Adam Nowiński[1], Dariusz Kamiński[1], Marek Kram[2], Damian Korzybski[1], Anna Stokłosa[1], Dorota Górecka[1]

[1]2nd Department of Respiratory Diseases
Head: Prof. D. Górecka MD, PhD
[2]Physiotherapy Department
Head: M. Kram Msc.
National Tuberculosis and Lung Diseases Research Institute, Warsaw

Impact of mild anaemia on dyspnoea during exertion and exercise tolerance in patients with acute exacerbation of chronic obstructive pulmonary disease

Wpływ łagodnej niedokrwistości na duszność wysiłkową u chorych z zaostrzeniem przewlekłej obturacyjnej choroby płuc

The authors declare no financial disclosure.

Abstract

Introduction: Dyspnoea and decreased exercise tolerance are symptoms of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Anaemia is a risk factor for reduced functional capacity and dyspnoea in stable COPD. There is limited information about the impact of anaemia on functional capacity and dyspnoea of patients during AECOPD. The aim of this study was to evaluate the impact of decreased blood haemoglobin concentration on the results of six-minute walking test (6MWT) in patients during AECOPD.

Material and methods: A post hoc analysis of data collected from prospective long-term studies on AECOPD. Haemoglobin concentration from the first obtainable hospital measurement were included in the assessment. 6MWT was performed after clinical improvement of the patient. Dyspnoea at baseline and after exercise and oxygen saturation (SpO$_2$) during exercise was measured. Results: (presented as means ± SD): 402 patients with exacerbation of COPD (COPD stage 3.5 ± 0.6) were examined. Patients with anaemia (26% of those studied, age 74.5 ± 8.2 years) achieved 258.1 ± 125.1 m during 6MWT, with exertional desaturation of 2.9 ± 2.6%. Patients without anaemia (74% of those studied, age 70.2 ± 8.7 years) achieved 271 ± 136.0 m during 6MWT with exertional desaturation of 3.8 ± 3.7%. The haemoglobin concentration did not correlate with 6MWT, dyspnoea during 6MWT, or exercise oxygenation and blood desaturation during exercise.

Conclusion: Mildly decreased blood haemoglobin concentration did not influence the results of 6MWT in patients with AECOPD.

Key words: COPD, anaemia, exercise test, dyspnoea

Pneumonol. Alergol. Pol. 2013; 81: 200–206

Streszczenia

Wstęp: Duszność i zmniejszenie tolerancji wysiłku są objawami zaostrzenia przewlekłej obturacyjnej choroby płuc (POChP). Niedokrwistość stanowi czynnik ryzyka obniżonej tolerancji wysiłku i duszności w stabilnej POChP. Mało jest danych na temat wpływu niedokrwistości na tolerancję wysiłku i duszność u chorych z zaostrzeniem POChP. Celem pracy była ocena wpływu obniżonego stężenia hemoglobiny we krwi na wyniki 6-minutowego testu chodu (6MWT) u pacjentów w trakcie zaostrzenia POChP.

Materiał i metody: Retrospektywna analiza danych zebranych w trakcie badania u chorych z zaostrzeniem POChP. Do oceny wykorzystano pierwsze dostępne oznaczenia stężenia hemoglobiny, wykonane w trakcie hospitalizacji. 6MWT wykonano po uzyskaniu poprawy klinicznej pacjenta. Nasilenie duszności oceniano przed oraz po 6MWT. W trakcie 6MWT mierzono saturację krwi tlenem (SpO$_2$).

Adres do korespondencji: Adam Nowiński MD, PhD, 2nd Department of Respiratory Diseases, ul. Płocka 26, 01–138 Warszawa, Tel. +48 22 431 21 84, e-mail: a.nowinski@igichp.edu.pl

Wyniki: Zbadano 402 pacjentów z zaostrzeniem POChP (średnie stadium wg PTChP 3,5 ± 0,6). Chorzy z niedokrwistością (26% zbadanych, wiek średni 74,5 ± 8,2 roku) w teście chodu pokonali 258,1 ± 125,1 m, z desaturacją wysiłkową na poziomie 2,9 ± 2,6%. Chorzy bez niedokrwistości (74% zbadanych, wiek średni 70,2 ± 8,7 roku) w teście chodu pokonali 271 ± 136 m, z desaturacją wysiłkową na poziomie 3,8 ± 3,7%. Stężenie hemoglobiny nie korelowało z 6MWT, dusznością po 6MWT, saturacją w trakcie wysiłku i desaturacją krwi po wysiłku.
Wnioski: Łagodnie obniżone stężenie hemoglobiny we krwi nie wpływało na wyniki 6MWT u pacjentów z zaostrzeniem POChP.

Słowa kluczowe: POChP, niedokrwistość, test wysiłkowy, duszność

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases worldwide, and its incidence is constantly rising [1]. Dyspnoea is one of the main disease symptoms, with primary presentation exclusively during exertion [2]. Exertional dyspnoea occurs usually after longstanding disease course, when progressing airflow limitation has become irreversible, and forced expiratory volume at one second (FEV1) is about 50% of the expected value [2]. Disturbances in respiratory mechanics are the main cause of dyspnoea in COPD. These are due to restricted airflow within the respiratory tract (obturation) and hyperinflation of lung parenchyma, leading to air trapping phenomena. Marked hyperinflation during physical exertion, also referred to as "dynamic hyperinflation", is currently believed to represent the main pathogenetic mechanism of developing exertional dyspnoea [3]. Chronic obstructive pulmonary disease is an inflammatory process, with occurrence of many systemic symptoms and signs and frequent coincidence of other diseases. The latter include, among others, anaemia and progressive cachexia, caused mainly by loss of muscle mass [4]. Anaemia in patients with COPD is of the chronic disease type, most likely deriving from a long-lasting systemic inflammatory condition.

The impact of low haemoglobin concentration on dyspnoea in patients with COPD was investigated in the search for possible therapeutic interventions in this population. One of these studies concerned patients with stable disease, in whom decreased haemoglobin concentration correlated with increased dyspnoea reported by the patients [5]. There are, however, no reports in the literature concerning the influence of anemia on the exertional dyspnoea and exercise tolerance, during COPD exacerbation.

Aim

The aim of the presented study was to evaluate the potential impact of low haemoglobin concentration in the blood of patients with COPD exacerbation upon exertional dyspnoea and on the results of six-minute walking test (6MWT).

Material and methods

The study was based on post hoc analysis of the results of functional tests collected on a prospective basis as part of a single centre study, focusing on predictive factors in COPD. Tests were performed in patients with COPD exacerbation, hospitalized in the 2nd Department of Respiratory Diseases of the National Tuberculosis and Lung Diseases Research Institute. Diagnostic criteria of COPD were adopted from the guidelines published by PTChP (Polish Society for Lung Diseases) [2]. Excluded from the study were patients in whom 6MWT and spirometry could not be performed. In all the included subjects, diagnostic tests were performed, including morphological analysis of peripheral blood, 6MWT with assessment of exertional dyspnoea according to the pending guidelines [6], and spirometry. Test results were collected on a prospective basis. As spirometry was performed during regression of disease exacerbation, usually a couple of days after admission to hospital, the results did not reflect true values of lung volume in the analysed patients. Spirometry results were therefore not included in the final statistical analysis. Nevertheless, patient stratification according to the disease severity could be performed based on the obtained results of forced expiratory volume in one second (FEV$_1$), measured after inhalation of a broncholytic agent. The analysed parameters included haemoglobin concentration in peripheral blood, as well as blood gas analysis performed in arterialized venous blood, both sampled directly on admission. Forty-one of the studied patients with COPD had longstanding oxygen therapy at home. Those included persons with reduced blood haemoglobin level (2 patients) and subjects with normal haemoglobinaemia (20 persons). It was initially planned that patients remaining on oxygen therapy should not be included in final analysis, since this therapeutic modality affects tolerance

to physical activity in COPD. However, data concerning these subjects were finally included in the study, as tolerance of exertion is influenced not only by oxygen therapy but also by numerous other factors, including patient age, fitness, body mass, or concomitant diseases. Separate analysis of data concerning patients on oxygen therapy was not possible due to the low number of these subjects.

Six-minute walking test (6MWT) was performed several days after admission to hospital, when major symptoms and signs of disease exacerbation were under control, and the patient was clinically stable. The test was performed in a 50-meter-long corridor. Classification of perceived dyspnoea developed by Borg [7] was used for assessment of shortness of breath at rest, exertional dyspnoea, and feeling of dyspnoea after completion of the test. Continuous percutaneous measurement of peripheral blood saturation, and heart rate, was performed using a portable pulseoximeter during the entire 6MWT. Patients requiring oxygen therapy in hospital were breathing oxygen provided at the same flow rate as before the test or increased by 0.5–1 litre per minute, according to the orders of their treating physician. In both studied patients groups there were similar percentages of patients requiring oxygen therapy. These patients were not excluded from final analysis and no separate analysis was performed in this subpopulation as the low patient number and the overall study aim were considered. Based on the results of haemoglobin concentration analysis in peripheral blood, anaemia was diagnosed according to the respective World Health Organisation (WHO) criteria [8]. Anaemia was assigned when haemoglobin concentration was below 12 g/dL in women and below 13 g/dL in men.

Statistical analysis

Statistical analysis was performed using SigmaPlot 11 software (USA). Basic descriptive parameters were compared between the groups of patients with low haemoglobin concentration or with normal haemoglobinaemia. Descriptive statistical data are presented in tables as mean and standard deviation values. For comparisons between the groups, Student's t-test or Mann-Wilcoxon rank sum test were used, depending on the normal or non-normal distribution of parameters. The relative numbers of patients in groups were analysed using the chi square test. A statistical significance level was adopted for $p < 0.05$. Analysis of linear regression was performed for assessment of relationships between functional parameters and haemoglobin levels in peripheral blood.

Results

The entire analysed study population included 464 patients, of which 62 were excluded due to lack of complete data. Final analysis included data concerning 402 patients, including 165 women (41%) and 237 men (59%), for whom complete clinical and laboratory data were available.

Mean haemoglobin concentration in the studied patient group was 14.0 ± 1.7 g/L, and mean haematocrit was 43.5 ± 5.7. Decreased haemoglobin concentration was found in 104 patients (26% of all subjects).

Basic patient characteristics are presented in Table 1.

There were 54% women in the patient group with low haemoglobin levels, and 47% in the group with normal haemoglobin concentration; the diffe- rence was not statistically significant. These two groups did not differ according to disease severity classified according to PTChP. Patients with anaemia had significantly higher partial oxygen pressure in the arterialized venous blood.

Patients with COPD who had low haemoglobin concentration were significantly older (74.5 ± 8.2 years) than subjects with normal haemoglobin levels (70.2± 8.7 years). Patients with anaemia also had lower haematocrit as compared to patients with normal haemoglobin concentration, with respective median values of 37.3% (35.7–39.1%) and 44.9% (42.6–48.4%); $p < 0.001$.

Results of the 6MWT are presented in Table 2.

Decreased haemoglobin concentration in COPD patients did not affect the results obtained in the six-minute walking test. Patients with COPD and anaemia walked a similar distance during the test as persons with normal haemoglobin concentration.

Low haemoglobin levels in the investigated patients did not significantly contribute to a feeling of breathlessness. A similar degree of dyspnoea was reported by patients in both groups before the test, with increasing shortness of breath after exertion, though with no major differences between the groups. Patients with anaemia had significantly higher oxygen blood saturation (SpO2) before the test and less decrease of SpO2 on exertion as compared to subjects with normal haemoglobin levels.

Analysis of linear regression revealed no correlation between dyspnoea arising on exertion or dyspnoea increase in Borg scale and blood haemoglobin concentration (correlation coefficient = 0.0687, standard error = 0.0638, t = −1.077, p = 0.282).

The greatest percentage of patients with anaemia was observed in the group with stage II COPD (35%). Fewer patients with more severe COPD

Table 1. Patient characteristics in the study population

Variable	Patients with low haemoglobin concentration (%)	Patients with normal haemoglobin concentration (%)	p value
Number of patients (n = 402)	104 (26%)	298 (74%)	$p < 0.001$
Sex (M/F)	Men (M) 48 46%	Men (M) 189 63%	$p = 0.108$
	Women (F) 56 54%	Women (F) 109 47%	
Age (years)	74.5 ± 8.2	70.2 ± 8.7	$p < 0.001$
Haemoglobin concentration (g/dL)	11.9 ± 0.9	14.8 ± 1.3	$p < 0.001$
FEV1 (L)	0.96 ± 0.52	0.94 ± 0.48	$p = 0.721$
FEV1 (% of the predicted value)	35.6 ± 16.8	34.8 ± 19.6	$p = 0.711$
PaO2 (mm Hg)	63.3 ± 13.8	60.2 ± 11.9	$p = 0.023$
PaCO2 (mm Hg)	45.6 ± 10.7	47.0 ± 10.6	$p = 0.258$
pH	7.399 ± 0.217	7.370 ± 0.270	$p = 0.348$

Table 2. Six-minute walking test results in patients with COPD by haemoglobin concentration

Variable	Patients with low haemoglobin concentration	Patients with normal haemoglobin concentration	p value
6MWT distance (m)	258.1 ± 125	271.3 ± 136.0	$p = 0.389$
SpO2 before 6MWT (%)	94.6 ± 2.2	93.9 ± 3.1	$p = 0.048$
Desaturation (ΔSpO2,%)	$2.9 \pm 2.6\%$	$3.8 \pm 3.7\%$	$p = 0.048$
Dyspnoea before 6MWT (according to Borg scale)	0.4 ± 0.9	0.5 ± 1.0	$p = 0.513$
Dyspnoea after 6MWT (according to Borg scale)	2.5 ± 2.5	2.2 ± 2.4	$p = 0.309$
Dyspnoea Δ (dyspnoea increase; according to Borg scale)	2.1 ± 2.3	1.7 ± 2.2	$p = 0.154$

were anaemic (28% subjects with stage III, 13% of patients with stage IV disease) (Tab. 3).

Percentage of patients with COPD and anaemia increased with patients' age (Fig. 1). Pearson correlation analysis showed a strong relationship between age and haemoglobin concentration (R = −0.23; p = 0.00000613).

Discussion

The presented study confirms that low haemoglobin concentration, a crucial sign of anaemia, is a common phenomenon in patients with COPD. However, the definition of anaemia in this population and threshold levels of blood haemoglobin concentration should be reconsidered. The World Health Organisation criteria of anaemia [8] applied in this study are often used in epidemiological studies, thanks to their simplicity and availability

of numerous reference publications. The application of WHO criteria permits comparison of the incidence of anaemia in various populations and enables the assessment of the worldwide prevalence of this aberration. Studies based on the WHO definition of anaemia estimate that in Europe 8% of persons over 60 years of age (i.e. of similar age as the patients described in the presented study) are anaemic. American data state that as many as 10.6% of elderly persons have low haemoglobin concentration [9]. The percentage of patients with stable COPD and anaemia reported by Chambellan et al. [10] was higher (12%). The presented analysis does not fulfill criteria of an epidemiological study, and it was performed in a exertional dyspnoea, and is widely used in exercise tests. This scale was developed by Borg [7] and is applied in the presented study. The timing of the exercise test should also be mentioned here. The current study concerned

Table 3. Patients with COPD and anaemia or normal haemoglobin concentration by COPD severity

Patients with respective COPD stages according to PTChP	Patients with low haemoglobin concentration	Patients with normal haemo-globin concentration	p value
Stage I, n = 0	n = 0	n = 0	
Stage II, n = 31	n = 11 (35%)	n = 20 (65%)	p < 0.001
Stage III, n = 125	n = 35 (28%)	n = 90 (72%)	
Stage IV, n = 216	n = 29 (13%)	n =187 (87%)	
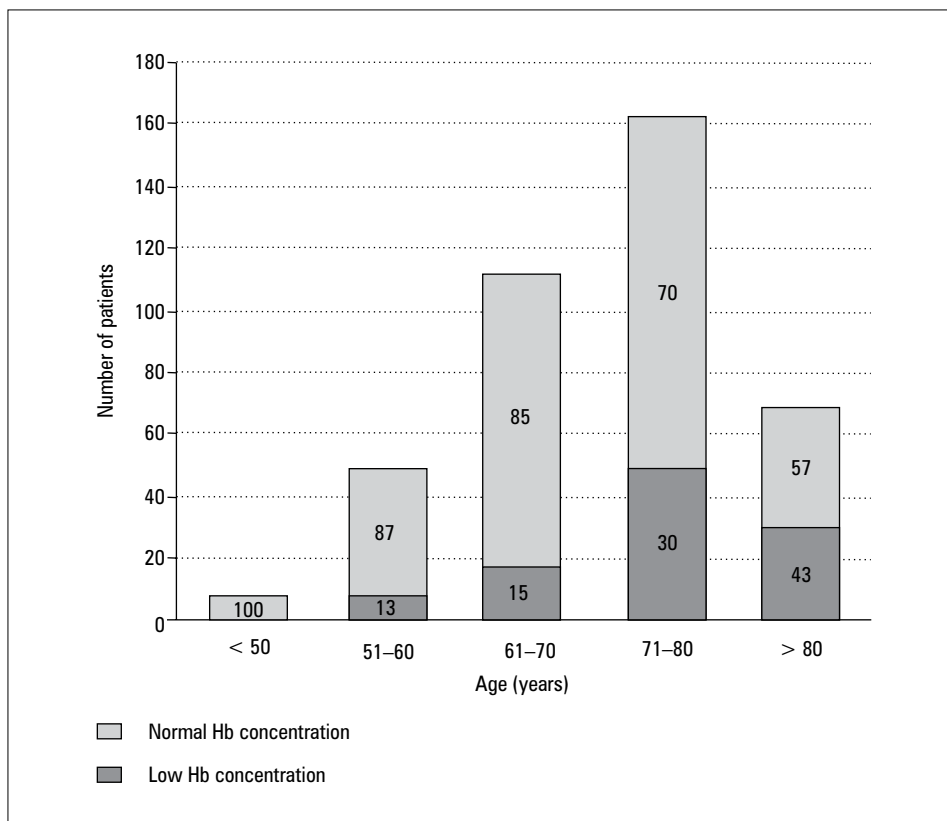
Figure 1. Patients with COPD and anaemia or normal haemoglobin concentration by age groups

patients hospitalised due to exacerbation of COPD. Exercise tests were not performed on the day of patient admission, due to clinical concerns, but were carried out after several days of treatment. However, as each COPD exacerbation is a process lasting usually for over 10 days, it can be stated that six-minute walking tests were actually performed during the disease exacerbation phase in the analysed patients [12].

Severe anaemia causes clinically notable dyspnoea due to tissue hypoxia, compensatory tachycardia, and tachypnoea. In cases of COPD exacerbation, anaemia is not a major cause of breathlessness and other causes population of patients experiencing a particular event in the course of the disease (exacerbation of COPD). However,

a significant amount of patients (26%) in the studied population had signs of anaemia.

The main aim of the presented study was to search for potential correlations between anaemia in patients with COPD and dyspnoea, as well as tolerance to physical exercise. The assessment of patient-reported shortness of breath most often refers to the MRC scale [11], which is easy to use and reproducible. This scale can be used for evaluation of dyspnoea over a longer period of time (e.g. a week or a month). Another scale is better suited for investigation of exertional dyspnoea, and is widely used in exercise tests. This scale was developed by Borg [7] and is applied in the presented study. The timing of the exercise test should also be mentioned here. The current study

concerned patients hospitalised due to exacerbation of COPD. Exercise tests were not performed on the day of patient admission, due to clinical concerns, but were carried out after several days of treatment. However, as each COPD exacerbation is a process lasting usually for over 10 days, it can be stated that six-minute walking tests were actually performed during the disease exacerbation phase in the analysed patients [12].

Severe anaemia causes clinically notable dyspnoea due to tissue hypoxia, compensatory tachycardia, and tachypnoea. In cases of COPD exacerbation, anaemia is not a major cause of breathlessness and other causes of dyspnoea play more important roles in the development of this symptom [3].

There are few studies published on the effect of anaemia on exercise tolerance in patients with COPD. Cote et al. studied patients with stable COPD and observed that the presence of anaemia affects, in general, the feeling of breathlessness measured in the MRC scale [5]. However, these authors did not analyze particularly dyspnoea on exertion, measuring only the general feeling of dyspnoea. Their conclusion was that anaemia decreases tolerance of exercise measured in 6MWT. However, there was no such correlation in the presented study. Discrepant results of the two studies can possibly be explained by the timing of patient assessment, since in the presented study dyspnoea was analysed during episodes of COPD exacerbation, whereas Cote and al. analysed patients with stable disease. It may therefore be implied that therapeutic intervention of compensating anaemia in order to decrease the feeling of dyspnoea, as proposed by Cote and al., may not have any major effect in the treatment of COPD exacerbations.

The differences between the groups in partial oxygen pressure of arterialized venous blood and blood oxygen saturation measured percutaneously also require some attention. Patients with normal haemoglobin concentration had significantly lower partial oxygen pressure and oxygen blood saturation before the exercise test, despite the fact that the percentage of patients on oxygen therapy was similar in both studied groups. This finding may be explained by some of the methodological limitations of the presented study. Saturation was measured in the standard way, by blood gas analysis and by percutaneous assessment of oxygen blood saturation (SpO_2). The lower amount of circulating haemoglobin in patients with anaemia was probably oxygenated more quickly in the lungs, thus producing higher oxygen saturation levels measured percutaneously. At the same time, lower oxygen absorption by haemoglobin resulted in the increase of oxygen amount dissolved in plasma, causing increased PaO_2.

The highest percentage of anaemic patients was found in the group with stage II COPD. In order to explain this mechanism, further studies would be necessary, including assessment of inflammation parameters. Most recent publications emphasise that anaemia in patients with COPD is of the chronic disease type, due to a systemic inflammatory process or, less likely, because of disturbed iron metabolism [13].

In the presented study there was no correlation between low haemoglobin concentration, exertional dyspnoea, and blood oxygen saturation measured percutaneously on exertion. However, anaemia correlated with patient age, which is in accordance with observations published by Guralnik [9], who noted a much higher incidence of anaemia in elderly patients.

To sum up, the presented study suggests that the mild decrease in haemoglobin concentration observed in some patients with COPD is not a major cause of increasing dyspnoea and decreased exercise tolerance during disease exacerbations

Conclusions

Patients with COPD and a mild decrease in haemoglobin concentration did not experience more dyspnoea on exertion during disease exacerbations as compared to patients with normal haemoglobin levels. Similarly, anaemia did not significantly contribute to shorter walking distance in 6MWT in patients with COPD exacerbation. Patients with COPD and anaemia were significantly older than subjects having normal haemoglobin concentration according to WHO criteria.

Conflict of interests

The authors declare no conflict of interest.

References

1. Jemal A., Ward E., Hao Y., Thun M. Trends in the leading causes of death in the United States, 1970–2002. JAMA 2005; 294: 1255–1259.
2. Pierzchała W., Barczyk A., Górecka D., Śliwiński P., Zieliński J.: Zalecenia Polskiego Towarzystwa Chorób Płuc rozpoznawania i leczenia przewlekłej obturacyjnej choroby płuc (POChP). Pneu- monol. Alergol. Pol. 2010; 78: 318–347.
3. O'Donnell D.E., Webb K.A. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2001; 164: 770–777.
4. Antonelli-Incalzi R., Fuso L., De Rosa M. et al. Co-morbidity con- tributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur. Respir. J. 1997; 10: 2794–2800.

5. Cote C., Zilberberg M.D., Mody S.H., Dordelly L.J., Celli B. Ha- emoglobin level and its clinical impact in a cohort of patients with COPD. Eur. Respir. J. 2007; 29: 923–929.
6. ATS Statement Guidelines for the Six-Minute Walk Test. Am. J. Respir. Crit. Care Med. 2002; 166: 111–117.
7. Borg G.A. Psychophysical bases of perceived exertion. Med. Sci. Sports. Exerc. 1982; 14: 377–381.
8. World Health Organization. Nutritional anemias: report of WHO scientific group. WHO Technical Report Series 405, Geneva,World Health Organization, 1968; 1–37.
9. Guralnik J.M., Ershler W.B., Schrier S.L., Picozzi V.J. Anemia in the elderly: a public health crisis in hematology. Hematology. Am. Soc. Hematol. Educ. Program 2005; 528–532.
10. Chambellan A., Chailleux E., Similowski T. ANTADIR Observatory Group. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. Chest 2005; 128: 1201–1208.
11. Bestall J.C., Paul E.A., Garrod R., Garnham R., Jones P.W., Wedzicha J.A. 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.
12. Aaron S., Donaldson G., Whitmore G., Hurst J., Ramsay T., Wedzicha J. Time course and pattern of COPD exacerbation onset. Thorax 2012; 67: 238–243.
13. Barnes P.J., Celli B.R. Systemic manifestations and comorbidities of COPD. Eur. Respir. J. 2009; 33: 1165–1185.