Non-Hyperinflated Lungs in Patients with COPD and Type 2 Diabetes

Ryuya Edahiro, Shuhei Nishina, Nachi Ishikawa, Yoshihiko Utsu, Seigo Ishii, Atsushi Kogetsu, Kenta Okuro, Mayumi Suzuki, Masahiro Koseto, Satoru Sumitani, Bunzo Sato, Soji Kasayama, and Isao Tachibana*

Department of Medicine, Nissay Hospital, Nippon Life Saiseikai Public Interest Incorporated Foundation, Nishi-ku, Osaka, Japan

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*Corresponding author: Isao Tachibana, Department of Medicine, Nissay Hospital, Nippon Life Saiseikai Public Interest Incorporated Foundation, Nishi-ku, Osaka, Japan, E-mail: tachibana.isao@k-nissay-hp.or.jp

Abstract

Background: Emphysematous, hyperinflated lungs are the hallmark of chronic obstructive pulmonary disease (COPD). COPD is recently recognized to occur along with systemic comorbidities, such as cardiovascular disease, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes. We investigated whether radiographic lung hyperinflation is affected by comorbidities in patients with COPD.

Methods: We analyzed chest X-rays of 91 patients with COPD out of 608 patients who underwent spirometry between April 2013 and December 2014. The lung was defined as hyperinflated when the posterior right 11th rib was above the diaphragm in the midclavicular line. The association between hyperinflated lungs and comorbidities was evaluated using univariate and stratified exact logistic regression models.

Results: When compared with patients with hyperinflated lungs, a higher proportion of patients with non-hyperinflated lungs had type 2 diabetes (3.7% vs. 31.3%, P = 0.0052), but not dyslipidemia, hypertension, or coronary artery disease. The association between non-hyperinflated lungs and diabetes remained after stratification with potential confounding factors.

Conclusion: Patients with COPD and diabetes may not show hyperinflated lungs on chest X-ray, suggesting that COPD could be under diagnosed in smoker patients with diabetes.

Keywords: Type 2 Diabetes; Chronic Inflammation; Chest X-ray; Chronic Obstructive Pulmonary Disease

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which varies between patients. These structural changes are mostly caused by cigarette smoking-induced chronic inflammation in the lung [1]. Emphysematous change and airflow limitation lead to air trapping and result in progressive lung hyperinflation [1,2].

In 2020, COPD is projected to rank fifth worldwide in terms of burden of disease and third in terms of mortality, highlighting the importance of early diagnosis and therapeutic intervention [1]. COPD is diagnosed when spirometry shows airflow limitation based on the global initiative for chronic obstructive lung disease criteria (GOLD). Clinical manifestations vary widely among patients and, even among patients with severe airflow limitation, a substantial proportion does not complain of symptoms, report exacerbation, or show impaired exercise tolerance, thus making early diagnosis difficult [3]. A chest X-ray is not necessary to diagnose COPD, but it can be suggestive in clinical practice, particularly in patients who have signs of emphysema, such as lung hyperinflation, a flattened diaphragm, hyperlucent lung fields, and peripheral tapering of the vascular markings [4,5].

COPD is increasingly recognized to occur along with systemic comorbidities, such as cardiovascular disease, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes [6,7]. These comorbidities are also caused by chronic inflammation, and often associated with obesity and metabolic syndrome [8,9], which influence clinical phenotypes and courses of patients [6]. We hypothesized that patients with such comorbidities may not display the typical signs suggestive of COPD on chest X-ray. We investigated the association between hyperinflated lungs and the presence of comorbidities.

Methods

Subjects

Out of 608 patients who underwent spirometry from April 2013 to December 2014 in the Department of Medicine, Nissay Hospital, 184 showed airflow limitation with a FEV1/FVC ratio < 0.70, the GOLD criteria for COPD [1]. Subjects were excluded if they had bacterial pneumonia, active or healed tuberculosis, or interstitial pneumonia on chest X-ray. Subjects were also excluded if they had a history of lung resection. Never-smokers were also excluded, because more than 95% of COPD cases in Japan are smoking-related [10]. Subjects diagnosed with bronchial asthma by pulmonary physicians were excluded, but subjects suspected of having asthma-COPD overlap syndrome [11] were included. Accordingly, 91 subjects diagnosed with COPD were further analyzed. Comorbidities including type 2 diabetes, dyslipidemia, hypertension, and coronary artery disease were based on self-report or medication history. The institutional review board for human studies of Nissay Hospital approved this study (No. 27-11-3). The characteristics of patients with COPD are shown in Table 1.

Chest X-rays

Standard posteroanterior chest X-rays were obtained with patients in an erect position as part of routine clinical care. A lung was defined as hyperinflated when the posterior right 11th rib was above the diaphragm at full inspiration in the midclavicular line on the chest X-ray. Two respiratory physicians, who were not informed of any information of study subjects, inspected images, and there were no mismatch in their decisions.

Statistical Analysis

Continuous variables were summarized as median and interquartile ranges, and compared using Wilcoxon rank-sum test for two-group comparisons. Categorical variables were presented as numbers and percentages, and compared using Fisher’s exact test. A univariate exact logistic regression model was used to evaluate the association between non-hyperinflated lungs and type 2 diabetes. A stratified exact logistic regression model was also used to reduce the confounding effects of background variables, including age, gender, height, weight, BMI, current smoking status, lifetime pack-year of smoking, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC, spirometric...
As shown in Table 1, median age of patients with COPD (n = 91) was 71 years, and 71 patients (78.0%) were men. The median FEV₁/FVC % was 60.8%. Regarding systemic comorbidities, 21 patients (23.1%) had type 2 diabetes, 31 patients (34.1%) had dyslipidemia, 40 patients (44.0%) had hypertension, and nine patients (9.9%) had coronary artery disease. Of 91 patients with COPD, 27 patients (29.7%) had hyperinflated lungs on chest X-ray, based on our criterion (See Methods). We also attempted to use another criterion, which defines the lung as hyperinflated, when the level of the right diaphragm dome was below the anterior end of the 7th rib [16,17]. However, referencing diaphragm position to the anterior ribs was difficult, as previously described [14], and there were a number of mismatches between the two physicians’ decisions with this criterion (data not shown). Compared with patients with hyperinflated lungs, those with non-hyperinflated lungs had higher BMI (p < 0.0001), and had better lung function based on FEV₁/FVC, PEFR/FVC, and peak expiratory flow rate (PEFR) values, corresponding to earlier GOLD stages. Notably, a higher proportion of patients with non-hyperinflated lungs had type 2 diabetes (31.3% vs. 3.7%, p = 0.0052), but not other comorbidities (Table 1). Of 21 patients with COPD, diabetes, only one patient (4.8%) had a hyperinflated lung, whereas of 70 patients with COPD without diabetes, 26 patients (37.1%) had hyperinflated lungs, as their characteristics were compared (Supplementary Table 1). The association between non-hyperinflated lungs and type 2 diabetes remained after stratification for each potential confounding factor (age, gender, height, weight, BMI, current smoking status, pack-year of smoking, lung functions, GOLD classification, and the other comorbidities) in the exact logistic regression analysis (Figure 1).

A representative case of a 72-year-old man with COPD, type 2 diabetes, and hypertension is shown in Figure 2. Based on spirometry, he had GOLD stage III disease. He was not obese (BMI = 21.2 kg/m²). Although emphysema was observed on chest computed tomography (CT) scan, his lungs were not hyperinflated on chest X-ray.

**Discussion**

As far as we know, there have been no studies investigating whether the chest X-ray appearance of COPD may be affected by systemic comorbidities. Our results suggested that the lungs do not appear hyperinflated on chest X-ray in COPD patients with type 2 diabetes, as opposed to those with dyslipidemia, hypertension, and coronary artery disease. The size of such populations may not be small, as approximately 10% of patients with diabetes also have COPD [15].

There could be several possible reasons for the association between non-hyperinflated lungs on chest X-ray and type 2 diabetes. First, patients with diabetes had slightly higher BMI than those without diabetes, although not statistically significant (Supplementary Table 1). It was previously shown that obese COPD patients have lower lung volume due to reduced functional residual capacity [16], and...
Figure 2: A representative case of a 72-year-old man with COPD, type 2 diabetes, and hypertension. The patient complained of shortness of breath. He was a current smoker with a 30 pack-year smoking history and not obese (BMI = 21.2 kg/m²). FEV1/FVC % and FEV1 % predicted were 46.6% and 44.2% (GOLD stage III), respectively, in a pulmonary function test. The HbA1c level was 7.1%. His lungs were not hyperinflated on chest X-ray (A), although pulmonary emphysema was observed on chest CT (B).

### Figure 1: Association between non-hyperinflated lungs and type 2 diabetes in patients with COPD. A univariate exact logistic regression model was used to evaluate the association between type 2 diabetes and non-hyperinflated lungs (top). Stratified exact logistic regression analysis was also performed to reduce the confounding effects of background factors, including age, gender, height, weight, BMI, current smoking status, lifetime pack-year of smoking, FEV1, FVC, FEV1/FVC, spirometric GOLD classification, dyslipidemia, hypertension, coronary artery disease, and asthma-COPD overlap syndrome. ORs for having hyperinflated lungs in COPD patients with diabetes were based on comparisons to those without diabetes.

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratification factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.09 (0.002–0.60)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Male</td>
<td>0.05 (0.001–0.42)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Height</td>
<td>0.09 (0.002–0.65)</td>
<td>0.0078</td>
</tr>
<tr>
<td>Weight</td>
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<td>0.0024</td>
</tr>
<tr>
<td>BMI</td>
<td>0.08 (0.002–0.63)</td>
<td>0.0087</td>
</tr>
<tr>
<td>Current smoker</td>
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<td>0.0214</td>
</tr>
<tr>
<td>Pack year of smoking</td>
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<td>0.0050</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.13 (0.003–0.99)</td>
<td>0.0474</td>
</tr>
<tr>
<td>FVC</td>
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<tr>
<td>FEV1/FVC</td>
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<td>0.0071</td>
</tr>
<tr>
<td>GOLD stage</td>
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<td>0.0060</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.11 (0.002–0.80)</td>
<td>0.0203</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>0.0061</td>
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<tr>
<td>Coronary artery disease</td>
<td>0.09 (0.002–0.61)</td>
<td>0.0053</td>
</tr>
<tr>
<td>Asthma-COPD overlap</td>
<td>0.08 (0.002–0.58)</td>
<td>0.0043</td>
</tr>
<tr>
<td></td>
<td>0.09 (0.002–0.61)</td>
<td>0.0054</td>
</tr>
</tbody>
</table>
in fact, patients with non-hyperinflated lungs had higher BMI than those with hyperinflated lungs (Table 1). However, the association between non-hyperinflated lungs and diabetes remained significant after stratification with BMI in the exact logistic regression analysis (Figure 1), suggesting that the non-hyperinflation was not simply due to obesity. Second, COPD in patients with diabetes may be less severe than in those without diabetes. Indeed, patients with diabetes had significantly better FEV1/FVC ratios (P = 0.0458) (Supplementary Table 1), and patients with non-hyperinflated lungs did as well (Table 1). However, the association between non-hyperinflated lungs and diabetes remained significant after stratification with lung functions and GOLD classification (Figure 1), again suggesting that the non-hyperinflation was not simply due to lower COPD severity. Third, airway disease, rather than emphysematous changes, may be more predominant in COPD patients with diabetes. It was suggested that inflammation in airway disease may be different from that in parenchymal emphysema in COPD patients [17]. Previous studies have reported emphysema is less common in COPD patients with diabetes. Based on quantitative CT analysis, Han et al. reported that type 2 diabetes was more prevalent in airway disease-predominant COPD, whereas osteoporosis was more prevalent in emphysema-dominant COPD [18]. Hersh et al. showed that non-emphysematous COPD on chest CT was associated with an increased risk with type 2 diabetes [19]. In diabetes, small, or possibly larger, airways could be preferentially affected by unique biological processes, contributing to non-emphysematous phenotypes. Fourth, non-hyperinflated lungs on chest X-ray may not necessarily reflect the degree of emphysema. Indeed, the representative case had pulmonary emphysema on chest CT, despite having no hyperinflation on chest X-ray (Figure 2). Diabetic phrenic neuropathy, which leads to respiratory weakness or failure [20–23], may reduce muscle tone and prevent the expansion of the diaphragm. Finally, disrupted glycemic control leads to non enzymatic glycosylation of lung collagen and elastin via advanced glycation end products (AGEs), resulting in reduced elasticity of the lung. These changes might render the diabetic lung more restrictive, thus preventing its hyperinflation [24,25].

Several limitations should be mentioned in this study. First, lung hyperinflation was simply based on chest X-ray and considered as a radiographic feature of COPD. There are other findings characteristic of COPD, including a flattened diaphragm, bathyocardia, hyperlucent lung fields, and rapid tapering of the vascular markings [4,5,26]. Parameters to assess these findings have also been proposed [13,14], but we speculate that lung hyperinflation is the most common radiographic clue of COPD in clinical practice. Second, we were not able to study the correlation between the extent of emphysema on CT and hyperinflated lungs on chest X-ray. Third, not all subjects were diagnosed with COPD based on the post-bronchodilator FEV1/FVC ratio. Although patients with physician-diagnosed bronchial asthma were excluded, those with undiagnosed asthma might have been included in the study population. Fourth, because this is a small cross-sectional study, larger studies and longitudinal data were necessary to confirm the association and to discuss the causal link.

Conclusions

This study has indicated that COPD patients with type 2 diabetes may have a propensity to have non-hyperinflated lungs on chest X-ray, suggesting that COPD could be overlooked in smokers with diabetes. Routine spirometry would help to detect COPD at an earlier stage in this population.

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References


*Corresponding author: Isao Tachibana, Department of Medicine, Nissay Hospital, Nippon Life Saiseikai Public Interest Incorporated Foundation, Nishi-ku, Osaka, Japan, E-mail: tachibana.isao@k.nissay-hp.or.jp

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