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EVALUATION OF INDICATORS OF ENDOTHELIAL DYSFUNCTION AND INTRACARDIAC HEMODYNAMICS OF THE LEFT VENTRICLE IN PATIENTS WITH CHRONIC PULMONARY HEART BRONCHOPULMONARY GENESIS OF COMORBIDITY WITH ESSENTIAL ARTERIAL HYPERTENSION

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is the main cause of progression chronic pulmonary heart (CPH), it is a serious worldwide problem. The combination of COPD with essential arterial hypertension (EAH) ranges from 4 to 27.7% with increasing age.

The aim: To evaluate endothelium function changes by the level of metabolites of nitric oxide, endothelin-1(ET-1), values of ultrasonic diagnosis of the humeral artery (HA), intracardial hemodynamics of the left ventricle in patients with CPH in combination with EAH.

Materials and methods: The research is involved 175 patients. Indicators of endothelial function by the level of nitric oxide metabolites, ET - 1, ultrasound intracardiac hemodynamics of the left ventricle of the heart were studied.

Results: The patients with CPH in combination with EAH in compensation stage have reduced level of nitric oxide in comparison with patients with CPH without EAH and healthy. To a large extent, reducing of nitric oxide level in decompensation stage indicates about contribution of combined pathology and requires ED correction. On the contrary increased concentration of ET-1 in decompensation stage indicate about combined pathology and demands correction of endothelial cell function.

Conclusions: Thus, patients with CPH in combination with EAH are characterized by more pronounced changes in endothelial dysfunction toward an increase in the level of vasoconstrictor factors, a decreasing of vasodilators, which is confirmed by ultrasound diagnosis of HA and reflected in the peculiarities of the intracardiac hemodynamic state.

KEY WORDS: chronic pulmonary heart, comorbidity, endothelial dysfunction, internal cardiac hemodynamics

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INTRODUCTION

For the global community of respiratory disease is a global health problem, primarily because of their widespread prevalence among the able-bodied population, the constant progression, the development of frequent various of extra-pulmonary pathologies and effects. Nowadays known probably 80 diseases are cause of CPH. But the main cause of progression CPH is COPD that represents a major global challenge. Also it is devastating pathology that reduce patients' quality of life and is a huge socio-economic burden for morbidity and mortality worldwide [1,2]. As reported by definition of Havrysyuka V.K. [3], CPH is circulatory failure syndrome with the progressing of peripheral edema, which complicates the course of many diseases with damage to the structure or only lung function. There are two types of CPH: compensated as a sign of the basic disease and decompensated is a sign of peripheral edema. According to modern data in the world about 600 millions of patients with COPD that increasing with age. Before forecasts of experts, COPD will take on the third place among of structure cause of mortality by 2020 year [4,5,6,7,8].

According to the results of large screening studies, the prevalence of COPD is greater in smokers than in non-smokers, in people over 40 years of age more than in young people, in men more than in women. At the same time, society has little knowledge of this problem and the cost of scientific research COPD is in 13th place.

Published articles in European White Book of Lungs (2013 year) are once confirms this pattern. Considering the high prevalence of COPD, the number of patients with CPH as its complication increased. As a result of this complication, the mortality rate is 67% and ranks third after arterial hypertension (AH), coronary heart disease (CHD), particularly among the causes of death of persons over 50 years of age. According to the concepts of the global strategy of diagnostic, treatment and prevention of COPD (Global Initiative for chronic obstructive pulmonary disease, GOLD (2017) [9], COPD is a disease with significant extrapulmonary manifestation such as arterial hypertension (AH), CHD , metabolic syndrome (MS), obesity, etc. They significantly complicate not only the course of the disease, but also lead to a deterioration in the quality of patient's life. COPD becomes not only a

pulmonary problem, but also a cardiac due to the frequent progressing of cardiovascular comorbid pathology in this category of patients [10,11].

The comorbidity of COPD and EAH remains the most important, their combination ranges from 4 to 27.7%, in the older age groups up to 62%, it increasing with age [12]. This has a significant impact on health, quality and life expectancy. Recently, in the pathogenesis of CPH of bronchial pulmonary genesis, AH, CHD pay much attention for studying endothelial dysfunction as a pathogenetic link of these diseases [13,14,15,16]. Activation or damage of the endothelium is fundamental in the development of a wide range of pathological processes.

THE AIM

To evaluate changes in endothelial function by the level of metabolites of nitric oxide, endothelin -1 (ET-1), indicators of ultrasound of the humeral artery (HA), intracardiac hemodynamics of the left ventricle (LV) in patients with CPH of bronchopulmonary genesis in combination with essential arterial hypertension (EAH).

MATERIALS AND METHODS

The study involved 96 persons with CPH in combination with EAH, II stage (the main group), from their the stage of compensation was detected in 32 (33.3%) patients is group 3 without heart failure (HF), stage of decompensation have 64 (66.7%) patients is group 4 with signs of HF. The comparative group consisted of 64 patients with CPH have identical gender, age, severity of illness of their 32 (50.0%) patients have the stage of compensation 0 without signs of HF is group 1 and 32 (50.0%) in the stage of decompensation with signs of HF is group 2. Thus, were 34 females and 62 males with an average age of 57.5 ± 1.2 years. The control group for patients with CPH with EAH were 15 healthy identical in gender and age. The basis for the causing of CPH was COPD.

The day before, all patients has signed an informed consent to be participation in the research in accordance with the requirements of the 1975 Declaration of Helsinki, its revision in 1983 and Order of the Ministry of Health of Ukraine № 690 of September 23, 2009 «About approval of the procedure for conducting clinical trials of medicinal products and examination of materials of clinical trials» and « The typical provision for ethics committees». Ethical and the moral and legal aspects of the research were agreed by the commission of bioethics in Ukrainian medical stomatological academy.

The total content of the stable metabolites of nitrogen oxide was determined in blood serum by the spectrophotometric method by the set of reactants (Total NO) made by "RL-system", USA in accordance with the kit instructions. Determination of ET-1 level was carried out by the enzyme immunoassay by the set of reactants BIG Endothelin-1 (HUMAN), Peninsula Laboratories inc., Division of Bachem.

An Aloca 5000 Pro Sound (Japan) ultrasonic scanner with a 13 MHz line sensor according to the D.S. Celermayer method was used to measure the diameter of the vessel. The research was carried out in the morning fasting before taking medicines in a special room. The study of the right HA was carried out 2-5 cm above the elbow joint, the cuff of the tonometer was applied on the forearm. The diameter of HA (mm) was measured in the transverse and longitudinal planes in order to obtain the same values to improve measurement accuracy, the location of the sensor was noted. The diameter of the HA was defined as the distance between the anterior and posterior walls of the artery on the face of the vessel intima/flow. The diameter measurement was carried out at the finite-diastolic phase of the blood flow, which was determined at the moment of appearance of the tooth R on the ECG synchronized with the ultrasonic image. Endothelium-dependent vasodilation (EDVD) was determined for 90 seconds after 5 minutes of shoulder compression with 300 mm Hg pressure by calculating the percent change in artery diameter with initial. Endothelium independent vasodilation (EIVD) was determined as the maximum percent artery expansion within 5 minutes after sublingual administration of 0.5 mg of nitroglycerine at minute-by-minute registration. The norm considered increasing the diameter of vessels more than 10% of the initial and 20% against the background of nitroglycerine action.

The assessment of the state of intradermal hemodynamics of LV was carried out using two-dimensional echocardiography on Toshiba SSA, 380 A Powervision (Japan) according to a conventional technique.

The following parameters were determined: left atrial diameter (LA, mm), cardiac (l/min (m^2) and percussion (ml/m^2) indices (CI and PI, respectively), thickness of the posterior septum of LV (TPWLV, mm), emission fraction (EF,%), maximal rate of transaortal blood flow(Vmax, m / s). The diastolic function of LV was evaluated by Doppler investigation of the transmitral blood flow of early E (m/s) and late A (m/s), their E/A ratio (conventional units), isovolumic relaxation time (IVRT) and the size of the interventricular septum (IVS, mm).

The criteria for diagnostics COPD were approved by the order of the Ministry of Health of Ukraine of № 555 from 27.06.2013 "About approval and introduction of medical and technical documents on standardization of medical care in case of chronic obstructive pulmonary disease" (order with change №270 from 16.04.14 "About amendments to the orders of the Ministry of Health of Ukraine "[17]. The severity of COPD was consistent with stage II and stage III and stage II pulmonary insufficiency (LF). The severity of COPD was in stage II-III pulmonary failure (PF).

The examination of EAH patients was carried out in accordance with order №384 from 24.05.2012 by Ministry of Health of Ukraine "About approval and introduction of medical and technological documents and standardization of medical care for arterial hypertension" [18]. The classification of the Association of pulmonologists and cardiologists of Ukraine was used to assess heart failure (HF) in patients with CPH. According to which CI of 1 stage is found in 6 (6.3%) patients, HF of II stage in 84 (87.4%) and HF of III stage in 6 (6.3%) patients.

The criteria for exclusion from the study were the presence of symptom hypertension, complications of EAH, endocrine diseases requiring correction, kidney pathology, systemic diseases of connective tissue, oncological diseases and other conditions. Statistical processing of the results was carried out by the method of parametric statistics.

The Student test was used to assess the significance of the differences. The difference of the indicators was accepted reliably at (P<0,05), as well as with the nonparametric Kolmogorov - Smirnov criterion. Correlation analysis was performed by a linear Pearson correlation coefficient method on a Celeron 650 computer with software SPSS11,0.

RESULTS AND DISCUSSION

Should note that the study of nitric oxide in the pathogenesis of EAH revealed a decrease in basal and stimulated production of NO [19]. Nitric oxide has proved ineffective in relaxing smooth muscles or reduced endothelium ability at all by its production. The patients with CPH with combined pathology (third, fourth groups) have the nitric oxide content metabolites was significantly reduced compared to patients with CPH without EAH. Thus, the 3rd group it has 16.2 ± 1.3 mmol / l (P_1<0.05), in the 4th group - 13.1 ± 1.2 mmol / l (P_2<0.05), whereas the patients with isolated CPH have in the 1st group - 26.5 ± 1.2 mmol / l (P_1 <0.05), in the 2nd group - 20.2 ± 1.1 mmol / l(P_2<0,05), the healthy persons have 36,3±0,8 mmol / l. So, the rate decreased by 10.3 and 7.1 mmol/L compared to the group of CPH patients without EAH and healthy individuals. The comparison of indicators of the 3rd and 4th group (CPH with EAH) reliable a difference between them - 3.1 mmol/l (P_3*/ ≠) that demonstrates that progressing of HF considerably influences damage of function of endotheliocyte, reducing synthesis of a vasodilator of nitrogen oxide. Its effect should be considered alongside ET-1 in these patients. According to the data obtained, in patients with CPH in combination with EAH in the stage of compensation (3rd group) the level of ET-1 was 5.2 ± 0.1 mmol / l, in decompensation (4th group) - 7.8 mmol/l. Whereas in patients with CPH without EAH, respectively, 4,0 ± 0,4; 6.2 ± 0.6 mmol/l. It increased significantly by 1.2 ± 0.09 mmol/l (P_1<0.05) in 3rd group and by 1.6 ± 0.06 mmol/l in 4th group. According to the obtained data, even in patients with CPH without signs of EAH in the stage of decompensation, along with the decrease of NO metabolites, an increase of ET-1 is observed, and especially in the combination of pathology in the stage of decompensation (7.8 mmol / l), i.e. 1.9 times more than for CPH in the non-EAH compensation phase.

This may indicate that several factors, such as arterial hypoxemia, increased intra-thoracic pressure (all patients had emphysema), and abnormal hemodynamics in the small circulatory tract, which are already characteristic for patients with COPD without CPH are important in the pathogenesis of these shifts. This is confirmed by the high degree of correlation in these patients between SaO2 and the level of metabolites of nitric oxide, ET-1. Studying the parameters of the morphometry of HA, we again indirectly evaluate the indices of nitric oxide. Therefore, to further study the state of endothelial dysfunction (ED), we conducted a non-invasive morphometric research of HA. patients with CPH without EAH in comparison with the group of healthy individuals already notice changes in the parameters of morphometry of HA. Thus, the initial diameter of HA in these patients in the stage of compensation increased by 1.3 ± 0.002 mm (P<0.05) in the stage of decompensation - by 1.6 ± 0.01 mm (P<0.05).

Significantly decreased in patients of the 2nd group of EDVD (by 5,0%, P<0,05), the initial rate of blood flow and increased the rate at hyperemia (P<0,05).

The significantly wider initial diameter of HA was determined in patients with CPH and EAH, such as, the 3rd group by 0.5 mm (P_1< 0.05); the 4th group by 0.8 mm (P_2<0.05) in comparison with patients with isolated CPH (1st and 2nd group). There were lower levels of dependent dilatation flow (DDF) in comparison with the 1st group by 3.5%, in the patients with the 2nd group by 4.4% (P<0.05), which indicates the depletion of the product nitric oxide due to an increase in vasoconstrictor factors. Reduced of induced dilation (EIVD), identical, but in a lesser extent. At patients of the 3rd group it decreased by 2,0 (P_1<0,05), at patients of the 4th group by 2,4% (P_2<0,05) in comparison to individuals with HPG without EAH.

In the patients of the 3rd and 4th groups are noted correlation communication between the level of EIVD and output diameter of HA(r = - 0,68, P<0,05 i r = - 0,70, P<0,01), and also the strong dependence is found between EDVD and ET-1 level (r = - 0,72, P<0,05).

The connection among during of diseases of CPH, COPD that is a cause and diameter of HA was studied. It is noted that the size of HA is more altered depending on the duration of COPD. The initial rate of blood flow in patients with CPH of the 1st and 2nd groups was 0.66 ± 0.005 m / s and 0.60 ± 0.002 m / s, the patients with CPH with high blood pressure - 0.54 ± 0.006 m / s (P<0.05) and 0.50 ± 0.003 m / s (P<0.05). The percentage increase in the rate of hyperemia also decreased in patients of the 3rd group by 6.6 ± 0.8% (P<0.05) and in patients of 4th group by 19.7 ± 1.0% (P<0.05).

Thus, summarizing the above data regarding the study of ED in patients with CPH in combination with EAH, it should be noted that ultrasound studies of HA indicators in combination with the level of nitric oxide, ET-1 indicate their significant role in the formation of CPH and more pronounced changes in ED in side of increasing factors of vasoconstruction and inhibition of formation of nitric oxide.

This contributes to the formation of HF, especially in patients with comorbid pathology, namely CPH with EAH. It should be noted, that EAH contributes significantly to the causing of hypertensive heart, so special attention is required to the study of the intracardiac hemodynamics of the right and left ventricle especially in the combination of CPH with EAH.

The research was revealed that patients with CPH combined with EAH even in the phase of compensation have significantly reduced CI and PI, a decrease in the rate of acceleration of blood flow through the aortic valve (P<0,05),

which led to a decrease in PV by 1.3 times (P<0,05) in compared to healthy persons, but it remained within the normal range (3rd group 50,0±2,5%). These changes indicate a additional contribution of the EAH to cause reduced systolic function on the period of hypoxia of toxic-infectious and metabolic effects of COPD. Even more pronounced were the changes revealed in patients with EAH of 4th group. All indicators (CI, PI, Vmax, size of LV) were significantly altered that confirms decrease of EF to 40,5±1,0%. Increasing hypertrophy of the posterior LV, especially of IVS, was also detected, but they did not reach the values that are characteristic of isolated EAH. The pathogenesis of these changes is explained by a decrease in inflow to the left heart due to increased total pulmonary resistance, pulmonary hypertension in the circulatory system and right ventricular failure.

The diastolic function of LV changed by relaxation type, it detected in 100% of patients. by relaxation type were also detected in 100% of patients. These changes were reflected in a decrease in the rate of early diastolic filling (E) to late (A) their ratio E/A, especially in patients with CPH in combination with EAH of 4th group, respectively by 0,3±0,001 m/s (P_2 <0,05) and 0,1±0,001 (P_1 <0,05) compared with the 2nd group of patients with CPH without EAH (P_1 <0,05) with increasing IVRT from 0,11±0,002s to 0,16±0,004s (P_2 <0,05). Significant thickening of the IVS is noted, which also plays a role in the formation of diastolic dysfunction of the LV. Violation of diastolic filling of the LV, along with changes in systolic function, was accompanied by its dilation by 7.6%.

Thus, the research showed that systolic dysfunction of LV heart is exacerbated by the adherence to essential hypertension in the CPH. pressure, decreased myocardial contractility on changes in LV, hypoxia, myocardial dystrophy, which are already present in COPD patients, are also important. Diastolic dysfunction of the LV heart appears already on the background of the formation of CPH in patients with COPD and is greatly exacerbated with EAH attachment and especially due to the development of HF.

CONCLUSIONS

1. The patients with bronchopulmonary genesis in combination with EAH are characterized by more pronounced changes in ED toward an increasing of the level of vasoconstrictor factors (ET-1), decreasing of vasodilators (metabolites of nitric oxide), which is naturally observed when joining arterial hypertension than in patients with isolated CPH and confirmed by ultrasound examination of the brachial artery, its high correlation with ED. This requires combination treatment to correct these changes and improve patients' prognosis.
2. The patients with CPH in combination with EAH as an indicators of metabolites NO, ET-1, ultrasonography of humeral artery indicate substantial contribution in progression endothelial dysfunction and circulatory insufficiency.
3. Changes in systolic and diastolic function of the LV the degree of which increases with the progressing of HF, combined pathology and correlates with the parameters of endothelial dysfunction (EF_{LV} – NO_2 - NO_3 r = 0,72, P<0,05; EF_{LV} – ET-1 r = 0,64, p<0,05) and deepened due to the development of decompensation.
4. Systolic dysfunction of the left ventricle is exacerbated when CPH joins to essential arterial hypertension. In addition, to the influence of high blood pressure, hypoxia, myocardial dystrophy, which are characteristic of patients with bronchopulmonary genesis are also important Diastolic dysfunction of the left ventricle of the heart appears already on the background of the formation of CPH and is greatly progressing in the combined pathology and especially, due to the progressing of EF, which is a predictive factor of aggravation.
5. The chronic pulmonary heart combined with essential arterial hypertension mutually exacerbate the disease in comparison with patients with isolated chronic pulmonary heart, indicating a syndrome of "mutual burden", which leads to a more severe course of the disease, that should be taken into account both in diagnosis and treatment.

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