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Regulatory peculiar features of uncontrolled bronchial asthma

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Abstract

Bronchial asthma (BA) is a multifactorial disease which develops under the influence environmental factors in the presence of individual’s genetic predisposition. The mechanisms associated with the respiratory system dominate in its pathogenesis. **The objective:** to determine the regulatory features of the uncontrolled course of asthma. **The results obtained.** At the outpatient stage of treatment 71 male and female patients, mean age 41.0 ± 0.8 have been examined with the use of spiroarteriocardiorhythmography (SACRG). The patients under examination were divided into 2 groups: the group of comparison (n = 20), and the main one (n = 51). Alfa - coefficient in high (BR_{HF}) and low (BR_{LF}) frequencies, hemodynamic and minute volume of blood circulation (HMV, l), indexes of cardiovascular and respiratory systems synchronization and parameters of the cardiovascular system in patients with asthma were determined. **Conclusions.** In BA at the background of total respiratory capacity significant increase and growth of neurohumoral regulatory influences there is a significant decrease of the sympathetic link activity in the regulation of uncontrolled respiration and relative reduction of the volume velocity of inspiration, which should be taken into account when determining the severity of asthma.

Key words: bronchial asthma, neurohumoral regulatory influences, uncontrolled breathing.

Introduction. Bronchial asthma (BA) is a chronic inflammatory disease combined with respiratory tract obstruction and bronchial hyperreactivity. It manifests itself in the form of episodes of wheezing, coughing, sensation of strangulation and compression in the chest [1, 2]. This is a multifactorial disease, which develops under the influence of environmental factors in the presence of individual's genetic predisposition [3].

Broncho-obstructive syndrome, which is at the basis of asthma clinical picture, is polymorphic by the mechanism of its formation, and determines the heterogeneity of BA pathogenesis [4, 5]. However, mechanisms associated with the respiratory system are dominant in it. Due to the anatomical and functional relationship with the cardiovascular system, these mechanisms should be considered comprehensively, as well as changes in the composition of the combined cardiopulmonary system [6, 7]. Recent advances in the study of BA pathogenical mechanisms and its basic concept are in the definition of asthma as an allergic inflammation of the respiratory tract, which involves bronchial hyperresponsiveness to various stimuli [8]. On this basis, one can assume that the efficiency of the cardiopulmonary system (CPS) functioning and the possibility of asthma development is largely determined by the peculiarities of its regulation.

Central, autonomic and humoral nervous system plays a pivotal role in the regulation of CPS function [9 - 11]. This, in its turn, ensures its functional homeostasis, which is the main, together with disregulation, pathogenic link in the development of various diseases [12, 13].

At present, asthma is considered as a heterogeneous disease in the pathogenesis of which, in addition to allergic inflammation, psycho-neurological disorders closely related to the somatic ones and play a significant role. A special role in the development of asthma is provided by vegetative dysfunction, which determines the formation of hypersensitivity and hyperreactivity of the bronchi [14, 15].

Considerable attention to the study of autonomic regulation in BA patients is associated not only with the understanding of the processes of pathogenesis [16, 17], but with the development of new approaches to therapy [18, 19]. That is why, the differences in the regulatory mechanisms that arise in the body of patients, including BA patients, make it possible to intensify the sanogenetic mechanisms of control of the disease [20].

The objective: to determine the regulatory features of BA uncontrolled course.

Results and discussion. To achieve the purpose set 71 patient of both sex, aged 41.0 ± 0.8 were examined at the outpatient stage of treatment. Complex multifunctional method of cardiopulmonary system examination - spiroarteriocardiorhythmography (SACRG) was used. All the patients under examination were organized into 2 groups, the first group, that of comparison (n=20, GC) included individuals with clinically confirmed intermittent or controlled asthma (9 men, 11 women, mean age 39.8 ± 1.7 y. o.). The second group, the main one, included 51 patients (30 men, 21 women, MG) with clinically confirmed persistent or uncontrolled BA, mean age 41.7 ± 0.9 y.o. Distribution of patients by groups is presented in Table 1.

Table 1

Age-matched BA patients' groups

	GP, n = 20	Main group, n=51
Age	39.8±1.7	41.7±0.9
Women	11	21
Men	9	30

As the control parameters of cardiorespiratory regulation, we used the results of examination of any pathology free persons of different sex and age [21]. Because of age variations, different levels of physical activity and functional state of the body, some indexes were further specified [22, 23, 24].

SACRG method allows to determine the activity of regulatory effects on the heart rate, systolic and diastolic blood pressure, and respiration [25] simultaneously. The patients were examined in the early hours, in the fasted state, examination included the registration of CRS activity throught SACRG. Additionally the registration of physical development indexes was carried out. The body mass (BM, kg), body length (BL, cm) and body area (BoA) were determined. The routine methods of systolic (SP), diastolic (DP) and pulse (PP) arterial pressure were carried out, as well as the calculation of a number of indices that characterize the functional state of the CRS and the body as a whole: Robinson's index (RI), Kerdo's index (KI).

Regulatory influences were determined on the basis of spectral analysis of cardiac rhythm variability (HRV), blood pressure and respiration. Spectral analysis was performed in three frequency bands: ultra-low frequency (VLF, 0-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.4 Hz), which were measured in absolute values of power

(ms^2 - for SP, mm Hg2 - for systolic BP and diastolic BP, $(l\ /\ min)^2$ - for uncontrolled breathing).

Herewith, both approaches to assessing the sensitivity of the baroreflex (BR) are implemented in SACRG software [26]. We analyzed the indicators calculated by the spectral method (α-coefficient). It was calculated separately in the ranges of high (BR_{HF}) and low (BR_{LF}) frequencies [27].

$$BR_{LF} = \frac{\sqrt{LF_{HR}}}{LF_{SP}} \qquad (1)$$

$$BR_{HF} = \frac{\sqrt{HF_{HR}}}{HF_{SP}} \qquad (2)$$

Hemodynamics and minute volume of blood circulation (VBC, l) were determined based on ECG data (1 derivation) by the two-phase reconstruction method [28]. According to the ultrasound spirometry, realized in SACRG device, the parameters of the respiratory pattern – RV, l; the volume rate of inhalation and exhalation – VRI and VIE / Tin (l / sec) and RV / Texh (l / sec), the ratio of the inhalation phases and exhalation Tin / Texh, as well as the minute volume of breath (MVB, l.) were registered.

Based on the data of hemodynamics and spirometry, the device has the ability to determine the parameters of cardiovascular and respiratory systems synchronization – Hildebrand's index (IH) and the VBC / MVB, which confirm the frequency and volume components of cardiorespiratory system synchronization.

To evaluate the results, non-parametric methods of statistical analysis with determination of Man-Whitney's and Wilcoxon's criteria were used. Statistical processing was carried out with the use of statistical package STATISTICA 10.

According to the data of general clinical observations of both groups patients, differences that characterize the clinical course of nosology under study were found (Table 2, 3).

Table 2

Data of blood clinical examination in the groups of patients under study, M (25; 75)

Index	GC	MG
Erythrocytes (10^{12}/l)	4,6 (4,1; 4,9)	4,7 (4,2; 4,9)
Hb (g/l)	146,0 (139,0; 150,0)	152,0 (142,0; 158,0) *
Leucocytes (10^{9}/l)	7,6 (6,9; 8,3)	6,9 (5,7; 7,8) *
Colour index	0,95 (0,90; 1,05)	0,95 (0,90; 1,05)
Lymphocytes, %	32,0 (25,0; 39,0)	34,0 (28,0; 38,0)
Monocytes, %	6,0 (2,0; 7,0)	6,0 (4,0; 8,0)
ESR, mm/h	8,0 (4,0; 13,0)	7,0 (4,0; 9,0)
Thrombocytes (10^{9}/l)	274,0 (187,0; 312,0)	267,0 (224,0; 301,0)

* *p<0.05*

Table 3

Data of blood biochemical examination in the groups of patients under study, M (25; 75)

Index	GC	MG
TP, g/l	73,1 (69,8; 83,5)	76,1 (69,0; 80,0)
BUN	5,4 (3,4; 6,4)	6,1 (5,4; 6,7) *
Alkaline phosphatase	77,0 (60,0; 93,0)	80,0 (67,0; 91,0)
Uric acid	288,0 (268,0; 345,0)	291,0 (237,0; 325,0)
Creatinine	79,0 (62,0; 97,0)	90,0 (73,0; 101,0)
TB	13,0 (9,4; 15,9)	11,6 (9,8; 15,4)
Cholesterol	4,1 (3,9; 5,2)	4,5 (3,9; 5,0)
SGPT	26,0 (24,0; 30,0)	29,0 (25,0; 33,0)
SGOT	22,0 (19,0; 26,0)	25,0 (22,0; 30,0) *

* *p<0.05*

Spirometric examination data, which indicate a significant deterioration of bronchodilation and obstruction in MG patients compared to GC ones are given in tabl. 4.

Table 4

Data of external respiration function examination in the group of patients under study, M (25; 75)

Index	GC	MG
Inhalation		
VC, l	3,350 (3,170; 4,870)	3,130 (2,750; 3,750) *
FVC, l	3,780 (3,350; 4,870)	3,290 (2,580; 3,760) *
FEV1, l	3,780 (3,350; 4,870)	3,290 (2,580; 3,760) *
FEV1/FVC	100,0 (100,0; 100,0)	100,0 (100,0; 100,0)
Exhalation		
VC, l	4,690 (3,020; 5,120)	3,110 (2,800; 3,660) *
FVC, l	4,840 (3,350; 5,270)	3,210 (2,740; 3,870) *
FEV1, l	3,720 (2,840; 3,960)	1,880 (1,680; 2,330) **
FEV1/FVC	74,3 (70,5; 78,2)	62,9 (60,2; 65,0) **

** p<0.05; **p<0.01*

The results of morphometric study indicate that BA uncontrolled course together with a significant increase in body mass 86.0 (78.0; 95.0) and BMI 29.1 (27.7; 30.5) versus 80.0 (60,0; 86,0) and 26,6 (25,4; 29,0), p <0.01, respectively, in GC, is accompanied by reorganization of patients' constitution. This is characterized by significant increase in double body hold and chest. If the first one is more often of an alimentary origin and associated with a violation of neuro-vegetative regulation and possible development of metabolic syndrome, the other can characterize changes in the structure of the chest in the development of emphysematous manifestations, which is sufficiently characteristic for BA course (Table 5).

Analysis of cardiovascular system parameters showed that in MG patients in comparison with those of GC, in the state of relative muscular and psychoemotional rest in the sitting position there is a significantly higher heart rate - 87.2 (78.3; 94.2) versus 80.6 (71.4; 97.2), p <0.05, which is accompanied by significant changes in the indexes of cardiointervalometry indices.

Table 5

Data of morphometric examination in the groups of patients under study, M (25; 75)

Index	GC	MG
Body mass, kg	80,0 (60,0; 86,0)	86,0 (78,0; 95,0)*
Body length (sm)	170,0 (152,5; 178,0)	169,0 (165,0; 176,0)
IMT, kg/m^2	26,6 (25,4; 29,0)	29,1 (27,7; 30,5)*
Waist-line (sm)	88,0 (83,0; 98,0)	88,0 (78,0; 96,0)
Belly circumference (sm)	93,0 (89,0; 103,0)	100,0 (91,0; 107,0) *
Hip circumference (sm)	56,0 (52,0; 60,0)	58,0 (49,0; 66,0)
Chest circumference (sm)	99,0 (95,0; 117,0)	108,0 (98,0; 117,0) *

* *p<0.05*

This is characterized by increased time of intraventricular conductivity QRS 0.092 (0.085; 0.100) versus 0.084 (0.080; 0.092), p <0.01, as well as the deterioration in the effectiveness of the reduction of QTC 0.435 (0.417; 0.461) versus 0.425 (0.402; 0.432), p <0.05, and ventricular repolarization 0.030 (-0.079; 0.144) against 0.111 (0.045; 0.183), p <0.01 (Table 6). The latter may be a manifestation of hypoxic states that develop during daily attacks of strangulation and cardiomyopathy development.

Table 6

The average parameters of cardiointervalometric examination in the groups of patients under study (according to SACRG), M (25; 75)

Index	GC	MG
HR, $min.^{-1}$	80,6 (71,4; 97,2)	87,2 (78,3; 94,2) *
P, c	0,099 (0,090; 0,102)	0,101 (0,084; 0,107)
PQ, c	0,137 (0,117; 0,155)	0,133 (0,118; 0,156)
QR, c	0,029 (0,028; 0,032)	0,030 (0,028; 0,033)
QRS, c	0,084 (0,080; 0,092)	0,092 (0,085; 0,100) *
QT, c	0,353 (0,344; 0,381)	0,362 (0,349; 0,385)
QTC, c	0,425 (0,402; 0,432)	0,435 (0,417; 0,461) *
ST, n.o.	0,111 (0,045; 0,183)	0,030 (-0,079; 0,144) *

* *p<0.05*

Analyzing the results of HRV examination, we paid attention to the characteristic differences between the indicators of GC and MC patients. They most related to the significant reduction of regulatory influences in the low-frequency (LF) and high frequency (HF) ranges from 772.8 (492.8, 1049.8) versus 424.4 (136.9; 750.8), p <0.01, and from 1149.2 (302.8; 1697.4) versus 216.1 (81.0; 1162.8), p <0.005, correspondingly. This is reflected in the total power of cardiac rhythm regulation (TP) from 2642.0 (1444.0; 4356.0) versus 1089.0 (576.0; 2662.6), p <0.01. The latter indicates a significant reduction of CVS reserve capacity. Decrease of LF absolute values (less pronounced) and HF (more pronounced) in MG patients occurs against the background of changes in their ratio. If high-frequency influences are prevalent in GC patients, in MG patients low-frequency ones prevale, which reflects the relative excess of ANS sympathetic part in the latter case (Table 7).

Table 7

Parameters of cardiac rhythm variability in the groups of patients under study (according to SACRG), M (25; 75)

Index	GC	MG
TP, ms^2	2642,0 (1444,0; 4356,0)	1089,0 (576,0; 2662,6) *
VLF, ms^2	475,2 (139,2; 718,2)	285,6 (114,5; 660,5)
LF, ms^2	772,8 (492,8; 1049,8)	424,4 (136,9; 750,8) *
LFn,n.u	37,7 (24,6; 57,6)	54,0 (30,5; 72,9)*
HF, ms^2	1149,2 (302,8; 1697,4)	216,1 (81,0; 1162,8) *
HFn,n.u.	52,4 (29,8; 69,9)	35,8 (24,5; 56,7) *
LFHF, ms^2/ms^2	0,64 (0,36; 1,96)	1,44 (0,49; 2,89) *

* *p<0.05*

These rearrangements of regulatory influences on the cardiac rhythm in GC patients occur at the background of significant differences in central hemodynamics, which is characterized by a significant increase in end – diastolic volume to 94.4 (83.4, 115.6) versus 79.8 (74.7; 90.5), p <0.01; end-systolic volume up to 32.7 (27.0; 42.4) versus 24.8 (23.1; 30.2), p <0.01; systolic output to 62.3 (56.3; 69.7) versus 55.2 (52.4; 64.9), p <0.05; and VBC to 5.5 (4.9, 6.2) versus 4.7 (4.1; 5, 3), p <0.01. At the same time peripheral vascular resistance (PVR) index significantly decreases from 1539.5 (1386.1; 1681.2) versus 1320.4 (1096.6; 1576.5), p <0.01. Such differences testify to the presence of hypokinetic type of circulation and reflect certain hemodynamic tension in the small circle of blood circulation in GC patients under the formation of obstructive changes in the respiratory system. The latter is confirmed by the data of Table 8.

Table 8

Parameters of central hemodynamics in the groups of patients under examination (according to SACRG), M (25; 75)

Показник	ГП	ОГ
ESV, sm^3	79,8 (74,7; 90,5)	94,4 (83,4; 115,6) **
EDV, sm^3	24,8 (23,1; 30,2)	32,7 (27,0; 42,4) *
SV, sm^3	55,2 (52,4; 64,9)	62,3 (56,3; 69,7) *
VBC, dm^3	4,7 (4,1; 5,3)	5,5 (4,9; 6,2) *
CI	2,52 (2,06; 2,81)	2,81 (2,57; 3,39) *
PVR	1539,5 (1386,1; 1681,2)	1320,4 (1096,6; 1576,5) *
SVI	29,1 (24,9; 35,2)	32,4 (29,5; 37,7) *

** $p<0.05$; **$p<0.01$*

Data presented in table 9 also confirm hemodynamic system tension.

Namely, arterial baro-reflex sensitivity decrease in the low-frequency (BR_{LF}) and high-frequency (BR_{HF}) ranges are significant enough with respect to the reserves of BP regulation due to the combined rigidity of blood vessels and increased variability in systolic and diastolic BP, which may further develop and lead to its steady increase. And although according to routine measurements in the patients under examination, BP's average values do not exceed the normal ranges, the corresponding preconditions are created. Decrease of baroreflex sensitivity parameters may indicate deterioration of neuro-reflex mechanisms of regulation of respiration, especially in the case of the patients excessive body weight [10, 29, 30].

For a more complete assessment of BA patientse regulatory features of CVS integral indices were calculated. The indicator of "double product" (DP), which is calculated on the basis of heart rate and systolic BP and describes the overall capacity of the cardiovascular system, does not significantly differ in both groups and is at a level of moderately increased power, which confirms the level of economy of cardiovascular system in the state of rest "below average". Kerdo's index (KI) used to evaluate the activity of ANS does not differ in the groups under discussion and generally characterizes the moderate prevalence of sympatheticotonia. The latter is confirmed by the data of HRV (table 9).

Table 9

Parameters of central hemodynamics in the groups of patients under examination (according to SACRG), M (25; 75)

Index	GC	MG
Systolic BP, mm Hg.	120,0 (110,0; 123,0)	120,0 (100,0; 130,0)
Diastolic BP, mm Hg.	70,0 (69,0; 80,0)	76,0 (65,0; 80,0)
DP, mm Hg*min^{-1}	96,5 (81,3; 115,9)	99,9 (82,6; 125,0)
KI	0,13 (0,02; 0,24)	0,15 (-0,01; 0,26)
BR_{LF}, ms/mm Hg	9,38 (4,92; 21,60)	6,58 (4,35; 10,95) *
BR_{HF}, ms/mm Hg	9,10 (6,08; 26,38)	5,34 (3,12; 12,07) *

* *p<0.05*

To estimate the functional state of respiratory system we analyzed indexes of variability of uncontrolled respiration at short registration which turned out to be informative.

In GC and MG patients the total respiratory capacity (TRC) significantly exceeds normative values, which range from 290.0 to 635.0 l / min^2 [31]. At the same time, in GP patients the average values are significantly higher than in MG patients - 1373.4 (721.0; 3378.1) versus 1162.8 (625.0; 1814.8), p <0.05. This indicator for practically healthy subjects is closely correlated with MVB, which in general determines the capabilities of the respiratory system and we could assume that it is for this parameter that the groups would vary significantly. However, the index under discussion has no significant differences in both group. Significant increase in BA regulatory influences in VLF-range in both groups indicates an increase of neurohumoral regulatory mechanisms contribution. It is noteworthy that in the low and high frequency bands, the power of uncontrolled respiration differs more significantly (p <0.05). GC patients have lower activity in LF and HF ranges - 26.0 (11.6, 64.0) versus 44.2 (29.7, 61.6) and 818.0 (453.7, 1267.4) against 1217.0 (622.5; 2987.9) in MG patients, respectively. Relative contribution of LF and HF-components of VA, shows no difference in the GC but has a significant decrease in MG. At the same time, comparing the relative values of ER LF-components with the normative parameters, it is necessary to indicate a clearly established tendency to their decrease in comparison with practically healthy persons. At the same time, taking into account the ratio of LF / $HF_{res,}$ which in practically healthy individuals normally fluctuates within the limits 0.025-0.150 $(l / min)^2 / (l / min)^2$, a balanced variant of uncontrolled respiration regulation in both groups is in evidence. In general, in BA at the background of significant increase in overall respiratory capacity and the growth of neurohumoral regulatory influences, there is a significant decrease of the sympathetic link activity in the regulation of uncontrolled respiration (Table 10).

Table 10

Parameters of uncontrolled breathing variability in the groups of patients under study (according to SACRG), M (25; 75)

Index	Norm	GC	MG
TP_{res}, $(l/min)^2$	**290,0-635,0**	1373,4 (721,0; 3378,1)	1162,8 (625,0; 1814,8)*
VLFres, $(l/min)^2$	**1,3-4,8**	8,1 (6,3; 14,9)	7,3 (3,6; 18,5)
LFres, $(l/min.)^2$	**7,9-33,6**	44,2 (29,7; 61,6)	26,0 (11,6; 64,0) *
LFres n, n.o.	**2,2-14,7**	2,9 (1,4; 5,7)	2,7 (1,6; 6,9)
HFres, $(l/min)^2$	**207,4-547,5**	1217,0 (622,5; 2987,9)	818,0 (453,7; 1267,4) *
HFres n, n.o.	**78,0-94,0**	92,1 (84,2; 94,3)	85,3 (45,9; 93,6) *
$LF_{HF\ res}$, $(l/min)^2/(l/min)^2$	**0,025-0,150**	0,031 (0,016; 0,063)	0,040 (0,023; 0,102)

* *p<0.05*

In Table 11 the results of respiratory patterns indices are quoted. MG patients had a significantly higher respiration rate (RR) 18.8 (16.0; 23.3) versus 16.5 (12.6; 19.6), p <0.05, which was characterized by a significantly shorter duration of inhalation and exhalation (Table 11), and a lower respiratory volume (RV) at uncontrolled respiration 0.680 (0.500; 0.870) versus 0.965 (0.660; 1.245), p <0.01; while MVB index was not significantly different. So, it can be assumed that the reduction of RV in MG patients is compensated by RR.

On the other hand, in both groups patients with uncontrolled respiration, RV is significantly greater than in a group of practically healthy individuals, in the latter it is within the limits of 0.430 - 0.710 liters. As to other indicators of the respiration pattern, the significantly lower volumetric rate of inhalation 0.48 (0.36; 0.60) versus 0.56 (0.34; 0.76), p <0.05 in MG patients with uncontrolled voluntary respiration. The latter can be explained by a decrease in the diameter of the upper respiratory tract due to swelling of the mucous membrane, a decrease of inspiration muscle strength [32], or a deterioration of the elastic traction of the lungs, which can be formed in the development of emphysematous manifestations. In this case, the increased chest circumference in most MG patients is accompanied by its reduced mobility. According to the volume exhaust velocity (RV / T_{exh}) and the ratio of inspiration and exhalation duration (T_{inh} / T_{exh}) the groups of patients do not differ.

Table 11

Parameters of the uncontrolled breathing pattern in the groups of patients under study (according to SACRG), M (25; 75)

Index	GC	MG
T_{inh}, sec	1,6 (1,4; 2,1)	1,4 (1,1; 1,8) *
T_{exh}, sec	2,1 (1,7; 2,6)	1,8 (1,5; 2,2) *
RV, l	0,965 (0,660; 1,245)	0,680 (0,500; 0,870) *
RF, $min.^{-1}$	16,5 (12,6; 19,6)	18,8 (16,0; 23,3) *
RV/T_{inh}, l/sec	0,56 (0,34; 0,76)	0,48 (0,36; 0,60) *
RV/T_{exh}, l/sec	0,41 (0,29; 0,69)	0,41 (0,31; 0,52)
T_{inh}/T_{exh}	0,80 (0,70; 0,91)	0,82 (0,68; 0,94)
MVB, l	13,7 (9,3; 21,7)	13,1 (10,1; 16,8)

* *$p<0.05$*

The differences among the integral parameters that characterize cardiopulmonary synchronization (Table 12) were informative. Hildebrandt's index is used for a long time and has a sufficiently clear justification [33, 34] related to the frequency synchronization of cardiac contractions and respiration. The ratio VBC / MVB characterizes the volumetric synchronization of heart's pumping function and respiratory tract. This ratio is possible to investigate if only the simultaneous registration of spirometry and indicators of central hemodynamics is performed, and this is implemented in the device SACRG [35].

Table 12

Indices of cardiorespiratory synchronization in the groups of patients under study (according to SACRG), M (25; 75)

Index	GC	MG
IH	5,3 (4,3; 6,4)	4,5 (3,5; 5,9) *
VBC/MVB	0,295 (0,234; 0,551)	0,403 (0,325; 0,533) *

* *$p<0.05$*

IH normative values in rest are considered to be 2.2-4.9 st/res. Its variation reflects the work of regulatory systems aimed to maintain body's optimal energy supply [35]. The critical IH values are the ones higher than 6.5 st/res. In GC persons this index is on the upper limit of normative values, whereas in MG persons it is significantly smaller and slightly exceeds normative values (Table 12). The latter characterizes a more pronounced cardiopulmonary desynchronization in GC individuals, which may indicate the course of adaptive-compensatory reorganization in the cardiovascular and respiratory systems.

According to a combined study of CRS with the use of SACRG, it was found that the indicator of volumetric synchronization of the cardiovascular and respiratory systems (VBC / MVB) is individually sufficiently stable and varies under various influences within the range of 0.30-0.65 [36]. According to our data, in MG patients it corresponds to normative, whereas in GC patients it is significantly smaller. The latter confirms our assumptions regarding the greater desynchronization of CPS under BA controlled course according to the data of IH.

In general, characterizing the regulatory features of BA course one should note that GC patients' values do not differ greatly from normative ones, while TP_{res} turned to be one of the most significant and exceeded the normative values due to the increase of high-frequency (HF_{res}) component of breathing variability. The same was increase of RV index under ultrasonic spirometry at rest.

The changes of MG patients regulatory parameters related to the cardiointervalometry and characterized worse intraventricular conductivity (QRS), ventricular electric systole (QTC) and their repolarization (ST), as well as HRV indices. These proved about lower regulation reserves of cardiac rhythm (TP, LF, HF) and sympathicotonia tendency (LFHF). Central hemodynamic indices indicated to their significant tension, parameters of baroreflexes activity (BR_{LF}, BR_{HF}) showed baroreceptors sensitivity decrease. This may be a significant marker of complications and concomitant pathology, in particular, AH. Significant differences were observed in indicators of uncontrolled respiration regulation (TP_{res}, LF_{res}, HF_{res}, $HF_{res}n$), which had lower values than GC patients, but nevertheless were higher than those in a group of practically healthy individuals. The same features were observed on the side of the RV. But that were the lower values of inhalation volume velocity (RV/ T), which most likely indicate a decrease in elastic traction of lungs due to emphysematous manifestations and which occured with a chest and abdomen volume increase accompanied by decrease in thoracic excursion. But the most significant peculiarities of the formation of regulatory mechanisms in the uncontrolled course of BA is the approximation to the normative values of the parameters of cardiopulmonary synchronization (IH and VBC/MVB) in comparison with GC persons, which showed a certain stabilization of intersystemic relationships at this stage of the pathological process. That is, against the background of CPS functional parameters deterioration at BA uncontrolled course in comparison with the controlled one stabilization of cardio- respiratory synchronization takes place and this may be a marker for the completion of adaptive-compensatory reconstructions at this stage of the pathological process development.

Conclusions: 1. According to the data of the comprehensive examination with the use of spiroarteriocardiorhythmography, the known regulatory features of the course of uncontrolled BA were confirmed and new ones were established. The data obtained can be used as criteria for determining the severity of the disease in the patients with asthma.

2. Indicators of uncontrolled respiration variability at short measurements show that in BA at the background of a significant increase in overall respiratory capacity and growth of neurohumoral regulatory influences there is a significant decrease in the activity of the sympathetic link in the regulation of uncontrolled respiration and the relative decrease of inspiration volume velocity. This should also be taken into account in determining the severity of asthma.

3. Taking into account the expressiveness and mobility of the methods under discussion, we consider expedient to use it in the practice of patients' monitoring and screening at the out- patient stage of treatment.

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