Journal of Cardiac and Pulmonary Rehabilitation

Tudorache et al., J Card Pulm Rehabil 2017, 1:2

Research Article Open Access

C-Reactive Protein and Endothelin-1 are Weakly Associated with Cardiovascular Diseases in Stable Chronic Obstructive Pulmonary Disease Patients. The Results of a Cross-Sectional Study

Emanuela Tudorache[1], Voicu Tudorache[1*], Cristian Oancea[1], Bogdan Timar[2], Ovidiu Fira Mladinescu[1], Diana Manolescu[3], Rodica Dan[4], Stela Iurciuc[5] and Lucian Petrescu[4]

[1]Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[2]Department of Biostatistics and Medical Informatics, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[3]Department of Radiology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[4]Department of Cardiology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[5]Department of Internal Medicine, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[*]**Corresponding author:** Voicu Tudorache, Professor, Department of Pulmonology, Victor Babes University of Medicine and Pharmacy, 2 Eftimie Murgu, 30041 Timisoara, Romania, Tel: +40722619148; E-mail: voicu.tudorache@yahoo.com

Received date: November 20, 2017; **Accepted date:** December 04, 2017; **Published date:** December 09, 2017

Abstract

Background and objectives: Exacerbations, systemic manifestations and comorbidities have a great impact on the morbidity and mortality of COPD. Our study aimed to evaluate the presence and the strength of a possible association between inflammatory biomarkers (especially CRP), the presence of CVD and muscular impairment in patients with stable COPD.

Materials and methods: We included 59 patients with stable COPD who were divided in two study cohorts: group A-27 COPD patients with normal levels of C-reactive protein (CRP) and group B-32 patients with increased levels of CRP at two measurements within 6 month. In group B were also analyzed Endothelin-1 (ET-1), Tumor Necrosis Factor Alpha (TNF-α) and Interleukin 6 (IL6). Both groups performed spirometry, 6 min walk distance test (6MWD), Maximal Expiratory Pressure (MEP) and Maximal Inspiratory Pressure (MIP), CAT (COPD Assessment Test), dynamometry, body composition, ECG, carotid ultrasound and echocardiography.

Results: Patients with persistent systemic inflammation when compared with normal CRP ones, had a higher age (64 yrs *vs.* 58 yrs, p=0.048), higher prevalence of CVD (3 *vs.* 1, p=0.005), dyslipidemia (61% *vs.* 39%, p=0.117), more pronounced upper extremity muscle weakness (dynamometry 4.5 *vs.* 5.5, p=0.048) and respiratory muscle weakness (MEP 50.3 *vs.* 57.3, p=0,038). They also had a slightly more limited exercise tolerance (6MWD 394.1 m *vs.* 430.6 m p=0.273), were slightly more symptomatic (CAT 21 pts *vs.* 16.5 points, p=0.141) and had a higher body mass index (26.5 kg/m^2 *vs.* 24.5 kg/m^2, p=0.187). Elderly patients had increased levels of CRP, TNF-α and IL-6.

Conclusion: In a context of stable COPD, persistently elevated CRP levels are associated with higher age, higher prevalence of CVD and more severe muscle weakness. Biomarkers like ET-1, TNF-α and IL6 do not reveal additional contributions in these systemic inflamed COPD group.

Keywords: Endothelin-1; CRP; Endothelium; Atherosclerosis; Muscular dysfunction; Stable COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the lungs to noxious particles and gases. Exacerbations, systemic manifestations and comorbidities have a great impact on the morbidity and mortality of this disease [1].

Systemic inflammation is common during COPD exacerbation periods. However, it has been reported a chronic elevated low-level of circulating inflammatory biomarkers in 16% of stable COPD patients [white blood cells (WBC), fibrinogen, C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α)]. This is described as a new COPD phenotype, different from the frequent exacerbator one, being associated with worse clinical outcome. These patients are more symptomatic, are having a higher prevalence of exacerbations, muscular dysfunction and cardiovascular morbidity despite similar lung function limitations [2-4].

The observed association between COPD and cardiovascular diseases (CVD) could be partly explained by the existence of common risk factors. Some of them are modifiable such as smoking or sedentary lifestyle, while others are not: genetic factors and aging [4-7].

Among COPD comorbidities, CVD (ischemic heart disease, atherosclerosis and heart failure) and muscular dysfunction (skeletal muscle weakness, muscle loss and malnutrition) are the most frequently met [2]. The anatomical and functional relationship between the lungs and the heart is such that any impairment which affects one organ will have consequences on the other one. Numerous

studies showed that COPD itself doubles the risk of hospitalization and mortality caused by CVD, independent of smoking history or aging. All the changes induced by COPD make the cardiovascular system vulnerable, particularly the endothelium, favoring atherosclerotic plaques development and destabilization. As a result, cardiovascular mortality represents about a quarter of all causes of death in COPD patients, and in mild-moderate stages of the disease, is even higher than that induced by respiratory failure [2,8]

Aging itself is associated with an increased incidence of COPD and other non-communicable diseases (CVD, diabetes, cancer, osteoporosis, etc.) [9].

On the other hand, the aging process is associated with a low grade of systemic inflammation. Pro-inflammatory cytokines, like TNF-α and IL 6, are increased in elderly people and are inducing senescence in adjacent cells [5].

Study Aims

Our study aimed to evaluate the presence and the strength of a possible association between inflammatory biomarkers (especially CRP), the presence of CVD and muscular impairment in patients with stable COPD.

Materials and Methods

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Subjects

In the study 59 patients with COPD, diagnosed according to the ERS/ATS guidelines were included. All patients were in a stable phase (clinically stable airway obstruction which did not required any change in therapeutic treatment plan in the last 3 months). The study cohort was divided in two sub-groups: group A-27 COPD patients with normal levels of CRP (<0.5 mg/dL) and group B-32 patients with increased levels of CRP at two measurements within a 6 months timeframe. No drop-outs were recorded.

As inclusion criteria, we used the following: age 45-75 years, COPD in a stable phase, history of smoking ≥ 20 packs-year and the ability to provide inform consent. In the study, following were exclusion criteria: asthma-COPD overlap syndrome (ACOS), pulmonary hypertension, pulmonary embolism, active infections, acute cardiovascular disease, malignancy, recent surgery, severe endocrine, hepatic or renal diseases, autoimmune diseases and inflammatory disorders (polyarthritis, chronic inflammatory bowel disease, lupus erythematous systemic). Also in order to exclude a confounder who might lead to CV and muscular dysfunction, we did not included patients with hypoxemia (defined as SaO_2<92% or PaO_2<60 mmHg).

We chose to divide our stable COPD patients in two groups according to CRP levels (normal and chronic elevated levels of CRP) and to study the possible differences in the characteristics of each cohort. Then in the group with elevated levels of CRP, we analyzed if additional exploration of other biomarkers such as ET-1, TNF-α and IL 6, could provide relevant insights with impact on the clinical practice or these patients prognosis.

Protocol and equipment

On admission day, blood samples (complete blood count, cholesterol, LDLc, HDLc, triglyceride, fasting glycaemia), blood gases and inflammatory biomarkers (leucocytes, fibrinogen and CRP) were collected from all subjects.

For group B, patients which were selected from our database based on previously elevated CRP levels measured within 6 month, we also collected blood samples for TNF-α, IL 6 and Endothelin1 (ET1). These inflammatory biomarkers were assessed using high-sensitivity kits and enzyme linked immunosorbent assay (ELISA) technique, according to manufacturer's instructions (Biomedica Medizinprodukte, Austria). The normal values for these assays are below 8.1 pg/ml for TNF-α, 7 pg/ml for IL-6 respectively 2000 pg/ml for ET-1.

Pulmonary function tests were evaluated using a Jaeger Spirometer. The FVC, FEV1, and the ratio FEV1/FVC were measured three times and the best value was reported (according to the ATS/ERS statement). Also, we recorded patients' medical history (CVD, dyslipidemia, diabetes and other comorbidities) and pulmonary-related treatment.

In the next two days, subjects completed CAT (COPD Assessment Test) questionnaire and performed the six-min walk distance test (6MWD), according to ERS/ATS statement, under the supervision of the same physiotherapist. We assessed the Maximal Expiratory Pressure (MEP) and Maximal Inspiratory Pressure (MIP) and evaluated the muscle strength using a dynamometer (Dynatest, Germany). Patients body composition (body fat-BF and Soft Lean Mass-SLM) was assessed by Biodynamics BIA 310e Bioimpedance Analyzer.

The ECG, carotid intima-media thickness assessed by ultrasonography (cIMT) and echocardiography (Siemens Medical Solution, USA) were performed by the same cardiologist in the second day of admission.

Statistical analysis

Data were collected and analyzed using SPSS v17 statistical software package (SPSS Inc, Chicago, IL, USA) and are presented as average ± standard deviation (numerical variables with Gaussian distribution), median and [interquartile range] (numerical variables with non-parametric distributions) respectively percentage from the sub-group total and (number of individuals). To assess the significance of the differences between groups, the Student t-test (means, Gaussian populations), Mann-Whitney U (medians, non-parametric populations) and Chi-square (proportions) were used. Continuous variables distributions were tested for normality using Shapiro-Wilk test, and for equality of variances using Levene's test. To evaluate the strength of the association between two continuous variables we used Spearman's correlation coefficient; the statistical significance of the correlation was evaluated using t-distribution test.

A p-value 0.05 was considered the threshold of statistical significance.

Results

The distribution of COPD stages in the entire group is presented in Table 1. In our study cohort we have not observed significant differences (p=0.620) between the COPD stages regarding elevated CRP or not.

We observed a significant association between elevated CRP and patients age (64 *vs.* 58 years median age; p=0.048) and the number of cardiovascular co-morbidities (3 *vs.* 1 median co-morbidities; p=0.005) and a marginally association between CRP and dyslipidemia (Figure 1). The other studied parameters had no significant differences in regard to elevated CRP or not. The stratified patient's characteristics are presented in Table 2.

	Group A	Group B	P
Stage I	7.4% (2)	3.1% (1)	0.620
Stage II	22.2% (6)	31.2% (10)	
Stage III	14.8% (4)	21.9% (7)	
Stage IV	55.6% (15)	43.8% (14)	

Table 1: Distribution of COPD stages in the study cohort.

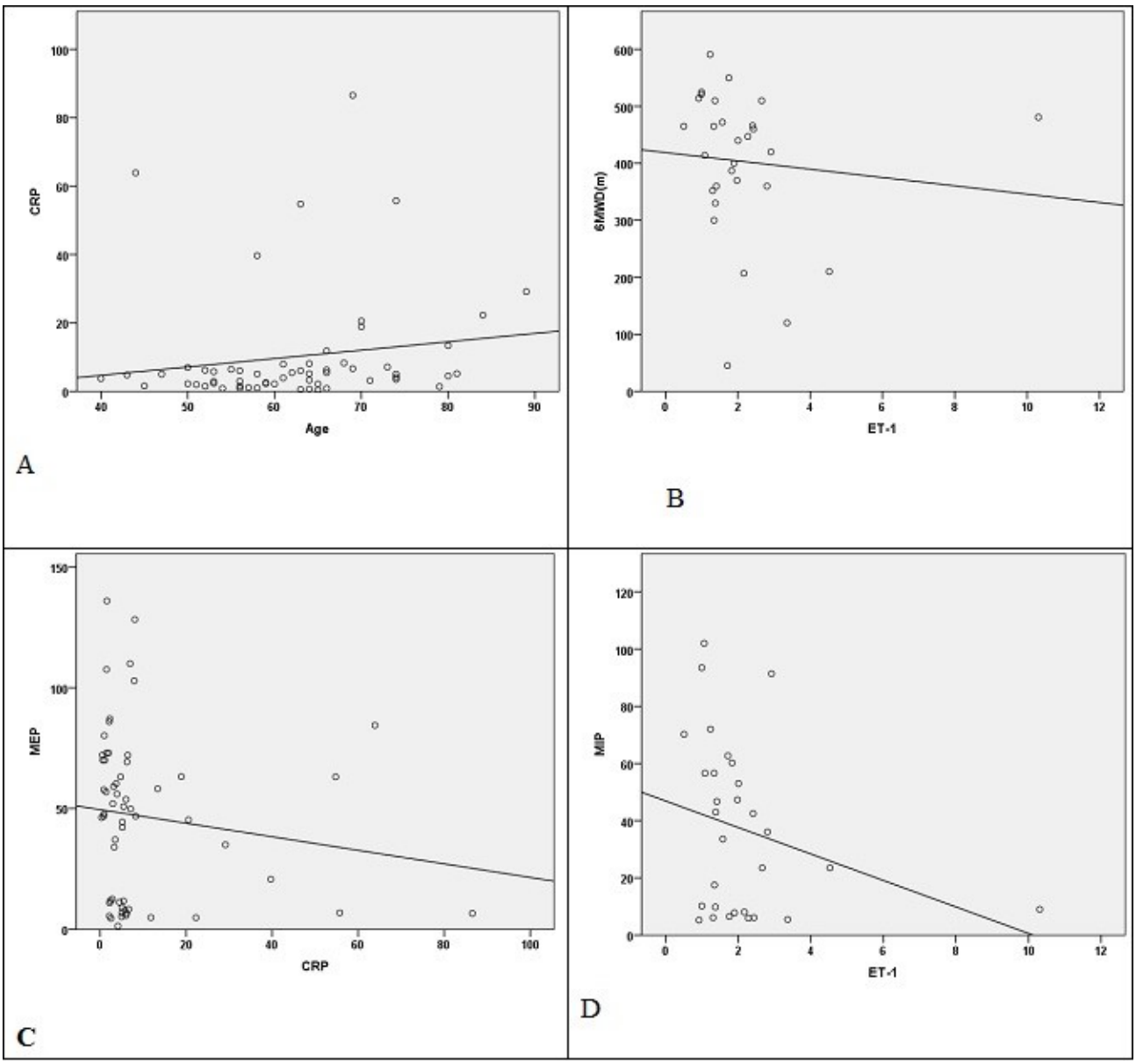

Figure 1: Correlations between inflammatory markers and other studied parameters: A. CRP and Age; B. ET-1 and 6 MWD; C. CRP and MEP; D. ET-1 and MIP.

In the same time, elevated CRP values were significantly associated with decreased values of MEP (50.3 *vs.* 57.3; p=0.038) and dynamometry (4.5 *vs.* 5.5, p=0,048). The differences in the FEV1/FVC (48.5 *vs.* 49, p=0.159) and CAT score (21 *vs.* 16.5, p=0,141) were only marginally significant, being most probably in our case caused by a type II statistical error. Regarding the laboratory parameters we studied, elevated CRP levels were associated with an increased fibrinogen value (3.56 *vs.* 2.86 mg/dL; p<0.001) and decreased HDLc (53.6 mg/dL *vs.* 64.1; p=0.043). Between the studied groups there was no statistical difference regarding cIMT. The detailed analysis is presented in Table 3.

	Group A	Group B	P
Gender (M)[a]	88.9% (24)	75.0% (24)	0.172
Age (yr)[b]	58 [12]	64 [12]	0.048*
Packs/year[b]	35 [27]	37.5 [40]	0.982
BMI(kg/m^2)[c]	24.5 ± 5.0	26.4 ± 6.1	0.187
No. of pulmonary therapeutic classes[b]	2 [1]	3 [1]	0.441
No. of CV comorbidities[b]	1 [2]	3 [3]	0.005*
Diabetes mellitus type 2[a]	46.9% (23)	53.1% (26)	0.688
Dyslipidemiaa	39.0% (16)	61.0% (25)	0.117

*Differences are statistically significant at a<0.05 threshold. [a]Dichotomous variables. Results are presented as number of individuals and (percentage from the sub-group). p value was calculated using chi-square test. [b]Numerical variables with non-parametric distribution. Results are presented as median and [interquartile range]. p value was calculated using Mann-Whitney U test. [c]Numerical variables with Gaussian distribution. Results are presented as average ± standard deviation. p value was calculated using unpaired t-student test.

Table 2: Patients characteristics stratified according to the presence *vs.* absence of elevated hs-CRP levels.

Between the values of CRP and the other inflammatory tests performed (ET-1, TNFα and IL-6) we found no relevant, significant correlations. The detailed analysis is presented in Table 4.

	Group A	Group B	P
Exacerbation/year[a]	2 [3]	2 [1]	0.796
FVC (%)[a]	63% [23.8]	67.1% [20.0]	0.465
FEV1 (%)[a]	35.9% [28.0]	30.5% [20.8]	0.743
FEV1/FVC[a]	49 [29.5]	48.5 [27.5]	0.159
SaO_2[a]	94.0 [5]	95.5 [10]	0.884
MIP[a]	42.1 [85.6]	47.0 [59.3]	0.235
MEP[a]	57.3 [62.5]	50.3 [58.6]	0.038*
CAT[a]	16.5 [10]	21.0 [10]	0.141
mMRC[a]	3 [1]	3 [2]	0.191
dynamometry[a]	5.5 [2.1]	4.5 [2.0]	0.048*
SLM (kg)[b]	51.2 ± 13.9	51.9 ± 14.6	0.844
BF (kg)[a]	23.3 [11.9]	24.4 [16.7]	0.433
6 MWD[b]	430.6 ± 121.1	394.1 ± 128.5	0.273
Fibrinogen (mg/dL)	2.86 ± 0.41	3.56 ± 0.98	<0.001*
Leucocyte (nr/uL)	8325 ± 2732	8071 ± 2025	0.684
Total Cholesterol (mg/dL)	212.6 ± 43.0	195.6 ± 34.5	0.101

LDLc (mg/dL)	144.2 ± 45.9	138.1 ± 36.0	0.572
HDLc (mg/dL)	64.1 ± 29.8	53.6 ± 13.0	0.043*
Triglyceride (mg/dL)	115.9 ± 54.0	98.6 ± 39.9	0.168
Fasting glycaemia (mg/dL)	110.6 ± 25.2	105.8 ± 29.4	0.507
SBP (mmHg)	130.0 ± 17.6	127.4 ± 16.9	0.576
DBP (mmHg)	76.7 ± 11.2	81.3 ± 19.0	0.267
cIMT(mm)	1.11 ± 0.23	1.09 ± 0.23	0.721

cIMT=Carotid Intima-Media Thickness; SBD=Systolic Blood Pressure; DBP=Diastolic Blood Pressure. *Differences are statistically significant at a<0.05 threshold
[a]Numerical variables with non-parametric distribution. Results are presented as median and [interquartile range]. p value was calculated using Mann-Whitney U test.
[b]Numerical variables with Gaussian distribution. Results are presented as average ± standard deviation. p value was calculated using unpaired t-student test.

Table 3: Comparison of studied parameters in the two sub-groups.

On the other hand, in group B, Endothelin-1 significantly correlated with cholesterol (p=0.027) and LDL (p=0.026). There is also a weak correlation between ET-1 and 6MWD test (p=0.084), MIP (p=0.111) and MEP (p=0.145). TNF-α significantly correlated with 6 MWD test (p=0.016) and correlated only marginally significant with patient's age (p=0.112), dynamometry (p=0.065), MIP (p=0.054) and IL6 (p=0.127), most probably due to a type II statistical error. IL6 is weakly associated with age (p=0.099) and smoking history PA (p=0.197). The other parameters are only marginally correlated: MIP with SLM (p=0.094), MIP with dynamometry (p=0.087) and MEP with dynamometry (p=0.115). The detailed analysis is presented in Table 5.

	CRP	P
ET-1	-0.139	0.465
TNF-α	0.075	0.848
IL-6	-0.263	0.495

Table 4: Correlation matrix for CRP and other inflammatory markers.

Discussion

Our results suggest that the presence of persistent systemic inflammation in COPD is associated with aging phenomenon, an increased prevalence of CV diseases in the medical history, dyslipidemia, upper extremity muscle weakness, respiratory muscular weakness and limited exercise tolerance.

The novelty of this article is the study design. Previous papers have assessed the CV and muscular systems in COPD, but this is one of the few studies, to our knowledge, which analyzed the implications of systemic inflamed COPD phenotype in these comorbidities [2,3,6].

We observed that there were small and inconsistent differences in inflammatory biomarkers levels between GOLD stages, observation also sustained by Agusti's study on systemic inflamed phenotype. He showed that persistent inflammation does not appear in all COPD patients and is not associated with the severity of FEV1 decrease [3].

In literature there are mentioned several common risk factors that can lead to CVD in COPD population: aging, smoking history, hypoxia, systemic inflammation, dyslipidemia, diabetes mellitus, obesity, sedentariness and others [3,10].

According to some authors, endothelial dysfunction could mediate the association between COPD and vascular related diseases, based on the increased risk of atherosclerosis correlated with decreased FEV1 [11]. One method to evaluate endothelium is to measure cIMT by carotid US. Although in general population inflammatory markers such as hs-CRP are correlated with increased cIMT, our study showed in COPD patients no differences of cIMT related to the CRP values [12]. This observation is consistent with data of Iwamoto et al. which demonstrated in a multivariate logistic regression of smokers with airflow limitation that CRP level was closely associated with frequency of plaques but not cIMT [13]. A possible explanation is that IMT reflects vessel remodeling in the early stages of the atherosclerotic process and can predict occurrence of plaques while low-grade systemic inflammation, indicated by hs-CRP, might be associated with the progression of atherosclerosis and plaque formation. In natural evolution of some COPD patients smoking-related vascular remodeling could probably appear before airflow limitation.

Other authors using invasive measurement of forearm vaso-reactivity to intra-arterial infusion of vasodilators (gold standard method) to assess endothelial function, reported that decreased FEV1 and endothelial dysfunction are unrelated and independent predictors of atherosclerosis. These results imply that the relationship between atherosclerosis, endothelial dysfunction and airflow limitation is very complex and poorly understood [11,14,15].

Endothelin is a vasoactive mediator that causes vasoconstriction and vascular wall proliferation and it is used as a main marker for endothelial dysfunction [16]. The present study showed no correlation between systemic inflammation markers (CRP, fibrinogen, leucocytes, IL 6 and TNF-α) and plasma levels of ET-1, which was also noticed by Gemici et al. [17].

The main inflammatory biomarker that we analyzed is CRP, released also as consequences of vascular damage stimulates IL6 and ET-1 production. Increased levels of CRP are related as worse cardiovascular outcomes in COPD patients, independent of the presence of ischemic heart disease. Stimulated by CRP, IL6 is facilitating the development of atherosclerotic plaque, a faster decline in lung function and a higher rate of exacerbations in these patients [10,18,19]. Our study showed that higher levels of CRP were associated with an elevate frequency of CVD.

Fibrinogen is also known for the involvement in atherosclerotic process: promoting plaque growing, stimulating platelets and white blood cells adhesion to the vessel wall and inducing muscle cell proliferation and migration [10]. From our results fibrinogen correlated with CRP and dyslipidemia but was not associated with IL6, TNF-α, leucocytes or ET-1.

	Endothelin1		**TNF-α**		**IL6**	
	Correlation Coefficient	**p**	**Correlation Coefficient**	**P**	**Correlation Coefficient**	**P**
Endothelin1	n/a	n/a	0.329	0.388	-0.033	0.932
TNF-α	0.329	0.388	n/a	n/a	0.548	0.127
IL6	-0.033	0.932	0.548	0.127	n/a	n/a
Age (yr)[b]	0.09	0.636	0.566	0.112	0.583	0.099
Packs/year[b]	-0.222	0.239	0.446	0.229	0.475	0.197
BMI(kg/m^2)[c]	0.109	0.565	0.164	0.673	-0.15	0.7
No. of CV comorbidities [b]	-0.049	0.795	-0.028	0.943	0.298	0.436
FVC (%)[a]	-0.221	0.241	-0.11	0.779	-0.067	0.865
FEV1 (%)[a]	-0.11	0.563	0.175	0.653	-0.008	0.983
FEV1/FVC[a]	0.123	0.516	-0.037	0.926	-0.283	0.46
MIP[a]	-0.297	0.111	-0.657	0.054	-0.217	0.576
MEP[a]	-0.273	0.145	-0.511	0.16	0.05	0.898
6 MWD[a]	-0.327	0.084	-0.767	0.016	-0.383	0.308
dynamometry[a]	-0.121	0.603	-0.783	0.065	-0.5	0.312
SLM (kg)[b]	0.167	0.395	-0.055	0.889	-0.3	0.433
BF (kg)[a]	-0.011	0.957	0.183	0.638	-0.383	0.308
hs-CRP (mg/dL)	-0.139	0.465	0.075	0.848	-0.263	0.495
Fibrinogen (mg/dL)	-0.059	0.762	0.304	0.464	0.357	0.385
Leucocyte (no/uL)	-0.153	0.42	-0.237	0.539	-0.167	0.668
Total Cholesterol (mg/dL)	0.411*	0.027	0.22	0.569	-0.025	0.949
LDLc (mg/dL)	0.413*	0.026	0.31	0.416	-0.067	0.865
Triglyceride (mg/dL)	0.253	0.186	-0.128	0.743	0.5	0.17
Fasting glycaemia (mg/dL)	-0.09	0.636	0.128	0.743	-0.017	0.966

*Correlations are statistically significant at p<0.05.
Numerical variables with non-parametric distribution. Results are presented as Spearman's correlation coefficient. P value was calculated using t-value distribution test.

Table 5: Correlations between inflammatory biomarkers (TNF-α, IL6) Endothelin1 and other parameters.

Systemic inflammation in COPD has also impact on the muscular system [20-22]. We found that patients with chronic inflammation compared with non-inflamed ones, have an advanced muscle weakness in both respiratory and peripheral areas. MIP was weakly correlated with CRP, TNF-α and ET1 whereas MEP significantly correlated with CRP and poorly with ET-1. Upper extremity muscle weakness, measured by dynamometry, was significantly associated with increased CRP. This group of patients had a greater limitation of walking distance performance (6 MWD) compared with the other group. Moreover, we found a significant correlation between TNF-α and 6 MWD test.

Increased airflow obstruction predicts a higher level of IL6, which, in turn, determines a decreased walking distance (6 MWD). A factor that influences this relation is the age. Baldi et al. considers that IL6 is an important signaling pathway that modulates the complex relationship between aging and chronic morbidity [18].

Agusti et al. showed that smokers without obstructive pulmonary diseases, have a chronic low grade systemic inflammation (leucocytes,

TNF-α) compared with the non-smoker cohort [3]. Further he defined the "inflammome" as patients with increased levels of fibrinogen, CRP and IL 6. The amount of pack-years is a determinant risk factor for COPD whereas in cardiovascular disease the risk increases from very low levels of smoke exposure [6]. In the present study, all the patients were ex-smokers and the cumulative exposure poorly correlated with IL6.

Our elderly subjects had increased levels of CRP, TNF-α and IL 6, compared to the younger ones, observation which was also supported by other authors [5,7] Aging is associated with a chronic low grade of systemic inflammation, known as "inflamm-aging", which contributes to the development and progression of obstructive pulmonary disease in older populations. On the other hand, aging is associated with an increased number of comorbidities such as CVD and muscle weakness [5].

Conclusion

In a context of stable COPD, patients with persistent elevated hs-CRP levels are older, have a higher prevalence of CVD and muscle weakness. Biomarkers like ET-1, TNF-α and IL6 do not reveal additional contributions in these systemic inflamed COPD phenotype.

Conflict of Interest

E Tudorache, V Tudorache, C Oancea, B Timar, OF Mladinescu, D Manolescu, R Dan, S Iurciuc, L Petrescu declare that they have no competing interests. Victor Babes University of Medicine and Pharmacy, Timisoara, Romania provided financial support for this research trough the PhD scholarship program.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, et al. (2017) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med 195: 557-582.
2. Barnes PJ, Celli BR (2009) Systemic manifestations and comorbidities of COPD. Eur Respir J 33: 1165-85.
3. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, et al. (2012) Persistent Systemic Inflammation is Associated with Poor Clinical Outcomes in COPD: A Novel Phenotype. Plos One 7: e37483.
4. Miłkowska-Dymanowska J, Białas AJ, Zalewska-Janowska A, Górski P, Piotrowski WJ (2015) Underrecognized comorbidities of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 10: 1331-1341.
5. Murray MA, Chotirmall SH (2015) The Impact of Immunosenescence on Pulmonary Disease. Media of Inflamm 692546.
6. Decramer M, Janssens W (2013) Chronic obstructive pulmonary disease and comorbidities. Lancet Respir Med 1: 73-83.
7. Fabbri LM, Rabe KF (2007) From COPD to chronic systemic infl ammatory syndrome? Lancet 370: 797-799.
8. Rabahi MF, Pereira SA, Silva Júnior JL, Rezende AP, Castro da Costa A, et al. (2015) Prevalence of chronic obstructive pulmonary disease among patients with systemic arterial hypertension without respiratory symptoms. Int J Chron Obstruct Pulmon Dis 10: 1525-1529.
9. Mercado N, Ito K, Barnes PJ (2015) Accelerated ageing of the lung in COPD: new concepts. Thorax 70: 482-489.
10. Campo G, Pavasini R, Malagù M, Mascetti S, Biscaglia S, et al. (2015) Chronic Obstructive Pulmonary Disease and Ischemic Heart Disease Comorbidity: Overview of Mechanisms and Clinical Management. Cardiovasc Drugs Ther 29: 147-157.
11. Chandra D, Gupta A, Strollo PJ Jr, Fuhrman CR, Leader JK, et al. (2016) Airflow Limitation and Endothelial Dysfunction: Unrelated and Independent Predictors of Atherosclerosis. Am J Respir Crit Care Med 194: 38-47.
12. Thakore AH, Guo CY, Larson MG, Corey D, Wang TJ, et al. (2007) Association of multiple inflammatory markers with carotid intimal medial thickness and stenosis (from the Framingham Heart Study). Am J Cardiol 99: 1598-1602.
13. Iwamoto H, Yokoyama A, Kitahara Y, Ishikawa N, Haruta Y, et al. (2009) Airflow limitation in smokers is associated with subclinical atherosclerosis. Am J Respir Crit Care Med 179: 35-40.
14. Satoh K, Shimokawa H (2014) High-sensitivity C-reactive protein: still need for next-generation biomarkers for remote future cardiovascular events. Euro Heart J 35: 1776-1778.
15. Maclay JD, David A, McAllister DA, Mills NL, Paterson FP, et al. (2009) Vascular dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 180: 513-520.
16. Kown YS, Chi SY, Shin HJ, Kim EY, Yoon BK, et al. (2010) Plasma C-Reactive Protein and Endothelin-1 Level in Patients with Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension. J Korean Med Sci 25: 1487-1491.
17. Gemici G, Erdim R, Tokay S, Tezcan H, Fak AS, et al. (2007) Interaction between C-reactive protein and endothelin-1 in coronary artery disease. Cardiology 107: 340-344.
18. Baldi S, Jose PE, Bruschi C, Pinna GD, Maestri R, et al. (2014) The mediating role of cytokine Il-6 on the relationship of FeV1 upon 6-minute walk distance in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 9: 1091-1099.
19. Sampsonas E, Lykouras D, Drakatos P, Moschopoulou A, Spiropoulos K, et al. (2011) Endothelin- polymorphisms involved in impaired exercise tolerance in COPD patients. A pilot study. Eur Rev Med Pharmacol Sci 15: 123-128.
20. Wüst RC, Degens H (2007) Factors contributing to muscle wasting and dys¬function in COPD patients. Int J Chron Obstruct Pulmon Dis 2: 289-300.
21. Sin DD, Man SF (2006) Skeletal muscle weakness, reduced exercise tolerance, and COPD: is systemic inflammation the missing link? Thorax 61: 1-3.
22. Ferrari R, Caram LM, Faganello MM, Sanchez FF, Tanni SE, et al. (2015) Relation between systemic inflammatory markers, peripheral muscle mass,and strength in limb muscles in stable COPD patients. Int J Chron Obstruct Pulmon Dis 10: 1553-1558.