Chaotic Dynamics of Long-term Prevention of Disorders of Central Hemodynamic Parameters and Parameters of Respiratory Function in Patients with Chronic Obstructive Pulmonary Disease with Comorbid Conditions in the North

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The aim of the study is to study features and prevention of complications in patients with chronic obstructive pulmonary disease (COPD) with comorbid conditions (CC). Clinical manifestations and dynamics of indicators echocardiography (EHCG) and spirography in visiting northern residents were evaluated for 10 years. We examined in dynamics 82 COPD patients with CC from the main and 85 from control groups in whom indicators of echocardiography and spirography were studied. The most pronounced therapeutic effect was observed in patients of the main group receiving the most optimal program for the management of patients.

Key words: Chronic obstructive pulmonary disease, Comorbid conditions, Indicators of echocardiography, Indicators of spirography, prevention, Rehabilitation.

The relevance of the study is determined by a significant prevalence (18% higher than in the Russian Federation) of chronic obstructive pulmonary disease (COPD) in the population living in specific ecological conditions at high latitudes, increasing morbidity and mortality indicators in the rapidly emerging cardiopulmonary failure[1,2,3]. According to the forecasts by 2020, COPD will cause 4.7 million. cases per year and will be released on the third leading cause of death[3]. The relevance of the topic is also determined by high prevalence (60-80%) of comorbid conditions in patients with COPD with complications (PAG with crises, stroke,

myocardial infarction, decompensation of chronic pulmonary heart, ARF and pneumonia), life-threatening, especially in the North[3,4,5].

Formation and decompensation of chronic pulmonary heart disease (the most serious complication of COPD) in modern therapeutic clinic is often associated with other cardiovascular diseases and life-threatening complications (ischemic heart disease, myocardial infarction, stroke), respiratory complications (ARF or adherence of asthma to COPD, viral and bacterial pneumonia after flu) in patients with COPD. This group of comorbid conditions leads to the mutual burden of the flow of cardiopulmonary process, accelerate the pace of morbidity and mortality in COPD patients[6,7].

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The pathogenesis of myocardial damage in COPD patients with CC (comorbidity conditioins) is due not only to chronic hypoxia, pulmonary hypertension, infectious and toxic factors, but also the CC (pneumonia, coronary heart disease, arrhythmias, systemic arterial hypertension, adherence asthma, type 2 diabetes, and others.) which can be as comorbidities in COPD in "starting period" and join in the process of long-term COPD. In this case, the CC, aggravating hypoxia, metabolic disorders (acidosis) of the myocardium and other changes of homeostasis, accelerate the development of systolic and diastolic dysfunction, decreased contractility of the heart, congestive heart failure, death[8,9]. Therefore, prevention of progression of EhoCG disorders in patients with this kind of mixed-pathology is an important component of clinical prognosis.

Prognosis is more unfavorable when the COPD is combined with the group of cardiovascular diseases. Patients with severe COPD forms are at high risk of sudden death, the causes of which are: severe pneumonia, dysrhythmia, myocardial infarction, stroke, adherence asthma to COPD with ARF episodes, inadequate treatment[10,11].

Practice has shown that conventional methods of clinical examination of COPD are not always suitable for the conditions of the North, because it does not take into account the peculiarities of the development and course of COPD in this region[5]. In the North people especially adapted to the cold, which is accompanied by the formation of stress syndrome of homeostatic systems, changes in lipid metabolism, activation of cardio respiratory function, alteration of hormonal function, increased respiratory minute volume, breathing performance, systolic pulmonary artery pressure[5,8, 12]. Secondary prevention of complications in this mixed-pathology is under development. Methods of primary and secondary prevention of COPD in specific environmental conditions at high latitudes are insufficiently developed. Questions of treatment, prevention of exacerbations of respiratory infections and complications of COPD in urban North, are directly related to the features of COPD, which are not well understood and taken into account in the preparation of regional standards. In this context it becomes especially urgent to develop new methods of diagnosis, treatment, health examinations, rehabilitation of patients with COPD in the framework of the system analysis, the dynamic of attractors of the state vector of the human body behavior (VSHB). It is related with the new understanding of the influence of the environment on the dynamics of functional systems of the organism (FSO), the quality of life of people living in high latitudes in the RF, since the dynamics of ecofactors of urbanized North often has a pronounced chaotic regime. In clinical practice guidelines for the management of patients with COPD, COPD treatment standards in outpatient there are no recommendations for optimal management program of clinical examination and rehabilitation of patients with COPD in the North[12,13,14]. In the available literature there are practically no studies on immunorehabilitation of this category of patients in the North.

The aim of our study was to evaluate the effectiveness of secondary prevention of violations of central hemodynamic parameters and parameters of respiratory function in COPD patients with comorbid conditions in the North.

MATERIALS AND METHODS

This study involved 167 outpatients with COPD with moderate and severe (according to the criteria GOLD, 2008) course[13] with comorbid conditions. All the patients were divided into 2 groups: Group 1 (main) - 82 patients with COPD in conjunction with the CC, the average age - 48,6 ± 2,8 years; Group 2 (control) - 85 COPD patients with CC, the average age - 48,5 ± 2,2 years; duration of the disease in both groups was similar and was 7,8 ± 3,3 years.

All patients underwent clinical study with the assessment of respiratory function (RF): analysis of flow-volume curve and indicators LVC, FEV1, MOS75 spirometry (MasterLabPro, "ErichJaeger", 1995). Peak flow rates were estimated with the definition of lability of daily peak expiratory flow (PEF). Biochemical parameters of blood (lipid) with the calculation of atherogenic index were defined, underwent ultrasound examination of the heart, blood pressure monitoring was performed.

Comprehensive ultrasound intracardiac hemodynamic study was performed on the unit

with vector sensor with a frequency of 3.5 MHz and 2.5 with M - and B - Doppler (PW, continuous, color Doppler) and computer processing of the data obtained by the standard method of precordial echocardiography synchronous recording of ECG in standard lead II.

Determination of the volume of the right ventricle was performed by the standard technique of two orthogonal planes of section. End-diastolic volume and end-systolic volume of the right ventricle were calculated, shock and cardiac index, ejection fraction (FE) of RV. Pressure in the LA was determined by pulsed dopplercardiografy by the standard technique. Systolic pressure, mean pressure in the LA and the total pulmonary resistance were calculated. The study of central hemodynamic parameters were determined by ehodopplerocardiografy in M -, and B - and Doppler modes according to the standard method proposed in 1981 by the American Heart Association[8,12].

Echocardiography in M -, and B - mode, dopplerechocardiography in pulse, continuous wave and color mode was made on echocardiograph «Acuson Sequoia-512» (Acuson, USA) according to traditional methods [8]. The following indicators were calculated: end-systolic size (ESS, cm), End-diastolic dimension (EDD, cm.), size of LV; the diameter of the right ventricle (DRV, cm.); the thickness of the anterior wall of the right ventricle (TAWRV, cm.); the size of the left atrium (LA RP, cm.); the thickness of the posterior wall of the left ventricle (TZSLZH, cm.). End-systolic (ESV ml) and end-diastolic (EDV ml) volumes of the left ventricle and RV were determined by the formula L. Teicholtz, calculated left ventricular stroke volume (SV, ml), left ventricular ejection fraction (EF%), ejection fraction (FI RV). The study of blood flow in the RV outflow tract was performed using pulsed Doppler echocardiography in the wave regime. Following indexes were calculated: Vp, m / s - maximum flow rate in the RV outflow tract; AT, m / s - while accelerating the flow in the outflow tract of the RV; ET, m / s time release from the RV into the pulmonary artery; AT / ET ratio of acceleration time to ejection time. The calculation of the maximum systolic pulmonary artery pressure (MPAP mm Hg. Art.) was carried out on the jet velocity of tricuspid regurgitation in continuous wave Doppler mode by formula: MPAP = RV

systolic pressure = systolic pressure gradient transtrikuspidal + pressure in right atrial. System blood pressure was measured by N.S. Korotkov method.

Diastolic function of LV and RV using doppleroehocardiografy in pulsed mode transtrikuspidalny and transmitral blood flow were studied. Following indexes (for RV and LV) were calculated: E, m / s - maximum velocity of early diastolic filling; A, m / s - the maximum speed of atrial diastolic filling; E / A - speed ratio E / A.

The main group of patients was intensified by surveillance program: as a basic therapy: formoterol 4.5-12 mg per day; budesonide 160 mcg 2-4 times daily or Symbicort 2-4 times a day, or Foradil Combi; tiotropium (18 ug per day); on the testimony beorodual, teopek 0.3 2 times a day. Also patients from the main group received: antihypertensive drugs (mikardis or lisinopril + indapamide), nebulizer therapy. Modern treatment of comorbid conditions was. All patients aged Ã50 years received aspirin-cardio, cardiomagnil on the testimony, xanthines (Crestor), drugs nitroglycerin (monocinque), Ca-antagonists (amlodipine), if arrhythmia: amiodarone, propafenone, dronedarone, ECS, in IHD - stenting; radiofrequency ablation and other treatment[15].

Rehabilitation programs include: chest massage, diathermic therapy, laser therapy, dosage walking, physiotherapy (drainage breathing exercises) by the method of V.F. Ushakov[4,16,17]. Patients with secondary bronchiectasis received medical BFS with inhalation solution dornase, with the introduction of antibiotics after the sanitization of the bronchi. All patients in the cold season had the prevented of cold BOS by the method of V.F. Ushakov[4]. The frequency of visits to the clinic was 8-12 times per year during the first two years. The observation period is 10 years.

Control group of COPD patients with CC had conventional clinical examination program, bronchodilator therapy: inhaled corticosteroid beclomethasone dipropionate 800mkg / day in combination with short-acting $ß_2$-agonists (salbutamol) or anticholinergic drug ipratropium bromide (Berodual). The frequency of visits to the clinic was 3-4 times a year, observation period - 10 years, regular comprehensive treatment (including physiotherapy) was not conducted.

Exclusion criteria were: severe liver

disease, cancer and associated hematologic disorders, renal, hepatic failure.

All patients had to written informed standard form consent, approved by the Ethics Committee HMGMA.

Systematization of the material and presented results of calculations were performed using spreadsheet software Microsoft EXCEL, statistical calculations were performed using the package Microsoft Statistica for Windows 2000, «Biostat» authors program (V.M. Es'kov)

Scientific and practical importance: allowing for the COPD with CC were developed an advanced program of secondary prevention of complications that threaten the life, improve the quality of life of patients, providing a reduction in disability 1.5-2, 3-4 times mortality in patients with mixed pathology, control of COPD with CC of 75-85% patients.

Possible applications: advanced management programs in COPD patients with CC will be implemented in cities hospitals, districts of Khanty-Ugra.

RESULTS AND DISCUSSION

In implementing the improved program for management patients for the prevention of complications in patients with COPD with the CC established a significant increase in quality of life (2 times), reduction in the frequency of exacerbations, episodes of acute respiratory failure in 3.3 times; the incidence of chronic pulmonary heart (compensated and decompensated) in 2 times. From the cardiovascular complications - reduction of chronic heart failure in 2.9 times, acute myocardial infarction in 16 times, stroke - 2,4 times; severe arrhythmias - 2.4 times. Reduced the burden of COPD, reduced the proportion of patients with disabilities II-III groups, and in general, decreased in 4 times mortality in patients observed by an improved program.

The studies of systolic and diastolic function indexes in patients from main and control group in the initial state found that rates UOLV (were: 89,0±1,2 and 85,8±1,54) INMMLV (were: 152,8±2,30 and 138,3±2,4), TPSRV (0,63±0,3 and 0,52±0,24), KSOLV (61,3±1,32 and 62,2±2,12), KDOLV (152,5±1,98 and 141,8±3,0), KDRRV (4,3±0,10 and 3,47±0,12), KSRLV (3,62±0,55 and

3,81±0,12), SDLA (55,4±1,8 8 38,4±1,72), SAP (162,8±4,2 and 165,2±3,8), DAD (90,4±2,4 and 92,5±2,6) were much higher ($p<0,05$; $p<0,001$) then in (table.1), indexes of FVLV (were: $53,7 \pm 1,76$ and $50,3 \pm 1,55$), FIRV ($52,1 \pm 1,44$ and $51,1 \pm 1,38$), E / APV ($0,77 \pm 0,045$ and $0,77 \pm 0.04$), E / ALV ($0,72 \pm 0,20$ and $0,79 \pm 0,05$) were reliably lower then ($r<0,05$; $r<0,001$) such in healthy people that indicates a violation of systolic and diastolic function of the left and right ventricles of the heart, as in patients with primary and in control subjects.

Along with this, in the course of clinical examination performance echocardiography in patients with a core group of 1-3 years as close as possible came to the level of healthy individuals or normalized. In this case, after 10 years of follow up in patients with a core group of systolic function of the left, right ventricle: UOLV, INMMLV, TPSPV, KSOLV, KDOLV, KDRPV, KSRLZH, PASP, SBP, DBP (were $73,5 \pm 0,46$; $128,0 \pm 0,46$; $0,41 \pm 0,017$; $47,6 \pm 2, 36$; $127,6 \pm 0,374$ $3,06 \pm 0,45$; $3,47 \pm 0,03$; $25,7 \pm 0,37$; $126,2 \pm 3,6$; $80,4 \pm 2,1$) did not differ from those in healthy subjects (Table 1), and rates of left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (FIPZH) as close as possible ($r<0,05$; $r<0,001$) to those in healthy individuals. However, the diastolic function of the left (E / ALV) and right (E / APV) ventricles were normalized by the end of the clinical examination (were: 1,18±0,007 and 1,13±0,005).

It should be noted that the sizes of KDRLV and KDRRV in individuals from main and control groups during the clinical examination was not significantly changed.

In this KDRRV ($3,06 \pm 0,45$) by the end of the clinical examination in patients of the main group did not differ ($r<0,05$) from that ($3,05 \pm 0,005$) in healthy individuals from control group (was: $3.64 \pm 0,11$). KDRRV considerably exceeded ($r<0,05$) that in healthy individuals (Table 1). In patients in the control group SBP (mm Hg) was significantly decreased (up to $147,8 \pm 3,4$), but not to normal.

At the same time it was found that the patients from the main group total volume (vX) and overall asymmetry (rX) during clinical examination decreased significantly with 1.12999848E0011 and 50.3595 in 2002-2005 to 198 and 349.2400 16.2300 in 2011, indicating a decrease of chaotic dynamics parameters echocardiography, stabilization of a functional system, the positive

therapeutic effect of an optimal program of treatment and rehabilitation of patients from the main group.

　　　At the same time in the control group vX and rX increased significantly (from 1.32121906 E0012 and 7.2098 in 2002 to 2.63955552E0012 and 11.6084 in 2011), indicating a significant spread indicators echocardiography in patients in the control group, a low therapeutic effect of clinical examination.

Table 1. Central hemodynamic parameters in patients from main(n = 28) and control (n = 28) groups of COPD in their clinical examination

S. No.	Indicators	Healthy Main group (n=28) Control group (n=28)	2002 Main group (n=28) Control group (n=28)	2011 between the rates in 2002 and 2011	Difference
1.	UOLV	73,6±2,2	89,0±1,2 85,8±1,54	73,5±0,46 82,3±2,22	p<0,001 p>0,05
2.	E/ARV	1,25±0,030	0,77±0,045 0,77±0,04	1,13±0,005 0,71±0,052	p<0,001 p>0,05
3.	e/ALG	1,28±0,02	0,72±0,020 0,79±0,05	1,18±0,007 0,75±0,066	p<0,001 p>0,05
4.	INMMLV	126,2±2,6	152,8±2,30 138,3±2,4	128,0±0,46 133,1±2,50	p<0,001 p>0,05
5.	TPSRV, cm.	0,33±0,04	0,63±0,03 0,52±0,24	0,41±0,017 0,31±0,13	p<0,001 p>0,05
6.	KSOLV, ml	50,6±2,20	61,3±1,32 62,2±2,12	47,6±2,36 66,5±2,43	p<0,001 p>0,05
7.	KDOLV, ml	127,4±2,5	152,5±1,98 141,8±3,0	127,6±0,37 149,6±2,56	p<0,001 p>0,05
8.	KDRLV, cm	5,15±0,04	5,13±0,16 4,76±0,21	5,06±0,058 5,4±0,25	p>0,05 p>0,05
9.	KDRRV, cm	3,05±0,05	4,3±0,10 3,47±0,12	3,06±0,45 3,64±0,11	p>0,05 p>0,05
10.	KSRLV, cv	3,44±0,04	3,62±0,055 3,81±0,12	3,47±0,03 3,86±0,12	p<0,05 p>0,05
11.	SPLA, mm hg.	23,1±0,5	55,4±1,8 38,4±1,72	25,7±0,37 43,0±2,60	p<0,001 p>0,05
12.	FElV, %	62,8±1,0	53,7±1,76 50,3±1,55	58,8±0,50 44,17±2,08	p<0,05 p<0,001
13.	FIRV, %	62,6±1,6	52,1±1,44 51,1±1,38	58,6±0,52 43,8±1,14	<0,05 p<0,001
14.	SAD, mm.hg.cm	122,0±3,2	162,8±4,2 165,2±3,8	126,2±3,0 147,8±3,4	p<0,001 p<0,001
15.	DBP, mm.rt.st.	81,2±1,8	90,4±2,4 92,5±2,6	80,4±2,1 86,8±2,3	p<0,05 p>0,05

Table 2.

	2002	2005	2007	2011
2002	0.0000	79.1328	45.3881	53.6597
2005	79.1328	0.0000	51.3972	55.1323
2007	45.3881	51.3972	0.0000	21.8643
2011	53.6597	55.1323	21.8643	0.0000

Table 3.

	2002	2005	2007	2011
2002	0.0000	9.3017	8.3413	12.0654
2005	9.3017	0.0000	6.0849	5.4803
2007	8.3413	6.0849	0.0000	5.9188
2011	12.0654	5.4803	5.9188	0.0000

Matrix identification of interattractors Zh distances between the centers of the chaotic state vector parameters of echocardiography in COPD patients from the main group with CC before and after clinical examination.

The calculation of matrices of distances between inter-attractors chaotic centers showed that in patients from the main group (Table 2), in contrast to those of the patients in the control group (Table 3) there is a more pronounced reduction in the distance between VSHB attractors only in the main group, suggesting stabilization of the FSO and a better therapeutic effect in patients of this group.

Matrix identification of interattractors Zh distances between the centers of the chaotic state vector parameters of echocardiography in COPD patients from the control group with CC before and after clinical examination.

Thus, long-term use of improved management programs in COPD patients with CC managed to significantly reduce the rate of the

complications of accession in 2-16 times (arrhythmias, asthma, bronchiectasis secondary, etc.). CC to COPD, which was accompanied during the decade of the clinical examination in the main group maximum close of systolic and diastolic function indexes of the heart to those in healthy individuals. Reverse pattern was observed in the control group whose echocardiography parameters have not changed significantly, or showed signs of worsening of cardiac dysfunction. So in the control group at the end of the clinical examination parameters of contractile function of the heart (FILV, FIRV) dropped significantly. The indicator TPSRV decreased (from 0.41 cm to 0,31 cm at a rate of - 0.33 norm), which can be explained by the appearance of degeneration of the myocardium of the right ventricle on the background of frequent exacerbations of COPD with progressive hypoxemia in patients with CC from control group. It should be noted that in the main group in spite of the positive developments in echocardiography indicators by the end of the

Table 4.

	2002	2005	2007	2011
2002	0.0000	7.9687	11.0793	12.4700
2005	7.9687	0.0000	8.3815	9.2736
2007	11.0793	8.3815	0.0000	1.5000
2011	12.4700	9.2736	1.5000	0.0000

Table 5.

	2002	2005	2007	2011
2002	0.0000	25.0243	25.0321	22.6795
2005	25.0243	0.0000	2.9942	4.4048
2007	25.0321	2.9942	0.0000	2.5123
2011	22.6795	4.4048	2.5123	0.0000

Table 6. Parameters spirographic indexes in patients from main (n = 28) and control (n = 28) groups of COPD with the CC in the course of their medical examination

Indicators	Healthy	2002 Main group (n=28) Control group (n=28)	2005 Main group (n=28) Control group (n=28)	2011 Main group (n=28) Control group (n=28)	2011 Main group (n=28) Control group (n=28)	Difference between the rates in 2002 and 2011
1. LVC (%D)	88,7±2,5	49,8±1,21 61,8±1,8 p<0,05	66,8±1,35 54,8±1,9 p<0,001	63,4±1,0 53,9±2,1 p<0,001	63,3±0,9 52,7±2,1 p<0,001	p<0,001 p<0,001
2. FEV$_1$	83,7±3,2	47,2±2,26 47,1±2,2 p<0,05	54,8±1,12 45,9±2,2 p<0,001	54,0±0,9 40,5±1,6 p<0,001	53,9±0,71 38,1±1,7 p<0,001	p<0,05 p<0,05
3. MOS$_{75}$	86,5±3,1	24,2±1,3 28,3±1,67 p<0,05	40,5±0,94 24,9±1,3 p<0,001	44,3±1,41 25,4±1,6 p<0,001	41,7±0,9 22,0±1,7 p<0,001	p<0,001 p<0,05

clinical examination a number of indicators (E / ARV, E / ALV, FILV) were lower than those in healthy individuals, although compared with the original data, these figures were significantly (rÂ0,001) higher, indicating a positive preventive effect of improved program of management of patients from the main group.

At the same time, a multivariate analysis of indicators of effectiveness of rehabilitation in COPD patients with CC showed that only patients from the main group had experienced marked reduction of rX and vX, the distance between the centers of chaotic and stochastic, that indicated a decrease in the chaotic dynamics of echocardiography indexes, stabilization of functional system, the positive therapeutic effect of medication and rehabilitation program in patients from the main group.

The studies of spirography indicators in patients from main and control group found that total volume of vX and total volume of asymmetry rX three-dimensional phase space that included in 2002: 104 728.0000 and 9.8949 during the clinical examination decreased by 2005 (according to 42 000.0000 and 7.1980) remained at a low level in 2007 (were respectively 52 360.0000 and 8.8781) and in 2011 (were: 19 250.0000 and 8.2083), indicating: a reduction of chaotic quasi-attractor, the stabilization of the FSO, the positive effect of control actions on the course of COPD in patients with CC from the main group.

At the same time, the control group had vX phase space volume and total volume of asymmetry rX, in 2002, respectively: 140 400.0000 and 12.3097 and decreased by 2005 (were following: 116 600.0000 and 8.8080) and remained at a high level in 2007 (were: 92 235.0000 and 8.0352) and in 2011 (were: 108 570.0000 and 9.0429), indicating of the instability of the functional system (FSO) and the instability of the therapeutic effect of clinical supervision in patients with a comparison group.

Matrix identification of inter-attraktor Zh distances between the centers of the chaotic state vector parameters of ERF control group patients with COPD and CC during the clinical examination.

Matrix identification of inter-attractor Zh distances between the centers of the chaotic state vector parameters of ERF from the main group patients with COPD CC during the clinical examination.

The calculation of matrix of the interattractor distances between the chaotic centers showed that in patients from the main group (Table 4), in contrast to those of the control group patients (Table 5) there is a more pronounced reduction in the distance between attractors VSHB only in the main group, suggesting stabilization of the FSO and a better therapeutic effect in the clinical examination of patients in this group.

In the process of clinical examination parameters LVC, FEV1, MOS75 (%) in patients from the main group significantly (r<0,001) increased accordingly: from $49,8 \pm 1,21$; $47,2 \pm 2,26$; $24,2 \pm 1,3$ (in 2002) to $63,6 \pm 0,9$; $53,9 \pm 0,71$; $41,7 \pm 0,9$ (in 2011), while in the patients from control group they significantly (r<0,05, r<0,001) decreased (Table 6)

Thus in the patients from the main group (in contrast to the control group) in the process of medical treatment and rehabilitation indicators LVC, FEV1, MOS75 are much closer to the level of healthy individuals, and indicators rX, vX decreased, indicating a stabilization of the functional system of the patients, the positive effect of the optimal program management of patients of the main group.

CONCLUSION

Enhanced long-term program of clinical examination and rehabilitation of COPD patients with CC helps to stabilize or proxy for echocardiography and spirography indexes to those in healthy individuals.

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