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Dynamic pulmonary hyperinflation and low grade systemic inflammation in stable COPD patients

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Abstract. – *Background and Objectives:* **It is increasingly recognized that a low grade of systemic inflammation occurs in patients with advanced chronic obstructive pulmonary disease (COPD). C-reactive protein (CRP), a marker of systemic chronic inflammatory response, has been related with decreased survival in large cohorts of COPD patients.**

The aim of the study was to assess if resting dynamic pulmonary hyperinflation (DH) is linked to the presence of systemic inflammation in COPD.

Materials and Methods: **In a 12-month retrospective study involving 55 out-patients with COPD (FEV_1 59±23% pred.) examined in stable conditions, inspiratory capacity (IC) was measured at rest and considered as index of DH when lower than 80% predicted. Simultaneously, CRP (by immuno-turbidometry) and white blood cells (WBC), uric acid and alpha-1 globulins were measured in the venous blood in the morning before eating.**

Results: **CRP was significantly increased in the COPD patients with IC <80% pred. (n=35; IC= 61+14% pred.) as compared with that measured in COPD patients with IC >80% pred. (n=20; IC = 97+13% pred.), amounting to 0.70±0.59 vs 0.29±0.28 mg/dl, respectively (p<0.01). CRP was inversely related to IC (% pred.) (r=0.45, p<0.01). WBC, serum uric acid (an endogenous danger signal), and albumin and alfa-1 globulins were not different between the two groups.**

Discussion: **These results show that the IC reduction is associated with higher serum levels of CRP in stable COPD patients, suggesting a potential role of dynamic pulmonary hyperinflation on development and maintenance of low grade systemic inflammation in COPD.**

Key Words:

COPD, Inspiratory capacity, Dynamic hyperinflation, C-reactive protein.

Introduction

Patients with advanced chronic obstructive pulmonary disease (COPD) very often suffer from extra-pulmonary (also called systemic) effects and, among others such as high oxidative stress, hypoxemia, malnutrition, reduced physical activity and drugs, low grade of chronic systemic inflammation has been implicated as potential underlying mechanism. Stable COPD patients exhibit enhanced activation of peripheral inflammatory cells such as neutrophils and lymphocytes[1,2] and have high baseline levels of several circulating inflammatory markers such as interleukin (IL)-6, IL-8, C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, TNF-alpha-receptors, FAS and FAS ligand as compared to controls[3].

Among various biomarkers of the systemic inflammatory status in COPD, serum CRP has been found significantly associated and inversely related with survival in large cohorts of COPD patients[4,5].

Although the presence and severity of systemic inflammation is now recognized as predictor of worse outcome in COPD patients[6], it is not entirely clear yet how systemic inflammation can develop in COPD. Ageing, smoking, spill-over of airway and lung inflammation, auto-immunity, respiratory and limb skeletal muscle abnormal activity have been proposed as factors or co-factors able to induce and maintain a low grade of systemic inflammation in COPD[7-13].

Moderate-to-severe airflow obstruction in COPD is often associated with the occurrence of dynamic pulmonary hyperinflation (DH) initially only during exercise and then at rest with the end-expiratory lung volume (EELV) that is increased and the inspiratory capacity (IC) that is decreased[14]. Recently, the IC reduction below

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80% of predicted at rest has been independently related to all and respiratory cause mortality in COPD[15]. Presumptive mechanisms could be less capacity of exercising[16], higher risk of exacerbations[15], greater autonomic imbalance[17] and more severe oxyhemoglobin desaturation during sleep[18]. In this context, another potential mechanism might be the development of pulmonary and systemic inflammation following the mechanical stress imposed by DH on lung structure and inspiratory muscles[19], but the potential relationship between DH and systemic inflammation in COPD has not been investigated.

The aim of the study was to assess if resting dynamic pulmonary hyperinflation, as defined by the presence of IC less than 80% predicted at rest, is associated to low grade systemic inflammation in stable COPD patients.

Materials and Methods

In a 12-month retrospective study, from February 2009 to January 2010, 55 COPD patients defined according to the presence of known risk factors, with a forced expiratory volume in one second/forced vital capacity (FEV_1/FVC ratio) less than 70% and an increase of FEV_1 less than 10% of predicted. and 200 ml after 400 mcg of inhaled albuterol [MDI (metered-dose inhaler) plus spacer], recruited through the Unit of Pulmonary Rehabilitation, Hospital "Domus Salutis" Brescia, Italy, were consecutively investigated.

None of the patients had suffered from an exacerbation or acute pulmonary complications in the previous 8 weeks and none had assumed systemic corticosteroids in the last 3 months. All patients had withdrawn long-acting bronchodilators, inhaled corticosteroids and theophylline for at least 48 hr before the functional assessment. All of them had pulmonary function testing (PFT) with determination of IC and lung volumes (Medical Graphics, St. Paul, MN, USA), measurements of maximal voluntary inspiratory (MIP) and expiratory (MEP) pressures and their Charlson Comorbidity index (CCI) was calculated[20]. Before performing PFT, a venous blood sample was collect in all these patients before eating in the morning of the same day to measure serum C-reactive protein (by immuno-turbidimetric method, with an upper normal limit equal to 0.5 mg/dl and a coefficient of variation of 6.2% in our laboratory) and serum uric acid, as expression of danger signal (ILab 600 analyzer, Shimadzu Corp., Kioto, Japan). Also white blood cells (WBC) (Coulter Hmx analyser, Beckman Coulter Inc., Miami, FL, USA) and serum levels of albumin and alpha-1 globulins (Hydrasys analyser, Sebia, Paris, France) were measured on the same occasion. The predicted values for IC were those proposed by Tantucci et al[21]. The study was approved by the local Ethics Committee and any patient gave a written informed consent to the treatment of data for research purposes.

Statistical Analysis

Variables were compared between COPD patients with IC ≥80% pred. and with IC <80% pred. by using a Student's t-test for unpaired data. Chi-square test was used for comparing categorical variables. Linear correlation analysis was performed between numerical variables of interest with determination of the Pearson's correlation coefficient. A p value lower than 0.05 was considered as significant. Statistical analysis was performed with STATISTICA data analysis system (Statasoft Inc., Tulsa, OK, USA). Data are expressed as mean ± SD. P value <0.05 was considered as statistically significant.

Results

The anthropometrical data and respiratory functional parameters are shown in Table I for all patients and for the two subgroups according to the IC value. COPD patients with IC <80% pred. had CRP serum values higher than those with IC ≥80% pred. (Figure 1 and Table II). Very few COPD patients with IC ≥80% pred. had CRP >0.5 mg/dl, while the vast majority of high values of CRP was observed in COPD patients with IC <80% pred. Only 43% of COPD patients with IC <80% pred., however, exhibited abnormal CRP serum values (Figure 2). A significant relationship was observed between IC (as % pred.) and CRP serum levels (r=0.45; *ps* <0.01), explaining 20% of variance of CRP in COPD patients ($r^2 = 0.20$) (Figure 2).

The relationship between FEV_1 (% pred.) and CRP serum levels was much weaker (r=0.31; p<0.05), and only COPD patients with FEV_1 <60% pred. had abnormal CRP.

No differences were found between COPD patients with and without resting DH for WBC, uric acid and albumin and alpha-1 globulins (Table II).

Table I. Anthropometric and functional parameters of the COPD patients.

	All	IC ≥ 80% pred.	IC < 80% pred.	p
n.	55	20	35	
Age (yr)	66 ± 10	65 ± 11	66 ± 10	ns
Gender (M/F)	37/18	14/6	23/12	/
BMI (Kg/m^2)	27 ± 5	26 ± 4	28 ± 5	ns
Smoking habit (p/y)	34 ± 8	33 ± 7	35 ± 8	ns
FEV_1 (% pred)	58 ± 23	66 ± 25	54 ± 21	ns
FEV_1/FVC %	51 ± 16	50 ± 18	51 ± 16	ns
IC (% pred)	74 ± 21	97 ± 13	62 ± 14	0.0001
RV (% pred)	124 ± 50	124 ± 44	123 ± 52	ns
TLC (% pred)	101 ± 23	110 ± 18	95 ± 24	ns
MIP (cmH_2O)	80 ± 24	88 ± 25	76 ± 23	ns
MEP(cmH_2O)	124 ± 42	117 ± 37	128 ± 45	ns
CCI (unit)	3.13 ± 0.9	2.95 ± 0.76	3.17 ± 0.98	ns

CCI = Charlson Comorbidity Index; see abbreviations in the text. Data are mean ± SD.

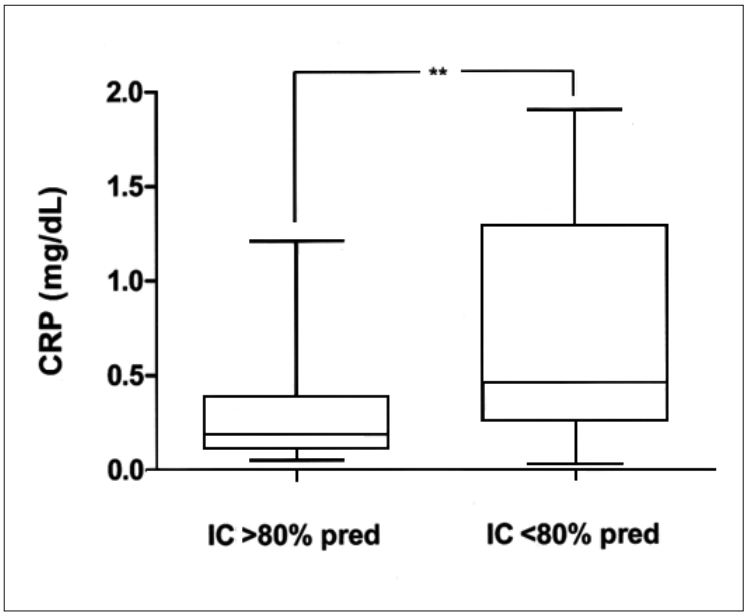

Figure 1. CRP serum values in stable COPD patients with IC ≥ 80% predicted and with IC < 80% predicted. COPD patients with IC < 80% predicted, show significantly higher values of CRP. ** = $p < 0.01$.

Table II. Systemic Inflammatory and metabolic parameters in the COPD patients.

	All	IC > 80% pred.	IC < 80% pred.	p
n.	55	20	35	
CRP (mg/dL)	0.55 ± 0.54	0.29 ± 0.28	0.70 ± 0.59	0.01
Uric acid (mg/dL)	5.77 ± 1.43	5.97 ± 1.12	5.68 ± 1.84	ns
WBC (× 1000/μl)	6.46 ± 1.23	6.37 ± 1.25	6.51 ± 1.24	ns
Albumin (g/dL)	4.37 ± 0.29	4.40 ± 0.31	4.35 ± 0.29	ns
α-1 globulins (g/dL)	0.21 ± 0.04	0.20 ± 0.04	0.21 ± 0.03	ns

CRP = C-reactive protein; WBC = white blood cells.

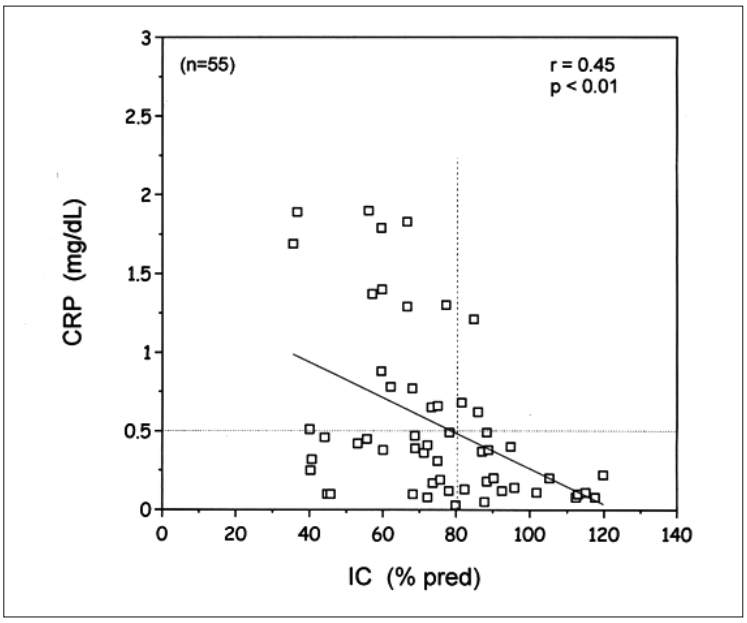

Figure 2. Relationship between CRP serum levels and resting IC (as % predicted) in stable COPD patients. CPR increases with decreasing IC at rest, but its values are elevated almost exclusively in COPD patients with IC lower than 80% predicted. In dynamically hyperinflated COPD patients, however, only about 50% of them exhibit abnormally high values of CRP.

Discussion

The information arising from this study is that in stable COPD patients a decreased baseline IC is frequently associated with an increase of serum CRP suggesting a potential relationship between resting DH and development of systemic inflammation in advanced COPD. This may contribute to explain a lower life expectancy in COPD patients with low IC at rest.

COPD patients with baseline IC lower than 80% pred. have been shown to survive significantly less in a 5-yr follow-up study[15]. In fact, both all cause and respiratory cause mortality was substantially higher in the presence of resting DH. Several could be the potential predisposing mechanisms for such a worse prognosis. Greater number of acute severe exacerbation requiring hospitalisation in COPD patients with IC <80% pred.[15] that is a well documented risk factor for mortality in COPD[22], a greater autonomic unbalance that recently has been shown independently related to mortality in a large cohort of COPD patients[17] and possibly a more severe oxyhemoglobin desaturation during sleep[18].

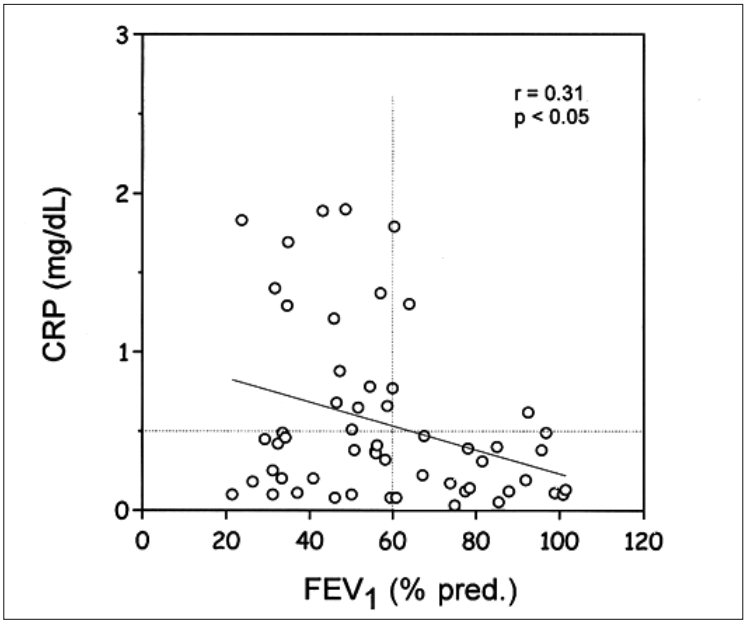

Figure 3. Relationship between CRP plasma level and FEV_1 (as % predicted). The correlation is weaker than that with IC. Only COPD patients with FEV_1 lower than 60% predicted, however, have elevated values of CRP.

Moreover, it has been elegantly demonstrated that COPD patients with low IC at rest exhibit lower exercise capacity essentially caused by mechanical constraints[16] that are known to induce intolerable dyspnea[23], and possibly by decreased cardiac function[24]. It is widely recognized, indeed, that poor or limited physical activity represents the most important risk factor for all cause mortality in every chronic disease included COPD[25] and that indices of physical performance predict all cause mortality in COPD patients[26,27].

Since the presence and severity of systemic inflammation, as inferred by the abnormal blood levels of various bio-markers and particularly of CRP, has been related to higher risk of mortality in COPD[5], the association of high values of plasma CRP and low IC at rest in our series of stable COPD patients strongly suggest another link between resting DH and greater risk of mortality in COPD.

Evidence exists supporting the possibility that inhomogeneous mechanical strain of the some regions of the lung can exert a pro-inflammatory stimulus by stretching alveolar epithelial cells that produce numerous inflammatory mediators such as IL-1beta, IL-8, IL-6 and TNFa and TNFa soluble receptors[28,29]. It is reasonable throughout this mechanism that DH, leading to different regional intrinsic positive end-expiratory pressures (PEEPi), could sustain part of pulmonary and systemic inflammation in moderate-to-severe COPD patients. Moreover, also the respiratory muscles could be a source of inflammatory mediators. In fact, DH by imposing a greater elastic work into inspiratory muscles functionally weaker because high operative lung volumes and possibly sick because of myopathic alterations, may markedly stress them[11]. In any case, our data seem to support these possibilities giving insights in the potential relationship between DH and systemic inflammation in moderate-to-severe COPD.

About half of the COPD patients with IC <80% pred. showed normal CRP serum levels indicating that a large quote of COPD patients with DH had not evidence of low grade systemic inflammation. This fact remains difficult to explain looking at our data, because no differences were found between COPD patients suffering from DH, with and without abnormal CRP, in the available anthropometric, functional, clinical (included pharmacological treatment) or metabolic parameters.

This could be due to either a different strategy to manage DH-induced alveolar strain and inspiratory muscle stress among different COPD patients, or ability to confine in the lung the inflammatory response elicited by the mechanical effects of DH in some of them. Moreover, ICS treatment added to long-acting bronchodilators could be more effective to control lung and systemic inflammation in some phenotypes of COPD patients.

Acid uric, a danger signal molecule that can be released by injured cells[30], was not increased in COPD patients with IC <80% pred. suggesting that DH-induced alveolar cells stretch is unable to release danger signals contributing to the enhancement of the inflammatory response.

In conclusion, resting DH when inferred by the presence of baseline IC lower than 80% pred. is associated with low grade of systemic inflammation, as shown by higher CRP serum levels. Only a subgroup of COPD patients with resting DH, however, exhibits abnormally raised values of plasma CRP. Low grade systemic inflammation might contribute to increase all cause mortality in some COPD patients with IC <80% pred. suggesting another link between DH at rest and less survival in COPD.

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