Association of Body-mass Index to Circumference of Body and Limbs, Inspiratory Capacity, and Inflammatory Biomarker in Emphysematous Patients

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Abstract

Although emphysema primarily affects the lungs, it also has systemic manifestations. Low body mass index (BMI) is a poor prognostic indicator in patients with emphysema. Low BMI, reduced quadriceps muscle mass and elevated inflammatory biomarker may present in emphysema. This study aims to investigate whether BMI is related to airflow limitation, exercise capacity and inflammatory biomarker. Twenty-eight patients with clinically stable emphysema were evaluated for BMI, circumference of chest, abdomen, quadriceps muscle and upper arm, and right upper arm muscle power, airway obstruction, inspiratory capacity (IC), distance of 6-min walking distance (6MWD), oxygen saturation, and serum inflammatory biomarkers [C-reactive protein (CRP), TNF-α and IL-6]. BMI was significantly associated with circumference of chest ($r = 0.716$, $p < 0.01$), abdomen($r = 0.783$, $p < 0.01$), quadriceps muscle ($r = 0.565$, $p < 0.01$) and upper arm ($r = 0.712$, $p < 0.01$), IC ($r = 0.451$, $p < 0.05$), muscle power of right upper arm ($r = 0.490$, $p < 0.01$) and oxygen saturation ($r = 0.380$, $p < 0.05$). However, the levels of CRP (1467 ± 202 μg/ml) and IL-6 (8.5 ± 4.2 pg/ml) in emphysematous patients ($n = 10$) with lower BMI (<21 kg/m^2) were significantly higher than those (CRP (911 ± 130 μg/ml, $p < 0.05$) and IL-6 (2.1 ± 0.5 pg/ml, $p < 0.05$)) of patients ($n = 18$) with higher BMI (>21 kg/m^2). BMI associated circumference of limbs, inspiratory capacity, and inflammatory biomarker in emphysematous patients. (J Intern Med Taiwan 2015; 26: 277-284)

Key Words: Body mass index (BMI), Emphysema, Inspiratory capacity, Circumference of body and limbs, Systemic inflammation

Introduction

Airflow limitation in emphysema involves airways (bronchitis), parenchyma (emphysema), or both and is responsible for exercise intolerance[1-3]. Emphysema can be considered a systemic disease

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since patients with emphysema may also suffer from weight loss and cachexia (which lead to muscle dysfunction, cardiovascular disease and osteoporosis)[4-8]. As weight loss is thought to be a major feature of emphysema[7], fat mass and skeletal muscle indexes are important prognostic indicator and are associated with a higher risk of death[9], as shown in previous studies. Weight loss also impair respiratory and peripheral muscle function and exercise capacity in emphysematous patients[6,10].

The mechanisms underlying weight loss and muscle wasting in emphysematous patients have not been well elucidated. However, hormonal changes associated with imbalances in protein degradation and replacement, and pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α), have been associated with weight loss, muscle wasting, and cachexia in emphysematous patients[11]. In addition, chronic pulmonary inflammation may lead to muscle wasting and reduced muscle regeneration through a TNF-α mediated mechanism in a murine model[12] (Langen et al., 2006). Furthermore, many reports have shown an association between increased inflammatory biomarker and reduced pulmonary function and disability in emphysematous patients[13-17].

Our aim was to determine if a relationship exists between reduction in body weight and elevated systemic inflammation in emphysema. We hypothesized that BMI is related to airflow limitation, reduced exercise capacity, and increased levels of inflammatory biomarker in emphysematous patients.

Materials and Methods

Subjects

From August 2007 to July 2010, patients with clinically stable emphysema some patients were refered from Taoyuan Saint Paul's Hospital. All patients completed study in Linkou Chang Gung Memorial Hospital were prospectively enrolled in this study. Diagnosis of emphysema according to the American Thoracic Society guidelines[3]. Emphysema was defined as an FEV1/FVC less than 0.70 with FEV1 less than 80% of predicted, consistent with Global Initiative for Chronic Obstructive Lung Disease stage 2 or higher, meanwhile, and radiologic images with chest high resolution computed tomography (HRCT) scan were compatible to emphysema.

This study was approved by Institutional Review Board of the institutes, and written informed consent from was obtained from all patients. The inclusion criteria were mild to moderate stable emphysema, FEV1 more than 30% of predicted value, FEV1/FVC < 70%, no exacerbations four weeks prior to the study, continuation of prescribed medication for emphysema, lack of enrollment in any physical exercise. The exclusion criteria were any history of heart disease, cor pulmonale, neurologic disorder, or cognitive disorder.

Assessment

Each examination included a variety of procedures, with blood sampling after an overnight fast (typically between 8:00 am and 9:00 am) and six minutes walking test (6MWT) performed according to our previous study[18]. Patients' age, gender, body weight and body mass index (BMI), parameter of 6MWT, pulmonary function, visual Borg scale dyspnea score, O_2 saturation and heart rate, and biochemical tests, at baseline, were all recorded in their medical charts.

The maximum circumferences (cm) of chest wall, abdomen, right thigh (quadriceps muscle) and right upper arm were measured when the patients took a deep inspiration maximum. Muscle power of right upper limbs was assessed by hand-held dynamometer (Hoggan Health Industry, West Jordon, USA). Biomarker including CRP, TNF-α and IL-6 were measured using an ELISA kit.

High Resolution Computed Tomography (HRCT)

Pulmonary emphysema was visually assessed by an expert chest radiologist unaware of the clinical and lung function data. The CT scans were performed on a GE SYTEC 3000 scanner (3 s, 160 mAs, and 120 kVp) without infusion of contrast medium. The patients held breath at full inspiration by using 1-mmcollimation (HRCT) scan. Hardcopy images were photographed using window settings appropriate for the lungs (level: -500 to -700 HU; width: 1,000 to 1,500 HU).

Measurement of 6MWT

In this study, patients who completed the 6MWD followed standard protocols for this test as methods in our previously published article[18]. Patients were instructed to walk back and forth at their own pace in a 35 m corridor. A physiotherapist supervised the test through the coure, telling the patient the remaining exercise time every 2 min. Dyspnea during the test was evaluated with the modified Borg dyspnea score. Pulmonary function test, inspiratory capacity, and dyspnea score, together with the walking distance were recorded before and after walking. Heart rate and oxygen saturation were monitored during the whole procedure.

Measurements of Pulmonary Function Tests

Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC ratio, inspiratory capacity (IC) and breathlessness (rated by Borg's scale dyspnea score) were measured before and immediately after the 6MWT.

Measurements of Muscle Strength

The elbow flexor muscle groups were assessed using a handheld dynamometer microFET2 (Hogan Health Industries, Inc, Draper, UT), which was the same as previously published article[19]. The isometric force of the elbow flexor was assessed with the elbow flexed 90 degrees. The strength of knee extensor muscle was measured with the subject seated with the leg fully extended. Strength was recorded as the peak force of three tests.

Statistical Analysis

All data were expressed as mean ± standard deviation or percentages (%). Since most continuous variables were skewed, nonparametric approaches were used in the study. Quantitative variables between two groups were compared using the Mann-Whitney test for continuous and ordinal variables. The relationship between BMI and other parameter (including FEV1, FVC, IC, biomarker, circumferences of chest wall, abdomen, right thigh (quadriceps muscle), and muscle power of upper limb) was assessed with the Spearman test. A p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS software (verion 10.0, SPSS, Chicago, IL) and Prism 4 for Windows (verion 4.03, Graphpad Software Inc., San Diego, CA).

Results

Twenty-eight patients with emphysema (26 males and 2 females; mean age: 71.4 year +/- 1.8 year) were included in this study. The baseline parameter and the results of the 6 minute walking test (6MWT) were shown in Table 1. These parameter included forced vital capacity (FVC) of 1.9 ± 0.1 liter; percentage of predicted values of forced vital capacity (FVC predicted value) of 59.0 ± 3.2%; forced expiratory volume in 1 second (FEV1) of 1.2 ± 0.1 L; percentage of predicted values of forced expiratory volume in 1 second (FEV1, % predicted) of 54.1 ± 4.8%; ratio of FEV1 to FVC (FEV1/FVC) of 60.8 ± 2.7%; inspiratory capacity (IC) of 0.4 ± 0.07 L; and walking distance of 236.1 ± 14.6 meter.

In Table 2, BMI was significantly associated with quadriceps muscle circumference ($r = 0.575$, $p = 0.0014$), chest circumference ($r = 0.716$, $p < 0.0001$), abdominal circumference ($r = 0.783$, $p < 0.0001$), upper arm circumference ($r = 0.712$, $p < 0.0001$),

and muscle power of right upper arm (r = 0.49, p = 0.0094), and oxygen saturation (r = 0.38, p <0.05).

No association was observed between BMI and FEV1 (r= 0.344, p = 0.074, Fig. 1) or between BMI and FVC (r = 0.255, p = 0.19, Fig. 1). However, the inspiratory capacity (IC) before exercise correlated with both BMI (r = 0.451, p = 0.016), and quadriceps muscle circumference (r = 0.45, p = 0.0163), as shown in Fig. 2. In addition, as shown in Fig. 3, the level of CRP (1467 ± 202 μg/ml) and IL-6 (8.5 ± 4.2 pg/ml) in emphysematous patients (n = 10) with lower BMI (<21 kg/m^2) was significantly higher compared to the CRP values (911 ± 130 μg/ml, p <0.05) and IL-6 (2.1 ± 0.5 pg/ml, p <0.05) in emphysematous patients (n = 18) with higher BMI (>21 kg/m^2).

Table 1. Patient Demographics, n=28

Age	71.4 ± 1.8
Gender, male/ female	26/2
BMI	20.8 ± 0.7
FVC predicted value, L	1.9 ± 0.1
FVC, % predicted	59.0 ± 3.2
FEV1 predicted value, L	1.2 ± 0.1
FEV1, % predicted	54.1 ± 4.8
FEV1/FVC, %	60.8 ± 2.7
IC, L	0.4 ± 0.07
O2 saturation, %	93.5 ± 0.9
Walking distance of 6MWT, M	236.1 ± 14.6
Cardiovascular diseases (With/Without)	6/22

BMI, body mass index; FVC, forced vital capacity; L, liter; FVC predicted value, predicted values of forced vital capacity; FVC, % predicted, percentage of predicted values of forced vital capacity; FEV1 predicted value, predicted values of forced expiratory volume in 1 second; FEV1, % predicted, percentage of predicted values of forced expiratory volume in 1 second; FEV1/FVC, ratio of FEV1 to FVC; IC, inspiratory capacity; 6MWT, six minutes walking test; M, meter.

Discussion

We found that emphysematous patients with lower BMI developed muscle dysfunction, impaired inspiratory capacity during exercise, and had higher inflammatory cytokines compared to those patients with normal BMI. In addition, the correlation between muscle wasting (as determined by chest wall, abdominal, and right thigh circumferences, and muscle power of upper limb) and BMI and the correlation between inflammatory cytokines (such as CRP, TNF-α, and IL-6) and BMI suggest that inflammation may be involved in the pathogenesis of weight loss in emphysema.

In our low-BMI patients, TNF-α plasma levels correlated with O_2 sat, suggesting interplay between hypoxia and inflammatory cytokines. Furthermore, TNF-α plasma levels and low O_2 sat may be responsible for the greater bone marrow involvement observed in these patients. Hypoxia and inflammation might also play an important role in trig-

Table 2. Correlation of BMI with chest and abdominal circumference, upper arm, thigh circumference and oxygen saturation

Variables correlated to BMI	N	R	P value
Chest circumference, cm	28	0.716	<0.0001
Abdominal circumference, cm	28	0.783	<0.0001
Right quadriceps muscle circumference, cm	28	0.575	<0.01
Upper arm circumference, cm	28	0.712	<0.0001
Inspiratory capacity, L	28	0.451	<0.05
Muscle power of right upper arm, lb/kg	28	0.49	<0.01
Oxygen saturation, %	28	0.38	<0.05

BMI, body mass index.

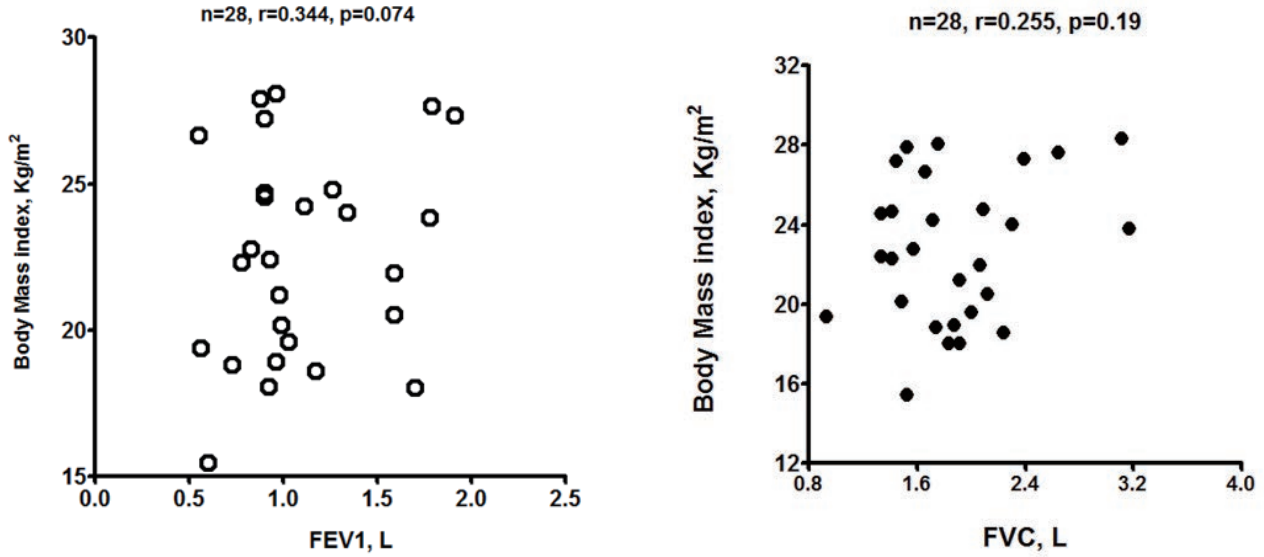

Figure 1. Body mass index does not correlate with FEV1 (r = 0.344, p = 0.074) or FVC (r = 0.255, p = 0.19).

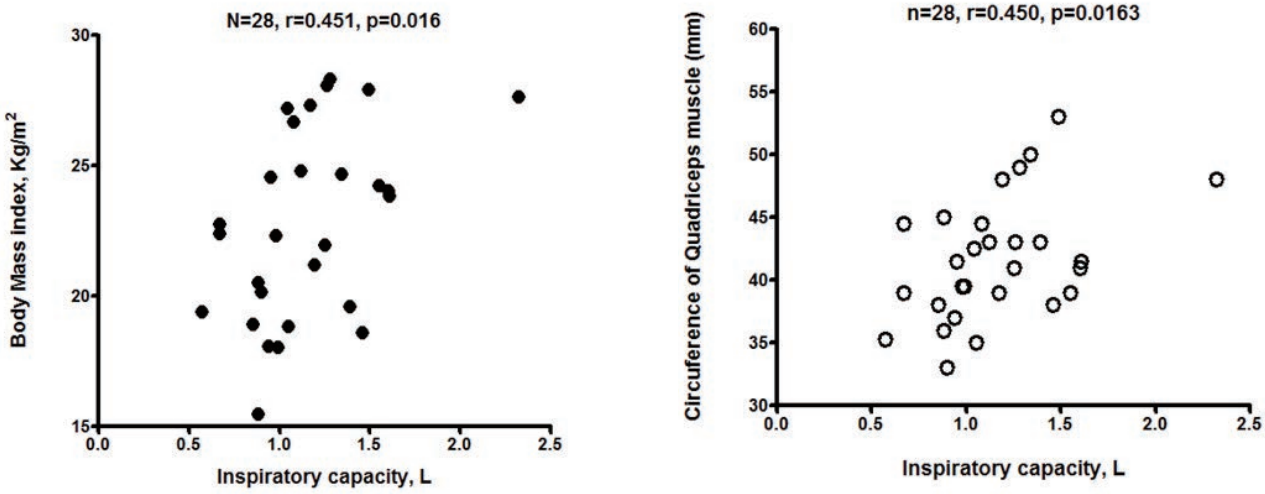

Figure 2. Inspiratory capacity (IC) before exercise correlates with BMI (r = 0.451, p = 0.016) and circumference of quadriceps muscle (r = 0.450, p = 0.0163).

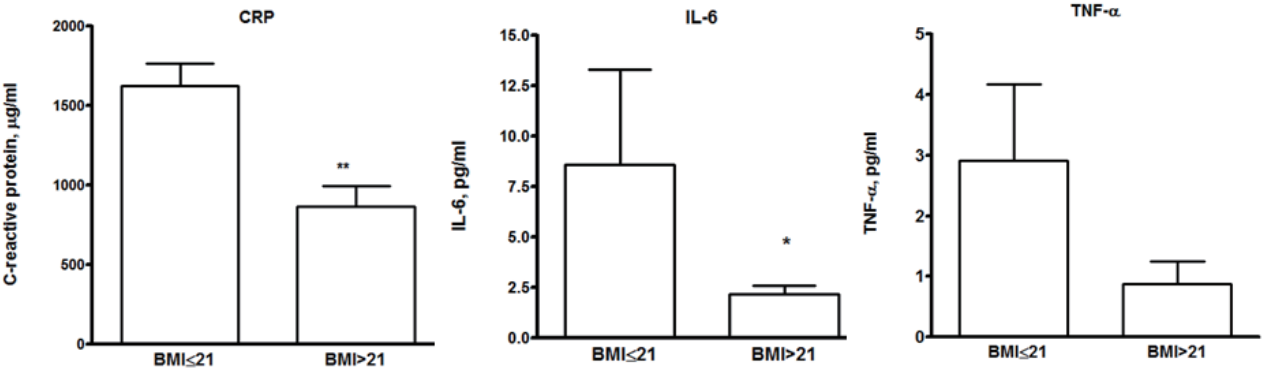

Figure 3. Emphysematous patients with lower body mass index (BMI) have increased serum levels of C-reactive protein (CRP) and interlukin-6 (IL-6) but not tumor necrosis factor - alfa (TNF-α), **p <0.01, *p <0.05.

gering the different bone marrow response seen in low versus normal BMI emphysematous patients, through different pathways, or interdependently.

In case-controlled studies, higher concentrations of IL-6, a cytokine that activates inflammatory cells, have been observed in exhaled breath condensate of emphysematous subjects, compared to control subjects[20-21]. Among participants in the seventh Framingham Heart Study, there was a consistent cross-sectional association between elevated IL-6 levels and lower levels of lung function.

The association between inflammation and muscle dysfunction in low body weight emphysematous patients has been previously reported[22]. Agusti et al. demonstrated a link between cytokine-related muscle apoptosis and weight loss in emphysematous patients via NF-kB. This factor upregulates the inducible form of the nitric oxide synthase by TNF-α, causing subsequent degradation of myosin heavy chains in skeletal muscle[23]. In addition, chronic pulmonary inflammation may lead to muscle wasting and reduced muscle regeneration through a TNF-α mediated mechanism in a murine model[12].

Additional reports have shown that systemic inflammation is associated with lower levels of pulmonary function and disability in emphysematous patients[13-17]. Oxygen-sensing and inflammation are already known to interact: TNF-αinduces nuclear accumulation and activity of HIF-1α [24-25], and more recently, hypoxia and TNF-α have been shown to act through a common HIF-1 pathway to increase the expression of TNF-α converting enzyme (TACE), leading to increased TNF-α shedding rates[26]. In addition, CRP may have direct immune-modulatory effect in the lung which had been previously associated with impaired lung function. In clinic-based samples, higher concentrations of CRP have been associated with the presence of emphysema and CRP concentrations appear to decline with inhaled corticosteroid treatment for stable COPD[27]. Higher levels of CRP have also been associated with lower levels of FEV1 in population studies[8,28].

Our study had several limitations. First, the numbers of this study were small. However, the study was conducted prospectively. To collect the measurement and data of these patients prospectively, the researches spend much time for it. Second, the co-morbidities such as cardiovascular diseases may interfere lung function. However, in our study, the lung function tests including FEV1 (1.19 + 0.1 vs. 1.21 + 0.1 L, p value, 0.78) and FVC (1.88 + 0.1 vs. 1.91 + 0.1 L, p value, 0.83) were not statistically significant between patients with and without cardiovascular disease (not list in results). Third, we observed a cross-sectional relationship between several circulating inflammatory biomarker and impaired lung function and BMI. A cross-sectional study may not definitively prove a causal link between the inflammatory cascades that incorporate these inflammatory marker and BMI in emphysema. Additionally, the relation between marker of inflammation and the tissue-level intrapulmonary processes that result in body weight loss and lower BMI in emphysema are not well understood. Whether the systemic inflammation is an epiphenomenon or contributes to the development of emphysema is unknown. Finally, we assessed circulating inflammatory marker, which may not adequately reflect local pulmonary tissue inflammatory concentrations.

Conclusion

In conclusion, BMI associated circumference of limbs, inspiratory capacity, and inflammatory biomarker in emphysematous patients.

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肺氣腫患者的身體質量指數和肢體周長、吸氣容量及發炎生物指標關聯性

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摘 要

雖然肺氣腫主要影響肺，它也有全身性的表現。較低的身體質量指數是肺氣腫患者預後不良的指標。低身體質量指數，低股四頭肌肌肉質量和高發炎生物指標可能存在於肺氣腫。本研究旨在探討身體質量指數與氣流受限，運動能力或發炎生物指標關聯性。將28例患者評估身體質量指數，身體及股四頭肌肌肉圍度和力量，氣道阻塞，吸氣容量，運動能力(6分鐘步行距離)，氧飽和度，血清炎症標記物(C反應蛋白，腫瘤壞死因子-α和細胞間素-6)和生活品質(聖喬治呼吸問卷)。身體質量指數與胸圍(R = 0.716，P <0.01), 腹圍(R = 0.783，P <0.01), 股四頭肌周長(R = 0.565，P <0.01)及上臂周長(R = 0.712，P <0.01)，吸氣容量(R = 0.451，P <0.05)，上臂肌力 (R = 0.490, p <0.01)及氧飽和度(R = 0.380，P <0.05)顯著有關。然而，C反應蛋白(1467±202微克/ml)和細胞間素-6 (8.5±4.2皮克/毫升)在低身體質量指數(<21公斤/平方米)的病患相較於高身體質量指數(>21公斤/平方米)的肺氣腫患者，具有較高的C反應蛋白(911±130 g/ml, p <0.05)和細胞間素-6 (2.1±0.5 pg/ml, p <0.05)。身體質量指數反映了肺氣腫患的肢體周長、吸氣容量及發炎生物指標關聯性。

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