

**СУКЦИНАТ И СУКЦИНАТДЕГИДРОГЕНАЗА  
МОНОЯДЕРНЫХ ЛЕЙКОЦИТОВ КРОВИ КАК МАРКЕРЫ АДАПТАЦИИ  
МИТОХОНДРИЙ К ГИПОКСИИ У БОЛЬНЫХ ПРИ ОБОСТРЕНИИ  
ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ**

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**Цель.** Изучить концентрацию сукцината и активность сукцинатдегидрогеназы (СДГ) мононуклеарных лейкоцитов крови как маркеров быстрой адаптации митохондрий к гипоксии у пациентов при обострении хронической обструктивной болезни легких (ХОБЛ).

**Материалы и методы.** В исследование было включено 58 пациентов с ХОБЛ и 13 условно здоровых добровольцев 40-75 лет. В соответствии с принципами комплексной оценки GOLD 2018 пациенты были разделены на группы В (n=18), С (n=20), D (n=20), сопоставимые по возрасту, уровню ОФВ<sub>1</sub> и индексу пачко-лет. Больные группы D отличались более выраженной гипоксемией. В выделенных из крови мононуклеарных лейкоцитах определяли активность СДГ и концентрацию сукцината.

**Результаты.** Больные с обострением ХОБЛ, разделенные на группы в соответствии с частотой обострений и выраженностью симптомов, характеризовались различной тяжестью нарушений функций митохондрий мононуклеарных лейкоцитов. Больные группы С имели наибольшую концентрацию сукцината (428 [357;545] нмоль / 10<sup>6</sup> клеток 1 мл суспензии) и активность СДГ (64[56;73] нмоль сукцината / мин \* 10<sup>6</sup> клеток 1 мл суспензии) в мононуклеарных лейкоцитах по сравнению с группами В (снижение сукцината в 1,43 раза, p=0,002; снижение СДГ в 1,88 раза p=0,0015) и D (снижение сукцината в 2,06 раза, p<0,0001; снижение СДГ в 4,26 раза, p<0,0001). Больные группы D демонстрировали наиболее выраженное снижение маркеров адаптации к гипоксии.

**Выводы.** Малое количество симптомов при обострении у больных ХОБЛ связано с наибольшими показателями механизма быстрой адаптации митохондрий мононуклеарных лейкоцитов к гипоксии. Наличие у пациентов выраженных симптомов и частых обострений связано с наиболее тяжелым нарушением механизмов адаптации митохондрий к гипоксии.

**Ключевые слова:** ХОБЛ; митохондриальная дисфункция; сукцинат; мононуклеарные лейкоциты.

**SUCCINATE AND SUCCINATE DEHYDROGENASE OF MONONUCLEAR  
BLOOD LEUKOCYTES AS MARKERS OF ADAPTATION OF MITOCHONDRIA  
TO HYPOXIA IN PATIENTS WITH EXACERBATION OF CHRONIC  
OBSTRUCTIVE PULMONARY DISEASE**

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**Aim.** To study the concentration of succinate and the activity of succinate dehydrogenase (SDH) of mononuclear blood leukocytes as markers of rapid adaptation of mitochondria to hypoxia in patients with exacerbation of chronic obstructive pulmonary disease (COPD).



**Materials and Methods.** The study involved 58 patients with COPD and 13 conventionally healthy volunteers of 40-75 years of age. In accordance with GOLD 2018 principles of complex assessment, the patients were divided to groups B (n=18), C (n=20), D (n=20) comparable in age, FEV<sub>1</sub> and in pack-of-cigarettes/year index. Patients of D group were characterized by more pronounced hypoxemia. Activity of SDH and concentration of succinate were determined in mononuclear leukocytes isolated from blood.

**Results.** Patients with exacerbation of COPD divided to groups on the basis of the frequency of exacerbations and evidence of symptoms, were characterized by different severity of disorders of mitochondrial functions of mononuclear leukocytes. Patients of C group had the highest succinate concentration (428 [357;545] nmol/10<sup>6</sup> cells in 1 ml of suspension) and SDH activity (64[56;73] nmol of succinate/min \* 10<sup>6</sup> cells of 1 ml of suspension) in mononuclear leukocytes as compared to groups B (1.43-times reduction of succinate, p<0.002; 1.88-times reduction of SDH, p=0.0015) and D (2.06-times reduction of succinate, p<0.0001; 4.26-times reduction of SDH, p<0.0001). Patients of D group demonstrated the most pronounced reduction of markers of adaptation to hypoxia.

**Conclusions.** A small amount of symptoms in exacerbation of COPD is associated with the highest parameters of the mechanism of rapid adaptation of mitochondria of mononuclear leukocytes to hypoxia. Existence of evident symptoms and frequent exacerbations in patients is associated with a severe frustration of mechanisms of adaptation of mitochondria to hypoxia.

**Keywords:** COPD; mitochondrial dysfunction; succinate; mononuclear leukocytes.

It was found that patients with chronic obstructive pulmonary disease (COPD) with marked broncho-obstructive disorders can adapt to respiratory failure that leads to reduction of complaints of dyspnea and, in turn, may influence the results of evaluation of severity of the disease [1,2]. Existence of the direct connection between respiratory failure and frustration of tissue respiration processes associated with functioning of mitochondria, permits to make suggestion that determination of the functional activity of mitochondria may be one of potential markers of adaptation of patients with COPD [3-5]. Active study of the role of the secondary mitochondrial dysfunction in COPD permitted to identify its systemic character and to determine disorders in the function of mitochondria not only in lung tissue cells, but also in cells of other organs, for example, of muscles, blood [5-8]. Therefore, of much interest is a study of parameters of adaptation to hypoxia of mitochondria of peripheral blood cells since they are cells most easily available for examination in routine clinical practice [9-11].

For functioning of mitochondria in the conditions of hypoxemia characteristic of COPD exacerbation, of high significance are processes of rapid adaptation of mitochondria associated with accumulation of intracellular succinate and increase in the activity of II complex of the respiratory chain of mitochondria that earlier were determined for neurons [12]. Failure of these adaptive mechanisms is associated with production of excessive active forms of oxygen, with oxidative stress and damage to cells [12].

Alterations in the functioning of mitochondria linked with development of respiratory failure in patients with COPD may be noted in leukocytes of peripheral blood flow. A study of the parameters of functioning of mitochondria of blood cells in groups organized on the basis of the combined assessment of COPD, will permit to understand the significance of the mechanism of rapid adaptation of mitochondria to hypoxia for development of clinical manifestations of COPD.

Thus, the *aim of the given study* was examination of the concentration of succinate

and of the activity of succinate dehydrogenase (SDH) in mononuclear blood leukocytes as markers of the mechanism of rapid adaptation of mitochondria to hypoxia in patients with COPD exacerbation.

### Materials and Methods

The conducted study was approved by Local ethic committee of Ryazan State Medical University (Protocol №2 of 7.10.2016) and corresponds to the requirements of Good Clinical Practice (GCP) and World Medical Association's Declaration of Helsinki «Ethical Conduct of Medical Studies with Participation of Humans Subjects».

The current pilot study included 58 patients with COPD and 13 conventionally healthy volunteers at the age from 40 to 75 years. The minimal sample size was calculated taking into account earlier studies, with use of Open Epi calculator with statistical assumptions of alpha-error 5 and 95% confidence interval (CI), with taking into consideration at least 25% reduction of the concentration of succinate of blood leukocytes in 98% of patients with COPD [11]. The group of patients with COPD included those who underwent treatment in the Regional Clinical Hospital of Ryazan and visited a pulmo-

nologist of Polyclinics №6 of Ryazan for exacerbation of the disease.

Criteria for inclusion into the group of patients with COPD were signing the Informed consent, age from 40 to 75 years, initial post-bronchodilation parameter  $FEV_1/FVCL \leq 0.7$ . Criteria for inclusion of healthy volunteers into the control group were signing the Informed consent, age from 40 to 75 years, absence of documented chronic diseases of lungs and diseases of cardiovascular system in history.

Criteria for exclusion for all the groups were surgical interventions on lungs in history, alcohol and drug abuse, pulmonary diseases other than COPD and chronic bronchitis, or significant inflammatory diseases, other inflammatory diseases of internal organs in decompensation phase, monocytosis in the results of clinical blood analysis. On the second day of hospitalization in all the patients functions of external respiration were measured using MicroLab spirometer (Micro Medical, Great Britain) including the forced expiratory volume in 1 second ( $FEV_1$ ). Pulse oximetry was conducted using Spirotel  $SpO_2$  (Medical International Research, Italy). Clinico-functional and demographic characteristics of the studied groups are presented in Table 1.

Table 1

### *Clinicofunctional and Demographic Characteristics of Studied Groups*

Parameter	COPD, n=58	Control, n=13
Age, years	67 [61;71]	54 [50;63], p=0.088
Gender:		
male, n	48	5
female, n	9	8
Smoking:		
smokers, n	34	0
ex-smokers, n	24	0
non-smoking before, n	0	13
$FEV_1$ , %	48 [38;61]	92 [91;93], p<0.0001
$SpO_2$ , %	92 [89;93]	97 [97;98], p<0.0001

*Note:*  $FEV_1$  – ratio of measured  $FEV_1$  to calculated due value taken for 100%;  $SpO_2$  – saturation of blood with oxygen

Within the general clinical studies, a combined assessment of COPD was performed taking into account the data about exacerbations of COPD in history and results of questionnaires of Modified Medical

Research Council Dyspnea Scale (mMRC) and The COPD Assessment Test (CAT) [2]. Patients with COPD divided to B, C, D groups were comparable in FEV<sub>1</sub>, pack/year index and SpO<sub>2</sub> (Table 2).

Table 2

*Clinicofunctional Characteristics of Studied Groups of Patients with COPD Classified According to Severity of Symptoms and Frequency of Exacerbation*

Parameter	Group B, n=18 (1)	Group C, n=20 (2)	Group D, n=20 (3)
Pack/year index	25 [20;30]	25 [20;30]	22 [20;28]
FEV <sub>1</sub> , %	48 [38;63]	55 [39;62]	45 [40;58]
SpO <sub>2</sub> , %	92 [91;93]	92 [91;94]	91 [87;93], p <sub>1-3</sub> =0.02, p <sub>2-3</sub> =0.003
mMRC, point	2 [1;4]	1 [1;1], p <sub>1-2</sub> =0.0001	3 [2;5], p <sub>2-3</sub> <0.0001
CAT, point	19 [12;31]	8 [6;9], p <sub>1-2</sub> <0.0001	28 [12;34], p <sub>2-3</sub> <0.0001

Note: FEV<sub>1</sub> – ratio of measured FEV<sub>1</sub> to calculated due value taken for 100%; SpO<sub>2</sub> – saturation of blood with oxygen

Blood was taken in the morning in fasting condition on the second day of hospitalization by venous puncture from the cubital access using blood sampling vacuum systems and tubes containing heparin sodium, barrier gel and ficoll solution for creation of density gradient (BD Vacutainer CPT, USA).

After centrifuging of blood in BD CPT test tubes at 1600 G within 16 minutes, mononuclear leukocytes were separated from plasma by centrifuging at 3000 rev/min within 10 min. The obtained cells were washed in 0.9% NaCl with subsequent centrifuging at 3000 rev/min within 5 min. three times.

The isolated mononuclear leukocytes were resuspended in 1 ml of distilled water with obtaining suspension. In 20 µl of suspension the number of cells stained with methylene blue was counted in the counting chamber with subsequent recalculation for the volume of suspension. After calculation of the number of cells, detergent (10 µl Triton X-100) was added to 1 ml of suspension, and it was frozen.

After defrosting the suspension was used for determination of the parameters of oxidative

stress, of concentration of succinic acid and of the activity of enzymes with recalculation of parameters for 10<sup>6</sup> cells/ml of suspension.

Activity of SDH was determined by photometry in reaction of reduction of potassium ferricyanide (III) [12]. Concentration of succinate was determined using Succinate Colorimetric Assay Kit (Sigma-Aldrich, USA).

Acquisition and processing of the data were implemented using Office Excel 2016 program (Microsoft Corporation, USA), statistical processing of the results was carried out using Statistica 10.0. (Stat Soft Inc., USA). Correspondence of samples to normal distribution was verified using Shapiro-Wilk test. Since distribution in samples was other than normal, Mann-Whitney test was used for paired comparison, for multiple comparison Kruskal-Wallis test and Mann-Whitney test with Bonferroni adjustment were used. Statistically significant were considered differences with the probability for null hypothesis of absence of differences p<0.05.

### Results and Discussion

According to the results presented in Table 3, in patients with COPD in exacerbation

tion, a significant reduction of the activity of SDH and of the concentration of succinic acid in the suspension of mononuclear leukocytes of peripheral blood was noted (Table 3). These alterations probably indicated an increase in the amount of cells in the suspen-

sion which were subjected to the secondary mitochondrial dysfunction that in turn created the basis for development of oxidative stress and disorders in functioning of mononuclear leukocytes of peripheral blood.

Table 3

***Parameters of Functioning of Mitochondria of Mononuclear Leukocytes in Patients with Exacerbation of COPD and in Control Group***

Parameter	COPD, n=58	Control, n=13
Activity of SDH, nmol of succinate /min* 10 <sup>6</sup> cells in 1 ml of suspension	34 [19;56]	94 [88;95], reduction in 2.76 times, p<0.0001
Concentration of succinate, nmol/10 <sup>6</sup> cells in 1 ml of suspension	319 [215;407]	731 [679;768], reduction in 2.29 times, p<0.0001

In comparison of parameters of patients with COPD identified according to the level of symptoms and frequency of exacerbations, it was found that they significantly differed from each other in the studied markers of adaptation of mitochondria to hypoxia. At the same time, patients of C group with minimal severity of symptoms had the highest activity of SDH and concentration of succinate in suspension of mononuclear leukocytes, which probably reflected preservation of mechanisms of rapid adaptation to hypoxia in most cells.

In patients of groups B and D, who had many symptoms, a significant decrease in the activity of SDH and in the concentration of succinate in mononuclear leukocytes was noted compared to the parameters of group C. With this, the lowest activity of SDH was

observed in group D, characterized by the most pronounced hypoxemia. This probably demonstrated the failure of the adaptive mechanism in this group of patients due to damage to the mitochondria against the background severe hypoxemia (Table 4). Previously it was found that a higher level of plasma succinate in patients with a stable course of COPD was associated with a more pronounced thickening of the bronchial wall, determined by high-resolution computed tomography. Here, this group of patients was characterized by better spirometric parameters and results of the SGRQ questionnaire in the course of treatment with inhalation glucocorticoids compared to patients who had emphysema without thickening of bronchial wall and statistically lower levels of succinate in plasma [15].

Table 4

***Parameters of Functioning of Mitochondria in Mononuclear Blood Leukocytes of Patients with COPD Classified Depending on Severity of Symptoms and Frequency of Exacerbations***

Parameter	COPD, B (1) n=18	COPD, C (2) n=20	COPD, D (3) n=20
Activity of SDH, nmol of succinate /min* 10 <sup>6</sup> cells in 1 ml of suspension	34 [25;48] ↓ <sub>1-2</sub> in 1.88 times p <sub>1-2</sub> =0.0015; ↑ <sub>1-3</sub> in 2.26 times p <sub>1-3</sub> =0.0019	64 [56;73] ↑ <sub>2-3</sub> in 4.26 times p <sub>2-3</sub> <0.0001	15 [11;20]
Concentration of succinate, nmol/10 <sup>6</sup> cells in 1 ml of suspension	299 [216;365] ↓ <sub>1-2</sub> in 1.43 times p <sub>1-2</sub> =0.002	428 [357;545] ↑ <sub>2-3</sub> in 2/06 times p <sub>2-3</sub> <0.0001	208 [157;276]



Analysis of relationship between the studied parameters revealed a strong negative correlation between markers of adaptation of mitochondria to hypoxia and severity of symptoms in patients with COPD (Table 5). Here, a reliable positive relationship was found be-

tween the activity of SDH and concentration of succinate, on the one hand, and between functional parameters (FEV<sub>1</sub>, SpO<sub>2</sub>) on the other hand. The duration of smoking determined by the pack/year index, was characterized by a negative relationship of moderate force.

Table 5

***Correlation Analysis of Relationship between Parameters of Adaptation of Mitochondria of Mononuclear Leukocytes and Main Clinicofunctional Parameters of Patients with COPD***

Spearman rank correlation coefficient R (p<0.05)	mMRC, points	CAT, points	ОФВ <sub>1</sub> , %	SpO <sub>2</sub> , %	Pack/Year Index
Activity of SDH, nmol of succinate /min* 10 <sup>6</sup> cells in 1 ml of suspension	-0.8380	-0.8586	0.7039	0.7433	-0.4277
Concentration of succinate, nmol/10 <sup>6</sup> cells in 1 ml of suspension	-0.8129	-0.8062	0.7070	0.7350	-0.5100

Thus, succinate-mediated mechanism of rapid adaptation of mitochondria to hypoxia probably plays an important role in adaptation of patients with COPD to respiratory failure in exacerbation of the disease. In this context, a study of the activity of SDH and of concentration of succinate in mononuclear leukocytes may be an additional method of evaluation of adaptation of patients with COPD to hypoxia.

### Conclusion

1. A small amount of symptoms in exacerbation of chronic obstructive pulmonary disease is associated with highest parameters of mechanisms of rapid adaptation of mitochondria of mononuclear leukocytes to hypoxia.
2. Existence of severe symptoms and frequent exacerbations were accompanied by most severe frustration of mechanisms of adaptation of mitochondria to hypoxia.

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#### Дополнительная информация [Additional Info]

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