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TNF-α, CXCL8, big ET-1 and hsCRP in Patients with Chronic Obstructive Pulmonary Disease

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COPD (chronic obstructive pulmonary disease) is a chronic progressive inflammatory disease characterised by limitations in lung airflow that is not fully reversible. The concentrations and correlations of TNF-α, CXCL8, big ET-1 and hsCRP were investigated in healthy non-smokers, healthy smokers and patients with COPD in order to study their possible role in the pathophysiology of COPD. The concentrations of TNF-α, CXCL8 and big ET-1 were not statistically different between the experimental groups. No significant differences for the measured analytes were found between smokers and the non-smokers in the control group. The Spearman coefficient of correlation between the concentrations of TNF-α and CXCL8 was $r = 0.638$ ($p<0.0001$). However, the concentration of hsCRP was significantly higher in patients with COPD than in the control group ($p = 0.0004$). hsCRP proved to be a more sensitive diagnostic parameter than TNF-α, CXCL8 and big ET-1 in the systemic circulation in patients with COPD.

Keywords
COPD
TNF-α
CXCL8
big ET-1
hsCRP

INTRODUCTION

COPD (chronic obstructive pulmonary disease) is, according to the Global Initiative for COPD, a chronic progressive inflammatory disease characterised by limitations in lung airflow that is not fully reversible.[1] According to the WHO, COPD could become until 2020 the third most common cause of mortality in the world.[2] The pathophysiology of COPD is not completely understood. The most common cause of COPD is tobacco smoke (80 % of COPD patients) and, as other causes, there are also air pollution, poor nutrition, professional risk at work and genetic factors.[3] Systemic inflammation seems to be a risk factor for various complications that occur during COPD, like atherosclerosis, cachexia and osteoporosis.[4] Various mediators released from structural and inflammatory cells in the lungs have been investigated and they probably participate in the pathophysiology of COPD.[2]

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TNF-α (tumor necrosis factor-α) is a glycoprotein, a strong inflammatory cytokine which has a key role in inflammation.[5] TNF-α induces the synthesis of IL-6 (interleukin-6) and stimulates the release of acute phase reactants from hepatocytes, activates macrophages, epithelial and mesenchymal cells and induces chemokine production.[2,5,6] Tobacco smoke induces the release of TNF-α and has an important role in the pathophysiology of COPD.[2,6] TNF-α influences gene expression of CXCL8 (interleukin-8) and ET-1 (endothelin-1) in human endothelial cells, and participates in bronchoconstriction through secondary release of ET-1.[7,8,9]

ET-1, a 21 aminoacid peptide, is one of the most potent known vasoconstrictors. ET-1 is cleaved from its precursor big ET-1 (38 aminoacids) by endothelin converting enzyme (ECE).[10,11] ET-1 is present in human lungs and has a potential role as a mediator in lung diseases like asthma, pulmonary hypertension and COPD.[12,13] ET-1 is presumed to participate in vasoconstriction, bronchoconstriction, remodelling of the airways, activation of inflammation cells, mucus secretion and hyperreactivity of the airways.[8,12] Increased concentration of ET-1 found in COPD patients in bronchoalveolar lavage, sputum and serum supports the role of ETs as potential bronchoconstrictors in the pathophysiology of this disease.[14] An increase of ET-1 in sputum and also a slight increase in plasma was found in COPD patients with exacerbation of the disease.[15]

CXCL8 (interleukin-8) is a glycoprotein from a group of chemokines which chemotactically attracts neutrophil granulocytes and, to a lesser extent, lymphocytes to the inflammatory site.[2,5] Epithelial cells from the airways and macrophages probably release CXCL8 under the influence of TNF-α, IL-1β, lipopolysaccharides and bacterial products, some viruses, oxidative stress and tobacco smoke extracts.[2] COPD patients have increased concentration of CXCL8 in sputum and serum, which correlates with the neutrophil number.[16] Cultivated epithelial cells obtained by bronchoscopy from COPD patients show increased synthesis of CXCL8 compared to cells from smokers.[17] The concentration of CXCL8 is increased in plasma of hospitalized COPD patients and correlates with muscle weakness.[18]

CRP (C-reactive protein) is an acute phase reactant and its concentration is increased in inflammatory diseases.[19] CRP is synthesised in hepatocytes under the influence of IL-6.[19] CRP concentration increases in bacterial infectious diseases and rheumatoid and malignant diseases; currently, with "high sensitivity" assays CRP is investigated as a prognostic factor in cardiovascular diseases present silent systemic inflammation, hence the name hsCRP.[19,20] hsCRP, as a systemic marker of inflammation, is increased in stable COPD patients and in COPD patients with complications when compared to healthy controls.[4]

As we described above, there was a number of investigations dealing with the concentration of these inflammatory mediators in specimens like induced sputum or bronchoalveolar lavage, and their results indicate a local inflammatory process.[14,15,21–23] However, it is known that COPD is a disease with prominent systemic inflammatory response.[4,24] The aim of this study was to identify whether the inflammatory process in stable COPD patients is powerful enough to produce significant changes in the selected inflammatory markers (TNF-α, CXCL8 and hsCRP). The role and concentration of big ET-1 in the peripheral circulation of COPD patients and relationship between big ET-1 and the concentration of TNF-α, CXCL8 and hsCRP have not been defined, as yet. Therefore, we also investigated the concentration of big ET-1 in plasma (half life ≈ 23 min), which is considered to be a reliable indicator of the activation of ET-1 (half life ≈ 7 min).[25] Big ET-1 is not believed to be subject to lung clearance and it provides better information on the secretion of ET-1.[13]

EXPERIMENTAL

Materials

The study was performed on specimens from patients with stable COPD (n = 27) or with exacerbations (n = 7) who were treated at the Jordanovac University Hospital for Lung Diseases, Zagreb. In the tested group there were n = 8 females and n = 26 males, thereof 6 non-smokers and 28 smokers. Except COPD, 15 patients also had another disease: hypertension (3), hypertension and angina pectoris (4), post-infarction status (4), hypertension and post-infarction status (1), osteoporosis (2) and stenocardia (1). Inclusion criteria for COPD patients was clinical diagnosis of COPD based on clinical features and spirometric findings (forced expiratory volume in 1 second (FEV1) < 80 %). There were 16 patients with moderate (FEV1 = 50–80 %) and 18 with severe COPD (FEV1 < 50 %). The control group consisted of healthy volunteers: smokers (37) and non-smokers (23), without any clinical signs of the disease and with normal spirometric findings (FEV_1 > 80 %). Venous blood was collected with K_3EDTA as anticoagulant for big ET-1 and hsCRP measurement and then centrifuged at 3000 *g* for 10 min, plasma was aliquoted and frozen at –20 °C until measurement. Venous blood for the measurement of TNF-α and CXCL8 was collected in vacutainer tubes without anticoagulant and, after coagulum formation, was centrifuged at 1000 *g* for 10 min, and serum was aliquoted and frozen at –20 °C until measurement. The study was approved by the Ethics Committee of the Jordanovac University Hospital for Lung Diseases and written informed consent was obtained from each participant.

Methods

Clinical evaluation of the examinees included medical history and spirometric analysis of lung function. The concentration of big ET-1 was determined with an ELISA test (Big

endothelin, Enzyme Immunoassay for the Quantitative Determination of Human Big Endothelin, Biomedica Gruppe) and the measuring range was 0.05–15.6 fmol/mL. hsCRP concentration was measured nephelometrically on an BN Pro Spec II nephelometer (N High Sensitivity CRP assay, Dade Behring). The analytical sensitivity of this assay was 0.159 mg/L. The measurements of TNF-α and CXCL8 were done using ELISA tests (Quantikine, Human IL-8 Immunoassay, R&D Systems; Quantikine Human TNF-α/TNFSF1A Immunoassay, R&D Systems). The analytical sensitivity was 0.5–5.5 pg/mL for the TNF-α test, and 1.5–7.5 pg/mL for CXCL8 test (data provided by manufacturer). Calibrators and control samples were commercially available from the same companies.

Subjects were divided in three groups: COPD patients smokers and non-smokers, healthy smokers and healthy non-smokers which served as a control group (Table I).

Statistical Analysis

Statistical analysis was performed by using the statistical software MedCalc, version 7.0.1.0. All data were tested for normal distribution with Kolmogorov-Smirnov test. The data for all measured analytes did not show normal distribution so results are presented as a median and the 25^{th}–75^{th} percentile. Figures present the median of the measured analytes and the 25^{th}–75^{th} percentile and outliers (Box and whisker plots). Statistical significance between groups was tested with the Mann-Whitney U test in relation to the control group (healthy non-smokers). The Spearman coefficient of correlation was used to study the relationship between the measured parameters. Values $p<0.05$ were considered statistically significant.

RESULTS

In this study we measured the concentrations and correlation of TNF-α, CXCL8, big ET-1 and hsCRP in healthy non-smokers, healthy smokers and patients with COPD (Table II, Table III and Figure 1).

Patients with COPD had a statistically significant increase in hsCRP (p = 0.0004), while healthy smokers

TABLE I. Clinical characteristics of the studied groups[a]

	COPD patients	Smokers	Non-smokers
Age / y	67 (64–72)	52 (45–58)	44 (40–59)
Smoking history (Pack/year)	45 (33–68)	28 (21–41)	0
FEV1 / %	44 (40–65)	> 80	> 80
Lkc counts / 10^9 dm^{-3}	7.50 (6.54–8.70)	6.60 (5.40–7.73)	5.55 (4.80–6.90)
Medication	Yes	No	No

[a] Data are presented as a median and 25^{th}–75^{th} percentile in parenthesis.

TABLE II. Concentration (γ) of measured analytes in serum (hsCRP, big ET-1) and plasma (TNF-α, CXCL8) of COPD patients, smokers and non-smokers (control group)[a]

	COPD patients	Smokers	Non smokers
γ(TNF-α) / (pg mL^{-1})	11.6 (7.7–15.3)	15.0 (11.4–20.9)	12.8 (10.0–24.9)
γ(CXCL8) / (pg mL^{-1})	33.8 (20.5–63.5)	29.4 (17.6–49.9)	29.7 (21.6–52.2)
γ(Big ET-1) / (fmol mL^{-1})	0.80 (0.70–1.14)	1.10 (0.90–1.50)	1.00 (0.76–1.20)
γ(hsCRP) / (mg L^{-1})	3.9 (1.52–5.39)[b]	1.52 (0.79–3.74)	1.10 (0.61–1.53)

[a] Data are presented as a median and 25^{th}–75^{th} percentile in parenthesis.
[b] p = 0.0004.

TABLE III. Concentration (γ) of measured analytes in serum (hsCRP, big ET-1) and plasma (TNF-α, CXCL8) in moderate (FEV1 > 50 %) and severe (FEV1 ≤ 50 %) COPD patients[a]

	COPD patients	
	FEV1>50 %	FEV1≤50 %
γ(TNF-α) / (pg mL^{-1})	13.5 (7.45–19.65)	11.60 (7.75–19.60)
γ(CXCL8) / (pg mL^{-1})	31.20 (19.45–113.38)	44.90 (18.88–73.38)
γ(Big ET-1) / (fmol mL^{-1})	0.80 (0.70–1.35)	0.80 (0.60–1.10)
γ(hsCRP) / (mg L^{-1})	4.90 (1.19–14.43)	3.90 (1.87–5.36)

[a] Data are presented as a median and 25^{th}–75^{th} percentile in parenthesis.

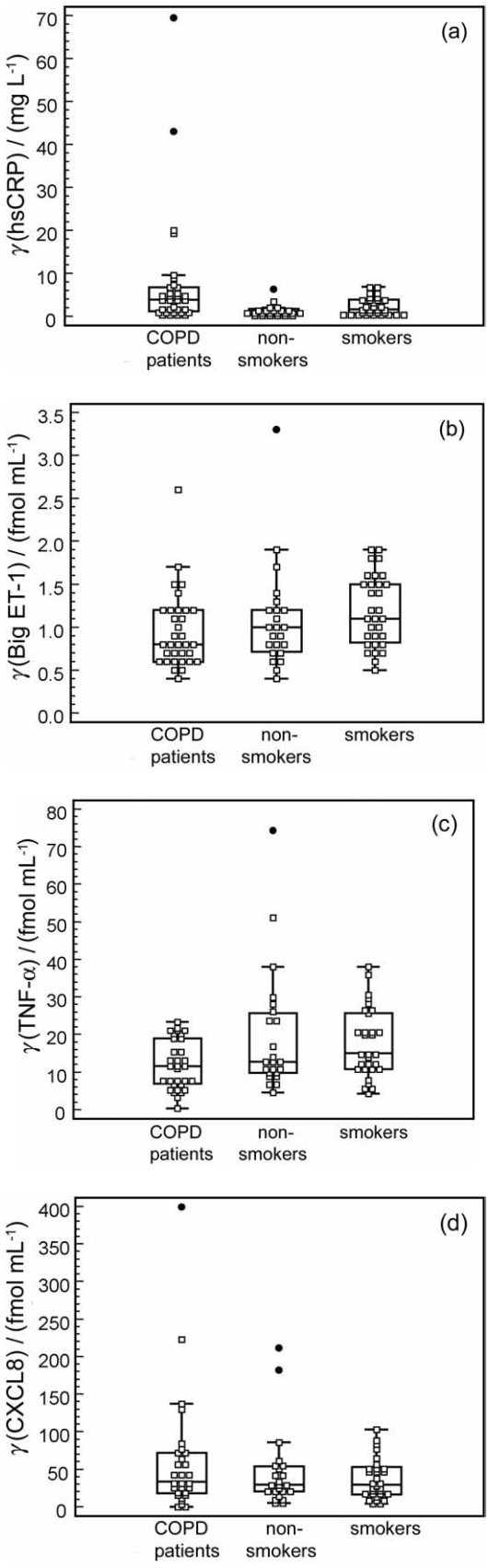

Figure 1. Concentrations (γ) of (a) hsCRP (b) big ET-1 (c) TNF-α (d) CXCL8 in healthy non-smokers (control group), healthy smokers and patients with COPD presented as box and whisker plots (*, $p < 0.05$).

had no increase compared to the control group (p = 0.1134). Fifteen COPD patients with increased hsCRP concentration (>3 mg/L) had additional complication (hypertension, angina pectoris, osteoporosis) and/or exacerbation of COPD, but five patients without any signs of complication and/or exacerbation also had elevated values of hsCRP. In comparison to severe COPD, patients with moderate COPD showed no statistically significant difference in hsCRP concentration (p = 0.5649). We also found a correlation between hsCRP concentration and smoking habit (pack/years) (r = 0.325, p = 0.0229). The concentration of big ET-1 was not statistically different in the COPD group (p = 0.3641), or in the group of healthy smokers (p = 0.1565) compared to the control group. In our study, there was no increase in TNF-α concentration in the sera of COPD patients (p = 0.0788) or in healthy smokers (p = 0.6472) compared to the control group. Compared to the control group, the concentration of CXCL8 in the sera of COPD patients was not statistically different (p = 0.4839). Also, there was no change in the concentration of CXCL8 in healthy smokers compared to the control group (p = 0.8717). In our study, we did not find any correlation between the concentration of CXCL8 and neutrophils in the peripheral concentration (results not shown).

Serum concentrations of TNF-α and CXCL8 showed (Figure 2) a statistically significant correlation (r = 0.638; p<0.0001). Our results also showed a certain correlation between the concentrations of big ET-1 and CXCL8 (r = 0.381; p = 0.0007). Correlation between other measured parameters was not found (results not shown).

DISCUSSION

A statistically significant increase was found in hsCRP concentration in the plasma of COPD patients as compared to the control group (healthy non-smokers). However, the concentrations of TNF-α, CXCL8 and big ET-1 in COPD patients did not exceed the values established for the control group. The concentrations of all four mediators were not statistically different in specimens of healthy smokers from those of the control group. A positive correlation was found between some mediators (TNF-α and CXCL8, and big ET-1 and CXCL8), which supports the assumption about interaction of these mediators in inflammatory process.

Systemic inflammation was present in COPD patients, which is supported by the fact that hsCRP was increased in systemic circulation in patients with stable and unstable COPD, and also in COPD patients with complications like atherosclerosis and osteoporosis. Increased values of hsCRP in stable COPD patients, determined regardless of complications or COPD exacerbation, confirmed the presence of systemic inflammation, which is in accordance with studies by other authors.[4] Man *et al.* found increased values of hsCRP in their prospective longitu-

dinal study and assumed hsCRP as a good predictor for mortality and cardiovascular events in patients with mild to moderate COPD.[26] Significantly increased hsCRP in plasma was also recorded in COPD patients without ischaemic heart disease.[20] The correlation between hsCRP concentration and smoking habit (pack/years) supports the assumption that tobacco smoke has an influence on systemic inflammation.[27] hsCRP indicates that COPD is a systemic inflammatory disease, and it could serve as a predictor for exacerbations.[28] Although COPD patients are mostly smokers, a small number of non-smokers also develop COPD, suggesting that there are also certain genetic components of the disease.[2]

Based on the results achieved by measuring the concentrations of TNF-α, CXCL8 and big ET-1 in peripheral circulation, it was not possible to demonstrate systemic inflammation in COPD.

Local effects of big ET-1, *i.e.* its half life and also the cleaving to ET-1 by ECE, can actually be some of the reasons why we did not find any change in the concentration of big ET-1 in circulation.[13,25] There was also no increase in cytokines like TNF-α and chemokines CXCL8 in our study; since some authors reported that they probably induce the expression of the endothelin system, we supposed that the release of big ET-1 was not induced.[7,8] TNF-α has a role in the mRNA expression of CXCL8 and ET-1 in human endothelial cells and in non-small lung cancer.[7,29] Our results also show a certain correlation between the concentrations of big ET-1 and CXCL8. However, it is not clear if big ET-1 release was induced by CXCL8, or *vice versa*. In *in vitro* experiments on endothelial cells, CXCL8 did not show any influence on the mRNA expression of ET-1 and ECE.[8] The studies done on melanoma cells showed that ET-1 induced the release of CXCL8.[30] Zheng *et al.* did not demonstrate any correlation between ET-1, CXCL8 and TNF-α in the serum of patients with bronchoectiasis.[31]

The negative results obtained for TNF-α and CXCL8 were in line with some results published previously. In peripheral circulation of COPD patients with malnutrition, there was no increase in TNF-α and leptin; it was also not recorded in COPD patients with exacerbations or stable COPD.[32] Calikoglu *et al*. found an increase in the concentration of TNF-α only in the sera of COPD patients with exacerbations, and Vernooy *et al*. found an increase in the concentration of soluble TNF-α receptors, while the concentration of TNF-α was within the reference range for healthy individuals.[33,34] Broekhuizen *et al*. found measurable values of TNF-α in sputum but not in the plasma of COPD patients.[35] Possible explanation for the unchanged concentration of TNF-α is its local and short-term effect, its degradation and its half life of aproximately 6–7 min, as well as its binding to receptors and renal clearance.[5,24]

Vernooy *et al.* found measurable values of CXCL8 in the plasma of four of 18 COPD patients and a statistically significant increase in the sputum when compared to healthy volunteers, which is explained by the fact that the regulation of local and systemic inflammatory response in COPD is different.[34] In the literature, we found that CXCL8 was mostly measured in the sputum of COPD patients.[21,22,23] Results of such measurements indicated a correlation between CXCL8 concentration and the number of neutrophils and eosinophils; the increased values are in accordance with the level of obstruction of the airways and it was thought that they could serve to assess inflammmation in the airways.[16,21] In our study, we did not find any correlation between the concentration of CXCL8 and neutrophils, which may be explained by the fact that this chemokine acts rather locally and thus attracts neutrophils to the local inflammatory site.[5]

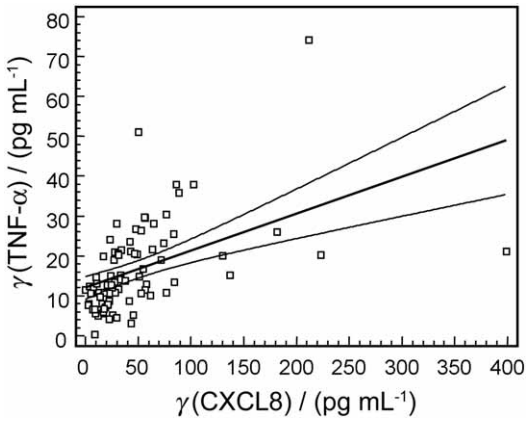

Figure 2. Plot of correlation for serum concentrations (γ) of CXCL8 and TNF-α presented by correlation coefficient (r) = 0.638, and level of significance $p<0.0001$; 95 % CI for r = 0.4889 to 0.7512.

The correlation found between TNF-α and CXCL8 confirmed that TNF-α, as one of the most important pro-inflammatory cytokines, induces the release of the chemokine CXCL8 and in this way contributes to chemotaxis of neutrophils to the inflammatory site.[2,5]

Local increase and the role of these mediators in COPD cannot be excluded based on our results. Some authors thought that systemic inflammatory response in COPD was not associated with local inflammation which takes place in the lungs.[4,24] hsCRP is synthetized in hepatocytes and has a long plasma half-life (19 h), as opposed to other measured mediators in this study.[19] However, some COPD patients were on therapy with corticosteroids and inhalators and some of them were on antihypertensive medications, which could also have an impact on the results of determination of the inflammatory mediators stated above.[36] However, regulation pathways between inflammation and endothelial functions are not yet clear and further *in vivo* and *in vitro* investigations are necessary to gain insight in interactions between these parameters, and the possible influence of tobacco smoke.

CONCLUSION

On the basis of our results and the reviewed literature, we can conclude that hsCRP is a valuable marker for disease follow-up and a predictor of COPD progression. Nevertheless, further investigations are needed for comparisons of systemic and local inflammatory markers in COPD, as well as *in vitro* studies of regulatory pathways and the manner of inducing cytokine, chemokine and endothelin release. The development of new potential terapeutic targets like antagonists of TNF-α, CXCL-8 and ET-1 will probably indicate the need for their local administration in the lungs.[37]

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SAŽETAK

TNF-α, CXCL8, veliki ET-1 i hsCRP u bolesnika s kroničnom opstrukcijskom plućnom bolesti

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Kronična opstrukcijska plućna bolest (KOPB; engl. *Chronic Obstructive Pulmonary Disease*, COPD) je progresivna kronična upalna bolest karakterizirana ireverzibilnim smanjenjem protoka zraka kroz dišne puteve. Cilj ovoga rada bio je ispitati koncentracije i korelaciju faktora tumorske nekroze-α (engl. *Tumor Necrosis Factor-α*, TNF-α), interleukina-8 (CXCL8), velikog endotelina-1 (engl. *big endothelin-1*, big ET-1) i visoko osjetljivog C-reaktivnog proteina (engl. *high sensitive C-Reactive Protein*, hsCRP) u zdravih nepušača, zdravih pušača i bolesnika s KOPB te ispitati njihovu ulogu u patofiziologiji KOPB i sistemskoj upali. Koncentracija hsCRP bila je statistički značajno veća u bolesnika s KOPB nego u kontrolnoj skupini (p = 0,0004), dok se koncentracija TNF-α (p = 0,0788), CXCL8 (p = 0,4839) i velikog ET-1 (p = 0,3641) nije statistički značajno razlikovala. Nije nađena statistički značajna razlika za izmjerene analite između pušača i kontrolne skupine. Spearmanov koeficijent korelacije za koncentraciju TNF-α i CXCL8 iznosio je r = 0,638 (p<0,0001). hsCRP se pokazao kao osjetljiviji dijagnostički parametar u usporedbi s TNF-α, CXCL8 i velikim ET-1 u sistemskoj cirkulaciji bolesnika s KOPB.