

Original article

Interaction of inflammatory parameters and thiol/disulfide system of antioxidant protection in chronic obstructive pulmonary disease

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Abstract: *Introduction* — Increased incidence and prevalence of chronic obstructive pulmonary disease (COPD) provides rationale for describing the disease progression mechanism, considering the interaction of key participants of this process. The *objective* of our study was to establish the dysfunction parameters of thiol/disulfide system components and adaptive immunity unit in patients with stable chronic obstructive pulmonary disease (COPD).

Material and Methods — We examined patients with stable COPD of moderate (62 subjects) or severe (50 subjects) grades. The control group included 32 subjects. Prooxidant and antioxidant markers of oxidative stress were investigated with ELISA. We determined cytokine levels in blood plasma and the number of T helper cells expressing IL-6R with flow cytometry (BD FACSCanto II, USA). Correlation pleiads *sensu* Terentiev were employed to visualize the data.

Results — Changes in both antioxidant and cytokine status of subjects with COPD of varying severity grades implied the progression of systemic inflammation in conditions of uncontrolled activation of adaptive immunity unit rather than just a shift in the peroxide balance and an increase in oxygen metabolites.

Conclusion — Accumulation of biomolecule peroxidation products, imbalance in the prooxidant-antioxidant system, and a change in pathogenetic mechanism of inflammation could lead to an aggravated course of bronchopulmonary pathology.

Keywords: Chronic obstructive pulmonary disease; parameters of thiol/disulfide system; inflammatory parameters, correlation pleiads *sensu* Terentiev.

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Introduction

Currently, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, and it is expected to become the third by 2030 [1]. COPD pathophysiology is associated with chronic inflammation and oxidative stress, causing lung parenchyma destruction [2]. Protective adaptive reaction is associated with the production of inflammatory mediators by the effector cells and regulatory elements of immune system, which affect duration and intensity of the immune response [3]. Such changes in the patient cytokine status could intensify the processes of biomolecule peroxidation. To prevent uncontrolled peroxidation of biological molecules and formation of toxic and mutagenic metabolites, there are special enzymatic systems aimed at neutralizing free radicals and reactive oxygen species. Such intracellular systems are glutathione and thioredoxin [1, 3].

Thiol/disulfide system components, in addition to inhibiting the reactivity of resulting oxygen metabolites, may affect the intensity of inflammatory process via phosphorylation and acetylation of redox-sensitive transcription factors of proinflammatory mediators [4]. There is also evidence that

antioxidants of different chemical structure and mechanism of action can affect the formation of NF- κ B signaling pathway or histone modification with a subsequent effect on inflammatory response gene expression in lung epithelial cells [2]. Concurrently, environmental and anthropogenic factors affect the activity of thiol/disulfide system in bronchoalveolar apparatus antioxidant defense, irreversibly damaging the redox components, thereby reducing the activity of transcription factors, such as Nrf2. The latter initiates the transcription of antioxidant genes and their proteins in conditions of oxidative stress [5].

At present, molecular mechanisms of the process intensification effect of the thiol/disulfide system on the severity and progression of systemic inflammatory process in patients with COPD require detailed examination, thereby making this problem relevant.

The *objective* of our study was to establish the dysfunction parameters of thiol/disulfide system components and adaptive immunity unit in patients with stable COPD.

Material and Methods

Study subjects

Our research was conducted in compliance with the requirements of the Declaration of Helsinki (2013 revision) and approved by the Ethics Committee of the Research Institute of Medical Climatology and Rehabilitation Therapy. The total of 112 subjects with moderate (Group 1) or severe (Group 2) COPD were included in the study. Voluntary informed consent was obtained from each subject prior to examination. All subjects were comparable regarding their age and gender. The mean age of subjects with COPD was 57.5±4.8 years. The control group comprised 32 relatively healthy subjects with no pulmonary dysfunction and mean age of 42.0±3.4 years.

The inclusion criterion was the presence of stable COPD of moderate to severe grade. The exclusion criteria were as follows: mild or extremely severe COPD, exacerbation of COPD, bronchial asthma, and severe decompensated diseases of internal organs.

Diagnosing COPD

We diagnosed COPD sensu GOLD 2021 guidelines [6] on the basis of medical history, physical examination, peak flowmetry, pulse oximetry, and spirometry with a bronchodilator test. Clinical and laboratory examination was performed according to the standards of pulmonological patient examination. To assess the symptoms of the underlying disease, testing with validated questionnaires was carried out: to evaluate the shortness of breath severity, we used Modified British Medical Research Council questionnaire (mMRC), to characterize the impact of COPD on the patient daily life and health status, the COPD Assessment Test (CAT) was applied. The examination of pulmonary function was performed on Master Screen Body apparatus (Care Fusion, Germany). To determine the degree of severity, post-bronchodilator parameters were examined: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and their ratio (FEV1/FVC). COPD was diagnosed at FEV1/FVC<0.7. The degree of bronchial obstruction was identified based on FEV1 values: medium (GOLD II) if values were ≥50% and <80% of predicted magnitude, and severe (GOLD III) if values were ≥30% and <50% of predicted.

Laboratory methods

Blood serum was used to examine the cytokine status. The levels of interleukins (IL) IL-4, IL-6, IL-10 and IL-17A; tumor necrosis factor (TNF-α), interferon γ (IFN-γ), and transforming growth factor (TGF-β1) were determined by flow cytometry, according to the principle of multiplex quantitative analysis (BD FACSCanto II cytometer; Cytometric Bead Array test system, BD, USA). The data were processed with FCAP 3.0 (BD, USA). To detect CD antigens on the surface of T cells, labeled monoclonal antibodies (CD45⁺ (APC-H7), CD4⁺ (PE-Cy7), CD126⁺ (APC): CD4⁺CD126⁺, which are the cells expressing the IL-6 receptor) were used. To identify expression of clonally determined markers, we used BD FACSCanto II flow cytometer and BD reagents (USA). The obtained results were processed and systematized with FACS Diva (BD, USA). The shares of cells carrying the test antigens on the cell membrane were expressed as percentages. We also studied prooxidant and antioxidant markers of oxidative stress in peripheral blood: 8-OH-deoxyguanosine (8-OHdG), protein carbonyl (PC), glutathione, glutathione reductase (GR), glutathione peroxidase (GP),

thioredoxin-1 (TR1) and thioredoxin reductase-1 (TRR-1) (Northwest Life Science Specialties, USA).

Statistical data processing

Correlation analysis sensu Spearman was employed to examine the relationship between the adaptive unit of immunity and oxidative stress parameters. Statistical analysis was carried out using Statistica 10.0 (StatSoft). Data are presented as median and interquartile range – Me (LQ-UQ). Differences between groups were analyzed via Mann-Whitney test. Statistical significance of differences was assumed at p<0.05. Data visualization was performed using the method of correlation pleiads sensu Terentiev.

Results

Our study yielded the data on the features of prooxidant and antioxidant systems (Table 1). In contrast to healthy volunteers, the level of 8-OHdG in subjects with COPD significantly increases (by 86% in moderate disease, and by 168% in severe disease), which implies intensification of free radical oxidation of nucleic acids in the cell. The effect of reactive oxygen species on protein molecules leads to their irreversible chemical modification by carbonylation of amino acid residues, as evidenced by enlarged levels of PC in subjects with COPD (by 39% in the group with moderate COPD and by 135% in the group with severe COPD). In subjects with severe COPD, there is a significant increase in the content of oxidative damage products, in contrast to subjects with moderate COPD, which indicates the role of thiol/disulfide system of antioxidant defense in disease progression.

Glutathione levels in the peripheral blood of subjects in groups 1 and 2 increased by 36% and 40%, which was indicative of the active action of the glutathione component of the antioxidant system (Table 2). The difference between glutathione levels in the studied groups is insignificant: probably, reactive oxygen species in subjects with severe COPD prevent intracellular synthesis of this antioxidant component, disrupting the membrane transport of the amino acid cysteine by the antiport mechanism. Constant supply and activation of GR enzyme in the cell is required for restoration of oxidized glutathione [7]. Its concentrations in the peripheral blood of subjects in groups 1 and 2 increased by 1 and 10%, respectively. Peripheral blood content of GP (which is directly involved in neutralization of free radicals and reactive oxygen species), in contrast to GR, increased by 50% and 69%, compared with the control group. In the study, subjects of groups 1 and 2 had increased content of TR1 (by 50% and 110%, respectively) and TRR-1 (by 22% and 72%, respectively), which was the result of compensatory reactions.

Table 1. Parameters of prooxidant system in patients with stable COPD of moderate and severe grades

Group	8-OH-deoxyguanosine, ng/mL	Protein carbonyl, nmol/mg
Control	7.98 (7.2-8.4)	0.51 (0.45-0.58)
COPD (moderate)	14.88 (13.7-15.4)	0.71 (0.67-0.8)
	p<0.001*	p=0.038*
COPD (severe)	21.4 (18.2-24.7)	1.2 (0.98-1.36)
	p=0.003#, p<0.001*	p=0.041#, p<0.001*

* statistical significance of differences vs. the control group; # statistical significance of differences between groups of patients with COPD of varying severity.

Table 2. Parameters of glutathione and thioredoxin components of antioxidant system in patients with stable COPD of moderate and severe grades

Groups	TR1, ng/mL	TRR1, ng/mL	GR, ng/mL	GP, ng/mL	Glutathione, µg/mL
Control	9.12 (7.8-10.1)	2.27 (1.9-2.25)	1.38 (1.1-1.5)	0.54 (0.48-0.62)	54.06 (47.4-61.9)
COPD (moderate)	13.7 (12.6-15.1) p=0.002*	2.76 (2.2-2.96) p=0.081*	1.40 (1.1-1.62) p=0.326*	0.81 (0.67-0.89) p=0.026*	73.3 (68.8-79.2) p=0.034*
COPD (severe)	19.2 (18.7-20.0) p<0.001#, p<0.001*	3.9 (3.37-4.83) p=0.004#, p<0.001*	1.53 (1.42-1.65) p=0.072#, p=0.124*	0.91 (0.86-0.97) p=0.095#, p=0.002*	76 (69.5-79.7) p=0.116#, p=0.021*

* statistical significance of differences vs. the control group; # statistical significance of differences between groups of patients with COPD of varying severity.

Table 3. Blood serum cytokine levels in patients with stable COPD of moderate and severe grades

Parameter, pg/mL	Control group	Moderate COPD	Severe COPD
IL-4	77.9 (66.2-81.0)	45.4 (43.0-52.3) p=0.039*	81.2 (77.0-99.4) p=0.072*, p=0.006#
IL-6	38.2 (35.7-39.0)	40.0 (37.1-46.2) p=0.367*	79.0 (69.1-84.5) p<0.001*, p=0.008#
IL-10	32.4 (31.1-33.7)	36.5 (29.0-41.0) p=0.284*	69.8 (61.0-92.1) p=0.007*, p<0.001#
IL-17A	378.4 (360.0-395.1)	402.0 (352.0-412.0) p=0.517*	640.1 (526.1-705.3) p=0.018*, p=0.035#
IL-21	75.5 (74.0-82.0)	81.6 (72.3-92.4) p=0.329*	254.0 (250.0-276.0) p=0.006*, p=0.005#
TNF-α	46.3 (43.2-48.9)	93.0 (89.6-107.5) p=0.021*	70.2 (60.0-84.0) p=0.037*, p=0.064#
IFN-γ	103.5 (91.6-125.7)	325.3 (308.1-344.0) p<0.001*	108.0 (102.0-161.1) p=0.173*, p=0.003#
TGF-β1	150.0 (118.0-180.0)	162.0 (88.0-184.0) p=0.486*	280.0 (240.0-340.0) p=0.005*, p=0.002#
CD4 ⁺ CD126 ⁺ , %	1.75 (1.62-1.79)	2.40 (2.26-2.72) p=0.043*	6.75 (5.50-8.50) p=0.002*, p=0.004#

* statistical significance of differences vs. the control group; # statistical significance of differences between groups of patients with COPD of varying severity.

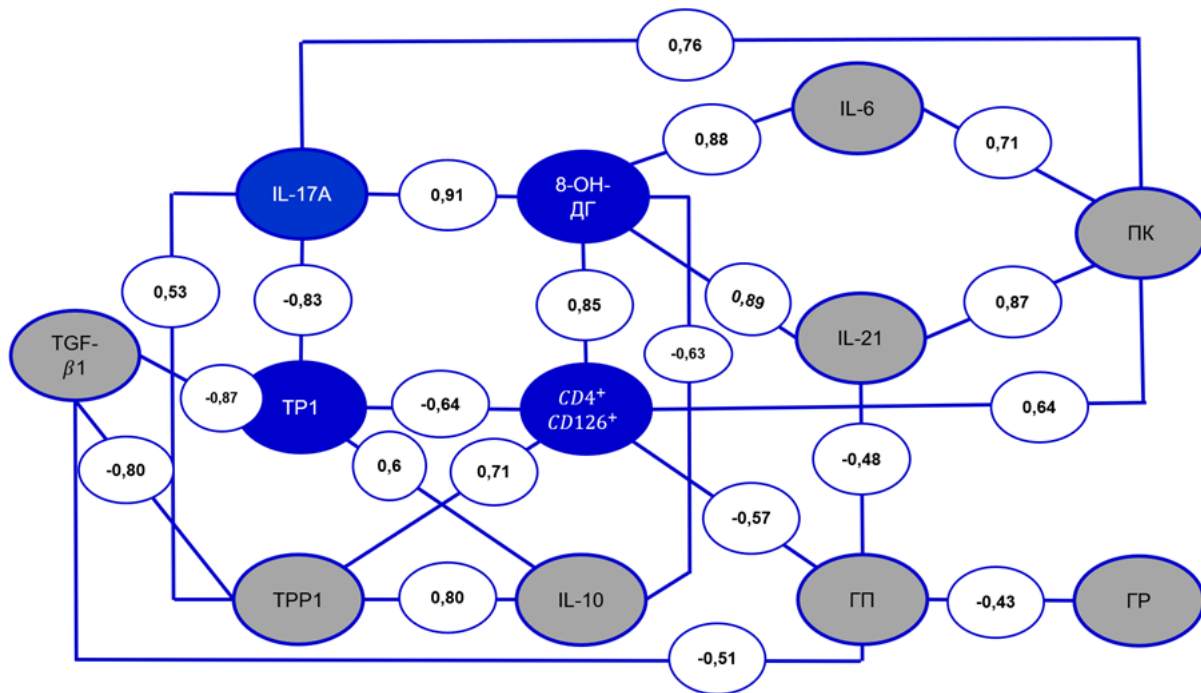


Figure 1. Correlation pleiads sensu Terentiev in COPD patients, reflecting the intra- and intersystem relationships of immunity components and oxidative stress.

Analysis results of levels of proinflammatory and anti-inflammatory cytokines and cells of the effector unit of immunity, expressing the receptor for interleukin 6 in the peripheral blood of subjects with COPD are presented in *Table 3*. Cytokines, such as IL-6, IL-17A, IL-21, TNF- α and IFN- γ , are proinflammatory molecules responsible for inflammatory process. As can be seen from *Table 3*, the levels of these mediators increase in COPD subjects, compared with the control group. Pleiotropic IL-6, which is a key inflammatory mediator, increases in subjects with moderate COPD by 5%, while in subjects with severe COPD by 106%, compared with the control group. At the same time, the percentage of cells expressing the IL-6 receptor (CD126) grow exponentially. In the peripheral blood of subjects of groups 1 and 2, the levels of IL-17 increase by 6% and 69%, respectively. The difference between subjects with moderate and severe COPD is 60%. The dynamics of changes of IFN- γ and TNF- α in serum is unclear. These cytokines provide long-term activation of innate immunity unit, in particular, pulmonary macrophages and blood neutrophils [8]. Their blood levels in group 1 increased by 101% and 214%, respectively. In group 2, they declined to 52% and 4% vs. the control group. Such biological effect is associated, on the one hand, with the activity of the regulatory immunity unit, which is confirmed by an increase in levels of IL-10 and TGF- β 1 in subjects with severe COPD by 87% and 115%, respectively, compared with the control group; and on the other hand, with switching the strategy of immune response to the disease progression, according to another pathogenetic mechanism.

We employed the method of correlation pleiads sensu Terentiev, allowing to identify and visualize the development of the pathogenic process as an apparatus for calculating the formation of systemic inflammation processes and oxidative stress in subjects with stable COPD (*Figure 1*).

The following parameters exhibited the largest number of correlations in COPD: 8-OHdG, CD4⁺CD126⁺ cells, TR1 and IL-17. Consequently, these indicators were the centers of the pleiad (i.e., predictors). 8-OHdG, which characterizes the functional activity of prooxidant system, had a positive correlation with IL-6, IL-21, IL-17A and CD4⁺CD126⁺ cells, which implied systemic inflammation and increased damage to bioorganic molecules.

Discussion

The study demonstrated statistically significant increase in oxidative modification of DNA and proteins in subjects with COPD, associated with severity of this pathology. Due to topographic peculiarities of the alveolar epithelium cells and alveolar cell polarization, the oxidation of deoxyribonucleic acid begins, primarily, with interaction of free radicals and reactive oxygen species with circular mitochondrial DNA [9]. Since in most cases, mitochondrial and nuclear DNA molecule contains high concentration of guanine and cytosine in its two-stranded chain, as a result of a chemical reaction between 2'-deoxyguanosine nucleotide and hydroxyl radical, superoxide anion radical, and hydrogen peroxide, the DNA adduct 8-OHdG is formed [10]. Unlike other modified nucleosides, 8-OHdG can penetrate the plasma membrane of endothelial cells in blood vessels; hence, it can be detected in the patient bloodstream [11]. This metabolite is the most dangerous compound in organs and major vessels, since it could cause irreversible damage to the cells of tissues and organs. This may lead not only to integrity disruption in the cytoplasmic membrane of cells, but also to the release of endogenous free

radicals and other reactive molecules, thereby causing progression of systemic inflammation via the inclusion of proinflammatory signal transduction. Protein modification could launch the specific NF- κ B signaling pathway, aimed at the expression of genes encoding proinflammatory cytokines, or else it could result in conformational rearrangements of integral proteins acting as receptors and carrier proteins [2, 9, 11]. The consequence of the former is active production of such inflammatory mediators, as IL-6, IL-8, IFN- γ , and TNF- α , aimed at enhancing the immunological response and connecting specific immunity factors [12]. As for the latter, the toxic effect of oxidized polypeptides could cause not only disruption of the integrity of the cell membrane bilipid layer, but also inability of exogenous carrier molecules to induce signaling pathways.

The thiol/disulfide system plays a significant role in maintaining the peroxidative balance. The increased levels of GP imply compensatory mechanisms directed at reducing the oxidative effect of reactive molecules, which may also affect the innate and adaptive mechanisms of the immune response in case of systemic inflammation [13]. The activity of glutathione component of antioxidant defense is aimed at inhibition of free-radical damage to biomolecules in the cell, thereby reducing the likelihood of signaling cascade activation. The latter leads to production of systemic inflammatory mediators in COPD [14]. The redox elements of glutathione component actively interact with thioredoxin system. The main elements of thioredoxin system are TR1 (involved in neutralizing oxygen metabolites and in the synthesis of deoxyribonucleotides for repairing damaged DNA) and TRR-1 that helps reducing oxidized TR1. A twofold increase in these antioxidant markers indicates the active onset of repair processes in damaged DNA [15]. It is necessary to exclude induced mutations and further destruction of deoxyribonucleic acid in the nucleus and mitochondria of the cell. Timely activated mechanisms of damaged DNA repair may preserve the integrity of two-stranded DNA molecules, along with preventing cell destruction [16]. Avoiding the progression of alterative processes in bronchoalveolar apparatus, the thiol/disulfide system directly affects the development of systemic inflammation. Oxidation of free radicals, along with leveling their toxic effect, can prevent hyperacetylation of DNA molecules and phosphorylation of NF- κ B complex component to repress the transcription of proinflammatory cytokines [2]. With COPD progression, an intensification of antioxidant defense functions is observed; but, as shown in *Table 1*, an increase in redox processes of antioxidant defense is directly proportional to augmented free radical oxidation and an increase of secondary metabolites in the peripheral blood of COPD subjects.

Therefore, in subjects with COPD of moderate grade, oxidized adducts of proteins and DNA are observed in peripheral blood. This phenomenon may lead to signal transduction and, consequently, to an increase in proinflammatory mediators, which may cause the progression of this pathology. An increase in the parameter values of glutathione unit (primarily GP) indicates an intensification of antioxidant defense reactions, aimed at inhibiting the processes of oxidative modification. The addition of redox components of thioredoxin system leads to the restoration of damaged DNA and further utilization of oxidative stress products. Nonetheless, observed oxidative damage to bioorganic molecules, formed in subjects with stable COPD of moderate or severe grade implies an increase in oxidative stress, which could trigger worsening the course of bronchopulmonary pathology.

A simultaneous increase of IL-6 and its receptor cells demonstrates uncontrolled cellular immune response. Besides, increased levels of IL-6 lead to active proliferation of naïve T cells, which acquire a specific cell phenotype with altered immune response strategy via the stages of blast transformation [12]. Consequently, the pool of T helper cells of T_H17 type increases, starting to produce IL-17 mediator. Relatively high correlation coefficients of proinflammatory cytokine IL-17A and IL-6 with 8-OHdG denotes the leading role of these bioregulators in inflammatory process development and intensification of the processes of oxidative DNA damage in COPD cells [17]. Additionally, enlarged levels of 8-OHdG indicate high concentrations of hydroxyl radical, which, through affecting the epigenetic modification of deoxyribonucleotides, could induce the expression of adaptive immunity proinflammatory unit, along with triggering apoptotic mechanisms of cell death [4, 8, 17]. Negative association of 8-OHdG with cytokine IL-10 designates suppression of immune response regulation and free-radical damage to the genes of anti-inflammatory mediators. Cells expressing receptors for interleukin-6 on their membrane have an inversely proportional relationship with the components of the thiol/disulfide system, e.g., TR1 and GP. Increased concentrations of CD4⁺CD126⁺ cells denote an emerging role of these cells in systemic inflammation progression and inhibition of oxygen metabolite neutralization [18]. Additionally, CD4⁺CD126⁺ cells are positively associated with PC, which, being an indicator of irreversible carbonylation of protein molecules, correlates with interleukin-17A. An increase in this cytokine concentrations indicates processes of alternative blast transformation of T lymphocytes into the T_H17 cell type, one of the functions of which is to suppress the production of IFN- γ and TNF- α by macrophages and cells of the lymphocytic series [19]. The positive dynamics of IL-17A in subjects with severe COPD and its negative relationship with TR1 proves its important role in the pathogenesis of respiratory pathology. TGF- β 1 is characterized by an inverse relationship with components of the thiol/disulfide system of antioxidant defense, such as TR1 and GP. High level of this inflammatory mediator leads to hyperactivation and proliferation of fibroblasts in the connective tissue of the lungs, contributing to the remodeling of alveolar epithelium and irreversible fibrotic changes [20]. Positive correlation between the immunity proinflammatory unit and the components of prooxidant system implies systemic alterative processes. A large number of weak correlations in the markers of glutathione system of antioxidant defense with proinflammatory unit indicate the suppression of restoring peroxide homeostasis and progression of bronchoalveolar pathology. Changes in the antioxidant and cytokine status of patients with COPD of varying severity grades indicate not only a shift in peroxide balance and an increase in concentrations of oxygen metabolites, but systemic inflammation progression in uncontrolled activation of adaptive immunity unit as well.

Conclusion

Accumulation of biomolecule peroxidation products, imbalance in the prooxidant-antioxidant system, and a change in the pathogenetic mechanism of inflammation development result in aggravated bronchopulmonary pathology.

Study limitations

Small sample size is a main limitation of our study.

Funding

The study did not have external funding.

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

All procedures in clinical studies were conducted in accordance with the ethical standards of the Institutional and/or National Research Committee, as well as 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

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