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КЛИНИКО-ФУНКЦИОНАЛЬНАЯ ОЦЕНКА ДЕСАТУРАЦИИ ГЕМОГЛОБИНА ПО КИСЛОРОДУ ПРИ НАГРУЗОЧНОМ ТЕСТЕ С 6-МИНУТНОЙ ХОДЬБОЙ У БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ

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Clinic-Functional Assessment of Hemoglobin Desaturation by Oxygen in 6-Minute Walk Test Among Patients with Bronchial Asthma

Резюме

Цель — оценить распространённость и клиническое значение феномена десатурации гемоглобина при нагрузочном тесте с 6-минутной ходьбой у больных бронхиальной астмой. Материалы и методы: обследовано 75 больных с обострением аллергической (n=39, 52 %) и смешанной (n=36, 48 %) бронхиальной астмы. Всем пациентам проводили физикальное обследование, спирометрию, СО-метрию выдыхаемого воздуха для определения HbCO, транскутанную 2-волновую пульсоксиметрию (в покое и при проведении 6-минутного нагрузочного теста) со спектральным анализом и коррекцией на уровень карбоксигемоглобина. 6-минутный тест проводили после купирования обострения бронхиальной астмы (перед выпиской из стационара), оценивая desaturation-distance ratio — отношение площади кислородной десатурации гемоглобина к пройденной дистанции и O₂-GAP index — потребность в дополнительном потоке кислорода для поддержания SpO₂ на уровне ≥88 % при проведении теста с 6-минутной ходьбой, а также динамику усталости и диспноэ до и после нагрузочного теста. У курящих больных астмой (n=36, 48 %) оценивали индекс курильщика по показателю пачка/лет. В зависимости от результатов оксиметрии во время 6-минутного теста пациентов разделили на «десатураторов» (n=28, 37 %) и «недесатураторов» (n=47, 63 %). Результаты. Оказалось, что десатурация гемоглобина по кислороду, выявленная по снижению SpO₂ ниже 90 % в ходе выполнения теста с 6-минутной ходьбой, ассоциирована с тяжестью обострения данного заболевания, более выраженными нарушениями лёгочной вентиляции и оксигенации крови и потребностью в более длительной госпитализации. Распространённость табакокурения и индекс курильщика в обеих группах были идентичными, однако у «десатураторов» мы обнаружили более высокую распространённость сочетания бронхиальной астмы и ХОБЛ по сравнению с «недесатураторами». У «десатураторов» были выявлены достоверно более высокий уровень десатурационно-дистанционного отношения и повышенная потребность в дополнительном потоке кислорода для поддержания SpO₂ на уровне ≥88 % при проведении теста с 6-минутной ходьбой, что свидетельствует о более высокой «кислородной цене» поддержания физической работоспособности. Заключение. Таким образом, высокая распространённость феномена десатурации гемоглобина по кислороду во время 6-минутного нагрузочного теста у больных бронхиальной астмой и ассоциированные с ним клиничко-функциональные нарушения подтверждают целесообразность и клиническую значимость проведения нагрузочного теста с 6-минутной ходьбой не только пациентам с ХОБЛ, но и больным бронхиальной астмой.

Ключевые слова: бронхиальная астма, 6-MWT: «десатураторы» и «недесатураторы», desaturation-distance ratio, O₂-GAP index

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Abstract

The main purpose of the study is to assess the prevalence and clinical significance of hemoglobin desaturation by oxygen during the 6-minute walk exercise test in patients with bronchial asthma. Material and methods: 75 patients with exacerbation of mixed (48 %) and allergic (52 %) bronchial asthma were examined. Research explored following methods: collecting complaints and anamnesis, physical examination, spirometry, CO-metry of exhaled air to determine carboxyhemoglobin, transcutaneous 2-wave pulse oximetry (at rest and during 6-minute walk exercise test) with spectral analysis and correction for COHb. 6-minute walk exercise test was performed after relief of asthma exacerbation (before discharge from the hospital), assessing the desaturation-distance ratio (the ratio of the area of oxygen desaturation of hemoglobin to the 6-minute walk exercise test distance), O₂-GAP index, the dynamics of fatigue and dyspnea before and after 6-minute walk exercise test. In smoking patients (n=36, 48 %), the smoker index was calculated. Based on oximetry results during the 6-minute walk exercise test, patients were divided into "desaturators" (n=28, 37 %) and "non-desaturators" (n=47, 63 %). Results. The findings of the research illustrated that hemoglobin desaturation by oxygen, detected by reducing SpO₂ to <90 % during 6-minute walk exercise test, was associated with the severity of this disease exacerbation, more pronounced impairment of pulmonary ventilation and blood oxygenation, and the demand for longer hospitalization. The prevalence of tobacco smoking and the magnitude of the smoker index in both groups were identical but in "desaturators" we found a higher prevalence of the combination of asthma and COPD compared to "non-desaturators." The "desaturators" had significantly higher level of desaturation-distance ratio and increased demand for additional oxygen flow to maintain SpO₂ at ≥88 % during a 6-minute walk test, which indicates a higher "oxygen price" of physical activity in this group of patients. Conclusion. Thus, the high prevalence of the phenomenon of hemoglobin oxygen desaturation during 6-minute walk exercise test in patients with asthma and associated clinic-functional disorders supports the feasibility and clinical significance of conducting a stress test with a 6-minute walk not only in COPD patients, but also in bronchial asthma patients.

Key words: bronchial asthma, 6-MWT: "desaturators" and "non-desaturators", desaturation-distance ratio, O₂-GAP index

Conflict of interests

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BA — bronchial asthma; COPD — chronic obstructive pulmonary disease; 6-MWT — 6-minute walking test; DDR — desaturation-distance ratio at 6-MWT; SpO₂, % — hemoglobin oxygen saturation, measured transcutaneously; HbCO, % — carboxyhemoglobin; O₂-GAP index — demand for additional oxygen flow to maintain SpO₂ at ≥88 % during a 6-minute walk test; FEV₁ — forced expiratory volume in 1 second; VC and FVC — vital and forced vital capacity of the lungs; FEV₁/FVC — Gensler index; IBM/FG — ipratropium bromide monohydrate/fenoterol hydrobromide; Q25, Q75 — upper and lower quartiles

Introduction

In pulmonology, the 6-minute walking test (6-MWT) is actively used in patients with chronic obstructive pulmonary disease for the assessment of their physical capability and prognosis. Not only the distance walked is analysed, but also blood oxygenation, because some patients have oxygen desaturation of haemoglobin. Oxygen desaturation of haemoglobin during 6-MWT means reduction in oxygen saturation (SpO₂) of haemoglobin below 90 % or reduction in SpO₂ by ≥ 4 % vs. baseline oxidized hemoglobin values at rest before the 6-minute walking test [1].

It has been shown that, in patients with chronic obstructive pulmonary disease (COPD), oxygen desatu-

ration of haemoglobin during 6-MWT has negative prognostic value of mortality, rate of complications, rate of pulmonary function reduction, and lean body mass [2]. COPD patients with desaturation during 6-MWT had a two-fold increase in the risk of mortality; the risk of moderate and severe exacerbations of this disease was 1.5 times higher; the rate of pulmonary function reduction was twice as high and was associated with many-fold increase in the risk of lean body mass reduction [1-3]. A number of studies identified an inverse relationship between the ratio of the area of oxygen desaturation of haemoglobin to the distance walked during 6-MWT and such clinical and functional parameters as forced expiratory volume in 1 second (FEV₁) and transfer factor [4].

Physical exercise is known to be one of the risk factors of bronchial asthma (BA). In 2020, a study was performed in Italy to identify a clinically significant minimal change in the distance during 6-MWT in patients with BA undergoing rehabilitation [5]. Besides, some smokers can have bronchial asthma alongside COPD, and the golden standard to diagnose this condition is to perform 6-MWT.

Therefore, the study of the incidence as well as clinical and functional consequences of oxygen desaturation of haemoglobin during the 6-minute walking test in patients with BA is relevant. The purpose of this paper is to assess the incidence and clinical significance of oxygen desaturation of haemoglobin during the 6-minute walking test in patients with bronchial asthma.

Materials and Methods

We examined 75 patients with exacerbated allergic (n = 39; 52 %) and mixed (n = 36; 48 %) bronchial asthma, who were undergoing inpatient treatment for disease exacerbation. Exclusion criteria: contraindications for 6-MWT; inability to take the 6-minute walking test [6]; pneumonia; life-threatening exacerbated BA; uncontrolled arterial hypertension; diabetes mellitus with off-target HbA1c levels.

Diagnosis and therapy followed 2021 Bronchial Asthma Clinical Guidelines [7]. Bronchodilators with a fixed combination of ipratropium bromide monohydrate/fenoterol hydrobromide (IBM/FH) were used mainly in the form of nebulisation of respective solutions; also, system glucocorticosteroids were used in generally accepted dosages. Besides, during the inpatient therapy, desaturators and non-desaturators continued

inhaled glucocorticosteroids or their combination with the highest doses of long-acting β_2 -agonists.

Desaturators (n = 28; 37 %) included patients with SpO_2 reduction to < 90 % during 6-MWT. All other patients with blood oxygenation of over 90 % during the 6-minute walking test were non-desaturators (n = 47; 63 %). Detailed clinical characteristics of patients are presented in Table 1.

Unlike non-desaturators, desaturators had severe BA exacerbation significantly more often; at the same time, age, male/female ratio, eosinophilia levels in induced sputum and the rate of comorbidities in both groups were similar ($p > 0.05$).

All patients underwent a physical examination, measurement of CO in exhaled air in order to calculate carboxyhaemoglobin levels based on expiratory carbon oxide (Micro CO-monitor, UK); respirometry and transcutaneous dual-frequency pulseoximetry at rest and during 6-MWT (Spirodok SpO_2 , Italy). 6-MWT was performed after arresting exacerbated BA (before discharge), taking into account generally recognised absolute and relative contraindications [6]. During 6-MWT, the distance walked was measured; changes in fatigue and shortness of breath before and after the test were analysed; blood oxygenation was measured and adjusted for carboxyhaemoglobin (HbCO) values; DDR was evaluated using the following formula:

$$DDR = \frac{DA (\%) }{Distance (m) },$$

where *DA* is desaturation area, *Distance* is distance walked during 6-MWT; as well as desaturators' need in additional oxygen to maintain SpO_2 at ≥ 88 % during the 6-minute walking test (O_2 -GAP index) [8].

Table 1. Clinical characteristics of bronchial asthma patients

Parameters	«Desaturators»	«Non-desaturators»
Age, years	50,9±1,87	55,0±2,18
M/W	15/13	24/23
BMI, kg/ m ²	29,4±1,3	28,7±0,92
Height, m	1,7±0,02	1,7±0,01
Allergic bronchial asthma, n(%)	14 (50)	25(53)
Mixed bronchial asthma, n(%)	14 (50)	22(47)
Moderate exacerbation of BA, n(%)	6(21)*	26(55)
Severe exacerbation of BA, n(%)	22(79)*	21(45)
Eosinophilia of sputum, n(%)	3(12)	6(13)
Arterial hypertension, n(%)	16(57)	31(66)
Obesity, n(%)	9(32)	14(29)
Angina pectoris II functional class, n(%)	10(37)	13(27)

Note: BA — bronchial asthma; * — probability of α -error = 0,009 when comparing the prevalence of moderate and severe exacerbations of asthma (Chi-square test with Yates' correction); BMI (BMI) — body mass index; M/W (M/W) — ratio of men to women

In order to adjust the results of blood oxygenation monitoring based on HbCO, we used a proprietary developed application [9]. Statistical processing was performed using Statistica 13.3 software. Mann — Whitney U test, χ^2 (Yates corrected, if necessary) or two-tailed Fisher's exact test were used. Depending on the distribution type, quantitative data are presented as $M \pm m$ or $Me[Q_{25}-Q_{75}]$. The differences between the analysed values and their changes were significant at α -error probability of < 0.05 .

Results and Discussion

The key results of the 6-minute walking test are presented in Table 2.

Distance walked, degree of shortness of breath and fatigue, systolic and diastolic blood pressure (SYS; DIA) before and during 6-MWT in the study group and controls did not have any significant difference. However, after an additional physical stress, desaturators demonstrated more pronounced tachycardia ($p < 0.03$). **The “oxygen cost” (an author-created term) of the similar (same as for non-desaturators) distance in desaturators was significantly higher** and was confirmed with comparison of blood oxygenation levels and changes in haemoglobin oxygen saturation during 6-MWT in both groups. It is worth noting that both SpO_2 value during 6-MWT (an attribute used to form the groups) and baseline blood oxygenation levels were low. Moreover,

a higher “oxygen cost” of physical stress in desaturators vs. controls is confirmed by a higher desaturation/distance ration (DDR) and desaturators’ need in additional oxygen to maintain SpO_2 of $\geq 88\%$ during 6-MWT. Non-desaturators did not require additional oxygen. Thus, when walking the same distance during 6-MWT, desaturators required higher activity of the cardiovascular system; also, patients needed additional oxygen to maintain an adequate SpO_2 level ($\geq 88\%$).

During the next stage of the study, we compared pulmonary ventilation upon admission to the inpatient unit and before discharge. Both groups demonstrated bronchial tree obstruction (desaturators — severe, non-desaturators — moderate) in combination with reduced vital and forced vital lung capacity (VLC; FVLC), as well as Gensler index, since in obstruction, VLC and specifically FVLC can decrease [10-11]. The degree of pulmonary ventilation obstruction and the rate of FVLC reduction were significantly higher in desaturators vs. non-desaturators, correlating with a higher incidence of severe exacerbations and more severe obstruction in the main group (Table 3).

The therapy had proven positive impact on the status of lung ventilation in both groups, and the baseline difference in key parameters of pulmonary function disappeared. Improved lung ventilation in desaturators was achieved mainly due to a longer inpatient therapy, which was 13.3 ± 0.77 days vs. 11.4 ± 0.35 days in controls ($p = 0.031$).

Table 2. Main results of 6-minute walking test

Parameters, $M \pm m$ or $Me[Q_{25}; Q_{75}]$	«Desaturators»		«Non-desaturators»		p	
	Initially	6-MWT	Initially	6-MWT	1	2
Distance, m	396,4 $\pm$ 12,41		402,8 $\pm$ 13,80		0,325	
Distance, %	73,3 $\pm$ 2,36		71,9 $\pm$ 3,17		0,736	
Dispnoea	0,5[0,5-1,5]	4,0[3,0-5,0]*	0,5[0,5-1,0]	3,0[2,0-5,0]*	0,21	0,07
Fatigue, points	0,5[0,5-1,0]	3,0[2,0-4,0]*	0,5[0,5-1,0]	3,0[2,0-5,0]*	0,95	0,49
HbCO, %	1,3 $\pm$ 0,18		1,4 $\pm$ 0,17		0,502	
SpO_2 corr, %	93,9 $\pm$ 0,52	87,3 $\pm$ 0,57*	95,2 $\pm$ 0,25	92,9 $\pm$ 0,25*	0,001	0,001
ΔSpO_2 corr $\geq$ 4%	11,1 $\pm$ 4,15%		0,2 $\pm$ 0,08		0,014	
DDR, %/m	0,95[0,30-1,30]		0,10[0,00-0,40]		<0,001	
O_2 GAP, L/min	0,24 $\pm$ 0,120		0		-	
SBP, mm Hg	121,8 $\pm$ 2,61	139,6 $\pm$ 2,30	120,4 $\pm$ 2,29	136,5 $\pm$ 3,02	0,69	0,41
DBP, mm Hg	75,9 $\pm$ 1,48	81,4 $\pm$ 1,15	75,7 $\pm$ 1,17	80,6 $\pm$ 1,07	0,94	0,62
HRinit	85[74-94]		82[74-91]		0,256	
HRmax	130[116-154]		108[101-126]		0,001	
HRmean	105[96-113]		97[92-105]		0,028	

Note: Blood oxygenation indicators are shown with HbCO correction; Distance, % — the ratio of the actual distance traveled to the calculated (due) distance in %; HbCO — carboxyhemoglobin; SpO_2 corr — blood oxygenation measured transcutaneously and corrected by HbCO; ΔSpO_2 corr $\geq$ 4% — % of SpO_2 values measured during 6-MWT (corrected for HbCO level) reduced by $\geq$ 4% of the initial SpO_2 level before 6-MWT; DDR — desaturation-distance ratio; O_2 GAP — the need for additional oxygen flow to maintain SpO_2 at $\geq 88\%$ during 6-MWT; SBP, DBP — systolic and diastolic blood pressure; Heart rate initial, Heart rate Max, heart rate mean- initial, maximum and average heart rate during 6-MWT; * — probability of a-error in assessing the dynamics of indicators in the control or main groups as a result of 6-MWT (t-test or Wilcoxon test); p — the probability of a-error when comparing indicators in the main and control groups initially (1) and during (2) the 6-MWT test (Mann-Whitney test)

Table 3. State of pulmonary ventilation in patients with bronchial asthma

Parameters, M±m	«Desaturators»		«Non-desaturators»		P ₁	P ₂
	before treatment	after treatment	before treatment	after treatment		
VC, %	64,8±2,98	85,1±5,91*	71,5±2,91	78,3±4,9*	0,112	0,383
FVC, %	51,2±2,88	72,4±4,93*	60,9±2,68	79,6±4,45*	0,016	0,287
FEV ₁ , %	46,0±2,97	68,6±6,21*	57,0±2,89	76,7±5,38*	0,010	0,329
FEV ₁ /FVC, %	73,5±2,46	74,7±3,05	78,3±2,64	78,3±2,21	0,183	0,347
Duration of hospitalization, days	13,3±0,77		11,4±0,35		0,031	

Note: VC — vital capacity of the lungs; FVC — forced vital capacity of the lungs; FEV₁ — volume of forced exhalation in 1 second; FEV₁/FVC — Gensler index; p₁, p₂ — probability of α-error when comparing parameters in the main and control groups before and after treatment, respectively (Mann-Whitney test); * — reliable dynamics of spirometric parameters under the influence of treatment (Wilcoxon test)

Table 4. Comparative analysis of the blood oxygenation state under the influence of hospital treatment

Parameters, M±m или Me[Q ₂₅ -Q ₇₅]	«Desaturators»		«Non-desaturators»		P ₁	P ₂
	before treatment	after treatment	before treatment	after treatment		
HbCO, %	1,4±0,18	1,3±0,15	1,5±0,17	1,4±0,13	0,502	0,602
SpO ₂ min, %	90,4±0,94	91,4±0,58	93,4±0,41	93,9±0,37	0,006	0,001
SpO ₂ max, %	97,2±0,29	96,8±0,33	97,8±0,20	97,8±0,18	0,086	0,010
SpO ₂ mean, %	94,4±0,47	94,8±0,45	96,3±0,25	96,4±0,20	0,001	0,001
SpO ₂ [95-100%], %	51[20-93]	55[5-98]	100[90-100]	100[97-100]	0,001	0,001
SpO ₂ <95 %, %	49[7-73]	45[2,5-91]	0[0-8]	0[0-3]	0,002	0,001
HR mean	85,4±2,25	82,6±2,58	81,5±1,85	79,4±1,64	0,180	0,297

Note: HbCO — carboxyhemoglobin; SpO₂ min, max, mean — minimum, maximum and average SpO₂ values; SpO₂ [95-100%], SpO₂<95% — the proportion of measured SpO₂ values related to the specified oxygenation spectra; HR mean — average heart rate; p₁, p₂ — the probability of α-error when comparing parameters in the main and control groups before and after treatment, respectively (Mann-Whitney test for independent samples); dynamics of oximetric parameters and heart rate after inpatient treatment is unreliable (p>0.05; Wilcoxon test)

Taking into account more pronounced lung ventilation disturbance in desaturators, we compared blood oxygenation at rest and monitored SpO₂ in both groups before therapy and before discharge from the inpatient unit (Table 4).

Baseline blood oxygenation in non-desaturators was normal, while desaturators had hypoxemia: mean SpO₂ was below the acceptable level of 95 %. The highest difference was observed in spectrum characteristics of blood oxygenation. The share of normal blood oxygenation values [95–100 %] in the main group was just 51 [20-93] % vs. 100 [90-100] % in non-desaturators (p = 0.001). Lower values (< 95 %) of SpO₂ in desaturators were observed in 49 [7–73] % vs. 0 [0–8] % in controls (p = 0.002). A longer inpatient therapy improved lung ventilation and approximated the average oxygen saturation of haemoglobin in desaturates to the lower limit of normal — SpO₂ of 94.8 ± 0.45 %. At the same time, desaturates did not demonstrate any clinically significant improvement in spectrum characteristics of blood oxygenation.

The incidence of smoking and smoking index (packs of cigarettes/year) in the main and control groups were

identical; however, desaturates demonstrated a higher incidence of BA with COPD. The incidence of smoking in desaturates was 50 % (n = 14), with the smoking index of 32.8 ± 4.62, while in non-desaturates — 47 % (n = 22), with smoking index of 31.2 ± 5.15 (p > 0.79). Nevertheless, the incidence of BA with COPD in desaturates was significantly higher: 32 % (n = 9) vs. 9 % (n = 4) in non-desaturates (p = 0.022).

Discussion

Based on the results, reduced physical capacity in one third of BA patients is associated with oxygen desaturation of haemoglobin, where SpO₂ falls below 90 % during the 6-minute walking test. It turned out that oxygen desaturation of haemoglobin during 6-MWT is associated with an increase in the desaturation/distance ratio and a higher need in additional oxygen to maintain SpO₂ of ≥ 88 %, thus requiring a **higher oxygen cost** of maintaining physical capacity at a level, which is typical for non-desaturates. Besides, this phenomenon was associated with poorer lung ventilation and blood oxygenation, as well as a higher incidence of BA with COPD.

At the same time, desaturators required longer hospitalisation to arrest a more severe BA exacerbation, typical for the main group.

Conclusion

Therefore, a high incidence of oxygen desaturation of haemoglobin during 6-MWT in BA patients and associated clinical and functional disorders prove usefulness and clinical significance of the 6-minute walking test not only in patients with COPD, but also with bronchial asthma.

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