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Systemic Inflammation in Patients With COPD and Pulmonary Hypertension*

Pavol Joppa, MD; Darina Petrasova, PhD; Branislav Stancak, MD, PhD; and Ruzena Tkacova, MD, PhD

Study objectives: **COPD is a systemic disorder that is associated with increases of inflammatory proteins in systemic circulation. However, no data on the potential role of systemic inflammation in pulmonary hypertension secondary to COPD are available. Therefore, our aim was to investigate the degree of systemic inflammation reflected by circulatory levels of C-reactive protein (CRP), tumor-necrosis factor (TNF)-α, and interleukin (IL)-6 in COPD patients with and without pulmonary hypertension.**

Design: **Cross-sectional study.**

Setting: **University hospital, tertiary referral setting.**

Patients and measurements: **In 43 consecutive patients with COPD (mean [± SD] age, 65.0 ± 10.5 years; mean FEV_1, 46.2 ± 18.1% predicted), lung function was assessed using body plethysmography; pulmonary artery pressure (Ppa) levels were measured by echocardiography. Serum TNF-α and IL-6 levels were assessed by enzyme-linked immunosorbent assay, and high-sensitivity serum CRP levels were measured by chemiluminescent immunoassay.**

Results: **Pulmonary hypertension was present in 19 patients and was absent in 24 patients. In patients with pulmonary hypertension, serum CRP and TNF-α levels were significantly higher than in those patients without hypertension (median, 3.6 mg/L [25th to 75th percentile, 1.4 to 13.0 mg/L] vs 1.8 mg/L [25th to 75th percentile, 0.8 to 2.8 mg/L; p = 0.034]; and median, 4.2 pg/mL [25th to 75th percentile, 3.4 to 10.9 pg/mL] vs 3.1 pg/mL [25th to 75th percentile, 2.1 to 4.2 pg/mL]; p = 0.042, respectively). No differences were seen in serum IL-6 (median, 10.4 pg/mL [25th to 75th percentile, 8.8 to 12.2 pg/mL] vs 10.5 pg/mL [25th to 75th percentile, 9.4 to 39.1 pg/mL]; p = 0.651) between the groups. In multiple linear regression analysis, the following two variables were independent predictors of systolic Ppa (R^2 = 0.373): Pa_{O_2} (p = 0.011); and log-transformed serum CRP level (p = 0.044).**

Conclusion: **We conclude that increases in Ppa in patients with COPD are associated with higher serum levels of CRP and TNF-α, raising the possibility of a pathogenetic role for low-grade systemic inflammation in the pathogenesis of pulmonary hypertension in COPD patients.**

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Key words: COPD; C-reactive protein; pulmonary hypertension; systemic inflammation; tumor necrosis factor-α

Abbreviations: CRP = C-reactive protein; IL = interleukin; Ppa = pulmonary artery pressure; TNF = tumor necrosis factor

Pulmonary hypertension will develop in a significant number of patients with COPD over the course of their disease, and they will experience increased morbidity and mortality as a result.[1,2] In the last decade, the traditional view that hypoxemia and emphysema explain the presence of pulmonary hypertension in COPD patients has been challenged.[2] Indeed, structural and functional changes in pulmonary arteries have also been observed in normoxic patients during the initial stages of the disease.[3] In patients with mild-to-moderate COPD, histopathologic studies[4] have shown inflammatory infiltrates in pulmonary arterial walls. In addition, experimental data have suggested that several inflammatory proteins play an important role in pulmonary artery physiology and in the regulation of pulmonary artery pressure (Ppa).[5–8] Subsequently, the concept of chronic inflammation as one of the key factors involved in pulmonary vascular remodeling has emerged.[1,9]

Besides the presence of chronic local inflammation in both the airways and lung parenchyma, there is increasing evidence of systemic inflammation in patients with COPD.[10–12] Levels of inflammatory proteins such as C-reactive protein (CRP), tumor necrosis factor (TNF)-α, and interleukin (IL)-6 are increased in systemic circulation in such patients.[10–12] However, the potential role of systemic inflammation in the pathogenesis of pulmonary hypertension secondary to COPD has not yet been established.[1] At the same time, the associations between the circulatory levels of TNF-α, CRP, and IL-6, and Ppa have been described in patients with other pathologic conditions such as primary pulmonary hypertension,[13] chronic thromboembolic disease,[14] polyneuropathy-organomegaly-endocrinopathy-M protein-skin changes syndrome,[15] connective tissue diseases,[16] and Gaucher disease.[17] At present, the prognostic value of the measurement of CRP levels is being evaluated in a multicenter prospective study in patients with pulmonary arterial hypertension.[18] If the concept of the relationship between levels of systemic inflammatory proteins and Ppa applies also to patients with COPD, one would expect higher circulatory levels of such proteins in patients with pulmonary hypertension compared to those without pulmonary hypertension secondary to COPD. Therefore, the aim of the present study was to investigate the degree of systemic inflammation, as reflected by circulatory levels of CRP, TNF-α, and IL-6, in COPD patients with and without pulmonary hypertension.

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Materials and Methods

Subjects

Patients with a diagnosis of COPD, determined according to the American Thoracic Society/European Respiratory Society guidelines,[19] were consecutively recruited to the study in a university hospital setting. Exclusion criteria were respiratory disorders other than COPD, pulmonary embolism, left ventricular systolic or diastolic dysfunction, malignancy, systemic autoimmune disorders, infectious diseases, recent surgery, and severe endocrine, hepatic, or renal diseases. The study had local ethics committee approval, and all subjects gave written consent to participate in the study.

Pulmonary Function Tests

Pulmonary function was evaluated with body plethysmography (Jaeger; Wuerzburg, Germany); all testing was performed according to the European Respiratory Society standards with patients in a sitting position at the same time of the day by the same technician in order to ensure the consistency of the technique. Three technically acceptable measurements were performed in each patient, and the highest one was included to the analyses.

Ppas

Mean and systolic Ppas were assessed by Doppler echocardiography[20] by a single investigator (B.S.) who was blinded to the results of the biochemical analyses. Continuous Doppler wave assessment of the peak velocity of the tricuspid regurgitation jet as well as pulsed Doppler recording of the time to peak velocity curves of pulmonary artery blood flow and right ventricular outflow tract were used to assess Ppas. Tricuspid regurgitant flow was identified by color flow Doppler techniques, and the maximum jet velocity was measured by continuous-wave Doppler recording. Right ventricular systolic pressure was estimated based on the modified Bernoulli equation. The diameter of the inferior vena cava and its respiratory variations were used to estimate right atrial pressure, which was added to the right ventricular systolic pressure in order to calculate the systolic Ppa. The acceleration times of the systolic blood flow in the pulmonary artery (*ie*, the time between the onset of systolic flow to the peak systolic flow) and the right ventricular outflow tract were determined with pulsed Doppler recordings from the parasternal short axis, with a two-dimensional-guided Doppler probe placed at the level of the pulmonary valve. The time to peak velocity curves of the systolic blood flow in the pulmonary artery and right ventricular outflow tract were used to assess the mean Ppa.[20] These estimations of Ppa have been shown to be accurate and to correlate well (up to 97%) with hemodynamic measurements during right heart catheterization in patients with cardiac diseases.[21] However, the accuracy of Doppler echocardiography in the assessment of Ppa may not be so high in patients with COPD. A study[22] from the consensus symposium on pulmonary hypertension that was held in Venice, Italy, in 2003 suggested that a systolic Ppa of 35 mm Hg represents the cutoff value for pulmonary hypertension when assessed by Doppler echocardiography. Therefore, we have divided patients into those without pulmonary hypertension (systolic Ppa, < 35 mm Hg) and those with pulmonary hypertension (systolic Ppa, ≥ 35 mm Hg).

Transthoracic echocardiography also was used to assess systolic and diastolic left ventricular function. These assessments were performed at the time of Ppa measurements by the same investigator.

Measurement of CRP, TNF-α, and IL-6

In all patients, peripheral venous blood samples from the antecubital vein were collected between 6:00 and 8.00 AM after 10 h of fasting and abstention from the use of oxygen. Serum was separated from blood cells by centrifugation at 4,000 cycles/min. All samples were stored at −70°C until analyzed. High-sensitivity serum CRP levels were assessed by chemiluminescent immunoassay (Randox; Crumlin, UK). The analytical sensitivity of this CRP assay is 0.1 mg/L. Serum TNF-α and IL-6 levels were measured using commercially available enzyme-linked immunosorbent assay kits (Beckmann-Coulter Immunotech; Krefeld, Germany). At the time of the collection of venous blood samples, an arterial blood sample was obtained by puncture of the radial artery for blood gas analysis.

Statistical Analysis

The results are presented as the mean ± SD for all variables that were normally distributed, and as the median (25th to 75th percentile) for variables that were not normally distributed. Differences between the groups (*ie*, patients with vs those without pulmonary hypertension) were analyzed using a two-tailed unpaired *t* test for normally distributed variables and a Mann-Whitney *U* test for nonnormally distributed variables. Because the distributions of serum CRP, TNF-α, and IL-6 levels were all skewed, we used the log-transformed values of these variables in regression models. Least-squares linear regression analysis was used to assess the unadjusted relationships between systolic Ppa and log-transformed inflammatory protein levels. In the multivariate analysis, multiple linear regression models were used with systolic Ppa as the dependent variable, and age, gender, duration of COPD, Pa_{O_2}, and log-transformed CRP or log-transformed TNF-α as independent variables. A p value of < 0.05 was considered to be statistically significant.

Results

Patient Characteristics

Forty-three patients (29 male and 14 female) with COPD (mean age, 65.0 ± 10.5 years; range, 40 to 82 years; mean smoking history, 28.4 ± 25.9 pack-years) were recruited to the study. Fourteen patients were classified as having stage II COPD, 19 patients as having stage III COPD, and 10 patients as having stage IV COPD.[19] None of the patients had a history of exposure to noxious gases (*eg*, diesel fumes) or biomass exposure. Pulmonary hypertension was present in 19 patients (mean systolic Ppa, 47.7 ± 14.7 mm Hg) and was absent in 24 patients (mean systolic Ppa, 22.1 ± 5.8 mm Hg). No differences were seen between patients with and without pulmonary hypertension in the demographic data or in body mass index (Table 1). Also, no differences were observed in pulmonary function test results between the two groups (Table 2). Six patients without pulmonary hypertension and five patients with pulmonary hypertension denied current smoking. A trend toward lower FEV_1 and lower FVC in patients with pulmonary hypertension compared to those without was noted; however, it did not reach statistical significance (p = 0.052 and p = 0.054, respectively). Blood gas analysis revealed significantly lower Pa_{O_2} in patients with pulmonary hypertension compared to those without hypertension (p = 0.011) [Table 2]. The mean left ventricular ejection fraction was 58.3 ± 8.9% in patients without pulmonary hypertension and 59.3 ± 8.3% in patients with pulmonary hypertension. A clinical diagnosis of coronary artery disease in the medical history was present in 12 patients without pulmonary hypertension and in 11 patients with pulmonary hypertension. In patients without pulmonary hypertension, inhaled β_2-agonists were used by 14 subjects, anticholinergics were used by 17 subjects, inhaled corticosteroids were used by 9 subjects, and long-term domiciliary oxygen were used by 2 subjects. In patients with pulmonary hypertension, inhaled β_2-agonists were used by 11 subjects, anticholinergics were used by 14 subjects, inhaled corticosteroids were used by 5 subjects, and long-term domiciliary oxygen were used by 5 subjects.

Table 1—*Demographic Data in COPD Patients Without and With Pulmonary Hypertension**

Variables	Systolic Ppa		p Value
	< 35 mm Hg	≥ 35 mm Hg	
Patients, No.	24	19	
Men	18	11	0.381
Women	6	8	
Age, yr	62.5 ± 11.5	68.1 ± 8.3	0.082
Duration of COPD, yr	16.5 ± 13.4	14.6 ± 12.8	0.664
Smoking history, pack-yr	33.8 ± 29.1	21.4 ± 19.6	0.151
BMI, kg/m^2	24.6 ± 5.6	22.9 ± 6.0	0.352

*Values are given as the mean ± SD, unless otherwise indicated. BMI = body mass index.

CRP, TNF-α, and IL-6 in Patients With and Without Pulmonary Hypertension

Serum CRP and TNF-α levels were significantly higher in patients with pulmonary hypertension

Table 2—*Pulmonary Function Parameters and Arterial Blood Gas Levels in COPD Patients Without and With Pulmonary Hypertension**

Variables	Systolic Ppa		p Value
	< 35 mm Hg	≥ 35 mm Hg	
FEV_1, % predicted	51.1 ± 16.7	40.3 ± 18.4	0.052
FVC, % predicted	74.3 ± 20.0	61.9 ± 20.3	0.054
FEV_1/FVC ratio, %	54.5 ± 12.2	52.2 ± 14.3	0.586
RV, % predicted	180.9 ± 46.5	168.3 ± 72.2	0.509
TLC, % predicted	111.4 ± 14.9	102.1 ± 36.5	0.302
RV/TLC ratio, % predicted	160.7 ± 31.8	159.3 ± 29.7	0.884
Pa_{O_2}, kPa	9.1 ± 2.0	7.5 ± 2.1	0.011
Pa_{CO_2}, kPa	5.8 ± 0.9	6.3 ± 1.6	0.189

*Values are given as the mean ± SD, unless otherwise indicated. RV = residual volume; TLC = total lung capacity.

compared to those without (median, 3.6 mg/L [25th to 75th percentile, 1.4 to 13.0 mg/L] vs 1.8 mg/L [25th to 75th percentile, 0.8 to 2.8 mg/L; p = 0.034], and 4.2 pg/mL [25th to 75th percentile, 3.4 to 10.9 pg/mL] vs 3.1 pg/mL [25th to 75th percentile, 2.1 to 4.2 pg/mL]; p = 0.042, respectively) [Fig 1, 2]. No differences were seen between the two groups in terms of serum IL-6 levels (median, 10.4 pg/mL [25th to 75th percentile, 8.8 to 12.2] vs 10.5 pg/mL [25th to 75th percentile, 9.4 to 39.1 pg/mL]; p = 0.651) [Fig 3].

A significant linear relationship was observed between log-transformed CRP level and systolic Ppa in the whole group ($r = 0.337$; p = 0.027). No significant relationships were observed between log-transformed TNF-α or IL-6 and systolic Ppa. In multiple linear regression analysis with systolic Ppa as the dependent variable, and age, gender, duration of COPD, current smoking status, Pao_2, and log CRP as the independent variables, the following two variables were independent predictors of systolic Ppa ($R^2 = 0.373$): Pao_2 (p = 0.011); and log-transformed serum CRP (p = 0.044). In an analogic analysis, log TNF-α was not an independent predictor of systolic Ppa (p = 0.699).

Discussion

The present study provides a novel observation on the potential significance of systemic inflammation in patients with COPD who have pulmonary hypertension. Our data demonstrate that COPD patients with pulmonary hypertension have higher serum CRP and TNF-α levels compared to those with normal Ppa levels. In addition, in multiple linear regression analysis, log-transformed serum CRP level was an independent predictor of systolic Ppa. In previous studies, a relationship between Ppa and the levels of certain inflammatory markers was documented in patients with primary pulmonary hypertension,[13] thromboembolic disease,[14] and connective tissue diseases.[16] However, to our knowledge, our data are the first to suggest that systemic inflammation might be related to pulmonary hypertension in patients with COPD.

In the last decade, the concept of hypoxemia as the only major factor causing pulmonary hypertension in COPD patients has been challenged since structural and functional changes in the pulmonary arteries have also been observed in normoxic patients during the initial stages of COPD.[3] It has been suggested[1] that inflammation might be one of the key mechanisms involved in pulmonary vascular remodeling. Indeed, inflammatory infiltrates were seen in pulmonary arterial walls in patients who were in the early stages COPD.[4] It has been repeatedly reported that oxidative stress induced by cigarette smoke results in the local up-regulation of the synthesis of inflammatory cytokines.[23] However, besides local inflammatory processes in lungs, systemic

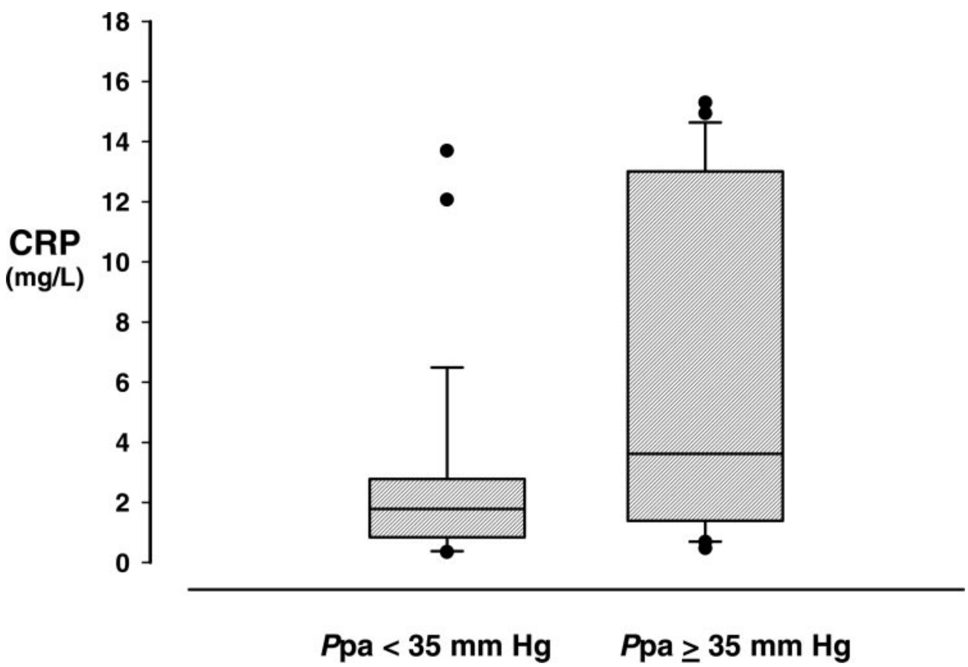

Figure 1. Serum CRP concentrations in COPD patients without and with pulmonary hypertension (p = 0.034). *P*pa = systolic Ppa.

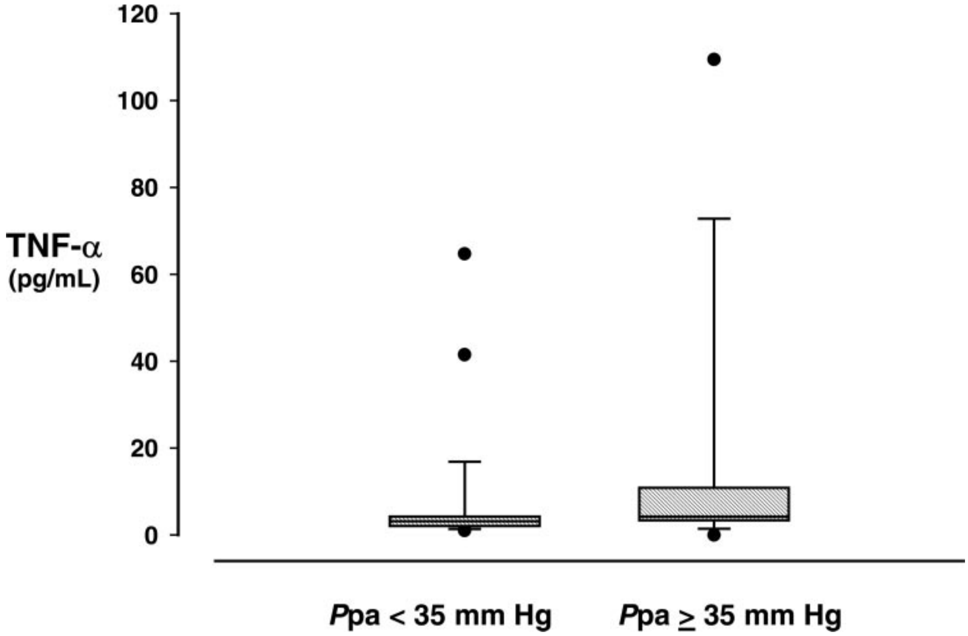

FIGURE 2. Serum TNF-α concentrations in COPD patients without and with pulmonary hypertension ($p = 0.042$). See the legend of Figure 1 for abbreviation not used in the text.

inflammation, as reflected by increases in several inflammatory markers in systemic circulation, is a key feature of COPD.[10–12] Nevertheless, the potential role of systemic inflammation in pulmonary circulation in patients with COPD is not well-understood.

There is an increasing body of evidence indicating that circulating CRP levels constitute an independent risk factor for cardiovascular diseases,[24] including systemic hypertension.[25] Some studies[26,27] have suggested that CRP may have complex direct modulatory effects on endothelial cells. In human aortic endothelial cells, CRP reduced endothelial nitric oxide synthase expression and bioactivity[26]; in saphenous vein endothelial cells, CRP increased endothe-

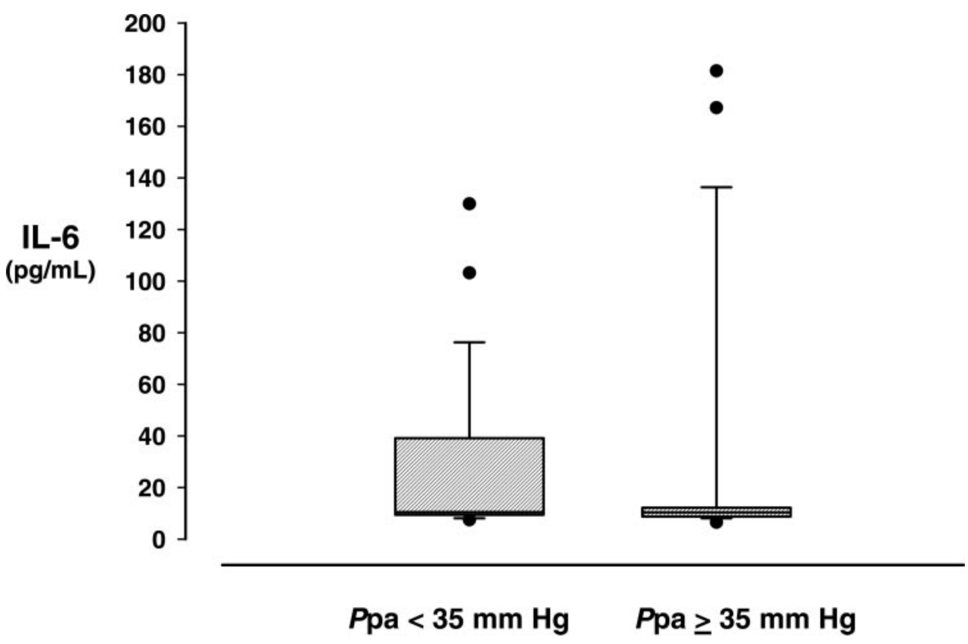

FIGURE 3. Serum IL-6 concentrations in COPD patients without and with pulmonary hypertension ($p = 0.651$). See the legend of Figure 1 for abbreviation not used in the text.

lin-1 release.[27] In patients with essential hypertension, the levels of CRP correlate with microalbuminuria, which is a consequence of endothelial dysfunction in the kidneys.[28] These studies have suggested that CRP may contribute to endothelial dysfunction and may potentially lead to vascular remodeling and increased vascular resistance in the systemic circulation. Nevertheless, the question remains whether CRP might promote similar pathologic processes in the pulmonary circulation as well. Some scarce data have suggested that this might be the case. In patients with Gaucher disease, CRP level was a strong predictor of the presence of pulmonary artery hypertension.[17] At present, the prognostic value of CRP level is being evaluated in a multicenter prospective study[18] in patients with pulmonary arterial hypertension. Data from the present study extend the concept of the link between circulating CRP level and Ppa further. In patients with COPD, CRP level was an independent predictor of systolic Ppa.

TNF-α is a proinflammatory cytokine with potent modulatory effects on the pulmonary circulation. In animal studies, TNF-α was shown to increase pulmonary vascular reactivity,[5] to decrease prostacyclin production in pulmonary artery smooth muscle cells,[29] and to potentiate platelet-activating factor-induced pulmonary vasoconstriction.[30] Emphysema and severe pulmonary hypertension developed in transgenic mice overexpressing TNF-α,[6] whereas TNF receptor-deficient mice were protected against pulmonary hypertension.[7] These data provide strong experimental evidence that TNF-α plays an important role in pulmonary vascular physiology. However, human studies on the potential link between TNF-α and the pulmonary circulation have yielded inconsistent results. Elevated serum TNF-α levels were observed in patients with pulmonary hypertension secondary to chronic thromboembolic disease.[14] In another study,[31] however, no correlation was seen between TNF-α levels and pulmonary vascular resistance in such patients. The findings of the present study showed higher average TNF-α levels in COPD patients with pulmonary hypertension compared to those with normal Ppa values. Further studies are needed to study this phenomenon in more detail.

IL-6 was measured in the present study because it is a powerful signaling cytokine for CRP expression by the liver and is a known independent risk factor for cardiovascular events.[32] Several reports have indicated the potential role of IL-6 in severe primary pulmonary hypertension[13] and pulmonary hypertension associated with connective tissue diseases.[16] However, no literary data have been published on the potential role of IL-6 in pulmonary hypertension secondary to COPD. In the present study, circulating IL-6 levels did not differ between COPD patients with and without pulmonary hypertension. The extent of the increases in Ppa in our patients with COPD was, however, much smaller compared to that seen in patients with very severe primary pulmonary hypertension.[13] In addition, it is important to notice that the mean IL-6 levels observed in the present study were comparable to those described by Humbert et al[13] in patients with COPD, and were much lower than those seen in patients with primary pulmonary hypertension (mean IL-6 level, 66 ± 20 pg/mL).

There are several limitations to this study. First, the study was based on observational data, and whether increases in circulatory levels of CRP and TNF-α represent contributing factors and/or a consequence of increased Ppa remains unclear. In addition, we cannot exclude the possibility that the relationship between CRP, TNF-α, and Ppa is only an epiphenomenon, albeit an interesting and thought-provoking one. However, this seems to be unlikely in the light of the previously discussed extensive body of experimental data[5–8,13–17] suggesting an important role for inflammatory proteins in the physiology of pulmonary circulation. The question of whether hypoxemia might affect serum CRP and TNF-α levels *per se* remains unclear, and was beyond the scope of the present study. Of interest, however, 3 days of marked altitude hypoxemia did not result in changes in serum levels of CRP or TNF-α in healthy subjects, whereas serum IL-6 levels increased significantly.[33] Further physiologic studies are needed to elucidate the exact mechanisms that are responsible for the increases in inflammatory mediators in patients with COPD. The second limitation of the present study is the use of transthoracic echocardiographic indexes to classify pulmonary hypertension. Although several studies have revealed significant statistical correlations between systolic Ppa estimated by Doppler echocardiography and that measured by right heart catheterization in patients with cardiac diseases[21] and pulmonary diseases,[34] the estimation of systolic Ppa by echocardiography may be inaccurate in patients with advanced lung disease.[35] Arcasoy et al,[35] in a cohort of lung transplant candidates, have documented that the correct estimation of systolic Ppa is particularly difficult in patients with interstitial lung disease and pulmonary vascular disease, and in those COPD patients who have marked air trapping. In the present study, no differences were seen in the prevalence of severe hyperinflation between patients with pulmonary hypertension compared to those without (29% vs 36%, respectively). Third, our analyses are based on single measurements of Ppa and inflammatory markers, which may not reflect these relationships over time. Therefore, this study does not provide information about the time-course relationship between systemic inflammation and Ppa. In view of the cross-sectional character of our data, our results should be considered as hypothesis-generating.

In conclusion, our study showed that increases in Ppa in patients with COPD are associated with higher serum levels of CRP and TNF-α, raising the possibility of a pathogenetic role of low-grade systemic inflammation in the pathogenesis of pulmonary hypertension in COPD. Further studies are needed to address this question in more detail.

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