CT Assessment of Lobar Heterogeneity and Fissure Integrity in Pulmonary Emphysema for Bronchoscopic Lung Volume Reduction with Valve

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Abstract

Background: Recently, advances in bronchoscopic techniques such as bronchial valves have been increasing in value for Chronic Obstructive Pulmonary Disease (COPD). Bronchial valve therapy has been proven to be useful for patients with lobar heterogeneous emphysema and complete fissure. In this study, we measured emphysema scores and fissure integrity in patients with emphysema, then classified these based on computed tomography image patterns to examine which patients were candidates for bronchial valve therapy.

Methods: Between February 2013 and May 2014, we studied 40 consecutive patients with CT-detected emphysema. Quantitative CT imaging analysis was performed using software. Emphysema scores per lobe were converted to the Likert scale, where a score of 1 equals 1 to 25%, 2 (26 to 50%), 3 (51 to 75%), and 4 (76 to 100%). Lobar heterogeneity of more than or equal to a 2-unit difference was needed between the adjacent lobes. The heterogeneous group was divided into complete and incomplete fissure groups. Fissure integrity scores of \( \geq 80\% \) and < 80% were defined as complete and incomplete fissure integrity, respectively.

Results: Forty patients were classified into either a heterogeneous group (5 patients), or a homogeneous group (35 patients). The heterogeneous group was then divided into a complete fissure group (2 patients) or incomplete fissure group (3 patients). In the homogeneous group, 14 patients were classified into the complete fissure group and 21 patients to the incomplete fissure group. This study revealed that, of the 40 patients who were indicated, only 2 patients met the criteria of heterogeneous and complete fissure for bronchial valve therapy.

Conclusion: We attempted to select candidates for bronchoscopic lung volume reduction with valve using VIDA Apollo software. However, we could not recruit a sufficient number of outpatients with CT-detected emphysema.

Key words

emphysema, quantitative, emphysema distribution, lobar heterogeneity, fissure integrity

Introduction

According to WHO estimates, 65 million people have moderate to severe chronic obstructive pulmonary disease (COPD). More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. In 2002, COPD was the fifth leading cause of death. Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. Estimates show that by 2030, COPD will have become...
the third leading cause of death worldwide\textsuperscript{11}. In addition, the PLATINO and BOLD studies have reported that the prevalence of COPD is about 10\% worldwide\textsuperscript{22,23}. In 2010, the number of deaths from COPD in Japan was 16,293, making COPD the ninth leading cause of death, and the number of deaths is increasing\textsuperscript{7}. A large-scale epidemiological study (Nippon COPD epidemiology study [NICE]) estimated the prevalence of COPD in Japanese patients older than 40 years at 8.6\%, and the number of patients at 5.3 million\textsuperscript{9}. CT is reportedly effective in detecting COPD and lung cancer, and a meta-analysis of 7,368 patients reported that 2,809 and 870 had CT evidence of emphysema and lung cancer, respectively, and that CT-detected emphysema was an independent risk factor for lung cancer\textsuperscript{6}.

COPD is a type of obstructive lung disease in which chronic, incompletely reversible poor airflow (airflow limitation) and the inability to breathe out fully (air trapping) occur\textsuperscript{7}. The poor airflow is the result of a breakdown of lung tissue (known as emphysema) and small airway disease (known as obstructive bronchiolitis).

Today, advances in bronchoscopic techniques such as bronchial valves have been increasing the value of CT quantitative analysis for COPD patients. Apollo software (VIDA Diagnostics, Inc.) is a quantitative lung imaging software which uses algorithmic workflow and automation features applicable to high-volume, repeatable parenchymal, airway, and fissure integrity analysis\textsuperscript{8–10}.

In the Endobronchial Valve for Emphysema Palliation Trial (VENT study), unilateral lobar treatment with bronchial valves resulted in modest improvements in lung function, exercise tolerance, and symptoms in patients with advanced heterogeneous emphysema\textsuperscript{11}. However, the presence of collateral ventilation (CV) could undermine the effectiveness of valve treatment. According to Gompelmann’s report, when evaluating patients for the likelihood of successful bronchial valve therapy, the Chartis system CV assessment and high-resolution computerized tomography (HRCT) fissure analysis appear to have comparable accuracy\textsuperscript{12}. Shah et al. proposed an algorithm for bronchoscopic lung volume reduction (BLVR) in patients with severe emphysema based on CT image analysis and stated that determination of the emphysema phenotype from the CT scan was important, because patients with predominantly paraseptal emphysema or with small airway disease were unlikely to respond. Furthermore, they stated that those with lobar heterogeneous emphysema and complete interlobar fissure might be considered for bronchial valve therapy\textsuperscript{13}. According to Mineshita et al., after CT review and once the fissure of at least one of both lungs is near complete (> 80\%), they functionally assess collateral flow using the Chartis system. Patients who have no collateral flow receive a bronchial valve\textsuperscript{14}.

Bronchial valve therapy has not yet been done in Japan, but it will be started soon. St. Marianna University School of Medicine and Gifu Prefecture General Medical Center are research institutions that will perform this therapy. This study is a pilot study to select patients for bronchial valve therapy using CT. In this study, using image analysis software, we evaluated the emphysema phenotype and measured the emphysema score and fissure integrity in patients with CT-detected emphysema, then classified these based on the image patterns to examine what proportion of patients with CT-detected emphysema were indicated for bronchial valve therapy according to CT image criteria.

Materials and Methods

Subjects

From February 2013 to May 2014, we studied 40 consecutive patients with CT-detected emphysema (4 women and 36 men, mean age 74±8 years). Inclusion criteria for this study included the following: (1) patients with emphysema confirmed by CT, (2) patients currently with or without treatment for emphysema; (3) 20 years of age or older with obtained consent; and (4) before study inclusion, all patients received a full explanation of the study, orally and in writing. Patients then gave written informed consent after obtaining a thorough understanding of the study. Exclusion criteria included the following: (1) patients with other major pulmonary disease such as interstitial pneumonia, lung cancer, respiratory tract infection; (2) patients unable to hold their breath sufficiently; and (3) patients judged to be inappropriate by physicians. All patients provided written informed consent, and the study was approved by the institutional review board at St. Marianna University School of Medicine and Gifu Prefectural General Medical Center.

Clinical and Physiologic Evaluation

Data on age, sex, body mass index (BMI), smoking history, modified medical research council (MMRC), COPD assessment test (CAT), St. George’s
CT image analysis of emphysema.

Respiratory questionnaire for COPD patients (SGRQ-C), exacerbation history, and receiving continuous oxygen were collected by patient interview using standardized instruments. Health status was assessed using CAT and the SGRQ-C. Dyspnea was assessed using MMRC. Patients underwent postbronchodilator spirometry, diffuse capacity of the lung for carbon monoxide (DLco), and 6-minute walk test (6MWT). The protocol used for 6MWT had been described in detail elsewhere\(^\text{15}\).

**CT and Quantitative Analysis**

All subjects were scanned with 64-detector CT (Aquilion-64; Toshiba Medical Systems, Tochigi, Japan) at full inspiration and full expiration (end-expiration), without receiving contrast medium. Every patient was carefully instructed on how to breathe before the study. Tube voltage was 120 kV, and tube current varied depending on the subject’s BMI (100 to 190 mA). CT images were reconstructed with 1.0 mm slice thickness at 0.5 mm intervals, using a normal mode reconstruction algorithm (kernel, FC 01).

Emphysema phenotype was visually assessed by three radiologists.

Quantitative image analysis was performed using Apollo software (VIDA Diagnostics Pulmonary Workstation Plus Software, Iowa City, Iowa, USA). The emphysema score was defined as % lung voxels less than or equal to −910 Hounsfield units (HU) on inspiratory CT. The emphysema score per lobe was converted to a Likert scale, with a score of 1 = 1 to 25%, 2 = 26 to 50%, 3 = 51 to 75%, and 4 = 76 to 100%. Lobar homogeneous emphysema was defined as fewer than 2-unit differences between adjacent lobes\(^\text{16}\). And lobar heterogeneous emphysema was defined as more than or equal to 2-unit differences between adjacent lobes\(^\text{11}\). Fissure integrity was assessed using VIDA software. This system is more accurate than simply visually determining the integrity of the fissure. Fissure integrity scores of ≥80% and <80% were defined as complete and incomplete fissure integrity, respectively\(^\text{14}\).

First, CT emphysema was classified into a heterogeneous emphysema group and a homogeneous emphysema group by emphysema scores. Second, the heterogeneous emphysema group and the homogeneous emphysema group were classified into a complete fissure group and an incomplete fissure group by fissure integrity scores.

**Results**

The patients’ characteristics are listed in **Table 1**.

<table>
<thead>
<tr>
<th>Patient characteristics (n=40)</th>
<th>Mean ±SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-years</td>
<td>74.1±8.4</td>
</tr>
<tr>
<td>Male - no. (%)</td>
<td>36 (90%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.6±4.4</td>
</tr>
<tr>
<td>Smoking history (never / ex / current)</td>
<td>0/27/13</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>55.8±28.6</td>
</tr>
<tr>
<td>Oxygen therapy - no. (%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>MMRC</td>
<td>1.5±1.2</td>
</tr>
<tr>
<td>CAT</td>
<td>15.5±7.9</td>
</tr>
<tr>
<td>SGRQ-C</td>
<td>34.2±19.5</td>
</tr>
<tr>
<td>COPD exacerbations (per year)</td>
<td>0.2±0.4</td>
</tr>
<tr>
<td>FEV1 % of predicted</td>
<td>70.8±22.5</td>
</tr>
<tr>
<td>FEV1 / FVC</td>
<td>52.5±14.0</td>
</tr>
<tr>
<td>DLco % of predicted</td>
<td>66.3±26.2</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>400.7±118.2</td>
</tr>
<tr>
<td>Healthy Smokers / GOLD(I/II/III/IV)</td>
<td>5/10/19/2/4</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or n (%), unless otherwise stated. MMRC: Modified Medical Research Council; CAT: COPD Assessment Test; the SGRQ-C: St. George’s Respiratory Questionnaire for COPD Patients; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLco: diffuse capacity of the lung for carbon monoxide; 6MWT: Six-minute walking test.
According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging\(^\text{17}\), 40 patients were classified as follows: healthy smokers = 5; GOLD stage I = 10 patients; stage II = 19 patients; stage III = 2 patients; and stage IV = 4 patients (mean forced expiratory volume [FEV] in 1 second of predicted, 71 ± 23%; FEV 1 range, 31 to 134%).

No large emphysema bulla and bronchiectasis were detected. For emphysema type, thirty-nine patients had centrilobular emphysema, and one patient had paraseptal emphysema.

An example of the quantitative analysis and qualitative assessment of emphysema is shown in Figure 1. First, the emphysema score per lobe was converted to a Likert scale; we classified patients into a heterogeneous group and a homogeneous group using 2 unit differences between adjacent lobes (Fig. 1). Second, the heterogeneous group and homogeneous group were divided into a complete and an incomplete fissure group by fissure integrity scores of 80% (Fig. 2). Finally, 40 patients were classified into a heterogeneous group of 5 patients, and a homogeneous group of 35 patients. The heterogeneous group was then further classified into a complete fissure

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**Figure 1.** Lobar homogeneous and heterogeneous emphysema patients with low attenuation cluster analysis.

The colored regions represent connected regions of the lung voxels below -910 HU. Each color represents a different lobe. The patient on the left belongs to the homogeneous emphysema group whose computed tomography (CT) scores have fewer than 2-unit differences between adjacent lobes. The patient on the right belongs to the heterogeneous emphysema group whose CT scores have more than or equal to 2-unit differences between adjacent lobes. In the patient on the right, the emphysema score of 63.8% for the left upper lobe is converted to a CT score of 3 on the Likert scale, and the emphysema score of 24.0% of the left lower lobe is converted to a CT score of 1.

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**Figure 2.** Complete and incomplete fissure integrity analysis.

Blue represents complete and green represents incomplete fissures. Sagittal views on computed tomography show a clear major fissure (white arrow) and a clear minor fissure (white arrow) in the left patient, and a clear major fissure (white arrow) and an unclear minor fissure (white arrow) in the right patient.
Discussion

In recent years, BLVR with valve has emerged as a new therapeutic option for severe emphysema. As we consider this therapy, it is also important to consider emphysema phenotype, heterogeneity, and fissure integrity from CT scans. In particular, patients with heterogeneous emphysema and complete fissure were candidates for bronchial valve therapy according to CT images. Venuta et al. reported on the long-term follow-up after BLVR with valve in patients with emphysema. They reported that survival rates at 1, 3, and 5 years were 81.6%, 47.4%, and 22.4%, respectively. They also noted an increase in mortality during the follow-up period in patients with nonvisible fissures at HRCT.

In this study, we focused on emphysema phenotype, heterogeneity, and fissure integrity. The highest frequency of emphysema phenotype was centrilobular pattern, and the homogeneous group was larger in number than the heterogeneous group. There were two patients with heterogeneous emphysema and complete fissure, and they were indicated for bronchial valve therapy according to CT images.

Gietema et al. reported that the highest frequency of emphysema phenotype was centrilobular pattern, and the highest frequency of emphysema distribution was the upper lobe in the visual score assigned by the radiologist. They also reported that the percentage of low attenuation area (%LAA) and visual scores of emphysema severity correlated well and that computer analysis of low attenuation cluster size helped quantitative algorithms discriminate low attenuation areas from gas trapping, image noise, and emphysema. Stavngaard et al. introduced a CT-based objective model for describing the distribution of different types of emphysema. Their methods were as follows: The relative area of emphysema in each CT slice was plotted against table position, and the cranio-caudal distribution was calculated as the slope of the regression line. They reported that the majority of patients with smoking-related emphysema had a homogeneous distribution and lower lobe predominance, although not as noticeable as in a 1-antitrypsin deficiency. In this study, the majority of patients with CT-detected emphysema had centrilobular pattern and homogeneous emphysema. However, there were no cases with emphysema of lower lobe predominance in the heterogeneous group.

Fissure integrity is important in considering the
bronchial valve treatment. Jian Tao et al. reported that there was no significant difference in fissure integrity for patients with different levels of disease severity, suggesting that the development of COPD does not change the completeness of pulmonary fissures, and that incomplete fissures alone may not contribute to the collateral ventilation\cite{20}. It can be said that COPD has not only a single pathology, but also a variety of pathological conditions.

To our knowledge, this is the first study that describes the classification by lobar heterogeneity and fissure integrity using Apollo software in Japan. The number of patients in the heterogeneous group in this study was too small to clarify the adaptation of bronchial valve therapy. Some severe COPD patients did not agree to this study because of dyspnea. Therefore, further analysis of a heterogeneous patient group is needed.

Since bronchial valve therapy is not performed in Japan, there is no data indicating the validity of this study. If this therapy is started, it will be necessary to evaluate the method of patient selection.

In this study, fissure integrity was evaluated using VIDA Apollo software since visual evaluation of fissure may not be reliable\cite{21}. VIDA Apollo software is a semi-automated software that evaluates the integrity of the fissure on a thin slice CT scan. This software may be more accurate than attempting to visually determine the integrity of the fissure\cite{13}. The assessment of fissure integrity has been developed, but its widespread use poses a problem in that data requires specialist analysis. Furthermore, the completeness of the fissure as determined by the software and its accuracy in predicting volume reduction has not been prospectively validated. Regarding its accuracy and relationship with collateral airflow, a comparative study with the Chartis system is necessary. Herth et al. noted that the Chartis system was a safe method to predict lung volume reduction, with accuracy of 75%-22).

COPD is a diverse disease. When detailed analysis of CT images becomes possible, in order to consider appropriate intervention, it is necessary to perform prospective analysis of emphysema, heterogeneity, and fissure integrity, thereby elucidating the pathogenesis and progression of emphysema. In addition, since various methods for BLVR are currently available, it is necessary to establish a treatment algorithm for BLVR based on clinical and CT findings. Furthermore, possible factors for the difference in the pathogenesis of emphysema among Japanese, Europeans, and Americans include external factors (such as air pollution) and internal factors (such as genetic predisposition). For example, 1-antitrypsin deficiency, as a genetic predisposition, is well known in Europe and the United States, but is extremely rare in Japan\cite{23}. Therefore, a treatment algorithm for BLVR in Japanese patients may be necessary.

**Financial Disclosure and Conflicts of Interest**

None of the authors have conflicts of interest associated with this study.

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