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Nitrosative and cytokine status in patients with COPD and chronic cerebrovascular diseases (CCVD)
Svetlana Soodaeva1, Timur Li2, Igor Klimanov1, Alexander Lisitsa1, Nailja Kubysheva1, Larisa Postnikova1, Olga Mironova1, Anatoly Fedin2.1Clinical and Experimental Pathobiology, Pulmonology Research Institute of Moscow, Russian Federation; 2Neurological Department, Russian State Medical University, Moscow, Russian Federation; 3Dept. of Internal Medicine, Municipal Hospital “Aibolit”, Nizhny Novgorod, Russian Federation; 4Department of Internal Medicine, The Medical Institute, Nizhny Novgorod, Russian Federation

The aim of the study was to investigate the dynamics of nitric oxide (NO) stable metabolites concentration in exhaled breath condensate (EBC) as markers of the nitrosative stress and circulating inflammatory cytokines in COPD and CCVD.

Material and methods: 50 males inpatients were enrolled in the study (age = 51-67 yrs). All patients were divided in two groups: group 1 contained 23 patients with COPD exacerbation and CCVD; group 2 contained 27 patients with COPD exacerbation only. The control group consisted of 21 healthy volunteers.

The investigation of NO metabolism was performed by the estimation of total nitrates/nitrites (TNN) level and 3-nitrotyrosine (3-NТ) concentration both in EBC and in blood plasma. The TNN concentration was measured using the spectrophotometric method; 3NT and cytokines (TNF-α, IL-8) concentrations in blood plasma were investigated with specific enzyme immunoassay.

Results: The TNN levels in EBC as well as in blood plasma were significantly higher in group 1&2 compared with control. The trend resulting to the increase of the TNN concentration in blood plasma was observed in patients with COPD and CCVD compared with COPD patients only (p<0.28). The 3-NТ concentration both in EBC and in blood plasma didn’t change in group 1&2 compared with control. So, the statistically significant increase of inflammatory cytokines level in blood plasma compared with control was demonstrated (p<0.001). The cytokines activity in group 1 was higher than in group 2.

Conclusion: The results obtained demonstrate the increase of nitrosative/cytokines stress parameters as a systemic reaction in patients with COPD and CCVD compared with COPD patients only.

P3895
Leptin modulates host defense against chronic cigarette smoke inhalation in mice
Juanita H.J. Vernooy1, Irene M.J. Eurlings1, Gonda F.J. Konings1, Dick Bonarius2, Marlies van Dijk1, Hub Kerkhoven1, Wim Timens1, 1Pathology and Medical Biology, University Medical Center Groningen, Groningen, Netherlands; 2J&J Therapeutics, J&J Therapeutics, Groningen, Netherlands; 3Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, Groningen, Netherlands

Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; 3Department of Respiratory Medicine, NUTRIM School for Nutrition, Toxicology and Metabolism/Maastricht University Medical Centre, Maastricht, Netherlands; 2Department of Medical Protein Research, Flanders Interuniversity Institute for Biotechnology/Ghent University, Ghent, Belgium; 1Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

Rationale: Several hallmarks of COPD, including pulmonary and systemic inflammation, can be mimicked in mice by cigarette smoke (CS) exposure. We recently revealed increased expression of the pleiotropic adipokine leptin by resident lung cells in smokers and patients with COPD versus never-smokers. To unravel the involvement of leptin in COPD pathogenesis, innate and adaptive immune cell recruitment and remodelling upon chronic CS-exposure was evaluated in leptin-receptor deficient (di/db) mice.

Methods: WT C57/BKS and di/db mice were exposed to air or CS for 16 weeks (4 exposures/5, 5 wk). At 24h after the final exposure, bronchoalveolar lavage fluid (BALF) and lung tissue were processed to examine pulmonary inflammation and remodelling.

Results: CS exposure significantly increased leptin expression in bronchial epithelial cells and pneumocytes as compared to air-exposed WT mice (p<0.05). CS exposure resulted in accumulation of neutrophils, dendritic cells, macrophages and T lymphocytes in BALF and lung tissue of both WT and di/db mice. However, CS-exposed di/db mice showed significantly higher number of neutrophils (p<0.05) and lower numbers of dendritic cells (DCs) and T lymphocytes (p<0.05), compared to CS-exposed WT mice. In addition, chronic CS exposure resulted in increased hyaluronan deposition in the airway walls and development of pulmonary emphysema in WT mice and di/db mice, which was not different between both strains.

Conclusion: These data suggest a central role for the pleiotropic adipokine leptin in innate and adaptive immune cell accumulation after chronic CS inhalation in mice.

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P3897
Towards understanding the role of autoreactivity in COPD
Jan Tavernier2, Guy F. Joos3, Guy G. Brusselle3, Emiel F.M. Wouters1, Ken Vervaet1, Juanita H.J. Vernooy1, Irene M.J. Eurlings1, Gonda F.J. Konings1, Dick Bonarius2, Marlies van Dijk1, Hub Kerkhoven1, Wim Timens1
1Pathology and Medical Biology, University Medical Center Groningen, Groningen, Netherlands; 2J&J Therapeutics, J&J Therapeutics, Groningen, Netherlands; 3Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, Groningen, Netherlands

Aim: Oxidant/antioxidant disequilibrium is an important problem in pathogenesis of COPD. This disequilibrium is effective in development and progression of COPD. The increased oxidative stress in COPD is not only associated with rise of oxidants but also associated with the decrease of antioxidant capacity.

Paraoxonase 1 (PON1) functions as one of the endogen free radical clearing system in human body. PON1 is localized in clara cells, endothelial cells and type 1 pneumocytes of the lungs.

In this study we aimed to study the PON1 activity in COPD patients with stable condition, had acute attack and developed respiratory failure.

Material and method: Twenty five patients with stable COPD (group1) (mean age 62.9±9.4), 25 cases with acute COPD attack (group2) (mean age 63.8±9.0), 25 patients with hypercapnic respiratory failure (group3) (mean age 65.0±12.9) and 25 healthy individuals for control group (mean age 34.8±9.8), totally 100 cases, were enrolled to the study. All cases enrolled to the study underwent routine biochemical analysis including PON1 activity and lipid profile.

Results: There was significant difference between groups with respect to PON1 levels (p<0.001). PON1 activities of COPD patient groups (group 1=96,8±57,4U/L, group 2=51,4±32,8U/L, group 3=47,1±27,5U/L) were lower than control group (185,4±110,1U/L) (p<0.001). Also PON1 activity of stable COPD patients was higher than the COPD cases admitted with acute attack or respiratory failure (group 2 and 3) (p<0.05).

Conclusion: This findings show that PON1 activity may have a role in COPD pathogenesis and endogen antioxidants might be depleted by increased oxidative stress in COPD. This also advocates that oxidative stress may have a role in acute COPD attacks.

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P3898

Model of staged development chronic obstructive pulmonary disease (COPD) in rats

Ivet Vopova-kovakova1, Elena Lebedeva1, Lev Danilov1, Nataliya Kuzubova2.
1 Department of Experimental Pulmonology and Pathomorphology, Research Institute of Pulmonology, St. Petersburg, Russian Federation; 2 Department of COPD Therapy, Research Institute of Pulmonology, St. Petersburg, Russian Federation

Models of COPD open ways of studying pathogenesis, searching for therapeutic targets and new health care trends.

Aim: To reproduce the successive stages of COPD in experiment.

Methods: Model of COPD was induced in Wistar rats by long-time intermittent nitrogen dioxide (NO2) inhalation (15 ppm, 1.5 h/day for 60 days). Histological specimens were stained with hematoxylin-eosin. CD3 expression in bronchial walls and interstitium was determined by immunohistochemistry. TNFα and TGFβ were determined in serum and bronchoalveolar lavage fluid (BALF).

Results: After 15-day NO2 exposure acute response to injury was observed: epithelium desquamation and focal proliferation, swelling of submucosa, bronchial gland degeneration, lung tissue hyperextension were revealed. After 30 days cell infiltration of submucosa and hyperplasia of goblet cells were added. After 60-day exposure squamous metaplasia of ciliated epithelium, muscle plate atrophy, focal sclerosis, emphysema were identified. At this stage increase of CD3 expression was revealed in walls of bronchi and interstitium that indicated the presence of large number of T-lymphocytes (61±6.15 vs. 28±1.23 in control intact rats, p<0.05). TNFα increased in serum (125.9±16.21 vs. 60.9±6.34 pg/ml in control, p<0.05) and BALF (204.9±25.76 vs 15±0.03 pg/ml in control, p<0.05). TGFβ increased in serum 18-fold and in BALF – 8-fold from control (p<0.01). TNFα and TGFβ have positive correlation (Rho=+0.66, p=0.01).

Conclusion: The model allows to reproduce stages of COPD from acute inflammation to lung tissue remodeling (emphysema and focal fibrosis). The model adequacy was revealed in walls of bronchi and interstitium that indicated the presence of large number of T-lymphocytes (61±6.15 vs. 28±1.23 in control intact rats, p<0.05). TNFα increased in serum (125.9±16.21 vs. 60.9±6.34 pg/ml in control, p<0.05) and BALF (204.9±25.76 vs 15±0.03 pg/ml in control, p<0.05). TGFβ increased in serum 18-fold and in BALF – 8-fold from control (p<0.01). TNFα and TGFβ have positive correlation (Rho=+0.66, p=0.01). Free fatty acids (FFA), compared with the control, increased by 47.2% (P<0.01) with a decrease in total phospholipids (TFL) by 17% (P<0.01). After 10 sessions of phototherapy we defined increase in PC and PE by 18.8% and 28.4% compared with the group of COPD without treatment, and this was accompanied by a decrease in LPC and LPE by 35.1% and 40.9% (P<0.05 in all cases). Tendency to normalization of FFA and TFL had no statistical significance.

Conclusion: Experimental COPD in the rats is accompanied by quantitative changes in the main fractions of phospholipids in the membranes of peripheral blood lymphocytes. Conducting a course of phototherapy by CPL contributes to positive change in membrane phospholipids of these cells.
Possible role of 25-hydroxycholesterol on the pathogenesis of chronic obstructive pulmonary disease

Hisatoshi Sugiura, Akira Koorai, Tomohiro Ichikawa, Masakazu Ichinose. Third Department of Internal Medicine, Wakayama Medical University School of Medicine, Wakayama, Japan

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Background: 25-Hydroxycholesterol (25-HC) is produced from cholesterol by cholesterol 25-hydroxylase and is related to atherosclerosis in vessels. Recently, 25-HC was reported to cause inflammation in various types of cells. The aim of this study is to assess the production of 25-HC in the airways of COPD and to elucidate the effects of 25-HC in neutrophil infiltration in the airways of chronic obstructive pulmonary disease (COPD).

Methods: Eleven healthy never-smokers, 6 healthy ex-smokers, and 13 COPD patients took part in the lung tissue study. The expression of cholesterol 25-hydroxylation in the lungs was investigated. Twelve healthy subjects and 17 COPD patients also took part in the sputum study. The amount of 25-HC in the sputum was also quantified. To elucidate the effects of 25-HC on neutrophil infiltration in the airways, 25-HC was intratracheally administered in mice. 

Results: The expression of cholesterol 25-hydroxylation was significantly enhanced in the lung tissue from COPD patients compared to healthy subjects. Cholesterol 25-hydroxylation was localized in alveolar macrophages and pneumocytes in COPD. The amounts of 25-HC in the sputum were significantly increased in COPD patients and the degree of 25-HC production was negatively correlated with the lung function. The amounts of 25-HC in the sputum had significant positive correlations with the interleukin-8 (IL-8) levels and neutrophil counts in the sputum. Treatment with 25-HC augmented neutrophil accumulation in the airways and the production of chemokines in mice.

Conclusions: 25-HC production was enhanced in the airways of COPD patients and could cause neutrophilic inflammation.

Time course analysis of lung function and morphometric parameters in a murine model of emphysema

Clarice Olivo, Bruna Scarpa, Francine Almeida, Petra Arantes, Fernanda Lopes, Milton Martins. Department of Medicine, Universidade de Sao Paulo, Sao Paulo, Brazil

Proteolytic enzymes have been used to induce emphysema in rodents to study mechanisms of this disease pathogenesis. However, few studies have evaluated the time course of the development of pulmonary emphysema after nasal instillation of elastase.

Objectives: To describe the progression of emphysema after porcine pancreatic elastase (PPE) nasal instillation in mice.

Methods: 64 adult male Balb/c mice received either a nasal drop of 60 μl (1.067 U) of PPE (PPE) or saline (S) and were studied on days 1, 7, 14 and 21 after PPE instillation. For each time, we analyze airway resistance (RAW), tissue damping (Gis) and tissue elastance (His). Inflammatory profile was performed in bronchoalveolar lavage (BAL) and both lungs were fixed with 10% buffered formalin infused through the trachea at 20cmH2O for 24h and paraffin embedded for measurements of mean linear intercept (Lm).

Results: There was an increase in inflammatory cells in PPE groups since the 1st day and was maintained throughout different times.

Conclusions: In this experimental model we observed an earlier inflammatory process concomitant with alveolar enlargement, suggesting that protease-antiprotease imbalance influence the development of emphysema. Supported by FAPESP, LIMHC-FMUSP, CNPq, Brazil

Effects of cancer cachexia on the alveolar morphology of the mouse lung

Tilmann Graulich1, Suman Kumar Das2, Gabriela Krasteva1, Lars Wessels1, Gerald Hoffer1, Christian Mühlfeld1. 1Institute of Anatomy and Cell Biology, Justus-Liebig-University Giessen, Giessen, Germany; 2Institute of Pathology, Medical University Graz, Graz, Austria

Cancer cachexia is a complex syndrome with a significant reduction of body weight and a variety of systemic symptoms including respiratory dysfunction. In rodents, calorie restriction causes loss of alveolar surface area, the so-called nutritional emphysema. We hypothesized that alveolar alterations and loss of gas exchange surface area are present in the cancer-cachectic mouse. C57Bl/6 mice were randomly assigned to subcutaneous injection of Lewis lung carcinoma cells (tumor group, TG) or saline injection (control group, CG). Mice were sacrificed 21 days later and lungs were processed for light and electron microscopy and biochemical analysis (n=6 in each group)

Body weight was reduced in TG vs. CG (17.4±0.6 g; CG: 22.1±1.0; p<0.05). Lung volume did not differ between TG (518.3±28.2 mm3) and CG (468.3±50.5 mm3). The alveolar surface area was similar in both groups (TG: 602.3±77.7 cm2; CG: 496.2±58.2 cm2). Although the total volume of lamellar bodies did not differ between the groups, the volume of lamellar bodies per unit alveolar surface area was significantly reduced in TG (TG: 26.5±3.7 mm3/μm2; CG: 40.2±13.05 mm3/μm2; p<0.05). Quantitative expression of surfactant proteins A, B, C and D was not different between CG and TG as shown by RT-PCR.

In summary, despite a reduced ratio between the volume of the intracellular surfactant pool and the alveolar surface area in TG, there was no evidence for a significant disturbance of the gas exchange region due to cancer cachexia. In particular, weight loss was not associated with loss of alveolar surface area.
P3907
Contribution of TGFβ1 and TIMP2 to clinical activity of asthma and COPD
Navid Abolfath Zade Ghalejoghli1, Mostafa Ghanel1, Mohammad Reza Neoumi1, Ali Ammi Harandi2, Abbas Ali Imani Fooladi2;1Research Center of Chemical Injuries, Baqiyatallah University of Medical Sciences, Tehran, Islamic Republic of Iran; 2Research Centers of Molecular Biology, Baqiyatallah University of Medical Sciences, Tehran, Islamic Republic of Iran

Introduction: The process of bronchial tissue repair and remodeling in airway diseases depends on balance between production and degradation of different cytokines, leading to the regulation of extracellular matrix turnover finally.

Objectives: This study was designed to evaluate contribution of Transforming Growth Factor β1 (TGFβ1) and Tissue Inhibitor of Metalloproteinase-2 (TIMP2) to clinical activity and reversibility of asthma and chronic obstructive pulmonary disease (COPD).

Methods: In a cross sectional study on two groups of 29 asthmatics (14 males and 15 females) and 13 male COPD patients, we evaluated TIMP2 and TGFβ1 expression using semi-quantitative PCR on induced sputum samples. The relation among TIMP2 and TGFβ1 and pulmonary function test (PFT) indices and disease free periods were assessed.

Results: Higher pulmonary function test (PFT) indices and longer disease free period was seen in COPD patients with raised expression of both TGFβ1 and TIMP2. On the other hand asthmatic patients had better pulmonary function status with raised TIMP2 and decreased TGFβ1 expression (p<0.05).

Conclusion: It seems that different effect of cytokines like TGFβ1 and TIMP2 in both diseases is dependent on underlying inflammatory process in airways epithelium. We supposed that TGFβ1 bidirectionally affects activity of disease in asthma and COPD. Furthermore TGFβ1 as a biomarker in sputum may have a role for evidence-based drug prescribing like corticosteroids in patients with COPD and asthma.

P3908
The role of cathepsin D, H & K in the regulation of tumstatin levels in asthmatic airways
Janette Burgess1,2,3, Karryn Grafton 1,2,3, Gavin Tjin1,2, Josephine Middelburg1,4, Beatriz Mangueira Saraiva 2, Milton Arruda Martins 2, Celso Ricardo Fernandes de Carvalho 3, Clarice Rosa Oliver2, Beatriz Mangueria Sarac2, Milton Arruda Martins 2, Clarice Rosa Oliveir2, Beatriz Mangueria Sarac2, Milton Arruda Martins 2, Celso Ricardo Fernandes de Carvalho 3

Introduction: Angiogenesis is a prominent feature of remodelling in asthma. We previously reported that tumstatin, an endogenous angiogenic inhibitor which is the non-collagenous domain-1 (NC1) of the collagen IV α3 chain is absent from asthmatic airways. Tumstatin is released from the basement membrane by specific proteases. Cathepsins D, H and K (members of a broad family of proteases that degrade ECM proteins including collagen IV in other organs) are increased in inflammatory diseases and modulate tumour angiogenesis. We hypothesised that cathepsin D, H and/or K plays a role in the absence of tumstatin in asthmatic airways.

Methods: Cathepsin mRNA expression was measured by real time RT-PCR. Immunohistochemistry was used to measure cathepsin D, H and K in human airway tissue sections. Recombinant tumstatin and airway tissue sections were digested with active recombinant cathepsin D, H and K and the resultant cleavage products analysed by polyacrylamide gel electrophoresis.

Results: Human airway smooth muscle cells express cathepsin D and H mRNA. In both asthmatic and nonasthmatic airway sections inflammatory cells exhibit strong staining for cathepsin D. Cathepsin H and K are also strongly expressed in asthmatic airway tissues. Recombinant tumstatin was completely degraded by recombinant cathepsin D and H whilst cathepsin K degradation produced a 10kDa cleavage product. In human tissue sections recombinant cathepsin D completely digested tumstatin. Digestion with cathepsin K resulted in greater detection of the tumstatin antigen.

Conclusion: These findings suggest that cathepsin D, H and K may play a role in the regulation of tumstatin levels in the asthmatic airways.

P3909
Inhibitory profiles of alpha-1-antitrypsin from PiZ & PiSZ individuals and implications for tissue destruction in emphysema
Nicola Sindel1, Timothy Dafforn1, Robert Stockley1;1ADAPT Project, Lung Function and Sleep Department, University Hospital Birmingham, Birmingham, West Midlands, United Kingdom; 2School of Biosciences, University of Birmingham, Birmingham, Birmingham, United Kingdom

Introduction: Neutrophil elastase (NE) causes emphysema in animal models. Homozygote (ZZ) deficiency of its inhibitor alpha-1-antitrypsin (AAT) is associated with human emphysema. The role of heterozygote deficiency (SZ) is unclear.

Aims: To compare the inhibitory profiles of equimolar amounts of AAT from Z & SZ serum with pure AAT & M serum. The hypothesis is that Z AAT inhibits NE less efficiently than SZ & M AAT.

Methods: AAT concentration was measured in serum from Z, SZ & M patients. Increasing amounts of AAT were added to a fixed amount of NE. Residual NE activity was measured spectrophotometrically using both a chromogenic substrate and elastin. This was repeated with pure AAT & alpha-2-macroglobulin (A2M).

Results: With a low molecular weight chromogenic substrate, M serum AAT increasingly inhibited NE as the inhibitor:enzyme molar ratio increased to 1:1. Beyond 1:1 inhibition 15% residual NE activity remained, but not for pure AAT. For SZ serum residual activity was 60%. For Z serum and pure A2M enhanced NE activity was seen as inhibitor:enzyme ratio increased.

Conclusion: Enhanced NE activity with Z serum likely represents binding to A2M. Deficiency of AAT means that NE is more likely to bind to A2M. A2M:NE complexes retain proteolytic potential. These data may have implications for tissue destruction in emphysema.

P3910
Acute effects of an aerobic exercise session on airway inflammation in a murine asthma model
Romana dos Santos da Silva1, Rodrigo de Paula Vieira4, Francine Marie de Almeida1, Clarice Rosa Oliveira2, Beatriz Mangueria Sarac2, Milton Arruda Martins2, Celso Ricardo Fernandes de Carvalho3, Clarice Rosa Oliveira2, Beatriz Mangueria Sarac2, Milton Arruda Martins2, Celso Ricardo Fernandes de Carvalho3

Background: Chronic effects of aerobic training (AT) seem to decrease inflammation in experimental asthma.

Introduction: Angiogenesis is a prominent feature of remodelling in asthma. We previously reported that tumstatin, an endogenous angiogenic inhibitor which is the non-collagenous domain-1 (NC1) of the collagen IV α3 chain is absent from asthmatic airways. Tumstatin is released from the basement membrane by specific proteases. Cathepsins D, H and K (members of a broad family of proteases that degrade ECM proteins including collagen IV in other organs) are increased in inflammatory diseases and modulate tumour angiogenesis. We hypothesised that cathepsin D, H and/or K plays a role in the absence of tumstatin in asthmatic airways.

Methods: Cathepsin mRNA expression was measured by real time RT-PCR. Immunohistochemistry was used to measure cathepsin D, H and K in human airway tissue sections. Recombinant tumstatin and airway tissue sections were digested with active recombinant cathepsin D, H and K and the resultant cleavage products analysed by polyacrylamide gel electrophoresis.

Results: Human airway smooth muscle cells express cathepsin D and H mRNA. In both asthmatic and nonasthmatic airway sections inflammatory cells exhibit strong staining for cathepsin D. Cathepsin H and K are also strongly expressed in asthmatic airway tissues. Recombinant tumstatin was completely degraded by recombinant cathepsin D and H whilst cathepsin K degradation produced a 10kDa cleavage product. In human tissue sections recombinant cathepsin D completely digested tumstatin. Digestion with cathepsin K resulted in greater detection of the tumstatin antigen.

Conclusion: These findings suggest that cathepsin D, H and K may play a role in the regulation of tumstatin levels in the asthmatic airways.

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Objective: Investigate the effects of a unique exercise session of aerobic exercise in a murine asthma model.

Methods: Male Balb/c mice were divided in 4 groups: Control, AT, ovalbumin sensitized (OVA) and OVA+AT. OVA sensitization groups received i.p. daily injections of OVA (10 μg/mL) for 7 days. OVA and OVA+AT groups performed a session of treadmill running for 1 hour (50% maximal intensity). Evaluations: In vivo respiratory mechanic (Fluxvent), different cell count in the BALF, and collagen fibers depositions and smooth muscle thickness in the airways were evaluated by an image analyzer.

Results: Initial physical capacity was similar among groups (p>0.05). BALF total and inflammatory cells, collagen fiber and the smooth muscle thickness were increased in sensitized groups (p<0.05). Parameters of respiratory mechanic (Gis and This) were also increased in groups sensitized groups (OVA and OVA+AT; p<0.05).

Conclusions: Aerobic exercise when performed for acutely does not decrease features of experimental asthma such as cell migration, airway remodeling and respiratory mechanic.

COPD and oxidative stress in patients with COPD

Valentina Kapustina1, Svetlana Ovcharenko1, Petr Litvicki 2.

High doses of N-acetylcysteine alone or in combination with inhaled corticosteroids and oxidative stress in patients with COPD

P3911

male, mean age 66.8±7.5 years, GOLD stage I-IV) were divided into two treatment groups. Group 1 received bronchodilators as basal treatment and NAC. Group 2 received NAC plus ICS in addition to basal treatment. Clinical examination, pulmonary function tests and blood collection were performed at baseline (T0) and repeated after 1 (T1), 3 (T3) and 6 months (T6) of treatment.

Results: Spontaneous ROS generation had trend to decrease at T3 in both groups, and achieved significant difference at T6 only in group 2 (p=0.0004). At the same time stimulated ROS generation did not significantly change in both groups (p>0.05). Antioxidant enzyme activity was increased from T0 to T1 however further levels did not substantially changed. We registered MDA plasma level decrease in both groups during all treatment period, but significant difference from T0 to T6 was observed just in group 2 (1.8 μmol/L vs. 1.4 μmol/L, p=0.017).

Conclusion: We conclude that combination of oral NAC 1200 mg/day with ICS for 6 months reduces the oxidant burden in airways of stable COPD patients and did not impact in patients treated with NAC alone.

Ceruloplasmin efficacy in patients with asthma exacerbations

Usman Farkhutdinov, Shamil Farkhutdinov. Department of Internal Diseases, City Hospital 21, Ufa, Russian Federation

Ceruloplasmin (C) proves to be a valuable preparation in the treatment of patients with lung diseases because it is a copper containing enzyme which is considered to be the basic antioxidant factor. The aim was to study the effect of C on the production of active oxygen forms (AOF) in patients with bronchial asthma (BA).

Methods: 40 patients with BA exacerbations were included in the study. The production of AOF in the blood of patients was studied by registration of lumilin dependent spontaneous (SP) and staphylococcus activated (SA) chemiluminescence (CLL). The patients were divided into 2 groups. The patients received standard therapy with different basic medications. The other 20 patients with BA received combined therapy including C.

Results: In comparison with normal findings SPCLL of blood in patients with BA was higher by 1.5-times and SACL was higher by 1.8 times. It indicated increased production of AOF by blood cells. Treatment with C was associated with reduced generation of AOF in the blood, positive dynamics of clinical and laboratory findings. Patients who received standard therapy demonstrated symptoms of the disease and enhanced CLl intensity of the blood for a long time.

Conclusion: AOF production in patients with BA exacerbations was found to be decreased. The use of C reduces AOF production and improves the treatment efficacy.