Phenotype of Chronic Obstructive Pulmonary Disease Based on Computed Tomography-Defined Underlying Pathology

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Running title: Phenotype of COPD based on CT-defined underlying pathology
Abstract

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease and not all patients respond to available drugs. Identifying respondents to therapy is critical to delivering the most appropriate treatment and avoiding unnecessary medication. Recognition of an individual patient’s dominant characteristics by phenotype is a useful tool to better understand their disease and tailor treatment accordingly. To look for a suitable phenotype, it is important to understand what makes COPD complex and heterogeneous.

The pathology of COPD includes small airway disease and/or emphysema, so COPD is not a single disease entity. In addition, there are two types of panlobular and centrilobular emphysema in COPD. It is therefore conceivable that the coexistence of different pathological subtypes could be the reason for the complexity and heterogeneity of COPD. Then it is necessary to look for the phenotype based on the difference in the underlying pathology.

Review of the literature has shown that there is a difference in the clinical manifestation and the therapeutic response to pharmacological therapy depending on the presence of computed tomography (CT)-defined airway wall thickening in COPD patients.

Defining the phenotype of COPD based on the underlying pathology is encouraging as most clinical manifestations can be distinguished by the presence of increased airway wall thickness. Pharmacological therapy has shown significant effects in COPD with airway wall thickening, but limited use in COPD without airway disease. The Phenotype of COPD based on the underlying pathology can be a useful tool to better understand the disease and adjust treatment accordingly.

Key words: Chronic Obstructive Pulmonary Disease; Phenotype; Small Airway Disease;
Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a common, preventable, and treatable condition that is characterized by persistent respiratory symptoms and airflow limitation resulting from abnormalities in the airways and/or alveoli, usually caused by significant exposure to harmful particles or gases and influenced by host factors, including abnormal lung development. COPD is a leading cause of morbidity and mortality worldwide, which creates a significant economic and social burden. In 2017, around 300 million cases were reported worldwide, with around 3.2 million deaths related to COPD, placing the disease seventh on a global list of causes of disability and third among the world's leading causes of death. COPD is also a leading cause of disability and death in the United States. In 2018, 16.4 million adults reported a diagnosis of COPD. This corresponds to 6.6% of adults, with the highest rates of illness occurring in those over 65 years of age. In the Republic of Korea, the prevalence of COPD over the age of 40 was estimated at 13.4% in 2015 by the Korea National Health and Nutrition Examination Survey using spirometry. In those over 65 years of age it was 28.1%.

Patients with COPD are characterized by a large clinical, functional, radiological, cellular and molecular variability of the phenotype, which in turn is reflected in an equally large variability in the course of the disease and in the response to pharmacological treatment. Therefore, COPD is a very complex and heterogeneous disease and not all patients respond to
available drugs. Identifying respondents is critical to delivering the most appropriate
treatment and avoiding unnecessary medication.

Recognition of an individual patient’s predominant characteristics by phenotype is a useful
tool in better understanding their disease and adjusting treatment accordingly. The phenotype
in COPD has been defined as a single or a combination of disease features that describe
differences between individuals in terms of clinically meaningful outcomes (symptoms,
exacerbations, response to therapy, disease progression, or death). The phenotype should be
able to classify patients into subgroups with prognostic value and determine the most
appropriate therapy to get better results. As the field of phenotyping of COPD is not
advanced enough to understand the mechanism behind each clinical presentation, there is an
urgent need to search for an identifiable phenotype of COPD. To achieve successful
phenotyping of COPD, it is necessary to understand why COPD is a complex and
heterogeneous disease.

The pathology of COPD includes small airway disease and/or emphysema, so COPD is not
a single disease entity. In addition, there are two types of emphysema in COPD, panlobular
and centrilobular emphysema. It is therefore conceivable that the coexistence of different
pathological subtypes of small airway disease and/or emphysema could be the fundamental
cause of the complexity and heterogeneity of COPD. Then it is necessary to look for the
phenotype based on the difference in the underlying pathology. To achieve this goal, it is
needed to discuss the pathophysiological difference between small airway disease and
emphysema, as well as the difference in clinical manifestation and response to
pharmacological therapy in these two distinct subtypes of COPD.
Pathophysiological Difference between Small Airway Disease and Emphysema

The pathological characteristics of COPD is an inflammation of the small airways (small airway disease) and destruction of the lung parenchyma (emphysema) of the lungs. Small airway disease contributes airflow limitation by narrowing and obliterating the airway lumen (Figures 1C and 1D) compared to normal small airway (Figure 1A) or small airway containing a mucus plug with relatively few cells (Figure 1B) and also actively narrowing the airway through an increased smooth muscle. Emphysema, on the other hand, helps restrict airflow by reducing the elastic recoil pressure available to drive air out of the lungs by destroying the parenchyma and decreasing tethering of small airways through low elastic load applied to the airways. In addition, the destruction of the alveolar attachments leads to narrowing and premature closure of the airways.

Difference between Panlobular and Centrilobular Emphysema

Two main types of emphysema have been recognized in COPD: panlobular emphysema (PLE), which is commonly associated with α₁-antitrypsin deficiency, but also smokers and centrilobular emphysema (CLE), known as smoker’s emphysema. Paraseptal emphysema is not associated with increased symptoms or reduced lung function. PLE shows diffuse even alveolar enlargement (Figure 2B). Therefore, PLE is associated with uniform damage of air space, affecting primarily the lower lobes of the lungs. CLE shows an uneven pattern of lung destruction with thickened wall of the terminal bronchiole (Figure 2C), affecting mainly the upper lobes. A schematic representation of the gross pathological difference between these...
two emphysemas is shown in Figure 3\textsuperscript{14}.

The original description of the autopsy study showed that all CLE lesions had a feeding bronchiole lined with abnormal epithelium, accompanied by varying degrees of thickening of the airway wall and narrowing of the lumen\textsuperscript{15}. In addition to this observational study, the objective quantitative morphometric measurement of small airway pathological scores in the surgically resected lung specimens indicated that CLE had a higher degree of small airway abnormalities than PLE, mainly due to higher muscle score and fibrosis\textsuperscript{16}. Direct microscopic measurement of the thickness of small airway walls in the resected lung samples also showed that the thickness of the small airway walls in CLE is greater than that of non-smoker control lungs and there was a significant correlation between the degree of airflow limitation and the small airway wall thickness in CLE\textsuperscript{17}. Further morphometric analysis of resected lung samples showed a significantly increased wall thickness of the small airways in CLE compared to non-smoker control or PLE lungs (Figure 4a)\textsuperscript{13}. Additional histologic analysis of cryosections cut from the frozen tissue blocks of isolated COPD lungs showed that CLE lungs had thickened airway walls compared to control lungs\textsuperscript{18}.

Immunohistochemical studies have shown that the volume fraction of CD8\textsuperscript{+} and granzyme B-positive cells in the small airway walls (Figure 4b)\textsuperscript{13} and the number of these cells on the alveolar walls\textsuperscript{19} in CLE lungs were greater than the same cells in non-smoker control or PLE lungs, suggesting a difference in cellular background between these two emphysema. In addition, mast cells were predominant in the smooth muscle of the small airways and alveolar walls of CLE compared to PLE\textsuperscript{20}. Blood interleukin (IL)-6, matrix metalloproteinase (MMP)-7 and tumor necrosis factor alpha (TNF-\(\alpha\)) were associated with emphysema, while IL-6, IL-13, IL-2 receptor, Interferon gamma (IFN-\(\gamma\)) and c-reactive protein (CRP) were associated
with bronchial thickening on quantitative computed tomography (QCT) in smokers, suggesting different inflammatory biomarker patterns in these COPD subtypes. QCT is the method of quantifying the presence and percentage of low attenuation areas of emphysema and airway wall thickness of the segmental and subsegmental airways of the lungs.

The fact that CLE shows uneven lung destruction with airway thickening and the preferential distribution in the upper lobes is consistent with the concept of airborne disease. On the other hand, the diffuse uniform destruction of the lungs without airway involvement and the preferential distribution in the lower lobes, where blood flow is greater than in the upper lobes, suggest that PLE may arise from a blood-mediated mechanism of protease-antiprotease imbalance.

The relative frequency of PLE and CLE was reported to be variable. Of the 19 series of random cases from mostly autopsy or necropsy studies, CLE was considered more common than PLE in 10, PLE more than CLE in 4, and PLE and CLE were considered equal in 5 studies. QCT examination of COPD patients showed 174 airway-predominant and 75 emphysema-predominant COPD. A study of the visual assessment of chest computed tomography (CT) scans of COPD patients found 63 predominant PLE and 55 predominant CLE.

### Relationship between Small Airway Disease and Centrilobular Emphysema

It was reported that young smokers who died suddenly outside the hospital had definite abnormalities in the peripheral airways. The authors hypothesized that these lesions may be the precursors of severe anatomical lesions in smokers. The MicroCT study of resected lung
samples also showed that the narrowing of the terminal bronchioles preceded the occurrence of centrilobular emphysematous destruction\(^{18}\). In lung tissue, remodeling of the terminal and transitional bronchioles not affected by emphysema provides further evidence that disease of the small airways precedes emphysematous lesions\(^{27}\). Therefore, it is believed that the pathogenesis of CLE begins with inflammation, remodeling and destruction of the small airways with subsequent spread into the peribronchiolar alveolar wall tissue and destruction of the center of the lobule\(^{28}\). Then the pathology of COPD can be redefined as small airway disease with CLE and PLE.

**Differential Diagnosis between Panlobular and Centrilobular Emphysema**

The differential diagnosis between PLE and small airway disease with CLE is not easy because the emphysema is shared by two. Chest CT scans are becoming routine for smokers with COPD to check for lung cancer and to evaluate pulmonary nodules. Fortunately, improved CT-based imaging of the lungs enables us to differentiate emphysematous phenotypes in a less invasive way\(^{29}\). QCT is useful to identify and sequentially assess the extent of emphysematous lung destruction and changes in airway walls in patients with COPD\(^{30}\). It was shown that CT measurements of the thickening and narrowing of the relatively large airways serve as a surrogate for the pathological changes in the small airways that cannot be measured in routine CT\(^{31}\). It is now possible to non-invasively assess the relationship of QCT-defined thickening of airways or emphysema with clinically relevant outcomes.
Different Clinical Manifestations of COPD Depending on the Presence of Increased Airway Wall Thickness

1. Clinical presentations

In a study with 463 COPD patients, the CT-measured airway wall thickness was significantly related to morning cough, chronic cough and wheezing\textsuperscript{32}. In 100 male smokers, smokers with chronic respiratory symptoms such as cough, excessive mucus, dyspnea, and wheezing had a CT-measured thicker bronchial wall than those with no symptoms\textsuperscript{33}. In 56 COPD patients, CT-measured thicker walls were associated with clinical features that may represent a bronchitic phenotype (Medical Research Council [MRC] bronchitis score, frequent exacerbations, total St. George’s score and body mass index [BMI]), independent of emphysema. BMI was negatively correlated with the degree of emphysema\textsuperscript{34}. The study of 3,171 current or former smokers found that patients with confluent or advanced destructive emphysema, likely equivalent to PLE, had a lower BMI than those with mild CLE\textsuperscript{35}. In 1,200 patients with COPD, CT-defined airway disease is closely associated with higher St. George's Respiratory Questionnaire (SGRQ) scores, and emphysema is closely associated with the higher \textbf{Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE) index}\textsuperscript{36}.

2. ACUTE BRONCHODILATOR RESPONSIVENESS

Preoperative methacholine challenge was compared to the morphologic and cellular
inflammatory features of the airways in the surgically resected lungs of CLE and PLE.

The reactivity of the airways was significantly higher in CLE than in PLE. The reactivity of the airways was determined by the degree of the pathological abnormality in the small airways. Small airway morphometry in the resected lungs was performed in 67 patients with advanced emphysema undergoing lung volume reduction surgery. The group with reactivity to bronchodilator had increased smooth muscle mass in the small airways compared to the irreversible group. Of 2,355 bronchodilator-negative COPD patients and 1,306 positive patients, bronchodilator-responsive patients had CT evidence of thicker airways than bronchodilator-unresponsive patients.

3. EXACERBATION OF COPD

In a study with 1,002 COPD patients with QCT measurements of emphysema and airway disease, the multivariate model showed that an increase in segmental bronchial wall thickness was associated with a higher frequency of exacerbations. Of 167 patients with COPD: patients with mild emphysema and severe airway changes had significantly more frequent exacerbations than patients with moderate emphysema with mild airway changes.

4. PROGRESSION OF COPD

In a follow-up study on 131 COPD patients over 3.7 years, the rapid fall in FEV1 was more strongly influenced by the emphysema-dominant than the airway-dominant phenotype. In 1,184 smoker and nonsmoker participants in a 6-year longitudinal study, the total airway count, possibly reflecting airway-related disease changes, was independently associated with
a decrease in lung function\textsuperscript{42}.

On the other hand, chest CT scans of 116 cigarette smokers showed that PLE was more frequent in individuals with Global Initiative for Obstructive Lung Disease (GOLD) 4 stage. The authors suggested that some people with predominant PLE might have a higher genetic susceptibility to emphysema or a faster disease progression\textsuperscript{25}. This finding is in line with the report of 3,171 ever smokers, showing that confluent and advanced destructive emphysema, equivalent to PLE, were more common in the GOLD 4 stage\textsuperscript{35}.

Although COPD is generally considered progressive, this disease is often remains stable\textsuperscript{28}. In more than half of 2,163 COPD patients, the rate of decline in FEV\textsubscript{1} over a 3-year period was no greater than in people without lung disease\textsuperscript{43}. A study to calculate the rate of lung function decline over a 5-year period showed that patients with a rapid decline had a lower proportion of regulatory T cells in the bronchoalveolar lavage fluid than patients with non-rapid decline. The authors suggested that the inability to upregulate regulatory T cells, i.e. the inability to suppress the inflammatory response after smoking, could lead to a more rapid decline in lung function\textsuperscript{44}. A cross-sectional study of surgically resected lung specimens showed that the number of alveolar granzyme B-positive cells was increased in CLE lungs compared to non-smoker controls, but not in PLE lungs. The number of their alveolar granzyme B-positive cells was positively correlated with FEV\textsubscript{1}\textsuperscript{19}. Another study also showed a positive correlation between the volume fraction of granzyme B-positive cells in small airways and FEV\textsubscript{1} in CLE lungs\textsuperscript{13}. These results mean that lungs with mild airflow limitation have more granzyme B-positive cells both in small airways and on alveolar walls than CLE lungs with severe airflow limitation. The authors postulated that the degree of lung destruction and thus the progression of airflow limitation in CLE might be determined by the
individual amount of available granzyme B-positive cells, which are thought to represent the
activated state of cells with regulatory function.19

5. MORTALITY

In 609 patients with severe emphysema, increased mortality was independently associated
with greater lower–lung zone emphysema. The 8-year mortality study in 947 ever smokers
showed that CT-measured airway thickness did not predict mortality, but emphysema was a
strong independent predictor of mortality.

6. ASSOCIATION WITH CARDIOVASCULAR DISEASE

Sixty COPD patients underwent a right heart catheterization and chest CT examination.
Airway wall thickness was the independent predictor associated with the increase in mean
pulmonary artery pressure. In contrast to the quantification of emphysema, the CT
measurement of the airway remodeling correlated with the mean pulmonary artery pressure.
Chest CT was used for emphysematous lesions, airway lesions, and epicardial adipose tissue
(EAT) in 180 smokers. EAT has been shown to be a non-invasive marker that predicts
cardiovascular disease (CVD) progression. The EAT area was independently related to the
wall thickness of the airway. It suggested a mechanistic link between the airway-predominant
COPD and CVD.

7. ASSOCIATION WITH LOW BONE MINERAL DENSITY
One hundred ninety subjects carried out dual X-ray absorptiometry measurements of bone mineral density. Quantitative emphysema, but not CT-measured airway wall thickness indices, was inversely associated with bone mineral density. Emphysema was a strong, independent predictor of low bone mineral density. In 3,321 current and former smokers, emphysema was associated with both low volumetric bone mineral density and vertebral fractures. Airway disease was associated with higher bone density. In 75 patients with emphysema-predominant and 174 with airway-predominant COPD, osteoporosis was significantly more common in emphysema-predominant COPD subjects.

8. ASSOCIATION WITH LUNG CANCER

CT scans were analyzed in 279 participants diagnosed with lung cancer. The emphysema index was most closely related, but the airway dimensions were not associated with lung cancer. In 947 ever-smokers followed for 10 years, baseline emphysema remained a significant predictor of lung cancer incidence. Airway wall thickness did not independently predict cancer.

9. ASSOCIATION WITH DIABETES MELLITUS

Of 75 patients with emphysema-predominant and 174 with airway-predominant COPD, diabetes was more common in patients with airway-predominant cases. Of 4,197 COPD subjects, non-emphysematous COPD, which is defined by airflow limitation with a lack of emphysema on chest CT, is associated with an increased risk of diabetes.
In summary, chronic respiratory symptoms, higher SGRQ score, positive bronchodilator responsiveness, exacerbation, cardiovascular disease and diabetes mellitus were associated with COPD patients with thickened airway walls. On the other hand, lower BMI, higher BODE index, rapid progression, mortality, low bone mineral density and lung cancer were associated with COPD without airway wall thickening (Table 1).

Different Response to Pharmacological Therapy Depending on the Presence of Increased Airway Wall Thickness

Lung samples were examined in 35 COPD patients within 12 months of administration of isoproterenol. Patients with an increased bronchial gland-bronchial wall ratio (Reid index) showed a significantly greater improvement in FEV$_1$ after bronchodilator therapy compared to patients with a normal Reid index$^{54}$. This index of the ratio of gland thickness to wall thickness measured between cartilage and epithelial basement membrane was introduced as a measure of chronic bronchitis.$^{55}$ In 85 COPD patients, increase in FEV$_1$ in response to treatment with inhaled corticosteroid for 2–3 months were significantly higher in emphysema with bronchial wall thickening on high-resolution computed tomography (HRCT) than in emphysema without airway thickening$^{56}$. Two hundred twenty six patients received combination of inhaled long-acting beta agonist and corticosteroid for 3 months. Internal perimeter of 10 mm measured by integral-based half-band method (Pi10-IBHB), which reflects severity of small airway disease on CT, was the only independent variable predicting an increase in FEV$_1$, suggesting that COPD with predominant airway disease is more
treatable than COPD with predominant emphysema. Sixty COPD patients were randomized
to receive bronchodilator or bronchodilator with corticosteroid for 16 weeks. Airway wall
thickening and airway narrowing on CT decreased after treatment with combination of
bronchodilator and corticosteroid, and changes in airway dimensions were proportional to the
improvement in FEV$_1$. Two hundred fifty four COPD patients were randomly assigned to inhaled corticosteroid or
placebo. Patients were followed up with annual CT for 2-4 years. There was no difference in
the annual decrease in FEV$_1$ between corticosteroid and placebo. Long-term inhalation of
corticosteroid showed a non-significant trend in reducing the progression of emphysema from
annual CT scans. One hundred sixty five COPD patients received inhalation of a long-
acting beta-agonist and corticosteroid for 3 months. CT-defined emphysema-dominant
patients showed no improvement in FEV$_1$ or dyspnea after 3-months of treatment.

The difference in response to pharmacological therapy is summarized in table 2.

Conclusion

Phenotyping of COPD based on the underlying subtype of pathology is encouraging, since
most clinical manifestations can be distinguished by the presence of increased airway wall
thickness on CT. Although further studies with large numbers of subjects are desirable, the
available data indicated that pharmacological therapy has a significant effect in COPD
patients with increased airway wall thickness, but has limited benefit in COPD patients
without airway thickening.

The phenotype of COPD based on the CT-defined underlying pathology was able to
describe differences in clinically meaningful outcomes between patients and also to classify
patients into subgroups with prognostic value of responsiveness to pharmacological therapy.
This phenotype can be a useful tool to better understand the disease and adjust treatment
accordingly

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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### Table 1.

**Different clinical manifestations depending on airway wall thickening**

<table>
<thead>
<tr>
<th>COPD with airway wall thickening</th>
<th>COPD without airway wall thickening</th>
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<tbody>
<tr>
<td>Chronic respiratory symptoms $^{32-34}$</td>
<td>Lower BMI $^{35}$</td>
</tr>
<tr>
<td>Higher SGRQ score $^{36}$</td>
<td>Higher BODE index $^{36}$</td>
</tr>
<tr>
<td>Positive bronchodilator response $^{37-39}$</td>
<td>Rapid progression $^{25,41}$</td>
</tr>
<tr>
<td>Exacerbation $^{24,34,40}$</td>
<td>Mortality $^{46}$</td>
</tr>
<tr>
<td>Cardiovascular disease $^{47,48}$</td>
<td>Low bone mineral density $^{24,49,50}$</td>
</tr>
<tr>
<td>Diabetes mellitus $^{24,53}$</td>
<td>Lung cancer $^{51,52}$</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; BMI: body mass index;
SGRQ: ST. George’s Respiratory Questionnaire;
BODE: Body mass index, airflow Obstruction, Dyspnea and Exercise capacity.

### Table 2.

**Different response to pharmacological therapy in COPD**

<table>
<thead>
<tr>
<th>Favorable response to therapy</th>
<th>Poor response to therapy</th>
</tr>
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<tbody>
<tr>
<td>Increased Reid index $^{24}$</td>
<td>Emphysema on CT $^{59}$</td>
</tr>
<tr>
<td>Emphysema with bronchial wall thickening on HRCT $^{56}$</td>
<td>CT-defined emphysema-dominant</td>
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<tr>
<td>Higher Pi10-IBHB on CT $^{57}$</td>
<td>COPD $^{60}$</td>
</tr>
<tr>
<td>Airway wall thickening on CT $^{58}$</td>
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COPD: chronic obstructive pulmonary disease; Reid index: bronchial gland-bronchial wall ratio; CT: computed tomography; HRCT: high-resolution computed tomography; Pi10-IBHB: internal perimeter of 10 mm measured by integral-based half-band method.
Figure 1. Small airway obstruction\textsuperscript{11}. (A) Normal small airway. (B) Small airway containing plug of mucus with relatively few cells. (C) Acutely inflamed airway with thickened wall, in which the lumen is partly filled with an inflammatory exudate of mucus and cells. (D) Airway surrounded by connective tissue, which appears as if it might restrict normal enlargement of the lumen and unfolding of the epithelial lining.
Figure 2. Representative microscopic images of the parenchyma of the lungs\textsuperscript{13}. (A) Image of a non-smoking control lung. (B) Image of a panlobular emphysema lung. (C) Image of a centrilobular emphysema lung with thickened wall of the terminal bronchiole. (D) Image of a mixed panlobular and centrilobular emphysema lung with thickened wall of the terminal bronchiole.
Figure 3. A schematic representation of the gross pathological difference between panlobular and centrilobular emphysema.14 (A) Panlobular emphysema shows enlargement and destruction of the air spaces that uniformly affect the acinus. (B) Centrilobular emphysema selectively and dominantly affects the respiratory bronchiole with inflamed terminal bronchiole. TB: terminal bronchiole; RB: respiratory bronchiole; AD: alveolar duct; AS: alveolar sac.
Figure 4. Thickness of small airway walls and volume fraction (Vv) of cells in small airway walls\textsuperscript{13}. (a) Small airway wall thickness is greater in CLE than in non-smoker control or PLE lungs. (b) The volume fraction (Vv) of CD8\textsuperscript{+} and granzyme B-positive cells in small airway walls is greater in CLE than in non-smoker control or PLE lungs.