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Correlation between hyperinflation defined as an elevated RV/TLC ratio and body composition and cytokine profile in patients with chronic obstructive pulmonary disease

Korelacje pomiędzy rozdęciem miąższu płucnego mierzonego wskaźnikiem RV%TLC i składem ciała oraz profilem cytokinowym u chorych na przewlekłą obturacyjną chorobę płuc

The study was performed as the part of National Center for Research and Development project "Chronic obstructive pulmonary disease (COPD) — systemic disease, the biggest threat of XXI century" (NO. 13 0034 06/2009).

Abstract

Introduction: Body composition is an important prognostic factor in patients with COPD. The decrease in fat free mass (FFM), muscle mass (MM) and increase in visceral fat is associated with an elevated secretion of cytokines which promote systemic inflammation.

The aim of the study was to evaluate body composition and the cytokine profile in patients with COPD in relation with the presence of hyperinflation.

Material and methods: The study group consisted of 149 patients (61F, 88M) with stable COPD in all stages of severity aged 68 ± 8.8 yrs. All the patients underwent spirometry and bodypletysmography with bronchial reversibility testing. Hyperinflation was defined as RV%TLC > 48% and > 126% predicted. Body composition was analyzed by bioimpedance. The following serum inflammatory markers were evaluated: C-reactive protein, IL-6, IL-8, TNF-α, CC16, adiponectin and resistin.

Results: Hyperinflation was found in 96 patients (group A) and it was more frequent in women than men (49/61 vs. 47/88, $p < 0.001$). BMI and age in this group were comparable to those in patients without hyperinflation (group B). Patients with hyperinflation have lover FFM, FFM index, MM and MM index and total body water and higher fat mass and fat mass index. We found significantly higher serum concentrations of inflammatory markers in group A: IL-6 – 6.4 ± 10.9 vs. 3.6 ± 4.2 pg/ml, resistin – 9.3 ± 4.2 vs. 7.6 ± 2.4 ng/ml, CRP 4.1 ± 2.3 vs. 2.9±2.1 mg/l, respectively.

Conclusions: Patients with hyperinflation have a lower FFMI, TBW and MMI and a higher proportion of fat tissue. Hyperinflation is associated with elevated concentrations of inflammatory markers what may be associated with more severe disease. Body compositions abnormality and higher activity of systemic inflammation could therefore be a negative prognostic factor in COPD patients.

Key words: COPD, RV%TLC, body composition, systemic inflammation

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Streszczenie

Wstęp: Skład ciała jest ważnym czynnikiem prognostycznym u chorych na POChP. Spadek beztłuszczowej masy ciała (FFM), masy mięśni (MM) i wzrost masy trzewnej tkanki tłuszczowej jest związane ze wzrostem wydzielania cytokin odpowiedzialnych za systemowe zapalenie.

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Celem pracy była ocena wpływu hiperinflacji układu oddechowego na stan odżywienia i profilu cytokin u chorych na POChP.
Materiał i metody: Grupa badana składała się z 149 chorych (61K, 88M), w stabilnym okresie POChP, którzy reprezentowali wszystkie stopnie ciężkości choroby, w wieku 68 ± 8,8 lat. Wszyscy chorzy mieli wykonaną spirometrię i pletyzmografię z próbą rozkurczową. Rozdęcie było definiowane, jako zwiększenie RV%TLC > 48% and > 126% wn. Skład ciała był mierzony metodą bioimpendancji. Wykonano pomiar następujących cytokin w surowicy: białko C-reaktywne (CRP), IL-6, IL-8, TNF-α, CC16, adiponektyna i rezystyna.
Wyniki: Rozdęcie stwierdzono u 96 chorych (grupa A), było ono częstsze u kobiet niż mężczyzn (49/61 *v.* 47/88, p < 0,001). Indeks masy ciała i wiek były podobne do grupy chorych bez rozdęcia (grupa B). Grupa A miała niższe FFM i FFMI, MM i MMI i całkowitą masę wody oraz wyższą masę tłuszczową i indeks masy tłuszczowej. W grupie A stwierdzono istotnie statystycznie wyższe stężenie w surowicy markerów zapalenia: IL-6 — 6,4 ± 10,9 *v.* 3,6 ± 4,2 pg/ml, resistin — 9,3 ± 4,2 *v.* 7,6 ± 2,4 ng/ml, CRP 4,1 ± 2,3 *v.* 2,9 ± 2,1 mg/l.
Wnioski: Chorzy, u których stwierdza się rozdęcie płuc mają niższe FFMI, TBW, MMI i więcej tkanki tłuszczowej. U chorych z rozdęciem płuc stwierdza się podwyższone stężenie markerów stanu zapalnego w porównaniu z chorymi bez rozdęcia, co może świadczyć o bardziej zaawansowanym procesie chorobowym. Zarówno zaburzenia w składzie ciała jak i wyższa aktywność zapalenia systemowego w grupie chorych z rozdęciem płuc może wskazywać na ich gorsze rokowanie

Słowa kluczowe: POChP, RV%TLC, skład ciała, zapalenie

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Introduction

Chronic obstructive pulmonary disease is characterized by progressive airflow limitation which is a result an inflammatory response in the airways to noxious particles and gases [1]. Pathological changes that lead to airway obstruction may have the form of chronic bronchitis and/or pulmonary emphysema. In patients with predominant chronic bronchitis the inflammatory process involves mainly the small airways and bronchioles, resulting in peribronchiolar fibrosis, muscular hypertrophy and mucus hypersecretion. Whereas in patients with predominant emphysema, pronounced lung parenchyma destruction is observed; the loss of lung elasticity impairs emptying of the lungs during expiration leading to an increase in the end-expiratory lung volume [2]. This process intensifies with increasing airway obstruction e.g. during COPD exacerbation. Irrespective of the predominant nature of pathological changes, inflammatory cells cumulate in the airways, secreting various mediators responsible for the above mentioned process and structural changes [3]. Systemic inflammation results in the development of extrapulmonary manifestations, including alterations in body composition. In some patients cachexia occurs, in the majority, the loss of fat free mass (FFM) is observed along with the progression of the disease. Nutrition disorders are associated with increased secretion of inflammatory mediators (TNF-α, IL-6, IL-8, CRP) [4]. Low body mass index (BMI) is believed to be an independent risk factor of mortality in COPD [5]. Lung hyperinflation has an impact on numerous factors that are taken into account in the evaluation of the COPD patient including the sense of dyspnoea assessed by the Medical Research Council (MRC) scale, quality of life, FEV_1 decline, energy balance and body composition disorders [6, 7].

The objective of the study was to evaluate the influence of lung hyperinflation on the nutrition status and cytokine profile in patients with COPD.

Material and methods

The study group included 149 patients with stable COPD (61 women and 88 men) aged 68 ± 8.8 years. COPD was diagnosed in accordance with the GOLD 2010 recommendations [8]. The criterion for stable COPD was lack of exacerbation for a period of at least 6 weeks prior to study inclusion.

The study group was divided into two subgroups: A — patients with hyperinflation, and B — patients without hyperinflation with predefined criteria as described below.

All patients underwent anthropometric measurements of height and body mass including: fat free mass (FFM, kg), muscle mass (MM, kg), total body water (TBW, kg), body fat content (BF, %). The measurements were performed under fasting condition in the morning. Body mass index (BMI), muscle mass (MMI) and fat free mass indices (FFMI) were calculated. Body composition was assessed using bioimpedance (Tanita T5896, TANITA Corporation of America, Inc, Arlington Heights, USA). Spirometry with bronchial reversibility testing (LungTest 1000, MES, Poland) according to the guidelines of the Polish Respiratory Society (Polskie Towarzystwo Chorób Płuc,

Table 1. Results of lung test in the studied groups

	Hyperinflation (+) Group A	Hyperinflation (−) Group B	p
FEV_1 (l)*	1.19± 0.42	1.88 ± 0.60	0.000
FEV_1 (%pred)*	48.30 ± 14.71	69.10 ± 15.65	0.000
Increase of FEV_1 (l)	0.16 ± 0.11	0.25 ± 0.18	0.0005
Increase of FEV_1 (%pred)	6.41 ± 4.13	9.15 ± 6.30	0.0018
FVC (l)*	2.66 ± 0.76	3.55 ± 0.88	0.0000
FVC (%w.n.)* FVC (%pred)	82.72 ± 15.17	99.58 ± 16.97	0.0000
Increase of FVC (l)	0.35 ± 0.26	0.32 ± 0.28	NS
Increase of FVC (%pred)	10.65 ± 7.38	9.17 ± 7.62	NS
TLC (l)*	7.1 ± 1.59	6.98 ± 1.36	NS
TLC (%w.n.)* TLC (%pred)	128.92 ± 21.4	113.29 ± 17.29	0.0000
RV (l)*	4.30 ± 1.09	3.29 ± 0.71	0.0000
RV (%w.n.)* RV (%pred)	195.54 ± 44.32	136.26 ± 23.45	0.0000
RV%TLC*	60.46 ± 6.27	47.44 ± 5.98	0.0000
RV%TLC (%w.n.)*	147.0 ± 15.0	114.0 ± 10.0	0.0000

*15 minutes after 400 μg salbutamol inhalation; FEV_1 — forced expiratory volume in 1 second); FVC — forced vital capacity; RV — residual volume; TLC — total lung capacity

PTChP) [9], bodyplethysmography (BodyBox, Medisoft, Sorinnes, Belgium and Vmax 6200 Autobox (SensorMedics, Yorba Linda, USA) were performed. Lung hyperinflation was defined as the residual volume/total lung capacity ratio (RV%TLC) > 48% and residual volume (RV) > 126% of predicted value [10]. The study was approved by the Bioethical Committee of the Warsaw Medical University (KB/207/2008).

Fasting venous blood samples were collected for the assessment of systemic inflammation: CRP, IL-6, IL-8, TNF-α, CCL16, adiponectin and resistin were evaluated (ELISA, R&D Systems Quantikinine, (Minneapolis, Minnesota United State).

Statistical analysis

Statistical analysis was performed with Statistica for Windows (StatSoft, Inc. version 10. www.statsoft.com). The values of variables with normal distribution were presented as mean ± standard deviation, the variables non-normal distribution were presented as median and interquartile range. Distribution normality was assessed using the Shapiro-Wilk test. Depending on the nature of distribution of the examined variable, comparisons between the groups were made using Student's t test or Wilcoxon test. To evaluate significance of correlation coefficient, Spearman correlation test was used. $P < 0.05$ was regarded statistically significant.

Results

Lung hyperinflation was found in 96 patients (49 women, 47 men). It was more frequent in the group of women — 49 (51%) vs. 47 (49%) $p < 0.001$. The age of patients from the two groups was comparable, the groups did not differ in BMI (27.5 ± 5.4 vs. 27.5 ± 4.8 kg/m^2). Both groups differed in the results of lung function tests (Table 1). Patients with hyperinflation had a lower pre and post- bronchodilator FEV_1. Pre-bronchodilator FVC was also lower, however there were no differences in post-bronchodilator FVC.

In patients with hyperinflation, lower fat free body mass and muscle mass were found, but a higher body fat and body water content measured in kilograms.

The analysis of body composition showed statistically significant differences between the study groups (Table 2).

The analysis of inflammatory markers showed statistically higher concentrations of serum IL-6, resistin and CRP in patients with lung hyperin-

Table 2. Body composition in patients with hyperinflations (group A) and without hyperinflations (group B)

	Hyperinflation (+) group A	Hyperinflation (−) Group B	p
Total body water (TBW. kg)	36.5 ± 8.0	40.9 ± 7.8	0.0006
Fat free mass (FFM. kg)	49.4 ± 10.2	55.9 ± 10.7	0.0003
Fat free mass	18.2 ± 2.5	19.6 ± 2.46	0.002
Fat mass (kg)	32.5 ± 7.9	28.8 ± 8.1	0.008
Index FFMI (kg/m^2)	12.3 ± 3.6	10.3 ± 3.6	0.002
Muscle mass (kg)	47.6 ± 10.6	52.4 ± 10.3	0.0005
Index MMI (kg/m^2)	17.5 ± 2.8	18.7 ± 2.4	0.001
Basal metabolic rate (kcal)	1472.6 ± 300.7	1646.0 ± 313.3	0.001

Table 3. Correlations between body mass compositions and lung test results

Parameters	R	p
FEV_1 (l)/FEV_1 (%w.n.) — FFMI	0.46/0.23	0.0000/0.0055
FEV_1 (lL)/FEV_1 (%w.n.) — TBW	0.56/0.20	0.0000/0.014
FEV_1 (l)/FEV_1 (%w.n.) — MMI	0.45/0.21	0.0000/0.011
FVC (l) – FFMI (kg/m^2)	0.41	0.0000
FVC (l) — TBW (kg)	0.61	0.0000
FVC (lL) – MMI (kg/m^2)	0.40	0.0001/0.0001
TLC (%w.n.) — FFMI (kg/m^2)	−0.42	0.0000
TLC (l)/TLC (%w.n.) — TBW (kg)	0.43/ −0.40	0.0000/0.0000
TLC (%w.n.) – MMI (kg/m^2)	−0.44	0.00000
RV (%w.n.) – FFMI (kg/m^2)	−0.40	0.000001
RV (%w.n.) – TBW (kg)	−0.32	0.0001
RV (%w.n.) – MMI (kg/m^2)	−0.41	0.00000
RV%TLC – FFMI (kg/m^2)	−0.34	0.000032
RV%TLC – TBW (kg)	−0.35	0.000025
RV%TLC – MMI (kg/m^2)	−0.33	0.000075

All abbreviations in the text

flation. The serum concentrations of the selected inflammatory markers in both study groups are presented in Table 4.

In the whole group, statistically significant correlations between level of adiponectin, resistin, TNF-α and CCL16 protein and spirometric and plethysmographic indices were shown. Correlations with the degree of hyperinflation measured with RV%TLC were shown only for adiponectin and CCL16 protein.

Discussion

The obtained results have shown differences in body composition of COPD patients, depending on the presence lung hyperinflation defined as an elevated RV/TLC ratio. Guera et al., while comparing patients with emphysema and chronic bronchitis, observed malnutrition defined as BMI < 18 kg/m^2 more frequently in patients with emphysema, compared to patients with chronic

Table 4. Serum concentrations of systemic inflammations markers

	Group A	Group B	P
IL6 (pg/ml)	6.4 ± 10.9	3.6 ± 4.2	0.004
IL8 (pg/ml)	12.9 ± 19.5	14.5 ± 35.0	NS
Adiponectin (mg/ml)	1.2 ± 8.7	1.1 ± 6.82.8	NS
Resistin (ng/ml)	9.3 ± 4.2	7.6 ± 2.4	0.0081
TNF-α (pg/ml)	2.4 ± 2.6	2.1 ± 0.8	NS
CCL16 (ng/ml)	29.1 ± 16.7	31.6 ± 15.3	NS
CRP (mg/ml)	4.1 ± 2.3	2.9 ± 2.21	0.003

All abbreviations in the text

Table 5. Correlations between lung test results and systemic inflammations markers

Adiponectin/FEV_1 (l)*	−0.3	< 0.0001
Adiponectin/FVC (l)*	−0.34	< 0.0001
Adiponectin/TLC (l)	−0.28	0.001
Adiponectin/RV%TLC*	0.24	0.004
Resistin/FEV_1 (%w.n.)*	−0.2	0.015
TNF-α/RV (l)*	0.26	0.002
CCL16/RV%TLC*	0.38	< 0.001

bronchitis and asthma, in whom BMI > 28 kg/m^2 was more frequent [11]. Kurosaki et al. showed that in patients with pulmonary emphysema diagnosed at chest CT, the severity of emphysematous lesions correlated with muscle and fat mass [12]. Furthermore, in COPD patients, a larger area of abdominal fat measured at CT was shown in comparison with the control group. This area increased with the severity of COPD, and correlated positively with the degree of dyspnea. In patients with emphysema, a negative correlation of the degree of emphysema with waist circumference, fat free body mass, body fat mass and subcutaneous fat area was shown [13]. We did not find differences in BMI between the groups. Patients with lung hyperinflation had a lower fat free body mass, muscle mass and body water and a higher proportional body fat content. The mean FEV_1% in the group was < 50% predicted and was statistically lower, compared to the group without hyperinflation, in addition, in the group with hyperinflation, improvement in FEV_1 after administration of salbutamol was smaller. The reversibility test was negative in both groups. In the study group, a negative correlation between the degree of hyperinflation and total body water and FFMI and MMI was shown, what confirms the presence of body composition disorders, particularly in patients with emphysema. The disorders may be the effect of lower physical activity [14], higher energy expenditure and systemic inflammation. The degree of hyperinflation and the values of FEV_1 are independent factors that influence mortality [15]. Patients with hyperinflation measured with IC/TLC ratio < 0.25, in the study by Casanova et al. had 3.15 times higher mortality risk than patients with IC/TLC > 0.25 [16]. What is the role of systemic inflammation in the process? Deterioration of functional parameters is related to increased inflammatory markers [3]. In the group with hyperinflation, patients with worse functional parameters had significantly higher serum levels of IL-6, resistin and CRP. The literature evaluates systemic inflammation in COPD in various aspects. Piehl-Aulin et al. showed an elevated level of high-sensitivity (hs)CRP in stable COPD patients, compared to the control group; in the same group, they observed an elevated concentration of IL-6 in patients in FEV_1 < 50% predicted, and IL-8 in patients with a severe stage of the disease. However, the authors did not show an elevated concentration of TNF-α, compared to the control group, or correlation of its level with the severity of the disease [17]. In another study, an increased level of TNF-α and IL-8 in COPD patients, compared to healthy smokers was not shown [18]. Whereas Pinto-Plata demonstrated that TNF-α and IL-6 levels increase with COPD severity of [19]. Engström et al. showed a negative correlation between concentration of CCL16 protein and the degree of hyperinflation measured with RV/TLC, whereas in patients with FEV_1%FVC < 0.7, a negative correlation between CRP and FEV_1, FVC, RV/TLC and DLCO was found [19]. Fat tissue is also the source of active substances that participate in systemic inflammation [20, 21].

Adiponectin, which is secreted by fat tissue, has an anti-inflammatory effect. Its level decreases in obese patients and increases with the degree of COPD progression [22]. In the study group, the level of adiponectin did not depend on the degree of hyperinflation. Another factor that is secreted by fat tissue is resistin [23]. Its main role is to maintain carbohydrate homeostasis. It was shown that resistin is related to obesity, type 2 diabetes, atherosclerosis and chronic inflammation [24]. Literature presents inconsistent data on the level of resistin in patients with obstructive diseases. Some authors have shown that the level of resistin increases with the severity of the disease [25], however, others have not found differences in its concentration between COPD patients and the control group [26]. In our study group, the serum resistin in patients with hyperinflation was statistically higher, furthermore, resistin correlated weakly but significantly with FEV_1 (% pred.), which indirectly proves its relation to systemic inflammation in COPD patients. It seems practical to assess body composition and systemic inflammation in COPD patients, particularly in those with predominant emphysema.

Conclusions

COPD patients with lung hyperinflation have had lower FFMI, TBW, MMI and more body fat.

In patients with lung hyperinflation, elevated levels of inflammatory markers was found, what may indicate a more advanced progression of the disease.

Body composition disorders and more active systemic inflammation in patients with lung hyperinflation may imply poor prognosis.

Conflict of interest

The authors declare no conflict of interest.

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