СРАВНИТЕЛЬНЫЙ АНАЛИЗ ПОКАЗАТЕЛЕЙ КАРДИОИНТЕРВАЛОМЕТРИИ, ЭРГОРЕФЛЕКСА И ДАННЫХ 6-МИНУТНОГО ШАГОВОГО ТЕСТА У БОЛЬНЫХ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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Цель. Изучить взаимоотношение показателей кардиоинтервалометрии и эргорефлекса с показателями 6-минутного шагового теста у больных хронической обструктивной болезнью легких (ХОБЛ). *Материалы и методы.* В исследование включено 63 пациента с ХОБЛ, 40 пациентов – контрольной группы (все – мужчины). Функциональную оценку внешнего дыхания и 6-минутный шаговый тест проводили с использованием оборудования Spiropalm 6 MWT (Cosmed, Италия). Оценку вегетативного статуса и влияние на него эргорефлекса проводили методом регистрации кардиоинтервалометрии до, во время и после пробы с внешней периферической сосудистой окклюзией на оборудовании аппаратно-программного комплекса «Варикард» (ООО «Рамена», Россия). *Результаты.* При выполнении 6-минутного шагового теста получены статистически значимые различия между группой пациентов с ХОБЛ и контрольной группой по большинству исследуемых показателей (p<0,01). 18 из 63 пациентов, страдающих ХОБЛ, за время проведения 6-минутного шагового теста, имели снижение уровня SpO_2 на ≥4% (p<0,01). При проведении пробы с внешней периферической сосудистой окклюзией в обеих группах увеличивался индекс показателей активности регуляторных систем (ПАРС), однако после завершения пробы у больных ХОБЛ показатель уменьшался ниже первоначальных величин (p<0,05), а у контрольной группы изменения оказались еще более выраженными (p<0,01). Пациенты с ХОБЛ были разделены на группы в зависимости от расстояния, пройденного за время теста с 6-минутной ходьбой: выявлена умеренная положительная корреляция между пройденной дистанцией и объемом форсированного выдоха за первую секунду (ОФВ$_1$, R=0,45, p<0,01). Максимальный уровень суммарного эффекта вегетативной регуляции кровообращения зарегистрирован у пациентов, преодолевших за время 6-минутного шагового теста минимальное расстояние (227,77±48,13 м). Также зарегистрирована умеренная отрицательная корреляция между индексом ПАРС и результатом теста с 6-минутной ходьбой (R=-0,34, p<0,01). *Выводы.* 1. При проведении теста с 6-минутной ходьбой важное значение для оценки функционального статуса пациентов имеет исследование сатурации на протяжении всего теста. 2. Изменение значений индекса ПАРС при проведении пробы с внешней периферической сосудистой окклюзией можно расценивать как снижение влияния рефлекса с эргорецепторов нижних конечностей на функциональное состояние пациентов. 3. У пациентов с ХОБЛ выявлен выраженный вегетативный дисбаланс. Индекс ПАРС имеет умеренную отрицательную корреляцию с пройденным расстоянием при тесте с 6-минутной ходьбой. 4. Максимальные значения индекса ПАРС получены у пациентов с минимально пройденным расстоянием при выполнении теста с 6-минутной ходьбой.

Ключевые слова: ХОБЛ, 6-минутный шаговый тест, эргорефлекс, вариабельность ритма сердца, проба с внешней периферической сосудистой окклюзией.

COMPARATIVE ANALYSIS OF PARAMETERS OF CARDIOINTERVALOMETRY, ERGOREFLEX AND DATA OF 6 MINUTE WALK TEST IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Aim. To study the relationship between parameters of cardiointervalometry and ergoreflex, and 6-minute walk test data in patients with chronic obstructive pulmonary disease (COPD). ***Materials and Methods.*** The study included 103 men, of them 63 patients with COPD, 40 patients of the control group. Functional assessment of external respiration and a 6-minute walk test were performed using Spiropalm 6MWT equipment (Cosmed, Italy). The autonomic status and the influence of the ergoreflex on it were assessed by the method of cardiointervalometry before, during and after the test with external peripheral vascular occlusion using Varicard hardware and software complex (LLC Ramena, Ryazan, Russia). ***Results.*** When performing a 6-minute walk test, significant differences were obtained between the groups of patients with COPD and of the control group in the majority of the studied parameters ($p<0.01$). In 18 of 63 patients with COPD, the level of SpO_2 in 6-minute walk test decreased by$\geq 4\%$ ($p<0.01$). The obtainedresult is of considerable importance for assessment of exercise tolerance in patients with COPD. In tests with external peripheral vascular occlusion in patients with COPD and of the control group, the index of activity of regulatory systems (IARS) increased in both groups. However, after completion of the test, the index in patients with COPD decreased below the initial values ($p<0.05$), and in patients of the control group the changes were even more pronounced ($p<0.01$). Patients with COPD were divided into groups depending on the distance covered in 6-minute walk test. Analysis of the data revealed a moderate positive correlation between the covered distance and the forced expiratory volume in the 1st second (FEV_1, $R=0.45$, $p<0.01$). The maximum level of the total effect of the autonomic regulation of blood circulation was recorded in patients who covered the minimum distance (227.77 ± 48.13 m) in 6-minute walk test. Besides, a moderate negative correlation between IARS and the results of 6-minute test was recorded ($R=-0.34$, $p<0.01$). ***Conclusions.*** 1. For assessment of the functional status of patients in 6-minute walk test it is important to take measurement of saturation throughout the whole test. 2. The change in IARS values in the test with external peripheral vascular occlusion can be regarded as a reduction of the influence of reflex from the lower limb ergoreceptors on the functional condition of patients. 3. Patients with COPD showed a marked autonomic imbalance. IARS showed a moderate negative correlation with the distance covered in 6-minute walk test. 4. Maximum value of IARS was obtained in patients with the minimal distance covered in 6-minute walk test.

Keywords: COPD, 6-minute walk test, ergoreflex, heart rate variability, test with external peripheral vascular occlusion.

Chronic obstructive pulmonary disease (COPD) presents a serious problem for public healthcare service. The disease considerably impairs the quality of patients' life. Patients experience impairment of the everyday activity, of physical working capacity, changes in the emotional status. Clinical manifestations of the disease, such as dyspnea, weakness of respiratory and physical muscles lead to reduction of tolerance to physical loads [1,2].

The diagnosis is verified on the basis of the parameter that reflects the ratio of the

forced expiratory volume in the first second (FEV_1) to forced vital capacity of lungs (FVCL) after use of a bronchodilator. The parameter <70% shows bronchial obstruction [3]. The diagnostic significance of FEV_1 is out of doubt, but this parameter does not show a good correlation with the severity of COPD course [4].

Along with disorders in the respiratory system, patients with COPD often present with extra pulmonary alterations manifested by the reduction of physical activity [5,6]. Negative influence of sedentary lifestyle on physical and mental condition of an individual has been discussed many times [7]. Tolerance to physical activity is evaluated in tests with physical loads and also by analysis of parameters that reflect the ability of a patient to do physical work [8].

The most common loading test is a 6-minute walk test (6MWT). It is used for determination of the functional status of a patient with diseases of respiratory organs, for assessment of the effectiveness of treatment and for making prognosis. An important matter is assessment of saturation before and after 6MWT. Analysis of saturation in 6MWT is included into recommendations of the Russian Respiratory Society as a method of additional confirmation of the COPD diagnosis [9,10].

There exist literature data about heart rate variability (HRV) in individuals with different diseases, however, little information is given on assessment of the autonomic status of patients with COPD [11,12]. One of methods of assessment of the autonomic status is a method of HRV analysis. Using HRV, it is easy to assess neurohumoral regulation of the cardiovascular system (CVS) and the activity of the autonomic nervous system (ANS) [13]. Patients with COPL exhibited the autonomic imbalance manifested by a stepwise reduction in the activity of parasympathetic division of the autonomic nervous system throughout a day. The cardiointervalogram (CIG) of the majority of patients with COPD showed reduction of all time parameters [11,14].

In the study of M. Pagani, et al. (1997), relationship between HRV and the extent of bronchial obstruction in patients with bronchial asthma (BA) was established – a considerable impairment of HRV parameters: of the total spectrum power, low frequency (LF) parameters, high frequency (HF) parameters. Reduction of HF (spectrum power of the high frequency component of variability) is interpreted as the result of predomination of sympathetic division of the ANS with reduction in the influence of parasympathetic division [15]. Reduction of LF (spectrum power of a low frequency component of variability) results from increase in the activity of sympathetic division of the ANS, since this parameter reflects the condition of regulation of the vessel tone. Change in LF/HF ratio indicates the autonomic imbalance with predomination of the sympathetic influence. These changes may probably be associated with increase in the respiratory rate (RR) [16].

In the study of O.V. Pilyasova, et al. (2008) moderate relationships were established between the values of peak expiratory flow rate in 1 sec and SDNN parameters (*Standard Deviation of Normal to Normal R-R Intervals*, standard deviation of totality of intervals), LF/HF, LF, and a moderate relationship between FEV_1/FVCL and the total spectrum power, which eventually confirms existence of interrelation between the autonomic regulation and parameters of respiratory function [17].

At present great attention is given to the systemic effects of COPD, to functional disorders in the peripheral muscles. In this connection, of interest is a study of ergoreflex [18]. Ergoreflex is one of reflex mechanisms that regulates adaptation of the respiratory and cardiovascular systems to the demands of an organism and maintains its homeostasis [19]. Muscle receptors are afferent receptors sensitive to products of metabolism of skeletal muscles. The object of study of M. Piepoli, et al. (1997) was activation of these receptors in patients with chronic cardiac failure where it could be provoked by

metabolic disorders in skeletal muscles, early acidosis and accumulation of metabolites in working muscles [20].

Activation of the ergoreflex seems to be a positive compensatory mechanism for maintenance of a stable homeostasis. In patients with chronic diseases of the respiratory and cardiovascular systems, the exaggerated activation of ergoreflex is considered to be a persistent source of enhanced influence of sympathetic division of the ANS [21].

Aim to study the interrelation between the parameters of cardiointervalometry and of ergoreflex, and parameters of 6-minute walk test in patients with COPD.

Materials and Methods

103 Male patients were studied: 63 patients with COPD (average age 65.8 ± 8.6 years) and 40 practically healthy volunteers (average age 59.8 ± 11.3 years). Individuals presenting with decompensated chronic diseases, serious organic pathology of the CVS (disorders in heart rhythm and conduction, history of cardiovascular accidents) were not included into the study.

Comparison between the two groups in age, FEV_1 and FEV_1/FVCL parameters is given in Table 1.

Table 1

Comparative Initial Clinical Characteristics of Patients
with COPD and Patients of Control Group

	Patients with COPD (n=63)	Control Group (n=40)
Age, years	65.73 ± 8.56	59.13 ± 11.24
FEV_1, L	1.57 ± 0.65*	3.38 ± 0.68
FEV_1/FVCL, %	49.85 ± 14.71*	78.89 ± 6.90

Note: * – $p<0.05$ in comparison with the results of control group

All the tested individuals were instructed in detail about the aim and tasks of the study, they received detailed answers to their questions, after which the Informed agreement was signed. The study was approved at meeting №3 of Local Ethics Committee (9 Nov 2016) at Ryazan State Medical University.

Functional capacities of the respiratory system of patients were studied according to ATS/ERS Standards (Series ATS/ERS Task Force: Standardization of Lung Function Testing, 2005) [22] and to recommendations of the Russian Respiratory Society on use of spirometry method, 2014 [23], on the equipment Spiropalm 6MWT (Cosmed, Italy). Within 12 hours before the study the patients refrained from use of short-acting and long-acting bronchodilators.

6MWT was conducted in compliance with Clinical recommendations of the American Thoracic Society (2014) [24]. In each test person spirometry was preliminary conducted.

The influence of ergoreflex was assessed by a method of registration of cardio intervals on Varicard hardware-software complex (LLC Ramena, Ryazan, Russia). Three parameters were recorded: the initial level within 5 minutes in the supine position in relaxed wake prior to the test with external peripheral vascular occlusion; with cuffs applied on the hips – within 3 min; and in the recovery period – 5 min. Simultaneously respiratory rate was measured.

The following parameters were studied: heart rate (HR), beat/min; RR per minute; SDNN, ms; RMSSD (*the Root Mean Square of Successive Heart Beat Interval Differences*), ms; HF, %; LF, %; VLF (very low frequency slow waves),%; LF/HF (ratio of power in the low frequency range to power in

high frequency range). Mathematical analysis of cardiointervalogram was conducted using ISKIM license software (LLC Ramena, Ryazan, Russia).

Statistical processing of the obtained results was conducted using license application program package Excel 2010 (Microsoft Corporation, USA) and Statistica 10 (Stat Soft Inc., USA). Correspondence of the variable to the normal distribution was determined using Kolmogorov-Smirnov test. The results were presented in the form of the average mean (M) ± standard deviation (σ). Quantitative signs not corresponding to the normal distribution were presented as median and interquartile range: Me [Q25;Q75]. Statistically significant were considered differences with probability of faulty judgment $p < 0.05$.

ResultsandDiscussion

In 6MWT the following results were obtained in the group of patients with COPD and in the control group: the distance covered within 6 minutes: 424.70 ± 162.46 m and 679.41 ± 136.42 m, respectively; the Borg scale score for the initial level of dyspnea was: 2.29 ± 1.44 and 0.28 ± 0.13, respectively; the Borg scale score for the level of dyspnea after 6MWT: 5.73 ± 1.71 and 1.41 ± 1.12, respectively; the Borg scale score for the initial level of muscle weakness: 1.16 ± 0.35 and 0.21 ± 0.21, respectively; the Borg scale score for the level of muscle weakness after 6MWT: 3.10 ± 1.80 and 0.61 ± 0.17, respectively ($p < 0.01$ for all the listed comparisons).

The saturation indices (SpO_2) in patients with COPD and of control group were: the initial level: $93.78 \pm 3.12\%$ and $95.91 \pm 1.54\%$, respectively ($p < 0.01$), after 6MWT: $91.53 \pm 5.23\%$ and $95.50 \pm 2.08\%$, respectively ($p < 0.01$). 18 of 63 patients with COPD showed reduction of SpO_2 level during 6MWT by $\geq 4\%$ ($p < 0.01$).

The results of the test with external peripheral vascular obstruction are given in Table 2.

Table 2

Comparative Analysis of HRV in Patients with COPD and of Control Group

Parameter	COPD (n=63)			Control Group (n=40)		
	Initial	**In test**	**In recovery period**	**Initial**	**In test**	**In recovery period**
HR, beat/min	72.47±11.04#	72.27±10.77*^	71.36±10.47	69.07±9.64	70.05±9.66	68.21±8.91
RR, per min	15.53±4.49	15.90±4.53	16.13±4.62	13.57±4.27	17.48±4.34	13.28±3.99
IARS	5.28±1.81*	5.61±2.03*^	4.92±1.96	4.76±1.74	5.15±1.74*^	4.02±1.74
RMSSD, ms Me [Q1;Q3]	24.0 [13.0;71.0]*	30.0 [11.0;62.0]	28.0 [13.0;79.0]	15.5 [10.0;26.5]	15.0 [10.0;26.5]	17.5 [10.5;28.0]
SDNN, ms Me [Q1;Q3]	28.0 [17.0;57.0]* #	28.0 [18.0;52.0] *^	33.0 [23.0;55.0]	22.5 [17.0;35.0]#	26.0 [16.5;37.0]	27.5 [19.5;37.0]
HF, %	47.50±25.23*	49.01±27.07	45.52±25.89	34.94±20.85	32.90±22.96	28.68±16.47
LF, %	28.67±14.93*	30.29±16.50	28.80±15.01	35.73±14.97	39.52±16.90	36.54±11.14
VLF, %	23.82±17.67	20.36±17.61*^	25.67±17.47	29.32±16.23#	27.58±17.81*^	34.52±14.70
LF/HF Me [Q1;Q3]	0.65 [0.25;1.39]	0.62 [0.27;1.70]	0.65 [0.31;1.66]	1.17 [0.58;2.59]	1.77 [0.76;2.92]	1.20 [0.84;2.38]

Note: *– $p < 0.05$ incomparison with the results of control group,*^– $p < 0.05$ in comparison of data during test and in the period of recovery, #– $p < 0.05$ in comparison of the initial data with the period of recovery

In patients with COPD the index of activity of regulatory systems (IARS) increased. After the test the parameter decreased below the initial values. The statistically reliable difference was obtained between IARS during test and recovery period (p<0.05).

Similar changes were more pronounced in the control group. Statistically significant differences were found between IARS in the test and in the recovery period (p<0.01).

Thus, the test objects shifted from the group of patients with expressed tension of regulatory systems (IARS 4-6) to the group with moderate tension of regulatory systems (IARS 3-4). On the basis of the obtained data it is possible to suggest hyperactivity of ergoreflex from the lower limbs in patients with COPD (delta of the total change of IARS in the testwith peripheral external vascular occlusion in the control group exceeded delta of the total change of IARS in the group of patients with COPD).

Then patients with COPD were divided into groups depending on the distance covered in 6MWT. Analysis of the distance covered in 6MWT and of FEV$_1$ revealed a moderate positive correlation (R=0.48, p<0.01).

The obtained results demonstrate dependence of distance covered in 6MWT on the functional condition of the patient, and in case of COPD – on the respiratory function.

With increase in severity of COPD the activity of parasympathetic regulation increased. The maximal level of the total effect of the autonomic regulation of circulation was recorded in patients who covered the minimal distance in 6-minute walk test (227.77±48.13 m). A reliable increase in the extent of dyspnea and in muscle weakness in the lower limbs was found in patients who walked the minimal distance in 6MWT as compared to patients with a higher level of tolerance to physical load (p<0.05). As to RR, no reliable differences between groups of patients with COPD were revealed (p>0.05).

IARS showed a moderate negative correlationwith the covered distance in 6MWT (R=-0.34, p<0.01, Fig. 1). In other words, the maximal IARS 6.23±1.8 relative units (RU) was obtained in patients who walked the minimal distance in 6MWT – 227.77±48.13 m; the minimal IARS 4.36±1.7 RU was obtained in patients who walked the maximal distance – 690.82±92.69 m.
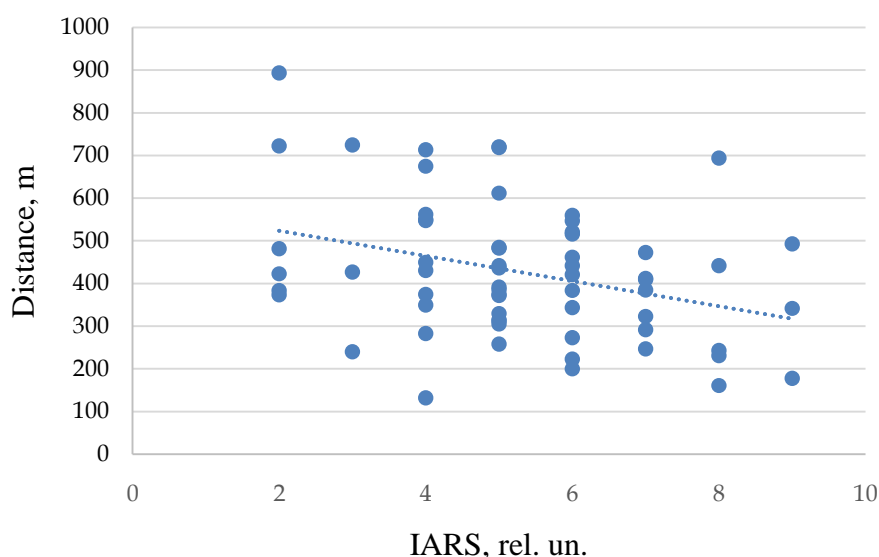

Fig. 1. Correlation analysis between the result of 6-minute walk test
and IARS in patients with COPD

Conclusions

1. In conduction of 6-minute walk test in patients with chronic obstructive pulmonary disease it is important to analyzesaturation throughout the whole test for assessment of the functional condition of patients.

2. Alteration of the values of IARS in the test with external peripheral vascular occlusion may be regarded as reduction of the influence of reflex from ergoreceptors of the lower limbs on the functional condition of patients.

3. Inpatientswith chronic obstructive pulmonary disease an evident autonomic imbalance was found – a moderate negative correlation of IARS with the distance covered in 6-minute walk test.

4. Maximal IARS values were obtained in patients with the minimal distance walked in 6-minute walk test.

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