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The influence of inflammatory process on the ventilatory impairment in patients with stable chronic obstructive pulmonary disease

Abstract

Introduction: At present, COPD is known to be a systemic disease resulting from generalized inflammation which affects the function of many organs. Generalized inflammation is recognized from increased serum concentration of inflammatory cytokines. The aim of the present study was to investigate the influence of inflammatory process on the respiratory impairment in patients with stable chronic obstructive pulmonary disease.

Material and methods: A group of 60 stable COPD patients (GOLD stages I–IV) participated in the study. Inclusion criteria were: confirmed diagnosis of chronic obstructive pulmonary disease, clinical stable state, established treatment which had not been changed for at least 3 months prior to the study or in the course of the study. Exclusion criteria included coexistence of other diseases and/or medication causing an increase of markers of inflammation. In all patients inflammatory markers (serum concentration of fibrinogen, hs-CRP, IL-6, TNF-α) were determined. In order to assess the stage of COPD, bodyplethysmography with bronchodilating test was conducted and lung hyperinflation parameters were assessed.

Results: Analysis of relationship between markers of systemic inflammation and spirometry variables revealed a significant negative correlation between the level of hs-CRP and signs of hyperinflation; IC% of predicted value ($r_s = -0.29$; $p = 0.023$) and IC/TLC ($r_s = -0.32$; $p = 0.014$). The IC/TLC index also tended to be related to the concentration of fibrinogen. Higher fibrinogen concentrations were associated with lower IC/TLC values, albeit without statistical significance ($r_s = -0.23$; $p = 0.074$). There was a positive relationship between serum concentration of TNF-α and arterial blood carbon dioxide pressure $PaCO_2$ ($r = 0.281$; $p = 0.03$) as well as right ventricle systolic pressure RVSP in echocardiography ($r = 0.332$; $p = 0.01$).

Conclusions: Severity of hyperinflation progression may be associated with the increase of inflammatory process in patients with stable COPD. Inflammatory process may have an adverse affect on the respiratory system increasing significantly static lung hyperinflation.

Key words: chronic obstructive pulmonary disease, proinflammatory cytokines, hyperinflation

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Introduction

Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disorder. It is estimated that in 2020 it will be the third most common cause of death worldwide [1]. The development of COPD is most commonly associated with smoking, but also with age, air pollution, occupational exposure [2], and socioeconomic status [3]. These factors lead to chronic inflammation in the airways, pulmonary parenchyma, and pulmonary blood vessels [4–6].

According to the definition, COPD is a disease characterised by an incompletely reversible airflow limitation. This limitation is usually progressive and associated with abnormal inflamma-

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Table 1. Characteristics of study group according to stage of COPD

Stage of COPD	Total		Males		Females	
	n	%	n	%	n	%
I	5	8.3%	5	10.2%	0	0.0%
II	26	43.4%	21	42.9%	5	45.5%
III	24	40.0%	18	36.7%	6	54.5%
IV	5	8.3%	5	10.2%	0	0.0%
Total	60	100.0%	49	100.0%	11	100.0%

tory response to noxious fumes or gases [4, 5, 7, 8]. The progression of the disease with increasing dyspnoea and exercise intolerance does not only result from airflow limitation but also from air trapping, which is a consequence of emphysema that leads to a loss of elasticity of the lungs and impairment of the patency of small bronchi [9]. This results in a decrease in the inspiratory capacity (IC) and an increase in the residual volume (RV), the RV to total lung capacity (TLC) ratio, and the respiratory effort during the inspiratory phase of breathing [10]. The forced expiratory volume in one second (FEV_1) is the parameter of greatest diagnostic and prognostic value. However, in patients with COPD, dyspnoea and limited exercise tolerance poorly correlate with FEV_1. On the other hand, it has been demonstrated that functional markers that define the severity of hyperinflation better correlate with these symptoms [11–15]. In COPD patients with reduced IC at rest, exercise tolerance decreased in proportion to the degree of IC reduction [13, 16–18]. An increase in exercise tolerance of 25% has been observed in patients whose IC increased by 10% predicted following a bronchodilator [13]. Hyperinflation is also defined as an increase in the functional residual capacity (FRC), whose main component volume is RV [16]. The increase in RV happens at the expense of reduced vital capacity (VC). The reasons why the vital capacity is reduced are: hyperinflation and increased RV%TLC above the upper limit of norm.

Smoking is one of the main risk factors for many chronic diseases. It stimulates inflammation not only in the pulmonary tissue, but also in blood vessels, causing the release of inflammatory mediators such as C-reactive protein (CRP), cytokines, and certain interleukins (IL), which both directly and indirectly affect specific organ functions [19, 20]. CRP is a commonly used marker of inflammation. Patients with COPD have higher concentrations of IL-6 than healthy controls [21]. IL-6 is believed to be responsible for target organ changes in COPD patients. Sin et al. emphasise that the intensity of inflammation (reflected by elevated CRP and IL-6 levels) in stable patients with COPD correlates with the severity of the disease (reflected by FEV_1) and is a risk factor for weakened peripheral muscles and reduced exercise tolerance [22]. The first mediator of inflammation the levels of which were found to be elevated in COPD was tumour necrosis factor α (TNF-α) [23]. TNF-α has been shown to positively correlate with muscle weakness in emaciated patients [24] and in patients with pulmonary hypertension [25].

The aim of the study was to evaluate the relationship between the signs of chronic inflammation and pulmonary function test results in patients with COPD.

Material and methods

Signing a written informed consent form was a condition of participation in the study. The study was approved by the Bioethics Committee.

The study included 60 patients with COPD (49 men and 11 women) selected according to the criteria given below. The mean age was 62.2 years (range, 45–80 years).

The inclusion criteria were as follows:

— Clinically stable COPD without acute exacerbations in the past 3 months. The severity of COPD was assessed in accordance with the GOLD scale [4] (Table 1);
— Stable treatment for at least 3 months prior to the study and during the study;

The exclusion criteria were as follows:

— Co-morbidities: rheumatic diseases, diabetes mellitus, thyroid disorders, cancer, infection;
— The use of systemic glucocorticosteroids, antiarrhythmics, digitalis, statins;
— Cardiovascular disease (congenital or valvular heart disease, ischaemic heart disease, cardiomyopathy, heart failure).

Investigations

The serum levels of fibrinogen, high sensitivity C-reactive protein (hs-CRP), IL-6, and TNF-α were determined. Determination of hs-CRP was by particle-enhanced turbidimetric assay (PETIA) using a Behring BN II nephelometer (DADE Behring). IL-6 and TNF-α were determined using quantitative enzyme-linked immunosorbent assay (ELISA) (R&D System).

Pulmonary function testing was performed with a constant-volume/variable-pressure MasterScreen Diffusion (Jaeger) plethysmograph. The flows in the cabin and at the mouth were recorded using a pneumotachographic head. The system was fitted with interface cards and contained a computer with the LAB 4.34 installed in the Windows environment. Three repeatable spirometric measurements were performed with an assessment of the dynamic parameters (FEV_1, FVC) and FEV_1/FVC. Predicted values for individual parameters were calculated from the regression equations proposed by the European Community of Steel and Coal and adopted by the European Respiratory Society (ERS) [26]. The predicted IC value equalled the difference between predicted TLC and predicted FRC.

The test was repeated following inhalation of 200 μg (2 inhalations) of salbutamol in order to evaluate the reversibility of bronchial obstruction and determine the stage of COPD. The spirometric classification of the severity of COPD used in the study followed the GOLD recommendations [4]. In order to evaluate resting hyperinflation the patients were divided into two groups according to baseline IC (< 80% and ≥ 80% predicted) [13] and baseline TLC ≥ 115% predicted [14]. RV was analysed as an additional parameter of hyperinflation. The following percentage indexes were also evaluated: IC/TLC and RV%TLC. The evaluation of baseline hyperinflation was performed in patients with IC% predicted < 80% and TCL > 115%. Hyperinflation reduction was evaluated on the basis of changes in the absolute and relative values of IC, RV, TLC following a bronchodilator, and on the basis of changes in IC/TLC and RV%TLC.

Arterial blood gas analysis included the measurement of pH, partial oxygen pressure (PaO_2), partial carbon dioxide pressure ($PaCO_2$), base excess (BE), bicarbonate levels (HCO_3), and haemoglobin oxygen saturation (SaO_2).

Echocardiography was performed with a Toshiba Vision Power echocardiograph with a head fitted with an electronic ultrasound transducer working in the range 2.5–3.5 MHz. The echocardiogram was obtained in the M mode and the 2D mode and using the Doppler method. The left ventricular ejection fraction was evaluated by Simpson's biplane method. Segmental contractility of the left ventricle was evaluated by analysing the biplanar image of the heart in the parasternal view in the long and short axes of the left ventricle and in the apical four- and two-chamber views. Patients with segmental contractility abnormalities were excluded from further testing. Cardiac chamber sizes were evaluated: the left ventricular end-diastolic dimension, right ventricular end-diastolic dimension, and left atrial dimension in the parasternal view in the long axis of the left ventricle. The right ventricular systolic pressure was evaluated on the basis of the velocity of the tricuspid regurgitation wave using a simplified Bernoulli's equation.

Statistical analysis

The description of the quantitative study variables included the arithmetic mean (x), standard deviation (s), and the minimum and maximum values (min–max). The qualitative parameters were described in contingency tables by absolute (n) and relative (%) frequency.

The differences between the groups of analysed parameters were verified with the t-test, analysis of variance (ANOVA), or non-parametric tests (U Mann-Whitney test). In the case of more than two groups, analysis of variance and Scheffe's test were used. Verification was conducted at the significance level of $p < 0.05$. Statistical calculations were performed using STATISTICA 7.1 for Windows.

Results

Among the 58 patients (96.7%) 24 were active smokers (40%), 34 were former smokers (56.7%), and 2 were never-smokers (3.3%). The mean number of packet-years was 45.

The severity of COPD in the study group is summarised in Table 1.

Evaluation of the relationship between the levels of chronic inflammation markers (fibrinogen, hs-CRP, IL-6 and TNF-α) and markers of obstruction, hyperinflation, and blood gas parameters revealed a significant correlation between hs-CRP levels and IC% predicted ($r_s = -0.29$; $p = 0.023$) and between hs-CRP levels and IC/TLC ($r_s = -0.32$; $p = 0.014$). At high levels of hs-CRP the values of IC% predicted and IC/TLC are low. As hs-CRP levels rise, the value of IC% predicted decreases (Fig. 1). The differences between the mean values of IC relative to hs-CRP = 3 mg/l are illustrated in Figure 2. For hs-CRP below 3 mg/l the mean IC was 86%

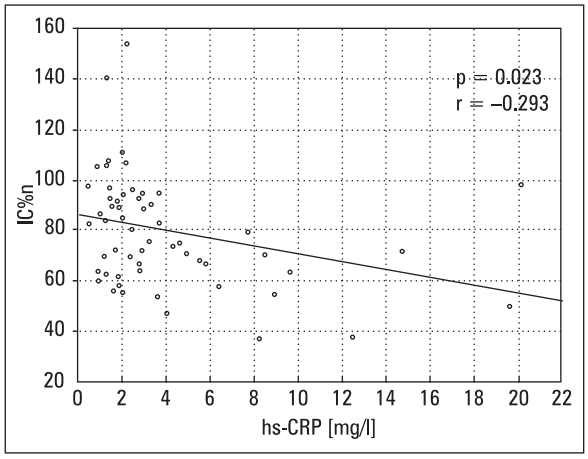

Figure 1. Correlation between IC% predicted value and serum level hs-CRP

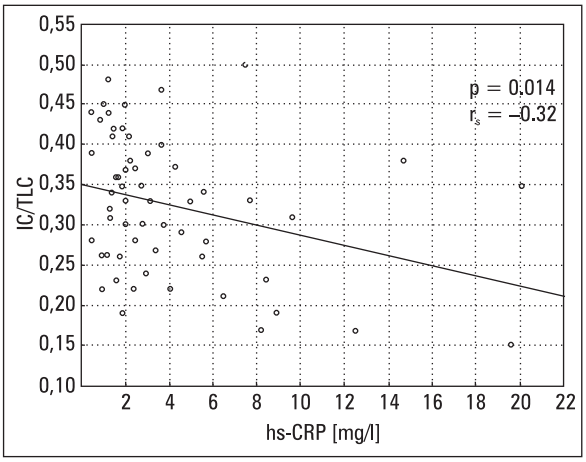

Figure 3. Correlation between serum level hs-CRP and IC/TLC

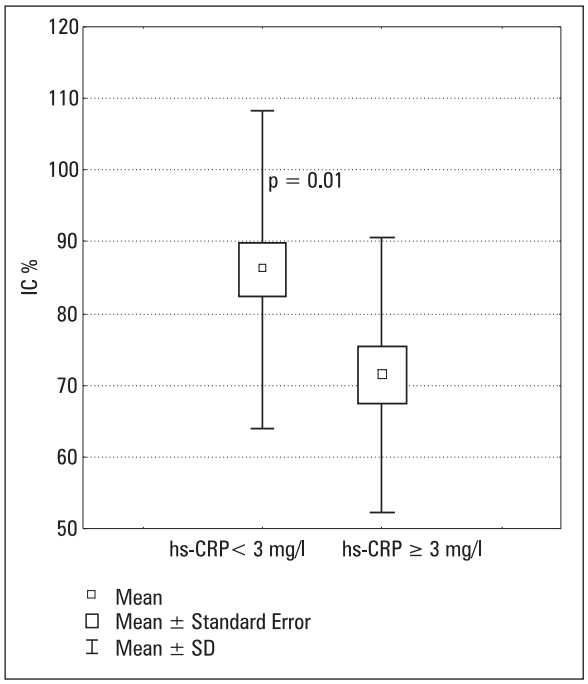

Figure 2. Correlation between IC% predicted value referring to hs-CRP < or > 3 mg/l

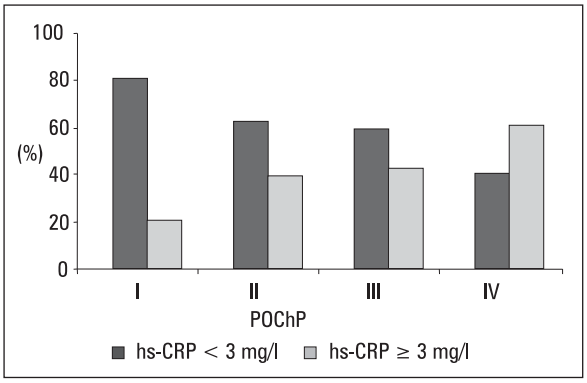

Figure 4. Correlation between stage of COPD and serum level hs-CRP

predicted, and for hs-CRP ≥ 3 mg/l the mean IC was 71% predicted. These differences were statistically significant (p = 0.01).

A significant negative correlation between hs-CRP and IC/TLC was observed (r_s = –0.32; p = = 0.014) (Fig. 3).

Figure 4 illustrates the relationship between the severity of COPD and CRP levels. In stage I disease hs-CRP below 3 mg/l was found in 48 patients (80%), while in stage IV disease the number of patients with high values of hs-CRP increased: hs-CRP ≥ 3 mg/l was found in 36 patients (60%). The relationship between CRP and FEV_1% predicted for hs-CRP above and below 3 mg is illustrated in Figure 5. At hs-CRP levels ≥ 3 mg/l lower values of FEV_1% predicted were observed, although the difference was not significant.

A statistically significant relationship between TNF-α and $PaCO_2$ was revealed (r = 0.281; p = 0.03) (Fig. 6). Also, a significant relationship between TNF-α and RVSP was found (r = 0.33; p = 0.01) (Fig. 7).

Discussion

Chronic obstructive pulmonary disease is an inflammatory condition in which epithelial cells and macrophages, once stimulated by irritants (mainly cigarette smoke), start to release various mediators. Endothelial dysfunction, which results in abnormal synthesis and release of inflammatory mediators, plays an important role in the pathogenesis of COPD [2, 27]. These changes make the inflammation detectable in the systemic circulation, as reflected by elevated leukocyte counts and elevated levels of fibrinogen, CRP, and proinflammatory cytokines, such as IL-6 and TNF-α [5, 8, 20,

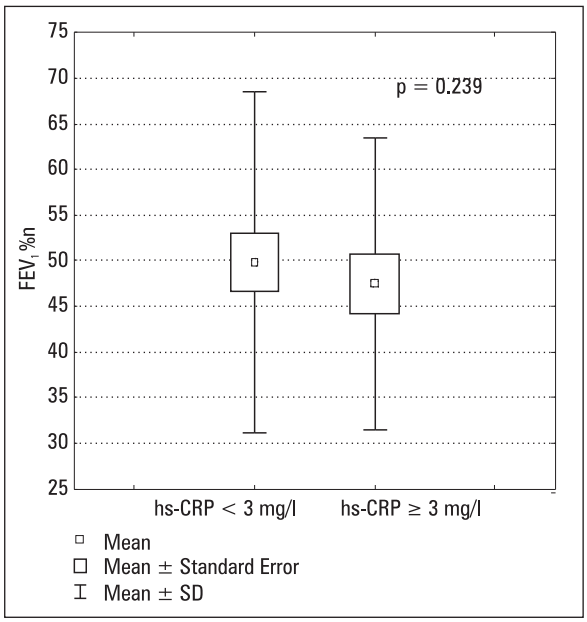

Figure 5. Correlation between FEV_1% predicted value and hs-CRP < or > 3 mg/l

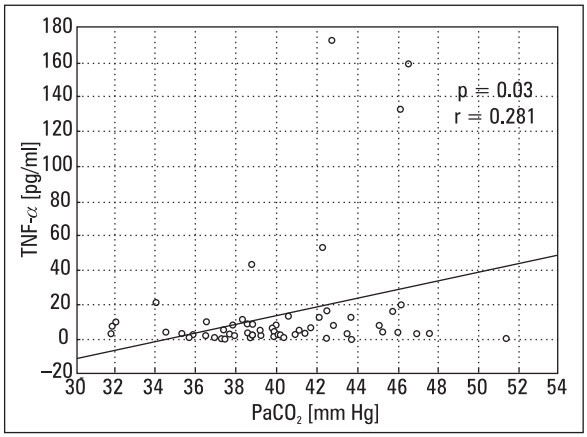

Figure 6. Correlation between serum level TNF-α and $PaCO_2$

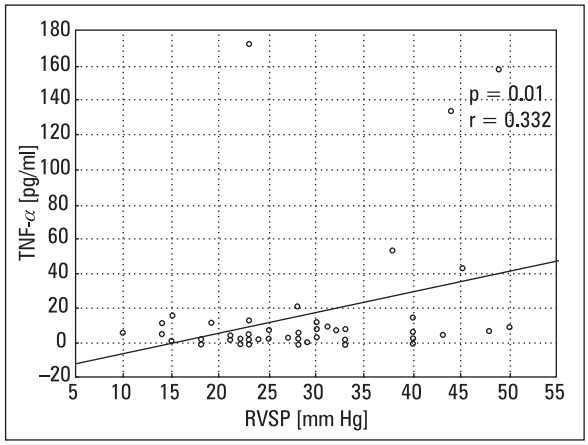

Figure 7. Correlation between serum level TNF-α and RVSP

28–30]. There are studies that confirm the presence of systemic inflammation in stable patients with COPD [30, 31].

A total of 60 patients with GOLD stage I to IV stable COPD were qualified for the study. In order to reduce the impact of other factors on the concentration of the inflammation markers the recruitment was very selective. Co-morbid inflammatory conditions were excluded, and the patients were also receiving a uniform treatment. The considerable difficulty in selecting such a predefined group results from the fact that more than 50% of COPD patients over 65 years of age have at least three other chronic co-morbidities, with 5 or more co-morbidities being seen in one fifth of these patients [32].

Analysis of the relationships between inflammation markers and spirometric parameters revealed a trend towards an increased hs-CRP level with increasing severity of COPD. These relations were not, however, statistically significant (p = 0.632). De Torres et al. [6] investigated 130 patients with stable COPD and showed that, compared to healthy controls, serum CRP correlated with prognostically important spirometric parameters, such as: FEV_1, FVC, IC/TLC, and the severity of the disease according to the GOLD classification. De Torres et al. conclude that their study has confirmed previous reports by Gan et al. [31] which showed that CRP levels rise with deteriorating lung function. In a large meta-analysis, Sin and Man [30] also demonstrated a statistically significant relationship between CRP levels and the severity of COPD, although the selection of patients in this study was random and the only inclusion criteria were pulmonary function parameters. It may be assumed that the presence of numerous co-morbidities in COPD patients in the studies cited above resulted in a considerable exacerbation of systemic inflammation reflected by the levels of inflammation markers.

For the purpose of analyses of the relationships between inflammation and functional parameters, the value of IC% predicted < 80% was adopted in accordance with previous bibliographical data [12, 13]. Statistically significant relationships between the severity of inflammation and the increase in static hyperinflation defined by IC and IC/TLC. Previously, hyperinflation was assessed by volume parameters (IC, TLC, IC/TLC, RV, RV/TLC, FCR), which reflected both static (at rest, post-bronchodilator) and dynamic (post-exercise) hyperinflation [11, 13–15, 17, 18]. De Torres et al. [6] found a relationship between CRP and IC/TLC in stable COPD patients. The relationship between other

inflammation markers and IC/TLC had not been previously investigated. Agusti and Rosiano [33] believe that inflammation plays a key role in the pathogenesis of emphysema and, as a consequence, in the pathogenesis of dynamic hyperinflation (DH). As the relationships between DH and inflammation have not been elucidated, gaining an understanding of these pathomechanisms may be of considerable clinical relevance, as both hyperinflation and chronic systemic inflammation are the key pathogenetic elements of COPD. The present study also revealed a near-significant relationship between serum hs-CRP and PaO_2 ($p = 0.055$) in arterial blood gas analysis. Similarly, in the study by de Torres et al. [6], in a group of stable COPD patients, multivariate regression analysis revealed that PaO_2 showed a statistically significant correlation with serum CRP levels. Patients with hypoxaemia in the course of COPD are at a higher risk of death. Hypoxaemia causes oxidative stress and inflammation present in the pathogenesis of this disease. Oxygen therapy is also known to improve the prognosis in these patients [34]. It is, however, unknown whether oxygen therapy could reduce the severity of systemic inflammation in COPD patients.

The present study revealed a significant positive correlation between serum TNF-α and $PaCO_2$. Tumour necrosis factor is one of the most potent proinflammatory cytokines. Sevenoaks et al. [35], referring to the central role of TNF-α in the pathogenesis of COPD, even proposed the term "inflammatory TNF-α phenotype" as being helpful in explaining the relationship between the presence of inflammation and the coexistence of other diseases in the course of COPD. Summarising numerous studies, the authors concluded that the negative correlations between PaO_2 and TNF-α may result from tissue hypoxia. Numerous researchers observed elevated TNF-α levels in groups of patients with severe COPD and in emaciated patients [4, 5, 24, 31]. The present study suggests that hypercapnia in the course of COPD may also be a cause of elevated TNF-α, in addition to hypoxaemia.

The present study showed a statistically significant relationship between the level of TNF-α and RVSP. Similarly, Joppa et al. [25], while investigating the relationship between systemic inflammation and pulmonary hypertension in COPD patients, found a significant correlation between TNF-α and CRP and RVSP. Median levels of both parameters (TNF-α and CRP) were higher than in the present study, which may have resulted from the fact that the only inclusion criterion in the study by Joppa et al. was a set of spirometric parameters, while in the present study, co-morbidities were also taken into consideration. Pulmonary hypertension in the course of COPD is associated with alveolar hypoxia. It leads to a vasospastic reaction followed by muscular hypertrophy of the arteriole walls and increased pulmonary vascular resistance [36]. Hypoxia may trigger both systemic and local production of TNF-α by cardiac myocytes [24, 37–40]. Joppa et al. draw a conclusion on the potential pathogenetic role of inflammation in the development of pulmonary hypertension in COPD patients, and it seems that the present study might support this.

In conclusion, the present study supports the essential role of inflammation in the pathogenesis of the functional abnormalities in patients with COPD. They seem to have potential practical implications. Because worldwide about 3 million patients die each year from COPD and mortality is expected to continue to increase, there is an urgent need for studies investigating drugs with a higher anti-inflammatory efficacy. It may well be that future studies of novel anti-inflammatory agents will offer new ways of treating and suppressing systemic inflammation and the worsening functional parameters.

Conclusions

Worsening of hyperinflation is associated with worsening of inflammation in patients with COPD. Generalised inflammation might increase static hyperinflation.

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