

C-reactive protein correlates with tissue oxygen availability in patients with stable COPD

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Background: Arterial oxygen tension, oxygen delivery to tissue, and systemic inflammation are recognized as pivotal factors in the progression of chronic obstructive pulmonary disease (COPD). However, interconnections between systemic inflammation and tissue oxygen availability are scanty investigated. Tissue oxygen availability depends on arterial PaO_2 , oxygen concentration, hemoglobin oxygen affinity (P_{50}), and hemoglobin oxygen binding capacity (ceHb). As the integrated changes of those indices are summarized by oxygen extraction tension (PaO_{2x}), the objective of this study was to explore the association between C-reactive protein (CRP) blood levels and either PaO_{2x} or each of its determinants, in stable COPD.

Materials and methods: Blood CRP and oxygen status of arterial blood were measured at rest while breathing room air in 44 moderate to severe stable COPD patients. PaO_{2x} was calculated along the shape of oxygen binding curve as the oxygen tension resulting from removal of 2.3 mmol of oxygen per liter of blood. Multiple linear regression analysis was performed with PaO_2 , ceHb , and P_{50} as independent variables, and CRP as the dependent variable, adjusting for age and sex. The analysis was repeated using PaO_{2x} as a sole independent variable.

Results: Multiple linear regression analysis indicated that ceHb , PaO_2 , and P_{50} , were significant and independent predictors of CRP ($R^2 = 0.52$, $p < 0.0001$). PaO_{2x} alone was an even stronger predictor of CRP ($R^2 = 0.62$, $p < 0.0001$).

Conclusions: These findings indicate that physiological determinants of tissue oxygen availability are independently associated with CRP blood levels. Thus, improvement of tissue oxygen availability is a central therapeutic option to modulate the severity of systemic inflammatory processes in patients with COPD.

Keywords: COPD, C-reactive protein, oxygen extractivity, systemic inflammation

Introduction

Systemic inflammation (Agustí et al 2003) together with arterial hypoxemia and oxygen delivery to tissue (Kawakami et al 1983) are known to influence the prognosis of chronic obstructive pulmonary disease (COPD). Nevertheless, whether systemic inflammatory process is primarily linked to the convective/diffusive process of oxygen transport from the lung to tissues or it is just a secondary phenomenon has not been well acknowledged yet, as the origin of systemic inflammation remains poorly understood in patients with COPD (Wouters 2005).

Recently published papers have reported that increased C-reactive protein (CRP) blood levels mark the metabolic and functional impairment in patients with stable COPD (Schols et al 1996; de Torres et al 2006; Broekhuizen et al 2006; Pinto-Plata et al 2006). Previous studies have also documented that wasting syndrome occurs in COPD patients with elevated arteriovenous oxygen difference, as a result of low arterial and mixed venous oxygenation (Filley et al 1968; Kawakami et al 1983). However, Broekhuizen and colleagues (2006) found no difference in arterial oxygen tension (PaO_2) between patients with normal and raised CRP levels, while de Torres

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and colleagues (2006) found that no more than 20% of the variability of CRP is accounted for by PaO_2 .

It is well acknowledged that hypoxia induces the synthesis of inflammatory cytokines and the expression of adhesion molecules in different cell types and tissues *in vitro* (Ghezzi et al 1991), as well as in humans exposed at high altitude (Hartmann et al 2000). We wondered whether the severity of systemic inflammation, as assessed by CRP blood levels, is instead associated with tissue hypoxia rather than with arterial hypoxemia alone in patients with COPD. To test this hypothesis, we explored the relationship between systemic inflammation, as assessed by CRP blood levels, and each single determinant of oxygen status of arterial blood, ie, PaO_2 , blood oxygen carrying capacity, and blood oxygen affinity. We also explored the relationship between CRP blood levels, and oxygen extraction tension (PaO_{2x}), as this is a noninvasive measurement of peripheral oxygen availability, which summarizes the degree of compensation among arterial oxygen tension, blood oxygen carrying capacity and affinity (Siggard-Andersen et al 1995) and reflects changes of cardiac output, which may affect extraction ratio and mixed venous oxygen tension (Ringsted et al 1990).

Methods

All COPD patients, consecutively referred to our in-patients pulmonary rehabilitation center of Montescano, Italy from January 2004 to January 2006, were considered eligible for the present study. They had to meet the American Thoracic Society (ATS) criteria for diagnosis of COPD (Pauwels et al 2001). Patients were excluded if they had: 1) idiopathic or acquired bronchiectasis; 2) COPD exacerbations within the last 4 weeks; 3) diagnosed cardiovascular disease (coronary artery, peripheral vascular, or cerebrovascular disease); 4) systemic confounding inflammatory disease, such as rheumatoid arthritis, psoriatic arthritis, systemic vasculitis, polymyalgia rheumatica, Crohn's disease, or allergic complication of infections: eg, erythema nodosum, rheumatic fever; 5) malignancies.

Patients had to be clinically stable at the time of examination (no exacerbation within the last 4 weeks) on a standard treatment regimen consisting of inhaled corticosteroids, and beta adrenergic, and/or anticholinergic drugs. None of the patients had to be on systemic corticosteroids. The presence of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia) was registered. It was also noted whether patients were currently smoking, and whether they were on long-term oxygen therapy (LTOT). The Medical

Ethics Committee at our institution approved the study design and a written informed consent was obtained prior to the study.

Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), inspiratory forced vital capacity (IVC), and total lung capacity (TLC) were determined using a Jaeger spirometer and body box (Masterlab, Jaeger, Würzburg, Germany). FEV_1 was also measured 15 minutes after four inhalations of salbutamol (400 μg) from a metered-dose inhaler. Predicted equations utilized were those of Quanjer and colleagues (1993). Carbon monoxide transfer factor (TL_{CO}) was measured (Baires System, Biomedin, Padua, Italy) using the single breath method and according to the ATS recommendation (ATS 1995). Reference equations utilized were those of Cotes (1979).

Functional status of the patients was assessed by BODE (body mass index, degree of airflow obstruction, dyspnea, and exercise capacity) index (Celli et al 2004). This is a multidimensional grading system based on: 1) the measurement of body mass index (BMI, Kg/m^2); 2) FEV_1 , % predicted; 3) degree of dyspnea, measured with the modified Medical Research Council (MMRC) dyspnea scale; and 4) the evaluation of exercise tolerance, as reflected by the distance walked at the 6 minute walking test (6MWD).

Fasting EDTA blood samples were collected, early in the morning (8:00–10:00 hours). CRP was measured in duplicate by high sensitivity turbidimetric immuno-assay (PETIA) (Dade Behring) with a lower detection limit of 0.5 mg/L .

Arterial blood samples were gently drawn from the brachial artery using a dedicated preheparinized blood sampler, while patients were seated and breathing room air. Oxygen breathing was temporarily withdrawn for at least 30 minutes in patients under oxygen therapy. Immediately after sample collection, mixing, and removal of the first drops of blood, the acid-base and oxygen status were analyzed. Arterial negative logarithm of hydrogen ion concentration (pH) and arterial carbon dioxide tensions (PaCO_2), together with arterial oxygen tension (PaO_2) and the oximetry parameters were measured using a blood gas analyzer (ABL Model 700 System Radiometer, Copenhagen, Denmark). The following oximetry parameters were directly measured: 1) concentration of total hemoglobin in the blood (tHb), which includes all types of hemoglobin ie, oxy- (O_2Hb), deoxy- (HHb), carboxy- (COHb), and meta-hemoglobin (MetHb); 2) arterial oxygen saturation

(sO₂) (ie, the ratio between the concentration of O₂Hb and HHb + O₂Hb); 3) fraction of oxyhemoglobin (FO₂Hb) (ie, the ratio between the concentration of O₂Hb and tHb); 4) fraction of carboxyhemoglobin (FCOHb) (ie, the ratio between concentration of COHb and tHb); 5) fraction of methemoglobin (FMetHb) (ie, the ratio between concentration of MetHb and tHb); 6) total arterial oxygen content (ct O₂) (ie, the sum of the concentration of hemoglobin-bound oxygen and the concentration of physically dissolved oxygen). The concentration of effective hemoglobin (ceHb) ie, the concentration of total hemoglobin (ctHb) corrected for fractions of carboxyhemoglobin (FCOHb) and methemoglobin (FMetHb), which are unable to bind oxygen reversibly was calculated as a measurement of hemoglobin oxygen binding capacity. Both oxygen tension at half saturation (50%) of blood (P₅₀), and oxygen extraction tension of arterial blood (PaO_{2x}), were calculated by extrapolation along the shape of the oxygen binding curve on the log PaO₂ – ctO₂ diagram, by a dedicated computer program (Siggard-Andersen and Siggard-Andersen 1990). The shape of the curve was modeled on the basis of the PaO₂ and the hemoglobin oxygen saturation fraction measured in the arterial blood, using a hyperbolic tangent function (Siggard-Andersen et al 1984).

Statistical analysis

The relationship between CRP and the determinants of oxygen extractivity (PaO₂, ceHb, and P₅₀) was assessed by multiple linear regression analysis, adjusting for age and sex. The same analysis was carried out to assess the relationship between CRP and PaO_{2x}, the latter being considered as a comprehensive index of oxygen availability. Descriptive statistics are expressed as mean, standard deviation (SD) or median and interquartile range (IQR). A p value <0.05 was considered statistically significant.

Results

A hundred and fifty-four patients with COPD were assessed for eligibility, and 101 of them were excluded from the analysis because they had either concurrent inflammatory disease or diagnosed cardiovascular disease that may raise CRP blood levels. The reasons and the numbers of excluded patients are detailed in Figure 1. Nine of the patients refused to participate in the study, therefore 44 COPD patients (34 men and 10 women) were recruited in the study. Anthropometric and functional characteristics are reported in Table 1. Most of the patients (41%) were in GOLD stage IV, 93% were exsmokers, and 11 current smokers, with a smoking history of 61 ± 31 (mean ± SD) pack-years.

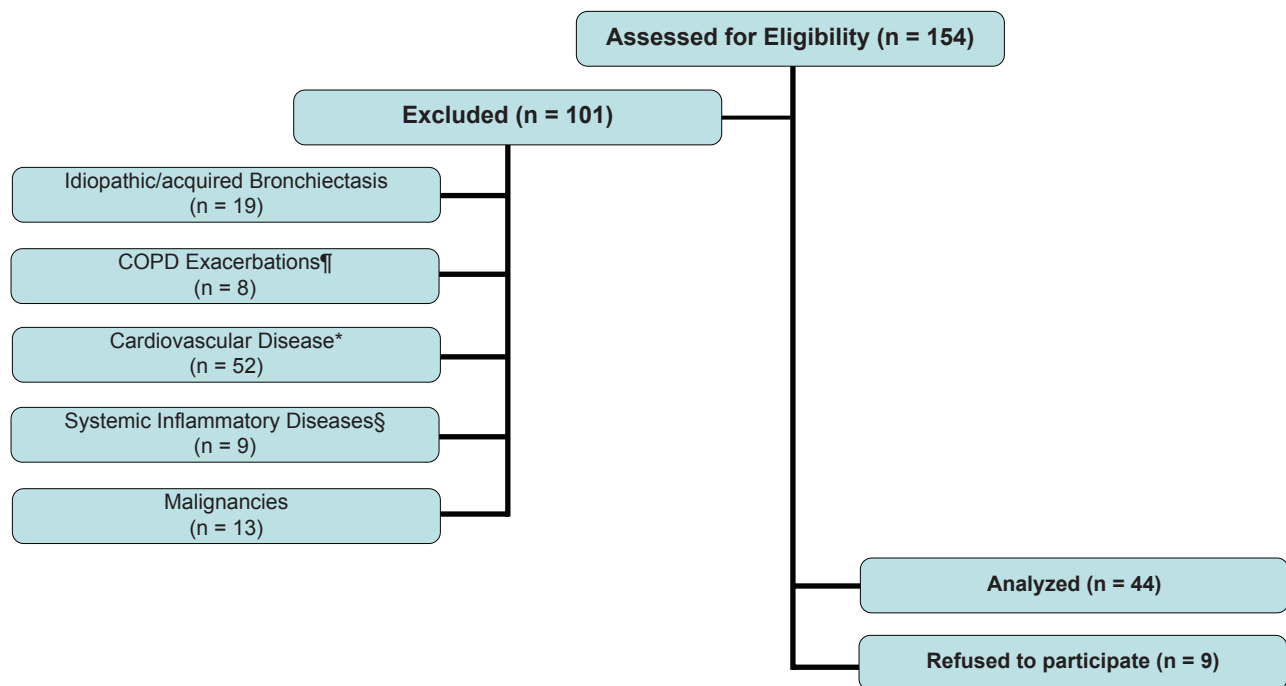


Figure 1 Flow of eligible COPD participants through the analysis.

Notes: Exclusion criteria: ¶COPD exacerbations within the last 4 weeks; *Diagnosed cardiovascular disease (coronary artery, peripheral vascular, or cerebrovascular disease); §Systemic inflammatory disease, such as rheumatoid arthritis, psoriatic arthritis, systemic vasculitis, polymyalgia rheumatica, Crohn's disease, or allergic complication of infections; eg, erythema nodosum, rheumatic fever, etc.

Cardiovascular risk factors were present in 64% of the patients. Out of 44, 43% of patients was on LTOT. The majority of patients (96%) was on inhaled corticosteroid therapy, none of them assumed systemic steroids at the time of the study; 61% was on antihypertensive drugs; 7% of patients was on statins.

The performance status as assessed by BODE index was scored ≥ 8 in 16% of patients, indicating a severely impaired performance. The median interquartile range CRP mg/L was 4.3 (3.0–8.4).

Multiple linear regression analysis indicates that ceHb, PaO_2 , and P_{50} were independently and significantly associated with blood CRP, ($R^2 = 0.52$, $p < 0.0001$). In Table 2, beta coefficients, standard errors, t values and p values are reported. An even stronger association was found when ceHb, PaO_2 , and P_{50} were replaced by PaO_{2x} ($R^2 = 0.62$, $p < 0.0001$), see Table 3. The specific contribution of PaO_{2x} to CRP variability was 56%.

Discussion

C-reactive protein is recognized as a biomarker of the systemic inflammatory response that characterizes patients with COPD (Agustí et al 2003; Schols et al 1996; Gan

et al 2004). The results of our study confirm previous data (Broekhuizen et al 2006; Schols et al 1996; Pinto-Plata et al 2006) that CRP levels are increased in stable COPD patients, and provide the novel finding of a strong association between reduced “oxygen extractivity” and CRP blood level in stable disease condition.

The term “oxygen extractivity” originally proposed by Siggaard-Andersen and colleagues (1995) indicates the property which allows tissues to extract the usual amount of oxygen without a fall in oxygen tension below the usual venous level. This is measured along the shape of the oxygen binding curve, and quantified as oxygen extraction tension (PaO_{2x}) (Siggaard-Andersen et al 1984). PaO_{2x} describes disturbances in oxygen availability depending on arterial oxygen tension, hemoglobin oxygen affinity and hemoglobin oxygen binding capacity, and reflects adjustments of cardiac output to maintain normal venous oxygen tension, if oxygen consumption is normal (Ringsted et al 1990). Thus, we take PaO_{2x} as a convenient estimation of the bio-energetic process of the convective/diffusive oxygen transport from the lung to tissues (Siggaard-Andersen et al 1995).

The finding of a strong association between CRP and PaO_{2x} , as assessed by the Siggaard-Andersen’s algorithm (Siggaard-Andersen and Siggaard-Andersen 1990), suggests a pathogenic link between systemic inflammation and reduced oxygen extractivity at tissue level. This result is also supported by the finding of a significant and independent predictive value of PaO_2 after adjustment for ceHb, P_{50} , age, and sex.

These data are not in contrast with those of de Torres and colleagues (2006), who report that CRP blood levels best correlate with PaO_2 in 130 stable COPD patients. Furthermore, dependence of PaO_{2x} on hemoglobin oxygen affinity, hemoglobin oxygen capacity, and PaO_2 forwards the idea that oxygenation state of hemoglobin, and total number of hemoglobin molecules play a regulatory role on peripheral oxygen availability, together with arterial hypoxemia.

Previous studies (Filley et al 1968; Burrows et al 1972) indicated that COPD patients with a low cardiac output pattern have more problems with tissue oxygenation during exercise than is apparent from their arterial hypoxemia at rest, and that tissue hypoxia may account at least in part for muscle weakness and impaired performance during physical activity. This issue has been further addressed by Schols et al (Schols et al 1996) who suggested the notion of a link between CRP and impaired exercise capacity and distress due to respiratory symptoms. Moreover, González-Alonso

Table 1 Clinical and physiologic characteristics of 44 patients with stable COPD

	Mean	(SD)	Range
Age, year	68.7	8.6	49–83
BMI, Kg/m ²	26.4	4.3	18–35
FEV ₁ , % predicted	47.9	20.9	12–76
MMRC-D, point	2.7	1.0	1–4
6MWD m	298	112	80–500
BODE, points	4.6	2.7	2–10
TL _{CO} , % predicted	49.3	22.4	6–75
tHb, g/dl	14.2	1.8	10–17
FCOHb, %	2.3	0.8	1.6–5.4
FMetHb, %	0.6	0.3	0.6–1.0
FO ₂ Hb, %	90.6	3.7	83–95
sO ₂ , %	92.8	3.8	85–96
PaCO ₂ , mmHg	40.5	6.7	27–53
PaO ₂ , mmHg	63.8	10.4	42–86
PaO _{2x} , mmHg	30.2	2.3	24–33
P ₅₀ , mmHg	23.2	1.9	18–26

Abbreviations: BMI, body mass index; BODE, BMI, degree of airflow obstruction, dyspnea, and exercise capacity index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FCOHb, fraction of carboxyhemoglobin; FMetHb, fraction of methemoglobin; FO₂Hb, fraction of oxyhemoglobin; MMRC-D, scores on the Modified Medical Research Council dyspnea scale; PaCO₂, arterial carbon dioxide tensions; PaO₂, arterial oxygen tension; PaO_{2x}, oxygen extraction tension; P₅₀, oxygen half saturation tension; sO₂, arterial oxygen saturation; tHb, total hemoglobin; 6MWD, distance walked in six minutes.

Table 2 Multiple linear regression analysis with CRP as the dependent variable

Independent variable	Beta coefficient	Standard error	T value	P value
ceHb, g/dl	-0.063	0.027	-2.32	0.025
PaO ₂ , mmHg	-0.028	0.006	-4.59	<0.0001
P ₅₀ , mmHg	-0.150	0.033	-4.50	<0.0001
Sex, M/F	-0.098	0.127	-0.77	0.45
Age, yr	-0.015	0.005	-2.67	0.011
Intercept	8.006	1.241	6.45	<0.0001

Note: R² = 0.52.

Abbreviations: ceHb, hemoglobin oxygen binding capacity; CRP, C-reactive protein; PaO₂, arterial oxygen tension; P₅₀, oxygen half saturation tension.

and colleagues (2006) reported that local regulation of skeletal muscle blood flow and O₂ delivery primarily senses alterations in the oxygenation state of hemoglobin, suggesting an important role of blood O₂ gradients in muscle microcirculatory control. Our findings further emphasize these concepts. They deserve further attention to unravel molecular responses elicited by tissue hypoxia within the lung, the systemic circulation, and the muscles, such as the hypothesized metabolic uncoupling between the citric acid cycle and the electron transport chain at mitochondria level in patients with COPD and chronic respiratory failure (Chance et al 1986; Saulea et al 1998).

Recent studies (Kishimoto et al 1989; Jakobsson 1990; Maltais et al 1996; Yu et al 1998; Semenza 2000; Takabatake et al 2000; Engelen et al 2000; Keller et al 2001) have begun to delineate pathophysiology of hypoxic chronic lung diseases in terms of changes in gene expression that are mediated by transcription factors like HIF1, tumor necrosis factor system and nuclear factor interleukin (IL)-6, among the others. As the pro-inflammatory cytokine IL-6 largely regulates plasma concentrations of CRP, the molecular mechanisms that link CRP blood levels and tissue hypoxia seem to be a crucial point for a better understanding of the origin of systemic inflammatory process in COPD.

Haagobian and colleagues (2006) documented the association between IL-6 mediated increase of CRP and

either hypoxia, or exercise, or caloric deficit in normal subjects, who exercise at high altitude. Furthermore, in healthy subjects exposed at high altitude, a moderate increase of CRP levels is reported to follow the upregulation of both cytokine IL-6 and interleukin-1 receptor antagonist (IL-1ra), arguing for the onset of a low-grade acute phase response to an inflammatory stimulus such as hypoxia at high altitude (Hartmann et al 2000). Similarly, in our COPD patients the reported increase of rest blood CRP levels below the range expected for acute inflammation invites speculation on a low-grade chronic IL-6 release in response to chronic hypoxia. The decreased CRP levels and IL-6 and spontaneous production of IL-6 by monocytes by n-CPAP in patients with obstructive sleep apnea syndrome (OSAS) might provide another evidence supporting this idea in relation to intermittent hypoxia (Yokoe et al 2003).

The exclusion from the analysis of about 2/3 of the patients with COPD according to the criteria detailed in Figure 1 could be regarded as a potential limitation of the study. However, out of 101 patients excluded from the analysis, 52 had a diagnosed cardiovascular disease. Therefore, the percentage of COPD patients showing the presence of cardiovascular risk factors or diseases (52%) does not differ from previously published data (de Torres et al 2006). Thus, we are confident that the patients included in the analysis were also representative of the general COPD population.

Table 3 Multiple linear regression analysis with CRP as the dependent variable

Independent variable	Beta coefficient	Standard error	T value	P value
PaO _{2x} , mmHg	-0.139	0.020	-6.91	<0.0001
Sex, M/F	-0.089	0.106	-0.84	0.41
Age, yr	-0.010	0.005	-1.98	0.054
Intercept	5.621	0.643	8.73	<0.0001

Note: R² = 0.62.

Abbreviations: CRP, C-reactive protein; PaO_{2x}, oxygen extraction tension.

Conclusion

Our findings clearly indicate that systemic inflammation is strongly related to reduced oxygen extractivity, and presumably tissue hypoxia, throughout the interplay of either intrapulmonary oxygen transport and blood supply mechanisms, or systemic regulatory aspects of hemoglobin oxygen transport. Our data allow some speculation on how the responses to chronic exposure to low oxygen concentrations have evolved into adaptive mechanisms operating at tissue level. To the extent that under conditions of tissue hypoxia these responses also promote a systemic damage, COPD would become a key element boosting other systemic inflammatory processes. As a practical implication, the improvement of tissue oxygen availability becomes a central therapeutic option to modulate the severity of systemic inflammatory process in patients with COPD.

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