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Immunological and functional predictors of chronic obstructive pulmonary Disease's combined with metabolic syndrome progression

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In modern clinical practice is more often possible to meet patients with a combination of three diseases - diabetes, the arterial hypertension in combination with ischemic heart disease, which are components of metabolic syndrome (MS) and chronic obstructive pulmonary disease (COPD). Combination of these socially - significant diseases reflects new period of new age diseases. The purpose of this study was to define the main clinical, structural, functional and immunological predictors of combined pathology advance - COPD and MS. The COPD diagnosis was verified among 143 patients, 75 patients out of them had a combination of COPD and MS (the main group), and 68 - separate disease (compare group). The clinical presentation of COPD progression among patients with MS symptoms unlike with separate COPD is characterized by heavier progression with growth of frequency of annual COPD recrudescences, respiratory function defects of the mixed type and myocardium remodeling with hypertrophy of the right and left heart. The patients with COPD combined with MS experience increasing of systematic inflammatory process activity in the form of concentration pro-inflammatory increasing (Interleukine - 1β, TNF-α, Interleukine -6, Interleukine -8) and deficit of anti-inflammatory (Interleukine -4) that is caused by production cytokines by excess of fatty tissue, and also cytokines synthesis activation in response to a hypoxia and inflammatory process in a bronchus- pulmonary system.

Keyword: Chronic Obstructive Pulmonary Disease, Metabolic syndrome, Immunity.

1. Introduction

The Chronic Obstructive Pulmonary Disease (COPD) is chronic diffuse evolving not allergic inflammation of bronhcus caused by long irritation and an inflammation of a mucous membrane of a bronchial tree, with primary affect the distal division of respiratory tract with partially inversum or non-inversum obstruction that is evident by constant or periodic cough with expectoration, short-windessness and conducting to progressive disruption of pulmonary ventilation and gas exchange on obstructive type [1,2].

For the last 15 years conceptualization about pathogenesis this pathology were significantly reconsidered and new approaches to diagnostics and treatment were developed. Earlier main mechanism of COPD development was considered the existence of chronic obstruction of respiratory tract, and correspondingly treatment was directed, first of all, on reduction of obstructive component effects. According to the new conceptualization about pathogenesis COPD reduction respiratory tract patency is connected with their inflammatory response to risk factors influence that further leads to mucociliary dysfunction, structural changes in bronchus and in pulmonary parenchyma, and also to systematic disease evidences [3]. In this context the COPD is considered as systematic pathology with the increased level of circulating proinflammatory cytokines, as a tumor necrosis factor-α (TNF-α) and interleukine -8 (IL-8) [3]. These and other mediators, probably, are responsible for chronic

catastatic state, that finally leads to such systematic effects as loss of weight, the muscular weight, dysfunction and damage of skeletal muscles, osteoporosis, damage of cardio-vascular and nervous systems functioning [4]. Development of inflammatory changes in a bronchial tree pries is constantly supported by inflammation mediators (leukotriene - B4, IL-8, TNF-α), and correlates with disease severity. As a result of prevalence of proteolytic activity the structural elements of alveoles are destructed, emphysema develops. Most quickly this process among patients with deficit α1 - antitrypsin - the main inhibitor of neutrophils elastase which is connected with development of COPD among persons who don't smoke, and are younger than 40 years [3].

The leading reason of a lethality among patients with COPD of minor and moderately-bad course is not respiratory distress as it was traditionally considered, but cardio-vascular diseases - arterial hypertension and ischemic heart disease (IHD), are components of the metabolic syndrome (MS) [4].

In modern clinical practice is more often possible to meet patients with a combination of three diseases - diabetes, the arterial hypertension in combination with IHD and COPD. Combination of these socially - significant diseases reflects new period of new age diseases. Thus, MS, on the one hand, as well as damage of bronchial patency and decrease in pulmonary function, on the other, can mutually potentiate each other [4].

According to literature data it is known that COPD is accompanied by elevation of inflammatory markers in blood even in the period of clinical remission [3]. The combination of COPD to MS leads to extreme increasing of pro-inflammatory markers level, is difficultly controlled by bronchodilators and statins and is clinically evident as frequent recrudescences of COPD with development of a bronchial tree remodeling, and ma complications of cardio-vascular system functioning and destabilization of an atheromatous plaque [4].

2. Work purpose: To define the main clinical, structural, functional and immunological predictors of combined pathology progression - COPD and MS.

3. Materials and methods

The COPD diagnosis was verified among 143 patients, 75 patients out of them had a combination of COPD and MS (the main group), and 68 - separate disease (compare group). Groups of patients with COPD were randomized according to age, sex and disease duration. All patients were examined during remission which was characterized by stable clinical symptoms and indicators of external respiration function. All patients had standard basic therapy according to a disease stage. The COPD diagnosis and its stage were determined according to the Order No. 128 Ministry of Health of Ukraine [5]. The MS diagnosis was determined on the basis of detailed anamnestic, clinical, laboratory and instrumental control methods of research for identification of the main criteria of a syndrome according to recommendations of the International diabetes Federation (IDF), 2005 [6]. The control group included 35 healthy people, randomized according to the age and a sex, without symptoms of COPD and MS.

Instrumental control methods of research included the spirography and an echocardiography (echocardiogram). The spirography was conduced with a help of "Spirosift SP - 5000" device (Fukuda Denshi, Japan). The following volume and speed factors were calculated: the vital lung capacity (VC), forced expiratory volume per 1 second (FEV1), the peak expiratory flow rate at the level of 25%, 50%, 75% of Forced vital lung capacity (PEF 25 %, PEF 50%, PEF 75%, Forced expiratory volume / Forced vital lung capacity (FEV1/FVC). These parameters are calculated as absolute values and as percent from due values. Echocardiogram in M and B modes was carried out with a help of echocardiograph "Sonoace X8" (Medison, Korea) with calculation of the following factors: end-systolic size (ESS, cm), end-diastolic size (EDS, cm) left ventricle (LV), diameter of the right ventricle (RVD, cm), right ventricle front wall thickness (RVFWT, cm), size of left auricle cavity (LAC, cm), left

ventricle back wall thickness (LVBWT, cm) and interventricular septum thickness (TMShP, cm), emission fraction (EF, %), left ventricle myocardial mass index (LVMMI).

Determination of serum concentration of the main pro- and anti-inflammatory cytokines was conducted by means certified in Ukraine sets for immunofermental research manufactured by Vektor-Best (Russia) according to the technique developed by the producer.

Statistical data processing was conducted by using of a package of the applied Microsoft XP programs "Excel", and also by means of the standard version of Statistical Package for the Social Sciences (SPSS) 17.0.

4. Results and Discussion

As a result of the conducted researches it was established that there are no significant differences in the average age of patients in both groups and it is 51.3 ± 4.2 years in the main group and 52.6 ± 3.8 years - in compare group. Smoking duration in group of patients who have separate COPD is 29.7 ± 3.7 years, and with combined pathology – 28.9 ± 2.4 years. Taking into account that smoking is the proved risk factor not only for COPD, but also for cardio - vascular diseases, it was estimated a smoking index which comprised 32.1 ± 2.6 packs / years among patients with the combined pathology and 27.2 ± 2.1 packs / years among patients with separate COPD ($p<0,05$).

The analysis of the anamnesis data showed also significant difference in recrudescence frequency per year. If among patients with separate COPD, more than in half of cases, recrudescence appear 2 times a year, among people in group with the combined pathology the frequency of recrudescence was 3 , 4 and more than 4 times a year ($p<0,05$). Significant increase of recrudescence frequency among patients of the main group can be connected with combination of bronchial- obstructive manifestations with MS which represents systematic inflammatory process in an organism with development of carbohydrate and lipid exchange damages. There for, MS is accompanied by abdominal and viscerogenic obesity type, patients with the combined pathology suffered form damage of pulmonary mechanics with restriction of diaphragm respiratory excursion. It led to strengthening of respiratory damages and hypoxia developments. So, indicators of blood saturation in both groups constituted respectively 94.8 ± 0.4% and 93.4 ± 0,3% ($p<0.05$).

The analysis respiratory function indicators, complaints, the anamnesis data and physical examination showed that all patients selected for research had the second stage of COPD. It is necessary to notice that among the patients in the main group was verified RFI damages of the mixed type (obstructive and restrictive) unlike in experimental group, where were verified only obstructive type damages (Table. 1).

Table 1: Main respiratory function indicators among patients with COPD, combined with MS (M±m).

Respiratory function indicator	Main group (n=75)	Compare group (n=68)	Significant difference
Vital lung capacity (% out of due)	63,8±3,1	74,4±2,9	p<0,001
Forced expiratory volume 1 (% out of due)	53,1±1,8	60,1±2,4	p<0,001
Forced expiratory volume 1/ Forced vital lung capacity,%	69,6±1,9	68,7±2,2	p>0,1
Peak expiratory flow rate 25% (% out of due)	46,2±2,3	49,6±2,4	p>0,1
Peak expiratory flow rate 50% (% out of due)	38,9±1,6	45,5±2,3	p<0,05
Peak expiratory flow rate 75% (% out of due)	39,6±2,4	47,5±2,9	p<0,05

Note: p - Significant difference of indicators between groups of patients

Apparently from the data presented in tab. 1, among patients in group with the combined pathology was observed the development and restrictive damages of respiratory function in the form of Lung capacity indicator decrease that is connected with abdominal obesity, as one of the MS components. Besides, there were discovered considerable damages of bronchial potency at the level of medium and small bronchus among the patients in main group, that obviously were smaller in comparison with Peak expiratory flow rate 50 and Peak expiratory flow rate 75 indicators in experimental group ($p<0,01$). Development of such significant respiratory function defects is a consequence of obstructive defects combination as a result of disease and the mediated influence of a "short circuit" phenomena which develops in the setting of abdominal and viscerogenic obesity in the presence of MS.

The hypoxia developed as a result of to respiratory function defects, is one of the causative factors of pulmonary emphysema. By results of clinical and radiological researches, pulmonary emphysema was diagnosed in 45.33% of patients of the main group and in 32.35% of compare group ($p<0.05$). According to literature data it is known that development of pulmonary emphysema gradually increases under influence the matrix metalloproteinase and the fucosic biocatalysts are release during a long hypoxia and aid to the respiratory defects.

The combination of COPD and MS has the extremely adverse influence on indicators cardiac muscle geometry, and is accompanied by hypertrophy of left and right heart combined with development of pulmonary hypertension and faster elaboration of circulatory collapse. The parameters of a heart geometrical structure comparative characteristic are provided in tab. 2.

Table 2: Main echocardiographic indicators among patients with COPD, combined with MS (M±m).

Indicators	Main group (n=75)	Compare group (n=68)	Significant difference
Aorta basis,см	2,2±0,12	2,3±0,15	p>0,1
Left atrium dimensions in diastole, cm	4,1±0,12	3,7±0,09	p<0,05
Left atrium dimensions in systole, cm	3,7±0,13	3,6±0,12	p>01
Right ventricle dimensions in diastole, cm	2,8±0,02	2,6±0,01	p<0,05
Right ventricle dimensions in systole, cm	2,8±0,11	2,1±0,09	p<0,05
End-systolic size cm	4,8±0,17	4,6±0,21	p>0,1
End-diastolic size, cm	3,1±0,24	3,0±0,26	p>0,1
Emission fraction%	56,4±3,68	69,2±4,29	p<0,05
Interventricular septum thickness, cm	1,31±0,06	1,10±0,08	p<0,05
Left ventricle back wall thickness, cm	1,35±0,05	1,10±0,04	p<0,05
Left ventricle myocardial mass index, g/m^2	123,7±4,3	102,5±2,7	p<0,05

Note: p - Significant difference of indicators between groups of patients

Apparently from data presented in tab. 2, patients with COPD and MS combination, despite the experience of smoking and duration of COPD changes of heart geometrical structure with development of a right ventricle hypertrophy and a left atrium dilation. At the same time the left ventricle size was increased due to arterial hypertension as MS constituent. Higher values of Interventricular septum thickness and Left ventricle back wall thickness were observed among the patients in the main group ($p<0.05$), and also was significantly higher than Left ventricle myocardial mass index ($p<0.05$).

Right ventricle and a left atrium dilation which was observed among patients with the combined pathology, is the extremely adverse sign of decrease of pumping function. During analysis of respiratory function indicators and the Echogram there was established that left atrium size increasing has strong negative correlation relation with decrease of Lung capacity (=-0.725, $p<0.05$). It confirms the existence of negative

cumulative effect from accession of the MS components to COPD as a result of body weight and volume of circulating blood growth, load growth of a myocardium which as well as all organism, is in a state of a chronic hypoxia and a systematic inflammation.

As a result of long influence of a hypoxia activation of processes lipid peroxidation process which already initiated development of systematic inflammatory process activates in patient's body.

Table 3: Indicators of serum level of cytokines and main specific markers of the inflammatory process among with COPD, combined with MS (M±m).

Indicators	Main group (n=75)	Compare group (n=68)	Significant difference
TNF-α, pg /ml	126,8±7,5	77,9±3,12	p<0,05
Interleukine-1β, pg /ml	110,1±6,8	72,6±3,82	p<0,05
Interleukine -6, pg /ml	68,3±2,2	18,7±1,31	p<0,001
Interleukine -8, pg /ml	29,2±1,8	18,5±1,1	p<0,05
Interleukine -4, pg /ml	17,5±1,1	22,7±1,2	p<0,05
SRP, pg /ml	13,2±0,9	7,8±0,6	p<0,05

Note: p - Significant difference of indicators between groups of patients

Apparently from the data presented in tab. 3, among patients with COPD and MS combination is found significantly higher values of pro-inflammatory cytokines serum concentration (TNF-α, Interleukine - 1β, Interleukine -6, Interleukine -8), and also nonspecific markers of an inflammation -SRP (p<0,05). Certainly, the a contribution to level, in particular, TNF-α level increase, brings existence abdominal - visceral type of obesity, as cells of this fatty tissue intensively produce this cytokine. On the other hand, existence of obesity limits respiratory excursion of lungs that strengthens a hypoxia even more and promotes additional production pro-inflammatory cytokines. Besides, growth of serumal concentration of pro-inflammatory mediators, namely a SRP, causes progressing reorganization of a bronchial tree with development of lungs emphysema.

Table 4: Indicators of serum level of circulating immune complexes among with COPD, combined with MS (M±m).

Indicators	Main group (n=75)	Compare group (n=68)	Significant difference
Circulating immune complex of big size (>19 S), c.u	21,17±1,49	35,28±2,07	p<0,05
Circulating immune complex of medium size (11-19S), c.u	61,55±2,34	52,73±2,85	p<0,05
Circulating immune complex of small size (<11 S), c.u	52,37±1,72	40,64±3,63	p<0,001

Apparently from the data presented in table 4, among patients of the main group serum concentration of the pathogenic Circulating immune complexes of an medium and the small size is significantly higher in case of lower values physiologic Circulating immune complexes of the big size level.

For tighter interaction between Left atrium geometry indicators, respiratory function indicators and level of pro-inflammatory mediators in blood serum was conducted correlation analysis with the use of Spearman rank correlation method. It is established that the patient with COPD combined with MS, has high positive a correlation interaction between such

indicators, as Left ventricle myocardial mass index and TNF-α level (r = 0.72), Left ventricle myocardial mass index and Interleukine-6 (r = 0. 73), and also between value of Interventricular septum thickness and TNF-α (r = 0.69), Interventricular septum thickness and Interleukine - 6 (r = 0.68). Also it was found significant positive correlation interaction between a concentration indicator Interleukine -8 in blood serum and value of Interventricular septum thickness (r = 0.56) and negative correlation interaction between level Interleukine -4 and as Left ventricle myocardial mass index (r = - 0.51). Respiratory function indicators too had correlation with level of pro-inflammatory markers. So, the indicator of Lung capacity had high negative correlation interaction with indicators of TNF-α (r = - 0.64) and Interleukine - 1β (r = - 0.71) concentration.

Thus, predictors of progressing and heavier COPD combined with MS progression, are such of Respiratory function indicators as the VC and FEV1; indicators geometrical heart structures: the left atrium, right ventrice sizes in a systole and diastole, indicators of Interventricular septum thickness, Left ventricle back wall thickness, Left ventricle myocardial mass index and also serum concentration of the Circulating immune complexes of an medium and the small size and the level Interleukine -6, Interleukine -1, TNF-α, Interleukine -8 and a SRP.

5. Conclusions

1. The clinical presentation of COPD progression among patients with MS symptoms unlike with separate COPD is characterized by heavier progression with growth of frequency of annual COPD recrudescences, respiratory function defects of the mixed type and myocardium remodeling with hypertrophy of the right and left heart.

2. The patients with COPD combined with MS experience increasing of systematic inflammatory process activity in the form of concentration pro-inflammatory increasing (Interleukine - 1β, TNF-α, Interleukine -6, Interleukine -8) and deficit of anti-inflammatory (Interleukine -4) that is caused by production cytokines by excess of fatty tissue, and also cytokines synthesis activation in response to a hypoxia and inflammatory process in a bronchus- pulmonary system.

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