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THE CHANGES OF THE FUNCTIONAL INDICES OF ENDOTHELIUM STATE AND CLINICOFUNCTIONAL PARALLELS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND IN CONDITIONS OF ITS COMORBIDITY WITH ESSENTIAL HYPERTENSION

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ПРОМЕНИ НА ФУНКЦИОНАЛНИТЕ ПОКАЗАТЕЛИ ЗА СЪСТОЯНИЕТО НА ЕНДОТЕЛА И КЛИНИКОФУНКЦИОНАЛНИ ПАРАЛЕЛИ ПРИ ПАЦИЕНТИ С ХОББ И ПРИ УСЛОВИЯТА НА КОМОРБИДНОСТ С ЕСЕНЦИАЛНА ХИПЕРТОНИЯ

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Abstract. *An analysis of the data about the functional state of endothelium, the structural-functional indices of the right and left ventricles and the indices of bronchial patency in 64 patients with chronic obstructive pulmonary disease (COPD), the II stage (females – 22, males – 42, mean age – 54.8 ± 2.5), among whom 32 patients had comorbid essential hypertension (EHT), is presented in the article. It has been showed that the patients with COPD in conditions of its comorbidity with EHT have the most apparent manifestations of the endothelial dysfunction. Participation of some indices of the endothelial function in mechanisms of early development of myocardial dysfunction of ventricles and intensity of the changes of bronchial patency was determined.*

Key words: *chronic obstructive pulmonary disease, essential hypertension, endothelial dysfunction, systolic myocardial dysfunction, diastolic myocardial dysfunction, external respiration function*

Резюме. *В статията се представя анализ на данни относно функционалното състояние на ендотела, структурно-функционалните индекси на дясната и лявата камера и индексите на бронхиалната проходимост при 64 пациенти с ХОББ, 2 стадий (жени – 22, мъже – 42, средна възраст 54,8 ± 2,5 г.), като 32 от пациентите са с коморбидна есенциална хипертония (ЕХТ). Доказва се, че пациентите с ХОББ в условията на коморбидност с ЕХТ имат най-силно изразени прояви на нарушена ендотелна функция. Направена е оценка на участието на някои показатели на ендотелната функция в механизмите на ранното развитие на нарушена миокардна функция на камерите и на интензитета на промените на бронхиалната проходимост.*

Ключови думи: *ХОББ, есенциална хипертония, нарушена ендотелна функция, нарушена систолна миокардна функция, нарушена диастолна миокардна функция, функция на външното дишане*

Introduction

The American physician and scientist A.R. Feinstein was the first to demonstrate the phenomenon "comorbidity" in the clinic of internal disease in 1970 [13]. A quarter of century afterwards, a most precise definition was given to this process. According to it, the comorbid pathology of a patient is determined as a combination of two and/or more chronic diseases which are interconnected pathogenically and contemporaneously regardless of activity of each of them [19, 24]. Nowadays, comorbidity is considered as a new pathology which complicates the course of the main disease from the clinical point of view, leads to the change of a regular clinical picture, becomes a reason for the fatal complications development and is an independent risk factor of lethal outcome [4]. Within this framework, we would like to cite the data by M. Akker et al. [9] and M. Fortin et al. [14] which testify about the following: a mortality risk increases to 5-10% in case of the simultaneous presence of two diseases, and to 70-80% in case of presence of 5 and more diseases.

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases, first of all, essential hypertension (EHT) leading in the structure of morbidity are considered as the main reasons for mortality in the developed counties of the world. The clinical significance of these diseases is constantly increasing [17, 18, 20], it happens especially often in cases of cardiorespiratory association [21]. Taking into account the significance of the functional state of the cardiovascular and bronchopulmonary systems changes as prognostic factors of the course of diseases [1], it is necessary to emphasize that every 10% of decrease of the forced expiratory volume per 1 second increases mortality of the patients with COPD by 28% [22]. Besides, the structural-functional state of the right ventricle is considered as an important mortality predictor [6], and myocardial dysfunction testifies about a high independent importance of cardiovascular factors in development of COPD [15] as well as the fact that the left ventricular hypertrophy is an independent factor which worsens the prognosis [23].

The foregoing and also the literary data about the role of endothelial dysfunction in genesis of COPD and EHT [5, 7] and their frequent combination – to 75% [12] were a precondition for carrying out this study.

The aim of the study was to reveal changes of the functional state of endothelium and determine their possible influence upon the structural-functional indices of ventricles and bronchial patency in patients with COPD combined with EHT.

Material and methods

The group of the examined individuals included 64 outpatients with COPD (the II stage) [16] (females – 22, males – 44, mean age – 54.8 ± 2.5 years), among whom 32 patients have comorbid EHT of the II degree [25]; the patients' status was medicamentous compensation. All the patients were divided into 2 groups: the main group (COPD combined with EHT) and a comparative group (COPD). The representatives of the both groups were of the same sex and age.

The carrying out treatment of both COPD and EHT met the requirements of the protocol.

The total content of the stable metabolites of nitrogen oxide (NO_X) was determined in blood serum by the spectrophotometric method by means of the assay kit "Total NO» ("RL-system", USA) in accordance with the kit instructions; the determination of a level of endothelin-1 (ET-1) was carried out by the immunoenzymatic method by means of the assay kit BIG Endothelin-1 (HUMAN), Peninsula Laboratories inc., Division of Bachem.

The diameter of the right brachial artery (D_{RBA}, mm) in transverse and longitudinal planes (ultrasound scanner Aloka 5000 Pro Sound (Japan), linear sensor and operating frequency 13 MHz) was taken into account for analysis of the endothelium's functional state. Endothelium-dependent vasodilatation (EDVD) was determined within 90 sec after a 5-minute compression of a shoulder by pressure 300 mm Hg by means of calculating the percentage of the change of an arterial diameter in comparison with the initial one. Endothelium-independent vasodilatation (EIVD) was determined as a maximal value of the percentage of arterial dilatation during 5 minutes after a sublingual intake of 0.5 mg nitroglycerin at once-a-minute registration.

Estimation of the functional condition of the right parts of a heart was carried out by means of two-dimensional echocardiography (Toschiba SSA, 380A Powerwission (Japan) by the generally adopted method. The following indices were estimated: diameter of the right atrium (D_{RA}, cm), end-diastolic dimension of the right ventricle (EDD_{RV}, cm), thickness of myocardium of the right ventricle (diastolic) ($TMRV_D$, mm), isovolumic relaxation time ($IVRT_{RV}$, sec), early diastolic filling velocity (E_{TT}, m/sec) and late diastolic filling velocity (A_{TT}, m/s) (by indices of transtricuspid blood flow by means of Doppler ultrasonography), ratio E/A_{TT} (conventional units). Systolic pressure in the pulmonary artery (SP_{PA}, mm Hg) was determined by the value of a transtricuspid gradient. Blood peak flow in the outflow tract

of the right ventricle ($V_{max\ RV,}$ m/sec) (by indices of transpulmonary blood flow) and shortening fraction (SF, %) were analyzed, too.

The following indices were taken into account for estimation of the functional condition of the left parts of a heart: diameter of the left atrium (D_{LA}, cm), end-diastolic dimension of the left ventricle ($ED-D_{LV}$, cm), thickness of interventricular septum (IVS_D, cm) and posterior wall of the left ventricle (PWLVD) (diastolic), stroke index (SI, ml/m^2) and cardiac index (CI, l/min/m^2), blood peak flow ($V_{max\ LV}$, m/s) in the outflow tract of the left ventricle (by indices of transaortal blood flow), ejection fraction (EF, %), isovolumic relaxation time ($IVRT_{LV}$, s), early diastolic filling velocity (ETM, m/s) and late diastolic filling velocity (A_{TM}, m/s) (by indices of transmitral blood flow by means of Doppler ultrasonography), ratio E/A_{TM} (conventional units).

Estimation of the external respiration function was carried out by means of spirometer Spirosift (Japan) with analysis of following indices: vital capacity (VC), peak expiratory flow rate (PEFR), forced expiratory volume per 1 second (FEV_1), forced expiratory flow 25%, 50% and 75% forced vital capacity (FEF_{25}, FEF_{50}, FEF_{75}).

The obtained research results in the patients of the main and comparative groups were compared between themselves and also with the indices of practically healthy individuals (n = 15) who were of the same sex and age.

Statistical proceeding of the results was carried out by parametric statistics. The arithmetic means (M), error in means (m) were calculated. Student's t-test and nonparametric Kolmogorov-Smirnov's test were used to estimate the significance of differences. The correlation analysis was realized by the method of linear correlation Pierson's coefficient (r) with the help of the computer Celeron 650, software SPSS 11.0.

Results

The results of the carried out research are given in the tables below. The most informative indices characterizing clinicofunctional and clinicolaboratory parameters of endothelial function (table 1), structural-functional indices of the right (table 2) and left (table 3) ventricles and a functional state of external respiration's apparatus (table 4) were analyzed. The significance of differences for the all indices is marked in this way:

*p < 0,05, **p < 0,01, ***p < 0,001 – with a group of practically healthy individuals

#p < 0,05, ##p < 0,01, ### p < 0,001 – between the patients of the main and comparative groups

Thus, the obtained results reflected objectively the functional indices of a bronchopulmonary system, the cardiac hemodynamics of the right and left parts of a heart, and also the clinicofunctional parameters of the endothelial function. Discussion of the obtained results is given below.

Table 1. Indices of the functional state of endothelium

Indices	Practically healthy individuals n = 15	Patients COPD (comparative group) n = 32	Patients COPD+EHT (main group) n = 32
D_{RBA}, mm	3.4 ± 0.2	4.7 ± 0.3**	5.2 ± 0.1***
EDVD, %	12.1 ± 0.6	13.7 ± 0.6	10.2 ± 0.4***###
EIVD, %	13.8 ± 0.7	9.0 ± 0.3***	7.0 ± 0.2***###
NO_X, mcmol/l	36.3 ± 0.8	26.5 ± 1.2***	16.2 ± 1.3***###
ET-1, pmol/l	3.2 ± 0.5	4.0 ± 0.4	5.2 ± 0.10***###

Table 2. Structural-functional indices of the right ventricle

Indices	Practically healthy individuals n = 15	Patients COPD (comparative group) n = 32	Patients COPD+EHT (main group) n = 32
D_{RA}, cm	3.29 ± 0.80	3.60 ± 0.20	4.00 ± 0.03
EDD_{RV}, cm	1.93 ± 0.6	3.00 ± 0.3	3.6 ± 0.3*
$TMRV_D$, cm	0.48 ± 0.01	0.51 ± 0.01*	0.61 ± 0.03**#
SF, %	23.5 ± 0.6	22.5 ± 0.8	19.8 ± 0.7***#
$V_{max\ RV}$, m/s	0.90 ± 0.003	0.50 ± 0.003***	0.60 ± 0.003***###
E_{TT}, m/s	0.69 ± 0.04	0.60 ± 0.004***	0.50 ± 0.003***###
A_{TT}, m/s	0.41 ± 0.03	0.40 ± 0.002***	0.70 ± 0.002***###
E/A_{TT}, conv. units	1.72 ± 0.11	1.50 ± 0.01**	0.70 ± 0.001***###
$IVRT_{RV}$, s	0.05 ± 0.003	0.06 ± 0.003	0.08 ± 0.002***###
SP_{PA}, mm Hg	19.9 ± 0.6	29.2 ± 1.1***	32.4 ± 0.9***#

Table 3. Structural-functional indices of the left ventricle

Indices	Practically healthy individuals n = 15	Patients COPD (comparative group) N = 32	Patients COPD+EHT (main group) n = 32
D_{LA}, cm	28.1 ± 0.7	29.8 ± 1.0	34.0 ± 0.8*** #
EDD_{LV}, cm	4.8 ± 0,2	4.9 ± 0.3	5.2 ± 0.3
IVS_D, cm	0.89 ± 0.02	0.80 ± 0.03*	1,04 ± 0.06* ##
$PWLV_D$, cm	0.91 ± 0.02	0.82 ± 0.04*	0.96 ± 0.04#
SI, ml/m^2	43.7 ± 1.9	42.0 ± 1.3	36.5 ± 1.2** ##
CI, l/min/m^2	3.1 ± 0.1	3.0 ± 0.3	2.4 ± 0.4
EF, %	65.7 ± 0.6	63.4 ± 1.2	50.0 ± 2.5*** ###
$V_{max\ LV}$, m/sec	1.2 ± 0.03	1.0 ± 0.02***	0.8 ± 0.002*** ###
E_{TM}, m/sec	0.84 ± 0.04	0.8 ± 0.003	0.6 ± 0.002*** ###
A_{TM}, m/sec	0.50 ± 0.04	0.5 ± 0.002	0.4 ± 0.001*** ###
E/A_{TM}, conv. units	1.74 ± 0.06	1.6 ± 0.02*	1.5 ± 0.02*** ###
$IVRT_{LV}$, sec	0.07 ± 0.001	0.09 ± 0.001***	0.13 ± 0.002*** ###

Table 4. Functional indices of external respiration's state

Indices	Practically healthy individuals, n = 15	Patients COPD (comparative group), n = 32	Patients COPD + EHT (main group) N = 32
VC, % of due	103.0 ± 1.1	68.8 ± 1.3***	60.4 ± 1.2*** ###
FEV_1, % of due	96.1 ± 2.0	66.8 ± 0.9***	58.2 ± 0.8*** ###
PEFR, % of due	85.2 ± 1.5	59.3 ± 1.1***	38.8 ± 1.1*** ###
FEF_{25}, % of due	82.7 ± 3.0	52.4 ± 1.1***	46.2 ± 1.3*** ###
FEF_{50}, % of due	88.9 ± 4.0	48.8 ± 0.9***	45.2 ± 1.3*** #
FEF_{75}, % of due	86.9 ± 2.2	42.4 ± 1.2***	40.3 ± 1.8***

Discussion

A disorder of the functional state of endothelium in the patients with COPD is demonstrated in Table 1. It was reflected in a significant decrease of the total content of the stable metabolites of nitrogen oxide (in 1.36 times) and in 1.53 – of EIVD index and also in tendency to increase of ET-1 level and decrease of EDVD index. The foregoing was considered as the manifestation of endothelial dysfunction [8], which plays a significant role in pathogenesis of COPD. P.J. Barnes [10] and R.G. Barr et al. [11] also paid their attention to it in their works. Taking into account the fact that endothelial dysfunction is one of the leading mechanisms in development of EHT [7], the significantly larger intensity of changes of endothelial function state in the patients with COPD combined with EHT becomes clear. They include a greater decrease of NO_X level in the blood (2.24 times as little as among practically healthy individuals and 1,63 times as little as among patients with COPD), the significantly increased ET-1 content both in comparison with practically healthy individuals (1.62 times) and in comparison with patients with COPD (1.3 times). Besides, the indices EDVD and EIVD were the lowest and correlated positively with NO_X index (accordingly, r = 0,36 и r = 0,44; p < 0,05). Negative relationship between NO_X and D_{RBA} (r = -0,49; p < 0,05) was also revealed. The indicated dynamics of the changes of indices of endothelial function in the patients with COPD combined with EHT reflected their pathogenic community in development of the comorbid pathology in spite of probably different starting mechanisms of their forming [4].

Signs of diastolic ventricular dysfunction (for right ventricle-decrease of E_{TT}, A_{TT}, E/A_{TT} at the tendency to the increase of $IVRT_{RV}$, for left ventricle – the tendency to the decrease of E_{TM}, A_{TM} at significantly low results E/A_{TM} and $IVRT_{LV}$) were revealed during the analysis of ventricular structural-functional indices. Significant changes of the global contractile function of ventricles were not revealed but the decrease of blood peak flow in the outflow tract of ventricles took place in comparison with practically healthy individuals ($V_{max\ RV}$ – 1,33 times and $V_{max\ LV}$ – 1,16 times). The obtained results associate with the data by Э.Г. Акрамова [1] who claimed that such changes are a stage of the following formation of the right ventricular hypertrophy.

Changes of structural-functional indices in patients with COPD with comorbid EHT were more significant, reflected aggravation of the diastolic and development systolic dysfunction of ventricles. It was revealed that not only elongation of $IVRT_{RV}$ but also increase of afterload play a significant role for development of the right ventricular diastolic dysfunction. It was confirmed by the presence of correlation relationship between indices SP_{PA} and E_{TT} (r = -0,36; p < 0,01), E_{TT} and $TMRV_D$ (r = -0,40; p < 0,01), and also between E/A_{TT} and $TMRV_D$ (r = -0,46; p < 0,05). Aggravation of right ventricular

diastolic dysfunction could be caused not only by development of secondary cardiopathy in conditions of chronic hypoxia but also by EHT, which the increase of myocardial rigidity is typical of [2, 3]. Decrease of E_{TM}, A_{TM}, E/A_{TM} and increase of $IVRT_{LV}$ characterized changes of the left ventricular diastolic function in the patients with COPD and comorbid EHT by relaxation type. Besides, intensity of the directed changes was much evident unlike among the patients with the isolated COPD.

It was claimed in the study by Э.Г. Акрамова [1] that the presence of cardiorespiratory association promotes not only the greater spreading of the right ventricular hypertrophy but also its earlier formation. It has been established in our study that there is a systolic dysfunction of ventricles in patients with COPD with comorbid EHT unlike among the patients with isolated COPD. It was manifested by significantly low EF (in comparison with healthy individuals and patients with COPD more than by 20%), SI (more than by 13%) at tendency to decrease of CI, and also decrease of SF (more than by 12%). It was revealed also that forming of systolic dysfunction of ventricles in patients with COPD and comorbid EHT occurs under the influence of the changed endothelial function. It was confirmed by presence of correlation relationship between NO_X and EF ($r = 0,52$; $p < 0,05$), ET-1 and EF ($r = -0,44$; $p < 0,05$), SF and NO_X ($r = 0,54$; $p < 0,05$), SF and ET-1 ($r = -0,46$; $p < 0,05$). Besides, both precapillary pulmonary hypertension and postcapillary hemodynamic disorders have influence on forming the right ventricular systolic dysfunction (correlation relationship between SP_{PA} and D_{LA} ($r = 0,48$; $p < 0,05$), between EDD_{RV} and EF ($r = 0,42$; $p < 0,05$).

In fact, the change of bronchial patency indices is a pathognomonic sign of the change of the ventilating function of the bronchopulmonary system in patients with COPD [16]. Besides, it is necessary to emphasize that intensity of the changes of bronchial patency prevailed significantly in the patients with the comorbid pathology and influence of the changed endothelial function on development of these disorders was also revealed (the presence of correlation relationships between FEV_1 и NO_X ($r = 0,58$; $p < 0,05$), and also between FEV_1 and ET-1 ($r = -0,56$; $p < 0,05$). It is necessary to note that intensifying of restrictive changes was under the influence of the changed left ventricular systolic function (the correlation dependence between VC and EF ($r = 0,66$; $p < 0,01$).

Thus, the foregoing assumes the following conclusions.

Conclusions

1. Patients with COPD have endothelial dysfunction that is characterized by a decrease of relaxing (NO_X) and increase of constrictive (ET-1) parameters. Besides, presence of comorbid EHT in them intensifies the dynamics of these indices' changes.

2. The tendency to the increase of the diameter of a brachial artery in patients with COPD, more strongly marked in its combination with EHT, is accompanied by significant disorders of the functional indices of endothelium (decrease of EDVD and EIVD) exactly in cases of comorbid EHT. It is reflected by negative correlation relationship between indices NO_X and D_{RBA}, and positive – between NO_X and EDVD, NO_X and EIVD; generally it is a reflection of endothelial dysfunction's presence.

3. The changes of endothelial function in the patients with COPD are accompanied by structural-functional changes of ventricles' myocardium which are typical of the diastolic dysfunction. Besides, a more expressed diastolic dysfunction and the development of systolic dysfunction are typical of the patients with COPD and comorbid EHT; decreased SF and EF have positive relationship with index NO_X and negative – with level of ET-1. It confirms their participation in forming of systolic myocardial dysfunction.

4. Presence of bronchial obstruction is pathognomonic for the patients with COPD; it is more expressed in the patients with comorbid EHT (FEV_1). Besides, the changed indices of the functional state of endothelium – NO_X (positive correlation) and ET-1 (negative correlation) influence its intensity. It reflects participation of endothelial dysfunction in forming of disorders of bronchial patency.

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