may further reduce exercise capacity in COPD patients.

The six-minute walk test (6MWT) is a valid and reliable tool for the evaluation of the pulmonary, cardiovascular, and musculoskeletal systems during exercise in chronic diseases patients, including those with COPD.[10] This test can indirectly determine the exercise capacity in moderate to severe COPD patients, and yields similar values of peak oxygen consumption (VO_2) to the incremental exercise test.[11] The six-minute walking distance (6MWD) was used to assess exercise capacity.[10] The 6MWD, heart rate, and oxygen saturation immediately after 6MWT (HRim and SpO2im, respectively) have been used as predictors of the prognosis in moderate to severe COPD patients .[10,12-13] A study with CHF and CKD

patients reported that anemia was the main factor that decreased exercise capacity as indicated by reduction in 6MWD.[7,9,14] However, a study of exercise capacity in anemic COPD patients were limited and small sample size.[15] Therefore, the present research was aimed to evaluate the exercise capacity in COPD patients with and without anemia, by using the 6MWT.

Materials and methods

1. Subjects

The study tentatively included 35 normal subjects, 30 COPD patients with anemia, and 35 COPD patients without anemia from the internal medicine outpatient clinic, Maharajnakorn Chiang Mai Hospital, Chiang Mai University and Mae Jun Hospital, Chiang Rai. Both male and female COPD patients were recruited and all clinically stabled, without any change in medication during the previous three weeks. They were classified as stage II-IV according to GOLD COPD guideline.[1] Anemia was defined as hemoglobin concentration below 12 g/dl in women and 13 g/dl in men. All subjects were matched in age, weight, height, and gender.

The patients were excluded from this study if they

1) required oxygen therapy,

2) used medication affecting exercise performance such as β-blocker,

3) had conditions that limited exercise: heart diseases, hypertension, diabetes mellitus, musculoskeletal disorder, and neurological diseases,

4) did not understand verbal communication,

5) had impaired vision and hearing after correction, or

6) had known vitamin B12 or folic acid deficiency.

2. Procedures

Prior to the study, written informed consents were obtained and questionnaires were filled out. Blood sample test, the spirometric maneuvers, and the 6MWT were performed on all subjects. All the tests were completed in one session. The data collection was begun in the morning and the subjects were asked to not to have alcohol, caffeine, or perform any vigorous exercise within 2 hours before the test.

The subjects came to the laboratory in the morning, and demographic data such as age, weight, and height were measured. After resting for 5 minutes, blood pressure and heart rate were recorded and the testing procedures were explained to the subjects.

Then, the 5 milliliter peripheral venous blood sample was collected. According to WHO guidelines, the standard hemoglobin test was performed.[16] This result was used to identify individuals' anemic condition. Then, the FVC, FEV_1, and FEV_1/FVC were measured with the standard spirometry maneuvers according to the ATS guideline.[17] The results of these tests were used to confirm the inclusion criteria.

Finally, the standardized 6MWT was performed.[10] Subjects were asked to walk from the starting point to the end point. They were asked to cover as much as distance as possible in 6 minutes. The subjects walked as fast as possible but running was prohibited. All subjects were permitted to slow down, to stop, or to rest as needed during the test. The same verbal encouragement "do your best" at the start of each minute was provided to all subjects. If the subjects took a rest, the verbal encouragement "begin walking as soon as you feel able" was given. Before and immediately after the test, the heart rate, the blood pressure, the oxygen saturation, the dyspnea scale, and the fatigue perception were recorded. In addition, the total walking distance covered in 6 minutes was recorded after the test. The second trial of 6MWT was repeated after 30 minutes rest, or after the heart rate returned to baseline. The best results of the 6MWT were used for further analysis.

The test was terminated if the subjects experienced chest pain, intolerance dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

3. Statistical analysis

Data was reported as mean ± SD. The significant level at 0.05 was selected. The descriptive statistics were used for demographic data, spirometry results, heart rate, oxygen saturation, and 6MWD. One way ANOVA was used to compare the differences among the normal subjects, COPD patients with anemia, and without anemia.

Results

One hundred sedentary elderly subjects were recruited into this study. Sixty five subjects were diagnosed as COPD. According to their hemoglobin level, they were divided into two groups: the anemic group (n=30) and the non-anemic group (n=35) (11.58 ± 0.72 g/dL vs. 13.21 ± 1.00 g/dL; $p<0.05$). Thirty five apparently healthy subjects were used as the control group. Their demographic data were showed in Table 1. There were no statistically significant differences in age, weight, height, and BMI among the three groups. The smoking period was over 45 years in both the anemic and the non-anemic group (51.43 ± 5.56 yrs and 50.76 ± 4.65 yrs, respectively).

Table 1. The subject's demographic data.

Variables	Control group	Pathologic group	
		Non anemic COPD	Anemic COPD
	(n=35)	(n=35)	(n=30)
Age (yrs)	68.35 ± 4.36	70.25 ± 5.47	70.44 ± 5.57
Gender (M/F)	26/7	25/8	23/7
Weight (kg)	53.25 ± 3.30	49.83 ± 4.76	49.38 ± 6.13
Height (cm)	160.64 ± 4.53	159.45 ± 6.36	161.88 ± 4.66
BMI (kg/m^2)	21.77 ± 1.25	20.99 ± 3.14	20.35 ± 2.53
Hemoglobin (g/dL)	13.08 ± 0.32[a]	13.21 ± 1.00	11.58 ± 0.72[c]
FVC (L/s)	2.56 ± 0.55[b]	2.04 ± 0.61	1.79 ± 0.53
% predicted FVC	95.88 ± 5.45a[b]	74.37 ± 15.24	69.35 ± 15.18
FEV1 (L/s)	2.05 ± 0.39a[b]	1.01 ± 0.29	0.92 ± 0.35
% predicted FEV1	97.33 ± 8.15[a,b]	47.82 ± 14.01	46.65 ± 13.22
FEV1/FVC	83.66 ± 2.56[a,b]	50.37 ± 7.71	52.28 ± 13.85

Data are presented as mean ± SD

Note; BMI = body mass index; FVC = forced vital capacity; FEV1 = forced vital capacity in 1 second

a = significant between normal and non-anemic group ($p<0.05$)

b= significant between normal and anemic group ($p<0.05$)

c= significant between anemic and non-anemic group ($p<0.05$)

The FVC, the predicted FVC, the FEV1, the predicted FVE1, and the FEV1/FVC showed the significantly differences between the pathologic group and the control group ($p< 0.05$). The degree of the airway obstruction in the anemic group was comparable to the non-anemic group. They were classified as moderate to very severe degree of COPD based on GOLD guideline.[1] The FVC and the predicted FVC were not statistically significant differences between the anemic and the non-anemic group. However, the results showed that the anemic group was more likely having the restrictive lung disease.

All subjects completed the 6MWT. The physiological responses during the 6MWT showed in Table 2. The lowest walking distance was found in the anemic group compared with the non-anemic and the control group.

Table 2. Physiological responses during 6MWT.

Variables	Control group	Pathologic group	
		Non anemic COPD	Anemic COPD
	(n=35)	(n=35)	(n=30)
6MWD	470.35 ± 43.10[a]	390.12 ± 50.75	300.12 ± 88.55[b]
RestingHR (beats/min)	73.73 ± 8.12[a]	84.65 ± 9.01	87.94 ± 9.09
HRim (beats/min)	97.00 ± 12.07	105.06 ± 10.42	111.35 ± 11.61
Resting SpO_2 (%)	97.35 ± 0.99	95.35 ± 2.42	94.65 ± 2.57
SpO^2im (%)	96.65 ± 2.62[a]	90.06 ± 7.11	84.82 ± 6.69[b]
Resting DBP (mmHg)	70.94 ± 5.88	72.76 ± 6.28	72.12 ± 6.63
DBPim (mmHg)	75.47 ± 7.92	77.94 ± 7.85	77.12 ± 8.70
Resting SBP (mmHg)	115.78 ± 13.15	116.08 ± 10.43	119.24 ± 10.86
SBPim (mmHg)	127.65 ± 10.33	129.41 ± 9.66	130.08 ± 9.05

Data are presented as mean ± SD

Note; HR = heart rate; HRim = heart rate immediately after the test; SpO_2 = oxygen saturation; SpO_2im = oxygen saturation immediately after the test; DBP = Diastolic blood pressure; DBPim = diastolic blood pressureimmediately after the test; SBP = Systolic blood pressure; SBPim = Systolic blood pressure immediately after the test

a = significant between control and pathologic group (p<0.05)

b= significant between anemic and non-anemic group (p<0.05)

All subjects completed the 6MWT. The physiological responses during the 6MWT showed in Table 2. The lowest walking distance was found in the anemic group compared with the non-anemic and the control group.

At rest, all the groups had the SpO_2 above 95% and there was no statistical difference on resting SpO_2 among the three groups. However, immediately after the test, the lower SpO_2im was found in the pathologic group when it was compared with the control group (p< 0.05). Furthermore, the anemic group showed the lowest SpO_2im among the three groups. There were no differences on blood pressure at rest and immediately after exercise among the groups.

Discussion

The control group had the highest walking distances among the groups. Additionally, the walking distances in the anemic group was lower than the non-anemic group. This result is comparable to the previous study (265 ± 122 m. for the anemic group vs. 325 ± 124 m. for the non-anemic group; p<0.05).[18]

This implies that the functional capacity is reduced in the anemic group via the reduction in oxygen carrying capacity. Additionally, the difference of walking distance between the anemic and non-anemic group is about 90 meters in our study. The evidence suggested that changing of the walking distances greater than 70 meters could alter the patient's clinical perception.[10] Additionally, this result was similar to the previous study about the six-minute walk distance and reaction time in anemia and non-anemia COPD.[15] Also anemia is the factor may be reduce exercise capacity in COPD.

In this study, the highest resting heart rate was found in the anemic group compared with the others. Physical inactivity can increase resting heart rate.[19] Also, dominant sympathetic outflow can increase heart rate and stroke volume in patients with anemia.[6] Thus, the anemic condition and the sedentary lifestyle, may affect their resting heart rate.

In this study, the HRim was higher in the pathologic group than the control group, though, it was not statistically significant difference among the three groups. This may be due to the effect of increase weak of breathing

primarily from the airway obstruction in the pathologic group.[1] Furthermore, the highest HRim was found in the anemic group. The anemic condition can increase plasma volume of the blood.[6,8] This consequently results in congestive heart failure leading to pulmonary hypertension and pulmonary edema, respectively.[20] Low lung compliance is occurred. Thus, the restrictive lung in the anemic group is possibly due to the low compliance. This restrictive type can increase the WOB and the heart rate, respectively.

The resting SpO_2 was over 95% in all groups. At rest, the oxygen availability can meet the basal metabolic rate. However, during the 6MWT the oxygen supply does not meet the oxygen demand due to high exercise intensity and gas exchange impairment.

It is known that the intensity of the 6MWT is comparable to the maximal exercise stress test in moderate to severe COPD patients.[11] The range of exercise intensity in that study between 67 to 105 percent predicted maximal heart rate.[11] In this study, the exercise intensity of the non-anemic and the anemic group was approximately 69.95 and 75.5 percent predicted maximal heart rate, respectively. Thus, the test can elicit the oxygen supply deprivation and is sufficient to stress the cardiopulmonary system in this study.

A previous study reported that the SpO_2im was significant lower in the COPD patients than the healthy individuals.[21] This result is repeated in this study. However, the SpO_2im comparison between the anemic and the non-anemic COPD patients has been made. This study is the first study demonstrated that the SpO_2im in the anemic group was statistically significant lower than the non-anemic group. Additionally, the greater deoxygenating and the greater reduction of the SpO_2im was found in the anemic group (from 94.65 ± 2.57% to 84.82 ± 6.69%) when it was compared to the non-anemic group (from 95.35 ± 2.42% to 90.06 ± 7.11%). This is because the higher the heart rate is the greater reduction of transit time at the pulmonary capillary. Thus, the severity of the gas exchange in the anemic group is greater than the non-anemic group.

Ozalevli et al[21] reported that the SBP and the DBP were not statistically significant differences between the COPD and the healthy group during at rest and immediately after the 6MWT. However, the SBP and the DBP during at rest and immediately after exercise was slightly higher than the healthy group. These are reproducible in this study. The comparison of the SBP and the DBP before and after the 6MWT between the anemic and the non-anemic group had been made in this study. The sympathetic activity was greater in the anemic group than the non-anemic group, even though this group tried to reduce the walking speed.

Pervious study showed that the dyspnea after the 6MWT in the anemic group was greater than the non-anemic group.[18] In this study, the fatigue and the dyspnea before and after the test were obtained. The pathology group had greater the fatigue and dyspnea than the control group before and after the 6MWT. Specific consideration between the anemic and the non-anemic group was made. The fatigue and the dyspnea were greater in the anemic group than in the counterpart before and after the test.

Hypoxemia in patients with severe COPD stimulate the EPO production in kidney and resulting in the increase of RBC production.[5] Thus, polycythemia should be frequently seen in the patients with COPD. In fact, it is not always the case. Form the epidemiologic study, the anemic prevalence in COPD was 23.1%.[5] Additionally, the EPO resistance was found in the anemic group.[22]

Both of COPD and CHF are considered as the systemic inflammatory disease.[2,3] The anemic mechanisms in CHF have been already proposed. Firstly, the increase level of inflammatory cytokines may reduce red blood cell survival. Secondly, there is the inhibition of erythropoietin production in bone marrow. Lastly, iron utilization is inhibited. Currently, the mechanisms of anemia in COPD are unknown. These mechanisms may cause anemia in COPD patients. Thus, further study needs to be clarified on these issues.

Some limitations were found in this study. Firstly, there was no physical examination on gastrointestinal (GI) bleeding and laboratory test on iron deficiency in all subjects. Since, GI bleeding and iron deficiency are commonly caused the anemia in elderly population.[23]

Secondly, pulmonary artery and capillary pressure were not directly measured. Lastly, objective physical examinations on the heart issues need to be done. This is because the cardiac disease is one of the most common co-morbidities in patients with COPD.[22] In conclusion, this study showed that the lowest 6MWD was found in the anemic group compared with the non-anemic group and the control group. However, the HRim was not statistically significant difference among three groups. Immediately after the 6MWT, the anemic group showed the lowest SpO_2 among the three groups.

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. Wouters EFM, Creutzberg EC, Schols AMWJ. Systemic effects in COPD. Chest. 2005; 121: 127-30.
3. Agustı 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.
4. Erschler WB, Chen K, Reyee EB, Dubois R. Economic burden of patients with anemia in selected disease. Value in health. 2005; 8: 629-38.
5. 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: 36570
6. Silverberg DS, Iaina A, Wexler D, Blum M. The pathological consequences of anaemia. Clin Lab Haem. 2001; 23: 1-6.
7. Calbet JAL, Lundby C, Koskolou M, Boushel R. Importance of hemoglobin concentration to exercise: Acute manipulation. Respir Physiol & Neuro. 2006; 51: 132-40.
8. Gabrilove J. Anemia and the elderly: clinical considerations. Best Prac & Research Clin Haem. 2005; 18: 417-22.
9. 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.
10. American Thoracic Society. ATS Statement: Guidelines for the six minute walk test. Am J Respir Crit Care Med. 2002; 166: 111-7.
11. Turner SE, Eastwood PR, Cecins NM, Hillman DR, Jerkins SC. Physiologic responses to incremental and self-paced exercise in COPD; a comparison of three tests. Chest. 2004; 126: 766-73.
12. Honeyman P, Barr P, Stubbing DG. Effect of a walking aid on disability, oxygenation, and breathlessness in patients with chronic airflow limitation. J Cardiopulm Rehabil. 1996; 16: 63-7.
13. Solway S, Brooks D, Lau L, Goldstein R. The short term effect of a rollator on functional exercise capacity among individual severe COPD. Chest. 2002; 122: 56-65.
14. 14. Roul G, Germain P, Bareiss P. Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? Am Heart J. 1998; 136: 449-57.

15. Mongkol S, Chaypech C, Pattanawong F, Thaithanee P, Suthasuwan A, Wongkokum P, et.al. Comparison of six minute walk distance and reaction time between anemic COPD and non-anemic COPD. Bull Chiang Mai Assoc Med Sci 2013; 46: 207-14
16. World Health Organization. Nutritional anemia: report of a WHO Scientific Group. Geneva: Switzerland; 1968.
17. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardizations of spirometry. Eur Respir J. 2005; 26: 316-38.
18. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J. 2007; 29: 923-9
19. Topp R, Ditnyer M, King K. Doheyty K. Hornyak J. The effect of bed rest and potential of rehabilitation on patients in the intensive care unit. AACN Clinical Issues. 2002.; 13: 263-76
20. Siverberg DS, Wexler D, Iaina A, Steinbruch S, Wollman Y. Schwartz D. Anemia, chronic renal disease and congestive heart failure the cardio renal anemia syndrome: the need for cooperation between cardiologist and nephrologists. Int Erol Nephrol. 2006; 38: 295-310
21. Ozalevli S, Ozden A, Itil O, Akkoclu A. Comparison of the Sit-to-Stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease. Respir Med. 2006; 101: 286-93.
22. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and Inflammation in COPD. Chest. 2005; 127: 825-9..
23. Mayhew M. Anemia of chronic disease in the elderly. JNP. 2006; 2: 261-7.