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E. M. Rekalova, O. R. Panasyukova, E. F. Chernushenko, Yu. A. Matvienko, S. G. Yassyr, M. B. Singaievskyi
SO «National Institute of phthisiology and pulmonology named by F.G. Yanovsky NAMS of Ukraine»

The features of immunological reactivity in patients with chronic obstructive pulmonary disease with concomitant cardiovascular disease

Keywords: *immunological reactivity, chronic obstructive pulmonary disease, cardiovascular disease.*

Cardiovascular pathology is the main cause of death in patients with chronic obstructive pulmonary disease (COPD) with mild and moderate severity forms [29], and the risk of such death increased by 2 –3 times [19].

Formation of various forms of comorbidity in patients with COPD, in particular – cardiovascular disease, musculoskeletal disorders, diabetes and others. Think of recent years, as the consequences of systemic inflammation that accompanies the COPD and contributes genesis of these diseases [2, 17, 20, 21].

Currently believe that an important reason for the combination of these pathologies, besides smoking, chronic viral infections and hypoxemia – can be persistent systemic inflammation [23, 31]. In particular, C-reactive protein, which increases with various inflammatory processes in the body, including the COPD – can activate the production of other pro-inflammatory factors – cytokines, complement, the adhesion of leukocytes to the endothelium and others [15]. His blood levels considered independent predictor of cardiovascular disease and mortality.

Multiple studies have shown that inflammatory markers in the body (serum levels of high sensitivity C-reactive protein (hsC-RP), proinflammatory cytokines) in patients with COPD, compared with subjects who do not have COPD is higher and probably associated with mortality in these patients [13, 20]. Found that many other markers of inflammation such as fibrinogen, white blood cell count and platelets in the blood are also associated with active smoking and reduced FEV1 in patients with COPD [25].

Increase in blood circulating CD8+ T cells, interleukin (IL) 6, 8, 1β, tumor necrosis factor (TNF-α), leukocyte adhesion molecules (sISAM-1) [16, 28], E-selectin and acute phase proteins, including C-reactive protein observed in patients with COPD as an exacerbation and in remission [4, 7, 18, 24, 27]. High levels of inflammatory mediators and cytokines may be a reflection of not only the activity and severity of bronchopulmonary pathological process, but also indicate the formation of new pathogenetic features of the disease associated with systemic inflammation and the development of comorbidities, in particular – cardiovascular diseases [11].

Indeed, in the pathogenesis of cardiovascular disease that occurs against the background of the formation of atherosclerotic plaques play an important role immunologic factor – inflammatory and anti-inflammatory cytokines, a variety of immune cells in various stages of activation [14, 32]. Atherosclerosis find local chronic inflammation with activation of NF-κB gene and participation of monocytes / macrophages (different phenotypes), dendritic cells, lymphocytes and endothelial cells, vascular smooth muscle cells, activation is determined (initiated, supported or decreases) cytokines. In the organized structure of plaques are present foamy macrophages and T cells at different stages of apoptosis (mainly T-helper of type-1), which can produce cytokines that support inflammation. Research on linear laboratory animals showed that reducing the total content of lymphocytes facilitates substantial reduction of atherosclerotic plaques [26].

In connection with the above, proinflammatory cytokines (IL-2, IL-6, IL-12, IFN-γ) consider proatherogenic factors that can lead to the spread of local inflammation in atherosclerosis and inflammatory (IL-4, IL-10, TGF-β) – antiatherogenic [26, 30]. Excessive production of interferon (IFN) and tumor necrosis factor (TNF) can play an important role in plaque rupture, by promoting vascular wall thinning and some other mechanisms [33]. It is believed that the severity of atherosclerosis depends strongly on the balance of Th1/Th2 factors, and the degree of activation of regulatory T-cells that inhibit the development of atherosclerotic lesions.

Thus, while the question remains about the features and symptoms of systemic inflammation in patients with COPD, its outstanding features and mechanisms of the overall impact on human organs and systems, in particular – cardiovascular systems.

The aim was to evaluate clinical and immunological features of the course of COPD patients according to the presence of diseases cardiovascular (ischemic heart disease and / or hypertension).

Materials and methods

There has been clinical, functional and immunological study of 65 COPD patients in the acute stage, held hospital treatment in pulmonary departments of the SO «National Institute of phthisiology and pulmonology named by F.G. Yanovsky NAMS of Ukraine». Clinical diagnosis of COPD was placed under the Ministry of Health of Ukraine Decree № 128 from 19.03.2007 h. [1]. Among surveyed were 42 men (64.6 %) and 24 women (35.4 %), average age (61,5 ± 1,6) years control group consisted of 25 healthy individuals – donors available without signs of respiratory tract diseases, including there were 10 men and 15 women, average age 45,9 ± 2,2 years. Spirometric examination was conducted of patients using the device «MicroLab» (UK).

Depending on the availability of the aforementioned diseases of the cardiovascular system examined COPD patients were divided into 2 groups: group 1 included 47 patients (mean age 66,8 ± 1,1 years) who were diagnosed: concomitant coronary heart disease, hypertension disease or a combination thereof; and group 2 included 18 patients (mean age 47,5 ± 3,4 years) without these characteristics.

Immunological examination consisted of evaluation methods systemic immunity in the acute phase of the disease in the early days of hospital treatment. State systemic immunity was assessed by indicators that characterized T-, B- and phagocytic its link: determine the total number of peripheral blood leukocytes (PB) calculation of relative and absolute lymphocyte content (Lf), monocytes (Mc), neutrophiles (Ng), eosinophils. The functional activity of T lymphocytes characterized by the reaction of blast transformation of lymphocytes with PHA (RBTL with PHA) [10]. Condition B - immune system was evaluated by determining the concentration of immunoglobulin (Ig) serum three main classes (Ig A, M, G), the level of circulating immune complexes (CIC) [5, 12, 22]. The functional activity of phagocytic cells was determined by their ability to absorbing latex particles, hoping index of phagocytosis (PF) – the percentage of cells with latex particles and the phagocytes number (Fn) – number of shares latex in a cell; the level oxygen-dependent metabolism NG and peripheral blood monocytes in the test with nitro-blue tetrazolium (NBT-test) and by the cytochemical index (CChI).

With flow laser cytometry (flow cytometer FACScan) using monoclonal antibodies (Saltag laboratories, USA) performed phenotyping major populations of lymphocytes for the expression of their differentiated surface antigens: CD3+ -Lf (Pan-T cells), CD4+ -Lf (T-helpers / inductors), CD8+ -Lf (T-suppressor / killer cells), CD19+ -Lf (B-cells). [9] Also counted immunoregulatory index (IRI) – the ratio of CD4+ -Lf to CD8+ -Lf in PB. Absolute lymphocyte content, their populations and subpopulations in peripheral blood was calculated on the basis of content and leukocytes, by counting leukocytes in smears stained with Romanovsky-Himza [6].

Serum was determined the content of pro-inflammatory cytokines (IL-8, TNF-α), E-selectin, high sensitive C-reactive protein (hs-CRP) and soluble adhesion molecule sICAM-1. The content of inflammatory cytokines and inflammatory mediators in serum were determined by enzyme immunoassay (ELISA) using commercial test kits: tumor necrosis factor-α (TNF-α) (Proteinovyi contur, Russia), IL-8 (Cytokine, Russia) E-selectin (Biomedica Gruppe, Austria), sICAM-1 (Bender MedSystems, Austria) hs-CRP (DA, USA).

Storage of research results and their mathematical processing was carried out using licensed software products that are included in the package Microsoft Office Professional 2000 (license Russian Academic OPEN No Level № 17016297). In analyzing the data obtained using parametric (t-test probability Students) or nonparametric (two selective Wilcoxon test) statistical methods [8]. Correlation ties between samples were calculated using methods of parametric Pearsons correlation or nonparametric Spearmans correlation. Check connection between samples with quality parameters evaluated using contingency tables using Pearson criterion $\chi 2$. Calculation of criterion values and confidence intervals (CI) was held at a given confidence level $p \le 0,05$. Were analyzed 83 quantitative and qualitative attributes that characterize the clinical and medical history, functional, immunological peculiarities of COPD patients.

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Results and discussion

It is established that the number of cardiovascular disease increased in patients with COPD with age and in surveyed 65 patients with COPD it is determined in 72.3 % of patients (table 1), corresponding to a total prevalence data on population after 60 years of cardiovascular diseases [3]. Age group 1 patients was higher by an average of 20 years, among them were 1.5 times more men and 2 times more smokers than in patients with COPD who did not have cardiovascular disease, indicating the probable participation smoking in their formation. The difference performance limitations of their disease COPD was not statistically confirmed, and indicators of lung function (forced expiratory volume in the first second (FEV1) and the FEV1 value/FVC) were lower than in group II patients ($p < 0, 05$), indicating a severe and very severe degree of bronchial obstruction (FEV1 < 50 % of predicted) in these patients, more severe course and rapid progression of COPD with concomitant diseases of the cardiovascular system.

In terms haemograms peripheral blood leukocyte count in the overall group of patients with COPD was significantly higher than normal (9,4 ± 0,5) % versus (5,9 ± 0,2) %, $p < 0,05$, in healthy individuals. This increase was carried out by lymphocytes (3,1 ± 0,2 g/l at a rate of 2,1 ± 0,1 g/l), neutrophiles (5,9 ± 0,4) g/l, the rate of (3,6 ± 0 2) g/l and monocytes PC (0,48 ± 0,05) g/l, the donors – (0,21 ± 0,03)

Table 1

Clinical and functional differences COPD patients according to the presence of diseases of the cardiovascular system (M ± m)

Indicator	Groups of patients			p
	Total (n = 65)	1 (n = 47)	2 (n = 18)	
Age (years)	61,5 ± 1,6	66,8 ± 1,1	47,5 ± 3,4	< 0,05
Men abs, %	42 (64,6 %)	34 (72,3 %, CI 57,4–84,4 %)	8 (44,4 %, CI 21,5–69,2 %)	< 0,05
Smokers, abs, %	31 (47,7 %)	27 (57,4 %, CI 42,2–71,7 %)	4 (22,2 %, CI 6,4–47,6 %)	< 0,05
COPD Age (years)	15,4 ± 1,4	16,5 ± 1,7	12,1 ± 2,3	> 0,05
FEV_1, %	45,1 ± 2,4	41,7 ± 2,6	54,0 ± 4,7	< 0,05
FEV_1 / FVC, %	50,1 ± 1,7	47,5 ± 2,0	57,1 ± 2,3	< 0,05

Table 2

Differences indicators of systemic immunity in patients with COPD depending on presence of diseases of the cardiovascular system (M ± m)

Peripheral blood	Group of donors (n = 20)	Groups of patients		
		Total (n = 65)	1 (n = 47)	2 (n = 18)
Lymphocytes, %	34,5 ± 1,0	32,8 ± 1,5	30,6 ± 1,6*#	38,4 ± 3,0
Neutrophiles, %	59,0 ± 1,2	57,8 ± 1,9	61,6 ± 2,0	48,2 ± 3,4*#
Neutrophiles, g/l	3,6 ± 0,2	5,9 ± 0,4*	6,4 ± 0,5*#	4,6 ± 0,7
CD3+ Lymphocytes, %	69,7 ± 1,5	65,9 ± 1,4	64,0 ± 1,7*#	70,9 ± 1,8
RBTL with PHA, %	55,8 ± 1,6	51,9 ± 1,6	49,0 ± 1,7*#	59,1 ± 2,9
Phagocytes number of neutrophiles Fn (c. u.)	6,8 ± 0,3	5,6 ± 0,1*	5,9 ± 0,4	5,1 ± 0,1*#

Notes:* the difference with an indicator of healthy statistically significant (p < 0,05); # the difference corresponding figure in 1 and 2 groups statistically significant (p < 0,05).

Table 3

Content of proinflammatory cytokines and inflammatory mediators in serum of patients with COPD depending on presence of diseases of the cardiovascular system (M ± m)

Indexes	Healthy persons (n = 25)	Groups of patients		
		Total (n = 65)	1 (n = 47)	2 (n = 18)
TNF-α, pg/ml	7,9 ± 0,8	15,4 ± 3,9	11,5 ± 2,9	25,7 ± 12,0
IL-8, ng/ml	45,0 ± 3,4	61,2 ± 21,7	62,4 ± 7,8*	57,9 ± 8,7
E-selectin, ng/ml	54,3 ± 7,1	119,8 ± 8,2*	118,3 ± 10,0*	123,8 ± 14,8*
sICAM-1, ng/ml	292,8 ± 24,2	336,7 ± 22,7	346,2 ± 26,3	308,0 ± 45,6
hsC-RP, mg/l	1,8 ± 0,4	7,5 ± 1,1*	9,1 ± 1,4*#	2,9 ± 0,9

Notes: * the difference with an indicator of healthy statistically significant (p < 0,05); # – the difference corresponding figure in the first and second groups being statistically significant (p < 0,05).

g/l, the absolute number was increased, p < 0,05. Thus the relative content of lymphocytes and neutrophiles not deviated from the norm, while the relative content increased in monocytes (4,8 ± 0,3 %, the rate of 3,8 ± 0,4 %, p < 0,05).

It was noted, that the authentic decrease in the percentage of the total pool of T lymphocytes are observed in the overall group of examined patients (64,3 ± 1,1) % at a norm of (69,7 ± 1,9) %, p < 0,05. The percentage of lymphocyte subpopulations of T-helper/inductor (CD4+) and T suppressor/cytotoxic cells (CD8+) were not significantly different from control.

From the B-system of immunity, changes are characterized only increased percentage (10,8 ± 0,8) %, the donors – (9,3 ± 0,8) %, p < 0,05 and absolute (0,36 ± 0,03) g/l, the donors – (0,21 ± 0,03) g/l, p < 0,05 content of B-lymphocytes (CD19+).

In the total group of patients the functional activity of neutrophiles in PB was reduced by suppressing their absorptive capacity with respect to polystyrene latex particles (PF): (50,8 ± 1,6) % in patients against (66,6 ± 2,4) % in blood donors ($p < 0,05$) and oxygen-dependent metabolism NG (NBT-test): (54,4 ± 1,9) % in patients against (64,2 ± 3,1) % in the control, $p < 0,05$. In NG was reduced production superoxide anion, which was reflected in a possible decline CChI to (0,68 ± 0,03) c. u. with control values (0,90 ± 0,10) c. u., $p < 0,05$. On the contrary, in another population of phagocytes cells PB – monocytes, against the it unchanged absorption capacity was identified it authentic reduction in the intensity of metabolic processes in them (NBT-test – (25,8 ± 1,6) % at a norm of (32,6 ± 2,0) %, $p < 0,05$ and CChI – (0,28 ± 0,02) c. u. (0,38 ± 0,01) c. u. in control, $p < 0,05$). The data showed, that suppression of phagocytes of immune system was in COPD on exacerbation.

The availability of diseases of the cardiovascular system, based on parameters the total immunogram, accompanied in patients with COPD differences (table. 2) – namely, significantly lower relative number of lymphocytes in PB due mainly CD3+ -lymphocytes, low functional activity of T-lymphocytes (RBTL with PHA) and higher relative and absolute number of neutrophiles in the blood of some indicators of activity (Fn) – that may have been caused not so much by the presence of cardiovascular disease as more severe course of COPD.

In examined patients during exacerbations of COPD was been elevated serum levels of E-selectin and hsC-RP, and do not been identified authentic rising of proinflammatory substances such as TNFα, IL-8 and soluble adhesion molecules sICAM -1 (Table 3). At the same time, only in the first group of patients was determined significant increase of IL-8 and hsC-RP, and only for hsC-RP was confirmed statistically significant difference between the first and second groups on the one hand, it could also be linked with severity of COPD, but on the other hand – confirmed that the level hsC-RP could be a marker for cardiovascular disease in patients with COPD.

Since patients with COPD 1 and 2 groups differed by age and severity of COPD (FEV1), to determine the influence of these factors on immunological parameters was performed a correlation analysis of the data obtained.

Established, that the age of patients had a positive correlation with the percentage neutrophiles in the PB ($r = 0,26$, $p < 0,05$) and their activity (PF NG: $r = 0,43$, SF NG: $r = 0,31$, NBT NG: $r = 0,31$, CChI NG: $r = 0,45$, adhesiveness NG – $r = 0,40$, $p < 0,05$), and monocytes activity in PB (Fn Monocytes: $r = 0,46$, Monocytes NST: $r = 0,63$, CChI P Monocytes: $r = 0,64$, $p < 0,05$) and E-selectin ($r = 0,26$, $p < 0,05$). A negative association was set for serum levels of CIC index ($r = -0,65$, $p < 0,05$). Thus, in patients with COPD the age increased the number of NG and activity of phagocytes in PB – that was probably due to the growth of the severity of inflammation in the body – in the lungs, and probably in vessels (a manifestation of systemic inflammation), – as evidenced by positive the relationship of age to the level of E-selectin. Along with age in patients with COPD decreased blood concentration of CIC – that, on the one hand, could be linked to increased activity of phagocytes in PB, and the other – the changing nature of inflammation.

There was no statistical confirmation between age and hsS-RP ($r = -0,04$, $p > 0,05$), indicating the independence of this indicator of age, which is accompanied by an increase in progression of COPD.

Correlation analysis of relations integral indicator of lung function (FEV1), which correlated with patient age ($r = -0,37$, $p < 0,05$), showed that FEV1 directly correlated with the relative number of lymphocytes PB ($r = 0,33$, $p < 0,05$) and the percentage of CD4 + lymphocytes in PB ($r = 0,26$, $p < 0,05$), is inversely correlated with the relative and absolute number of NG in PB (respectively $r = -0,32$, $r = -0, 27$, $p < 0,05$), indicators of functional activity of blood monocytes (source for the formation of alveolar macrophages) (NBT Monocytes: $r = -0,30$, TSHP Monocytes – ($r = -0,33$, $p < 0,05$). It also was not received confirmation statistical connection with FEV1 hsS-RP ($r = -0,05$, $p > 0,05$), indicating a lack of communication hsS-RP with progression of COPD. Thus, the increase bronchial obstructive disorders (decrease in FEV1) in COPD patients was accompanied by a decrease in the number of lymphocytes and the percentage of T-helper cells (CD4 +) in PB and the increasing number neutrophiles in PB and functional activity of monocytes in PB that reflected their involvement in the pathogenesis of bronchopulmonary inflammation in COPD [3].

Thus, the above analysis of these indicators showed that the presence of cardiovascular disease in patients with COPD and excluding the impact of the age of patients and the severity of COPD factor (in terms of FEV1) are connected with the level hsS-RP, which can be used in the presence of a marker of cardiovascular disease in patients with COPD.

Conclusions

1. In patients with COPD, cardiovascular diseases are defined mainly in older age (average age 66,8 ± 1,1 years), more often – in men (72,3 %), with a positive smoking status (57,4 %), on the background a drop in lung function FEV1 (41,7 ± 2,6) %, FEV1 / FVC (47,5 ± 2,0) %.

2. The features of the immune status of COPD patients with concomitant diseases of the cardiovascular system are significantly lower percentage of lymphocytes in the blood, preferably by pan-T lymphocytes (CD3+), low functional activity of T lymphocytes (the reaction RBTL on PHA) and higher (within normal range) absolute and relative number of blood neutrophils from increasing their activity (Fn) and increase the level of IL-8 and hsC-RP levels.

3. The increase in the number of blood neutrophiles and the activity of phagocytes (monocytes and neutrophiles) in patients with COPD due to age and fall in lung function (FEV1), probably due to the progression of lung inflammation due to COPD.

4. The presence of the marker of cardiovascular disease in patients with COPD may be elevated levels in the blood hsC-RP (9,1 ± 1,4) mg/l an exacerbation of COPD who require long-term therapy appropriate destination for the prevention of acute cardiac events, especially in mild/moderate severity of COPD.

Reference

1. *Nakaz* MOZ Ukrayiny № 555 vid 27 chervnya 2013 r. «Pro zatverdzhennya ta vprovadzhennya medyko-tekhnolohichnykh dokumentiv

zi standartyzatsiyi medychnoyi dopomohy pry khronichnomu obstruktyvnomu zakhvoryuvanni lehen'»: [Elektronnyy resurs]. – Rezhym dostupa: http://document.ua/pro-zatverdzhennja-ta-vprovadzhennja-mediko-tehnologichnih-d-doc166218.html

2. *Pertseva T. O.* Rol' sistemnih zapal'nih protsesv u patogenez hronchnogo obstruktivnogo zahvoryuvannya legen' [Tekst] / T. O. Pertseva, N. A. Sanna // Ukr. pul'monolog. zhurn. – 2012. – 4. – P. 48–50.

3. *Poshyrenist'* osnovnykh faktoriv ryzyku u khvorykh pislya infarktu miokarda / I. M. Sichkaruk ta in. // Zaporozh. med. zhurn. – 2010. – T. 12, № 4. – P. 37–41.

4. *Enikeev O. A.* Harakter ekspressii tsitokinov sistemnogo vospaleniya u bol'nyh hronicheskoj obstruktivnoj bolezn'yu legkih legkoj i srednej stepeni tyazhesti v dinamike obostreniya [Tekst] / O. A. Enikeev // Med. vestnik Bashkirostana. – 2012. – T. 7, 1. – P. 43–45.

5. *Ivchik T. V.* K otsenke diagnosticheskogo i prognosticheskogo znacheniya funktsional'noj aktivnosti al'veolyarnyh makrofagov u bol'nyh hronicheskim bronhitom [Tekst] / T. V. Ivchik // Klinika i lechenie hronicheskogo bronhita. – Leningrad, 1981. – P. 40–44.

6. *Immunotsitohimiya i* monoklonal'nye antitela v onkogematologii / Pod. red. V. G. Pinchuka, D. F. Gluzmana. – K.: Naukova dumka, 1990. – 229 p.

7. *Karoli N. A.* Hronicheskaya obstruktivnaya bolezn' legkih i kardiovaskulyarnaya patologiya [Tekst] / N. A. Karoli, A. P. Rebrov // Klinitsist. – 2007. – 1. – P. 13–19.

8. *Lapach S. N.,* CHubenko A. V., Babich P. N. Statisticheskie metodi v mediko-biologicheskih issledovaniyah s ispol'zovaniem Excel. – Kiev: Morion, 2001. – 320 p.

9. *Primenenie* protochnoj tsitometrii dlya izucheniya funktsional'noj aktivnosti immunnoj sistemy cheloveka: Posobie dlya vrachej laborantov. – Moskva, 2001. – 53 p.

10. *Unifitsirovannye* immunologicheskie metody obsledovaniya bol'nyh na statsionarnom i ambulatornom etapah lecheniya: Metod. rekomendatsii / Kievskij NII ftiziatrii i pul'monologii. – Kiev, 1988. – 18 p.

11. *Uroven'* provospalitel'nyh tsitokinov v otsenke aktivnosti vospalitel'nogo protsessa pri bronholegochnoj patologii u detej [Tekst] / Y. S. Guschina [i dr.] // TSitokiny i vospalenie. – 2006. – T. 5, 4. – P. 36–38.

12. *Haitov R. A.,* Pinegin, B. V. Ekologicheskaya immunologiya. – M.: VNIRO, 1995. – 168 p.

13. *Association* between C-reactive protein concentration and chronic obstructive pulmonary disease: a systematic review and meta-analysis [Text] / Y. Zhang [et al.] // J. Int. Med. Res. – 2012. – Vol. 40, № 5. – P. 1629–1635.

14. *Autieri M.V.* Pro- and Anti-Inflammatory Cytokine Networks in Atherosclerosis. Review [Text] / M. V. Autieri // ISRN Vascular Medicine. – 2012. – Vol. 2012. – P. 1 –17.

15. *Bucova M.* C-reactive protein, cytokines and inflammation in cardiovascular diseases. Topical rewiev [Text] / M. Bucova, M. Bernadic, T. Buckingham // Bratisl. Lek. Listy. – 2008. – Vol. 109, № 8. – P. 333–340.

16. *Chang K.* Cytokines in chronic obstructive pulmonary disease [Text] / K. Chang // Eur. Respir. J. Suppl. – 2001. – № 34. – P. 50– 59.

17. *Complex* chronic comorbidities of COPD [Text] / L. M Fabbri [et al.] // Eur. Respir. J. – 2008. – Vol. 31. – P. 204–212.

18. *Dahl M.* C-reactive protein is a strong predictor of prognosis in COPD [Text] / M. Dahl // Respiratory Medicine. – 2007. – Vol. 3, № 4. – P. 122.

19. *Ernst P.* Cardiovascular morbidity and mortality in COPD [Text] / P. Ernst, S. Suissa // Chest. – 2005. – Vol. 128. – P. 2640–2646.

20. *Fabbri L. M.* From COPD to chronic systemic inflammatory syndrome? [Text] / L. M. Fabbri, K. F. Rabe // Lancet. – 2007. – Vol. 370. – P. 797–799.

21. *Global* Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report. Last updated 2015. www.goldcopd.org/.

22. *Goldberg A. F.* Acid phosphatase activity in human blood cells [Text] / A. F. Goldberg, T. Barka // Nature. – 1962. – Vol. 195. – P. 297.

23. *Inflammatory* Cytokines and Risk of Coronary Heart Disease. New Prospective Study and Updated Meta-analysis [Text] / S. Kaptoge; et al. // Eur. Heart J. – 2014. – Vol. 35, № 9. – P. 578–589.

24. *Karadag F.* The value of C-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease [Text] / F. Karadag, S. Kirdar, A. B. Karulc // European Journal of Internal Medicine. – 2008. – Vol. 19. – P. 104–108.

25. *Majo J.* Lymphocyte population and apoptosis in the lung of smokers and their relation to emphysema [Text] / J. Majo, H. Ghezzo, M. G. Cosio // Eur. Respir. J. – 2001. – Vol. 17. – P. 946–953.

26. *Mallat Z.* Regulatory T cell responses: potential role in the control of atherosclerosis [Text] / Z. Mallat, H. Ait-Oufella, A. Tedgui // Current Opinion in Lipidology. – 2005. – Vol. 16. – № 5. – P. 518–524.

27. *Molecular* Mechanisms of Inflammation During Exacerbations of Chronic Obstructive Pulmonary Disease [Text] / A. L. Kersul [et al.] // Arch. Bronconeumol. – 2011. – Vol. 47, № 4. – P. 176–183.

28. *Mukhopadhyay S.* Role of TNF-α in pulmonary pathophysiology [Text] / S. Mukhopadhyay, J. R. Hoidaland, T. K. Mukherjee // Respiratory Research. – 2006. – Vol. 125, № 7. – P. 1465–1467.

29. *Recognising* heart failure in eiderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study [Text] / Rutten F.H. et al. // Br. Med. J. – 2005. – Vol. 331. – P. 1379.

30. *Schulte S.* Genetically programmed biases in Th1 and Th2 immune responses modulate atherogenesis [Text] / S. Schulte, G. K. Sukhova, P. Libby // Am. J. of Pathology. – 2008. – Vol. 172. – № 6. – P. 1500–1508.

31. *The cohorts* at the Research Centre for Prevention and Health, formerly 'The Glostrup Population Studies' [Text] / M. Osler, A. Linneberg, C. Glumer, T. Jorgensen // Int. J. Epidemiol. – 2011. – Vol. 40. – P. 602–610.

32. *The effects* of total lymphocyte deficiency on the extent of atherosclerosis in apolipoprotein E-/- mice [Text] / A. Daugherty, E. Pur´e, D. Delfel-Butteiger et al. // J. of Clin. Invest. – 1997. – Vol. 100. – № 6. – P. 1575–1580.

33. *Tissue* factor in the pathogenesis of atherosclerosis [Text] / M. B. Taubman, J. T. Fallon, A. D. Schecter et al. // Thrombosis and Haemostasis. – 1997. – Vol. 78. – № 1. – P. 200–204.

ОСОБЕННОСТИ ИММУНОЛОГИЧЕСКОЙ РЕАКТИВНОСТИ У БОЛЬНЫХ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ С СОПУТСТВУЮЩЕЙ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИЕЙ

Е. М. Рекалова, О. Р. Панасюкова, Е. Ф. Чернушенко, Ю. А. Матвиенко, С. Г. Ясырь, М. Б. Сингаевский

Резюме

Цель исследования: *оценить клинико-иммунологические особенности течения хронического обструктивного заболевания легких (ХОЗЛ) у больных в зависимости от наличия заболеваний сердечно-сосудистой системы (ишемической болезни сердца и/или гипертонической болезни).*

Работа выполнена за счет госбюджета.

Материалы и методы: *проведено клинико-функциональное и иммунологическое обследования 65 больных ХОЗЛ в стадии обострения. Среди обследованных – 64,6 % мужчин, 35,4 % женщин, средний возраст 61,5 ± 1,6 года. Контрольную группу составили 25 доноров крови, средний возраст 45,9 ± 2,2 года. В периферической крови (ПК) определяли уровни провоспалительных цитокинов (IL-8, TNF-a) и медиаторов воспаления (Е-селектин, высокочувствительный С-реактивный протеин (hsC-RP), растворимые молекулы адгезии (sICAM-1)) методом ИФА. Клеточное звено иммунной системы оценивали по количеству лимфоцитов и их субпопуляций (методом двухцветной проточной лазерной цитометрии с использованием моноклональных антител к дифференцирующим антигенам CD3+, CD4+, CD8+, CD19+); функциональную активность Т-лимфоцитов – в реакции бластной трансформации*

лимфоцитов с ФГА (РБТЛ с ФГА); состояние В-системы – с определением уровней иммуноглобулинов А, М, G, циркулирующих иммунных комплексов; функциональную активность нейтрофилов и моноцитов – по уровню кислородзависимого метаболизма в НСТ-тесте и их способности поглощать частицы латекса.

Результаты. *Сопутствующая сердечно-сосудистая патология определялась у 72,3 % больных (1-я группа), чаще у мужчин (72,3 %) с положительным статусом курения (57,4 %) и сопровождалась достоверно более низкими показателями функции внешнего дыхания ($ОФВ_1$ 41,7 ± 2,6 %, $ОФВ_1$/ФЖЕЛ 47,5 ± 2,0 %) по сравнению с группой больных ХОЗЛ без сердечно-сосудистой патологии (2-я группа) ($ОФВ_1$ 54,0 ± 4,7 %, $ОФВ_1$/ФЖЕЛ 57,1 ± 2,3 %, $p < 0,05$). У больных 1-й группы определялось достоверно более низкое количество лимфоцитов ПК, в основном за счет CD3+-лимфоцитов (64,0 ± 1,7 % против 70,9 ± 1,8 % во 2-й группе, у доноров – 69,7 ± 1,5 %), что сопровождалось угнетением их функциональной активности (РБТЛ с ФГА – 49,0 ± 1,7 %, 59,1 ± 2,9 %, 55,8 ± 1,6 % соответственно). Более высокое относительное и абсолютное содержание нейтрофильных гранулоцитов в ПК сопровождалось их более высокой активностью. Только у пациентов 1-й группы определялось достоверное повышение уровней IL-8, Е-селектина и hsC-RP по сравнению с группой здоровых, и только hsC-RP статистически значимо отличался от такого во 2-й группе (9,1 ± 1,4 мг/л против 2,9 ± 0,9 мг/л, $p < 0,05$, в контроле – 1,8 ± 0,4 мг/л) и не коррелировал с показателями возраста и $ОФВ_1$.*

Выводы. *У больных ХОЗЛ сердечно-сосудистая патология определяется преимущественно в более старшем возрасте, чаще у мужчин с положительным статусом курения, на фоне выраженного угнетения функции легких, и сопровождается лимфопенией, снижением количества Т-лимфоцитов (преимущественно CD3+) с угнетением их функциональной активности. Активация фагоцитов крови (нейтрофилоцитов и моноцитов) связана с возрастом и снижением легочной функции, что, вероятно, обусловлено прогрессированием бронхолегочного воспалительного процесса вследствие ХОЗЛ. Маркером наличия сердечно-сосудистых заболеваний у больных ХОЗЛ может быть высокий уровень С-реактивного белка в сыворотке крови (в фазе обострения), что требует назначения соответствующей длительной терапии с целью профилактики острых сердечно-сосудистых событий, особенно при легком/средней тяжести течении ХОЗЛ.*

Ключевые слова: *имммунологическая реактивность, хроническая обструктивная болезнь легких, сердечно-сосудистая патология.*

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Е. М. Рекалова
д-р мед. наук
ГУ «Национальный институт фтизиатрии и пульмонологии им. Ф. Г. Яновского НАМН Украины»
ул. Амосова, 10, Киев, 03680
тел.: +38(044) 275-42-22
e-mail: pulmonol@ifp.kiev.ua

THE FEATURES OF IMMUNOLOGICAL REACTIVITY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CONCOMITANT CARDIOVASCULAR DISEASE

E. M. Rekalova, O. R. Panasyukova, E. F. Chernushenko, Y. A. Matvienko, S. G. Yassyr, M. B. Singaievskyi

Summary

The aim – *to evaluate clinical and immunological features of chronic obstructive pulmonary disease (COPD) in patients, depending on the presence of cardiovascular disease (coronary heart disease and / or hypertension).*

This work was funded by the state budget.

Materials and Methods: *A clinical, functional and immunological examination of 65 patients with COPD was investigated. Levels of pro-inflammatory cytokines (IL-8, TNF-α) and inflammatory mediators (E-selectin, high sensitive C-reactive protein – hsC-RP), soluble adhesion molecule – sICAM-1) were determined in the peripheral blood serum (PB) with ELISA. Cellular immunity was evaluated by the number of lymphocytes and their subsets (with two-color flow laser cytometry using monoclonal antibodies to differentiating antigens CD3+, CD4+, CD8+, CD19+); functional activity of T-lymphocytes – with blast transformations reaction of lymphocytes with PHA (RBTL with PHA); activity of B-lymphocytes – by study of serum immunoglobulin A, M, G levels; the functional activity of neutrophils and monocytes – by the level of oxygen-dependent metabolism in HCT-tests and their ability to absorb the latex particles.*

Results. *The presence of concomitant cardiovascular disease (CVD) (1 group) was determined in 72,3 % of patients, more frequently in men (72,3 %) with a positive smoking status (57,4 %) and was accompanied by significantly lower rates of respiratory function (FEV_1 41,7 ± 2,6 %, FEV_1/FVC 47,5 ± 2,0 %) compared with patients without CVD (2 group) (FEV_1 54,0 ± 4,7 %, FEV_1/FVC 57,1 ± 2,3 %, $p < 0,05$). In 1 group the significantly lower number of lymphocytes, mainly due to the CD3+ lymphocytes (64,0 ± 1,7 % in 1 group, 70,9 ± 1,8 % in 2 group, and 69,7 ± 1,5 % in group of healthy), with inhibition of their functional activity (RBTL with PHA 49,0 ± 1,7 % and 59,1 ± 2,9 % and 55,8 ± 1,6 % respectively). The higher absolute and percentage level of blood neutrophills consistent their higher functional activity. Only in patients of 1 group significant increase of the serum levels of IL-8, E-selectin and hsC-RP were determined. hsC-RP only significantly different compared with relatively 2 group (9,1 ± 1,4 mg/l, 0,9 ± 2,9 mg/l, $p < 0,05$, and 1,8 ± 0,4 mg/l respectively) and did not correlate with patient's age and FEV_1.*

Conclusions. *In patients with COPD cardiovascular disease is determined, primarily in older age, more common in men, with a positive smoking status, with significant a significant reduction in lung function and is accompanied by lymphopenia, a decrease of blood T-lymphocytes (predominantly CD3+) and their functional activity. Activation of blood phagocytes (monocytes and neytrofilotsitov) is associated with aging and a decrease in lung function that is probably due to progression of the COPD inflammatory process. The marker presence of cardiovascular disease in patients with COPD may be a high level of C-reactive protein in serum (in exacerbation of COPD), which requires the appointment of an appropriate long-term treatment to patients for the prevention of acute cardiovascular events, especially in mild/moderate severity of COPD.*

Keywords: *immunological reactivity, chronic obstructive pulmonary disease, cardiovascular disease.*

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E. M. Rekalova
Dr. med. sciences
SO «National Institute of phthisiology and pulmonology named after F. G. Yanovsky NAMS of Ukraine»
Amosova str., 10, Kiev, 03680
tel.: +38(044)275-42-22
e-mail: pulmonol@ifp.kiev.ua