

Impact of Exacerbations on Emphysema Progression in Chronic Obstructive Pulmonary Disease

Naoya Tanabe¹, Shigeo Muro¹, Toyohiro Hirai¹, Tsuyoshi Oguma¹, Kunihiro Terada¹, Satoshi Marumo¹, Daisuke Kinose¹, Emiko Ogawa¹, Yuma Hoshino¹, and Michiaki Mishima¹

¹Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Rationale: Low-attenuation areas assessed by computed tomography reflect the extent of pathological emphysema and correlate with airflow limitation and mortality in patients with chronic obstructive pulmonary disease. The cumulative size distribution of low-attenuation area clusters follows a power law characterized by an exponent, *D*. The values of *D* reflect the complexity of the terminal airspace geometry and sensitively detect alveolar structural changes. Exacerbations of chronic obstructive pulmonary disease have a negative impact on lung function and prognosis. However, the impact on emphysema progression remains unclear.

Objectives: We investigated the relationship between exacerbation and emphysema progression assessed by computed tomography in patients with chronic obstructive pulmonary disease.

Methods: Exacerbations were prospectively recorded for 2 years. Annual changes in computed tomography parameters of emphysema were compared between patients with and without a history of exacerbations.

Measurements and Main Results: In patients with exacerbations, increases in the percentage of low-attenuation areas and decreases in *D* were greater than in patients without exacerbations. To interpret these results, we established a novel simulation model and found that not only enlargement of preexisting low-attenuation areas but also coalescence of adjoining low-attenuation areas due to alveolar wall destruction caused emphysema progression in patients with exacerbations.

Conclusions: This is the first longitudinal study to demonstrate that exacerbations are involved in emphysema progression in patients with chronic obstructive pulmonary disease. Emphysema progression should be evaluated as part of the outcomes of exacerbations in the management of chronic obstructive pulmonary disease.

Keywords: emphysema; exacerbation; computed tomography; chronic obstructive pulmonary disease; fractal

(Received in original form September 24, 2010; accepted in final form March 10, 2011)

Supported by grants-in-aid for scientific research (B) (no. 16390234) and (C) (no. 21590964) and a grant to the Respiratory Failure Research Group from the Ministry of Health, Labor, and Welfare, Japan.

Author contribution: N.T. contributed to study design, collection of data, analysis and interpretation of data, and writing the draft. S.M. contributed to study design, collection of data, analysis and interpretation of data, editing the draft, and acquisition of funding. T.H. contributed to the development of computer simulation analysis, editing the draft, and interpretation of data. T.O. developed the custom-made application for the analysis of computed tomography data, and contributed to interpretation of data and editing the draft. K.T. contributed to study design, collection of data, and analysis. S.M. contributed to study design, collection of data, and analysis. D.K. contributed to study design, collection of data, and analysis. E.O. contributed to study design, collection of data, and analysis. Y.H. contributed to study design, collection of data, and analysis. M.M. contributed to study design and analysis and interpretation of data, editing the draft, and acquisition of funding.

Correspondence and requests for reprints should be addressed to Shigeo Muro M.D., Ph.D., Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: smuro@kuhp.kyoto-u.ac.jp

This article has an online supplement, which is available from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 183, pp 1653–1659, 2011

Originally Published in Press as DOI: 10.1164/rccm.201009-1535OC on March 11, 2011
Internet address: www.atsjournals.org

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Pulmonary emphysema is the primary pathological change of chronic obstructive pulmonary disease (COPD) and can be assessed by computed tomography (CT). Exacerbations of COPD have a negative impact on lung function and prognosis. However, the relationship between exacerbations and progression of emphysema remains unclear.

What This Study Adds to the Field

This study shows that annual changes in CT parameters of emphysema are greater in patients with a history of exacerbations of COPD than in those without a history of exacerbations. This finding suggests that exacerbations accelerate emphysema progression in patients with COPD.

Chronic obstructive pulmonary disease (COPD) is a major public health problem. It is the fourth leading cause of death worldwide and is associated with increasing economic costs and social burdens (1). Emphysema, a main constituent of lung pathology in COPD, is characterized pathologically by abnormal and permanent enlargement of distal airspaces and destruction of alveolar walls (2). It causes airflow limitations (3) and impaired diffusing capacities (4), which are important determinants of COPD mortality. Investigating the mechanism of emphysema progression is therefore important to improve management of patients with COPD.

Exacerbations of COPD consist of acute episodes of worsening symptoms that may warrant changes in regular medications (1) and lead to worsening of the chronic progressive course of this disease. These exacerbations have negative impacts on lung function (5), health-related quality of life (6, 7), prognosis (8), and socioeconomic costs (9). However, it is not clear whether exacerbations of COPD promote emphysema progression.

Computed tomography (CT) has been previously used to assess the extent of emphysematous changes (3, 4, 10–14). The loss of lung tissue associated with emphysema can be measured by low-attenuation areas (LAA) in CT images, and the importance of such assessments of emphysematous changes is increasingly being recognized in clinical practice. In patients with α_1 -antitrypsin deficiency, emphysematous changes assessed by CT are more sensitive for detecting the efficacy of augmentation therapy than other conventional indices such as lung function tests (15). In typical patients with COPD, emphysematous changes assessed by CT are correlated with COPD mortality, independently of lung function (16). This finding suggests that CT assessment of emphysematous changes can provide additional information for managing patients with COPD.

The concept of fractal geometry is useful for analyzing the irregular and complex structures often seen in nature (17), and it has been applied to pulmonary physiology and histology (18, 19). We previously demonstrated that the cumulative size dis-

tribution of LAA clusters follows a power law characterized by an exponent, D . The values of D reflect the fractal dimension of the terminal airspace geometry, and could be sensitive to alterations in tissue structure that are not reflected in changes in the percentage of the lung field occupied by LAAs (LAA%) (4). Moreover, we also found that fractal analysis is useful in elucidating the mechanism of emphysema progression in an animal model (20). These reports suggest that the evaluation of LAA and fractal geometry could reveal faint alterations in lung structure in the clinical course of patients with COPD.

In the present study, we explored the impact of COPD exacerbations on emphysema progression by analyzing changes in both LAA% and D . We then investigated the underlying mechanism by establishing a novel simulation model.

METHODS

This is part of a prospective observational study investigating COPD exacerbation (21–23). The study protocol is summarized in Figure 1, and details of all protocols are provided in the online supplement. Briefly, from June 2006 to August 2008, we enrolled 101 of 105 patients with COPD who agreed to record exacerbations prospectively. The observation period was 2 years. The study was approved by the local ethics committee, and all patients gave written informed consent.

Exacerbation Criteria

We defined an exacerbation as a symptomatic deterioration requiring treatment with antibiotics and/or systemic corticosteroid. As previously reported (21–23), symptomatic changes were assessed by a modified version of the East London Cohort Study criteria (5, 6).

Pulmonary Function Tests, CT Acquisition, and Calibration of CT Numbers

As previously reported (24, 25), baseline and 2-year follow-up pulmonary function tests and CT scans were performed at least 4 weeks after resolution of the last exacerbation. In addition to routine calibration using air and water phantoms, CT numbers were corrected using air densities sampled from the intrathoracic trachea to eliminate the influence of X-ray tube aging (26).

Analysis of the Percentage of LAA and the Cumulative Frequency Distribution of LAA Size

We measured CT parameters according to our previous reports (4, 25). The cumulative frequency distribution of LAA sizes, Y , can be de-

scribed by a power law of LAA size X of the form: $Y = K \times X^{-D}$. Using all images of the whole lung (slice thickness, 0.5 mm), we calculated the values of LAA%, exponent D , and CT-derived lung volume.

Model Simulations

We established a simulation model using baseline CT images (*see* Figure E1 in the online supplement). One pixel in each image was randomly selected from the boundary of preexisting LAAs and changed into a new LAA pixel. This process was iteratively repeated, using the modified image as the starting point for the next selection until changes in LAA% reached 1, 3, and 5%. The procedure was performed according to various algorithms as follows. In model A, one pixel was randomly selected from all pixels in the boundary of LAAs, but not separating adjoining LAAs. This model simulates the simple enlargement of preexisting LAA. In model B, either 15% (model B15) or 30% (model B30) of pixels were randomly selected from all pixels separating LAAs, and then the remaining pixels were randomly selected from all those in the boundary of LAAs, but not separating LAAs. Model B simulates the situation in which lung destruction causes the coalescence of neighboring LAAs to some degree, with concomitant enlargement of LAAs. After these procedures, the values of exponent D were calculated.

Statistical Analyses

Statistical analyses were performed with JMP 7 software (SAS Institute, Cary, NC). Data are expressed as medians (25th, 75th percentile) unless otherwise indicated. Patients were divided into those with exacerbations and those without exacerbations, and differences between groups were evaluated with the Mann-Whitney U test. Data within groups were analyzed with the Wilcoxon signed-rank test. Relationships among data were assessed by the Spearman rank correlation test. To investigate the relative contribution of exacerbations to emphysema progression after adjustment for changes in CT-derived lung volume and baseline CT parameters of emphysema, multivariate regression analysis was performed. A P value less than 0.05 was considered significant.

RESULTS

Patient Characteristics

As shown in Figure 1, a baseline CT scan was performed on 101 patients who had already participated in our prospective observational study investigating COPD exacerbations (21–23). Of these patients, 17 were excluded because of abnormal chest shadows not associated with emphysematous changes obtained in CT images at entry. Over the next 2 years, 24 patients were excluded for the following reasons: withdrawal of consent, appearance of a new shadow on chest images, serious condition, death, or loss to follow-up. The final study population comprised 60 patients (Table 1). During the observation period, 26 patients experienced exacerbations requiring treatment with antibiotics and/or systemic corticosteroid at least once, and 34 patients experienced no exacerbations. Details of exacerbations are provided in Table E1. There were no significant differences in baseline clinical parameters, pulmonary function, or CT parameters between groups (Table 2). In addition, baseline pharmacological treatments and additional treatments were not significantly different between patients with and without exacerbations (Table E2).

Impact of Exacerbations on Lung Function and CT Parameters

We compared changes in lung function and CT parameters between patients with and without exacerbations (Table 3). There were significant annual decreases in FEV₁, %FEV₁ (FEV₁ expressed as a percentage of the expected value), and ratio of diffusing capacity to alveolar ventilation (DL_{CO}/V_A) in both groups, but the degrees of decline were not significantly

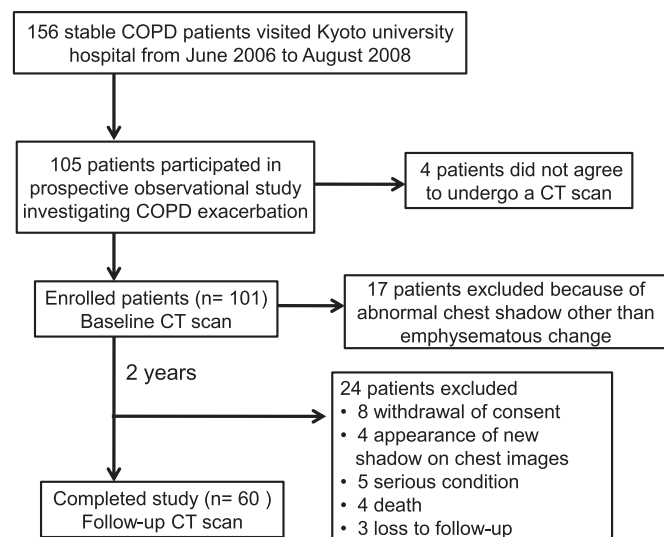


Figure 1. Patient disposition and reasons for exclusion. CT = computed tomography; COPD = chronic obstructive pulmonary disease.

TABLE 1. BASELINE CHARACTERISTICS OF STUDY PATIENTS

Characteristic	Value
Age, yr: median (25th, 75th percentile)	73.0 (68.3, 77.8)
Sex, male:female	56:4
Height, m: median (25th, 75th percentile)	1.62 (1.57, 1.68)
Weight, kg: median (25th, 75th percentile)	56.0 (49.0, 60.8)
Body mass index: median (25th, 75th percentile)	20.8 (19.5, 22.7)
Smoking status, current:former	8:52
Smoking history, pack-years: median (25th, 75th percentile)	55.0 (43.0, 84.0)
FEV ₁ , L: median (25th, 75th percentile)	1.27 (0.94, 1.67)
%FEV ₁ , median (25th, 75th percentile)	50.6 (38.2, 61.1)
D _{LCO} /V _A , ml/min/mm Hg/L: median (25th, 75th percentile)	2.67 (1.90, 3.25)

Definition of abbreviations: %FEV₁, FEV₁ as a percentage of the predicted value; D_{LCO}/V_A, ratio of diffusing capacity to alveolar ventilation. n = 60 study patients.

different between the two groups. On the other hand, significant annual increases in LAA% and decreases in D were detected only in patients with exacerbations. Furthermore, changes in LAA% and D were significantly greater in patients with exacerbations than in those without (Figure 2). Increases in LAA% significantly correlated with decreases in D both in patients with exacerbations ($r = -0.50$, $P = 0.009$) and those without ($r = -0.52$, $P = 0.002$) (Figure 3). There were no significant changes in CT-derived lung volume within patients. The degrees of changes were not significantly different between the two groups (Table 2). Baseline LAA% and D significantly correlated with FEV₁, %FEV₁, and D_{LCO}/V_A, whereas changes in LAA% or D did not correlate with changes in FEV₁, %FEV₁, or D_{LCO}/V_A (Table E3). In stepwise multivariate regression analysis, exacerbations contributed to changes in LAA% ($R^2 = 0.41$, $P < 0.0001$) or D ($R^2 = 0.48$, $P < 0.0001$) independent of changes in lung volume and baseline CT parameters of emphysema (Table 4).

Model Simulations Using Baseline CT Images

According to our previous findings (4), we supposed that when LAA% is increased, D would decrease only if exacerbations disrupted the alveolar wall and caused the coalescence of preexisting LAAs. To test this hypothesis, we established a novel simulation model using eight baseline representative CT images. As mentioned in METHODS, model A does not allow the coalescence of LAAs, representing a case in which exacerbations lead to simple enlargement of preexisting LAAs. On the other hand, models B15 and B30 allow coalescence by the destruction of lung parenchyma between LAAs. As shown in Figure 4, model A did not lead to a decrease in D when increases in LAA% were 1, 3, and 5%. However, both model B15 and model B30 resulted in an increase in LAA% and a decrease in D. The changes in D observed in model B15 were more like the actual values seen in patients with a history of exacerbations than those in model B30.

DISCUSSION

Our study demonstrated that annual changes in CT parameters of emphysema are greater in patients with exacerbations of COPD than in those without exacerbations, and that an increase in LAA% and decrease in D reflects not only the enlargement of preexisting LAAs but also the coalescence of adjoining LAAs.

To our knowledge, this is the first longitudinal study to demonstrate the relationship between exacerbations and emphysema progression in patients with COPD. Emphysematous

TABLE 2. COMPARISON BETWEEN PATIENTS WITH AND WITHOUT EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Parameter	Exacerbation (-)	Exacerbation (+)	P Value
Subjects, n	34	26	
Exacerbations, n/yr	0	0.54 (0.49, 1.00)	
Baseline characteristics			
Age, yr	72.0 (66.0, 79.0)	73.0 (69.8, 75.5)	0.80
Sex, male:female	32:2	23:2	1.00
Body mass index	21.2 (19.6, 23.7)	20.3 (18.7, 21.9)	0.19
Smoking status, current:former	4:30	4:22	0.72
Smoking history, pack-years	52.6 (43.3, 78)	57.0 (42.5, 84.9)	0.68
FEV ₁ , L	1.38 (0.88, 1.67)	1.18 (0.95, 1.73)	0.58
%FEV ₁	50.4 (39.2, 62.9)	51.4 (37.6, 58.4)	0.77
GOLD classification, n (%)			
Stage I	1 (2.9)	1 (3.8)	
Stage II	17 (50.0)	14 (53.8)	
Stage III	14 (41.2)	8 (30.8)	
Stage IV	2 (5.9)	3 (11.5)	
D _{LCO} /V _A , ml/min/mm Hg/L	2.68 (1.88, 3.27)	2.41 (1.95, 3.24)	0.85
LAA% (-910), %	55.2 (49.2, 62.3)	59.0 (50.8, 63.0)	0.67
LAA% (-930), %	47.2 (41.4, 54.3)	50.5 (42.0, 55.5)	0.67
LAA% (-960), %	33.8 (29.3, 41.1)	36.9 (28.5, 42.3)	0.54
D	1.45 (1.16, 1.78)	1.29 (1.12, 1.69)	0.40
CT-derived total lung volume, L	5.52 (4.58, 6.03)	5.27 (4.57, 6.04)	0.87

Definition of abbreviations: %FEV₁, FEV₁ as a percentage of the predicted value; CT = computed tomography; D_{LCO}/V_A, ratio of diffusing capacity to alveolar ventilation; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LAA%, percentage of low-attenuation area.

Data are expressed as medians (25th, 75th percentile) unless otherwise indicated.

changes have been assessed mainly by CT in cross-sectional studies (3, 4, 10, 11, 24, 25). Few longitudinal studies have been performed in patients with COPD without α_1 -antitrypsin deficiency.

Exacerbations are important events in patients with COPD because they contribute to the further decline of lung function (5), impaired health-related quality of life (6, 7), socioeconomic burden (9), and poor prognosis (8). Given that airway inflammation, oxidative stress, and proteolysis are involved in the pathogenesis of COPD (1) and are enhanced in exacerbations (1, 27–30), we assumed that exacerbations would affect lung pathological changes such as emphysema. However, their impact on emphysema progression has not been investigated. In addition, we previously demonstrated that emphysematous changes assessed by CT correlated with COPD mortality, independent of lung function (16). Therefore, this study gives us important insight into the mechanism of emphysema progression and the management of patients with COPD.

We analyzed not only LAA% but also D to explore the mechanism of emphysema progression. The cumulative size distribution of the LAA clusters has been shown to follow a power law characterized by exponent D (4, 31–33). The values of D can be obtained by linear regression and calculated as the slope of the straight line in the log–log plot. The goodness-of-fit was assessed by the correlation coefficients (r). We determined that the values of r in all images were greater than 0.941, and that the mean \pm SD values of r in patients with and without exacerbations were 0.988 ± 0.009 and 0.987 ± 0.009 , respectively. These values are consistent with those reported in our previous study (4). The exponent D reflects the fractal dimension of terminal airspace geometry (4). Analyzing the fractal property has been shown to be useful for detecting early stages of COPD, predicting survival (33) or exercise capacity after lung volume reduction surgery in patients with COPD (32), and discriminating between hyperinflation and emphysema in patients with asthma (31). Other investigators have reported that microscopically measured mean perimeters of alveoli and alveolar ducts and mean interwall distances are correlated with

TABLE 3. ANNUAL CHANGE IN LUNG FUNCTION AND COMPUTED TOMOGRAPHY PARAMETERS: INTRA- AND INTERGROUP COMPARISONS BETWEEN PATIENTS WITH AND WITHOUT EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Parameter	Exacerbation (-)		Exacerbation (+)		P Value (between Groups)
	Value	P Value (within Group)	Value	P Value (within Group)	
FEV ₁ , ml	-43.7 (-90.1, -3.38)	0.002	-73.9 (-91.9, -4.7)	0.0002	0.46
%FEV ₁	-1.10 (-3.02, 0.67)	0.05	-2.05 (-3.07, 0.29)	0.01	0.40
D _{LCO} /V _A , ml/min/mm Hg/L	-0.50 (-1.25, -0.08)	0.0008	-0.53 (-1.39, 0.03)	0.002	0.97
LAA% (-910), %	0.16 (-0.38, 0.98)	0.18	1.63 (0.80, 2.42)	<0.0001	0.0002
LAA% (-930), %	0.24 (-0.46, 0.66)	0.27	1.92 (0.92, 2.70)	<0.0001	<0.0001
LAA% (-960), %	0.13 (-0.34, 0.68)	0.21	2.10 (1.09, 2.82)	<0.0001	<0.0001
D	-0.015 (-0.027, 0.015)	0.09	-0.059 (-0.010, -0.041)	<0.0001	<0.0001
CT-derived total lung volume, ml	52.0 (-88.8, 273.3)	0.11	-45.5 (-255.0, 223.3)	0.52	0.14

Definition of abbreviations: %FEV₁, FEV₁ as a percentage of the predicted value; CT = computed tomography; D_{LCO}/V_A, ratio of diffusing capacity to alveolar ventilation; LAA%, percentage of low-attenuation area.

Data are expressed as medians (25th, 75th percentile).

LAA% but not D (14). These reports suggest that LAA% and D are complementary tools in the assessment of emphysema. Therefore, the combination of analyzing fractal properties by D and quantifying emphysematous change by LAA% could give us greater insights than measuring only LAA%.

In this study, increases in LAA% and decreases in D were greater in patients with exacerbations than in those without exacerbations. The relationship of exacerbations to changes in these CT parameters of emphysema persisted after adjusting for baseline CT parameters. Furthermore, changes in LAA% showed a significant inverse correlation with changes in D. In our previous report (4), patients with COPD had a smaller D than healthy subjects. We interpreted these results by simulations using a two-dimensional elastic spring network model, and demonstrated that a break of the alveolar wall and coalescence of preexisting LAA clusters could reduce values of D but leave LAA% unchanged. We thus supposed that the destruction of alveolar walls and the coalescence of neighboring LAAs occur more frequently in patients with exacerbations than in those without, and that these structural changes are reflected by an increase in LAA% and decrease in D.

Given that our previous study was cross-sectional and that its simulation included an unchanging LAA%, we established a new simulation model in the present study to assess our hypothesis. Consequently, our observed result could not be reproduced by model A, which does not allow the coalescence of neighboring LAAs due to alveolar wall destruction. We

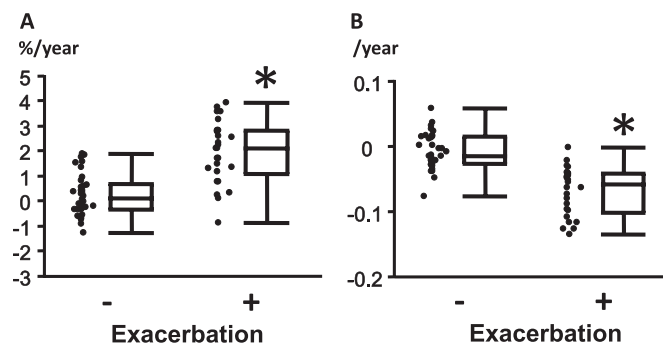


Figure 2. Change in (A) LAA% and (B) D in patients with and without a history of exacerbations (n = 26 and 34, respectively). *P < 0.0001 compared with patients without exacerbations. The horizontal line is the median value, the box is the interquartile range, and the whiskers indicate the range, excluding outlying and extreme values (i.e., points with values ≥ 1.5 box lengths from the upper or lower limits of the box). LAA% = percentage of the lung field occupied by low-attenuation areas.

therefore performed simulations using models B15 and B30, in which 15 or 30%, respectively, of selected pixels caused the coalescence of preexisting LAAs, while the remaining selected pixels only caused simple enlargement.

As shown in Figure 4, model B15 elegantly reproduced a reduction of D observed in patients with a history of exacerbations. This suggests that both destruction of the alveolar wall separating adjoining LAAs and enlargement of preexisting LAAs occur in exacerbations. We assume that preexisting LAAs could be more pathogenic than normal lung areas, and alveolar walls separating adjoining LAAs might be more vulnerable than those separating LAAs and normal lung areas. Enhanced airway inflammation, oxidative stress, and protease induction during exacerbation might contribute to this phenomenon.

We investigated the impact of exacerbations requiring systemic steroid and/or antibiotic treatment and then demonstrated that exacerbations are associated with emphysema progression. This suggests that the current dose and timing of such treatments might not be sufficient to prevent further emphysema progression in patients with COPD exacerbations. Although systemic steroid and antibiotics have been shown to be effective for relieving clinical symptoms and lung function (34–37), their

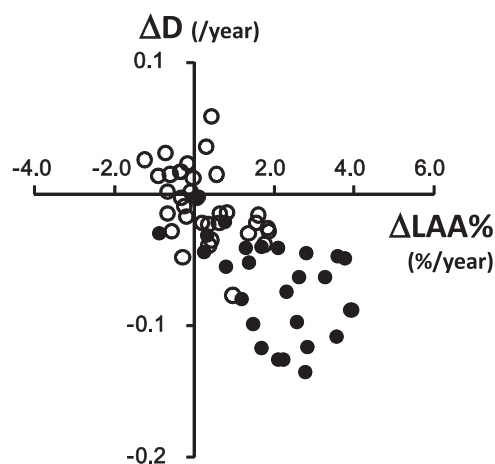


Figure 3. Relationship between changes in LAA% and D both in patients with and without a history of exacerbations. Solid circles and open circles show the change in patients with and without exacerbations, respectively. A significant correlation between an increase in LAA% and a decrease in D was found in each group ($r = -0.50$, $P = 0.009$ and $r = -0.52$, $P = 0.002$). LAA% = percentage of the lung field occupied by low-attenuation areas.

TABLE 4. STEPWISE MULTIVARIATE REGRESSION ANALYSIS SHOWING THE RELATIVE CONTRIBUTION OF EACH VARIABLE TO PREDICT CHANGES IN COMPUTED TOMOGRAPHY PARAMETERS OF EMPHYSEMA

	Coefficient	P Value	R ²
Change in LAA% (–960)			
Intercept	1.04		
Exacerbation (for the presence of a history of exacerbation)	0.92	<0.0001	0.41
Change in CT-derived lung volume, ml	0.001	0.001	0.10
Cumulative R ²			0.51
Change in D			
Intercept	–0.02		
Exacerbation (for the presence of a history of exacerbation)	–0.03	<0.0001	0.48
Cumulative R ²			0.48

Definition of abbreviations: CT = computed tomography; LAA%, percentage of low-attenuation area.

Exacerbation (two categories; the presence vs. the absence of a history of exacerbation), change in CT-derived lung volume, and baseline LAA% or D were included as candidate independent variables.

After stepwise variable selection, baseline LAA% was excluded in the model for change in LAA%, and baseline D and change in CT-derived lung volumes were excluded in the model for change in D.

suppressive effects on emphysema progression have not been evaluated in clinical studies. Our study is thus of great importance as it emphasizes the need to assess the progression of emphysematous change in studies of COPD exacerbations.

In the present study, the frequency of exacerbations observed was less than that seen in previous clinical trials. Prospective interventional studies such as the Understanding the Potential Long-term Impact of Tiotropium (UPLIFT) Study (38) and the Toward a Revolution in COPD Health (TORCH) Study (39) showed an incidence of exacerbations ranging from 0.73 to 1.13 per person per year. In our study, the rate of exacerbations in all 60 patients (including those with and without a history of exacerbations) averaged 0.36 per person per year (Table E1). There are several potential explanations for the discrepancy in the rate of exacerbations. First, our study design allowed for the prescription of all respiratory therapies, many of which have been shown to lessen the rate of exacerbations (38, 39). In addition, almost all patients received annual influenza vaccinations and about half also received a pneumococcal vaccination. These vaccinations could reduce the risk of exacerbations (40, 41). Second, during the study, we excluded four patients whose chest X-rays showed lung infiltrate suggesting pneumonia because the influence of pneumonia on CT parameters of emphysema is unknown. We also excluded two patients who died of pneumonia. The frequency of exacerbations has been shown to be associated with the risk of pneumonia (42). Third, the baseline and follow-up examinations were performed at least 4 weeks after resolution of the last exacerbation. We excluded three patients from the follow-up study who could not remain exacerbation-free. Fourth, to investigate changes in CT parameters of emphysema, we excluded five patients whose baseline CT showed bronchiectasis. Bronchiectasis has been reported to cause severe exacerbations and lower bacterial colonization (43), which might increase the exacerbation frequency. These exclusions may not have taken place in previous studies. According to the large Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort, there is one phenotype that is susceptible to exacerbations (44). Our exclusion criteria, including the appearance of pneumonia or existence of bronchiectasis, might have made the portion of these exacerbation-susceptible patients relatively low. However, it should be emphasized that even in patients with such a relatively low incidence of exacerbations, changes in CT parameters of emphysema have been shown to be greater than in those without exacerbations.

Although patients with exacerbations might have experienced more exacerbations in the past than those without exacerbations, baseline LAA% did not differ between the two groups. There are several potential explanations for this finding.

In addition to a history of exacerbations, other factors such as disease duration could affect baseline LAA%. Although the ECLIPSE Study showed that patients with a history of frequent exacerbations have been shown to experience exacerbations frequently in the following 3 years (44), the development and progression take a long time, and patients with exacerbations might not always have suffered from frequent exacerbations from disease onset to study entry.

We prospectively recorded changes in respiratory symptoms and health care utilization (HCU) events, using a diary card in the present study. Symptom-defined episodes and HCU events were found in 35 and 32 patients, respectively. When we alternatively defined symptomatic episodes or HCU events as an exacerbation, changes in LAA% or D were still significantly different between patients with and without exacerbations (symptomatic episode: median change in LAA%, 1.60 vs. –0.03%/yr, $P = 0.0001$, respectively, and median change in D, –0.05 vs. –0.01/yr, $P = 0.0001$, respectively; HCU: median change in LAA%, 1.62 vs. 0.13%/yr, $P = 0.0001$, respectively, and median change in D, –0.05 vs. –0.01/yr, $P = 0.0001$, respectively).

Failure to inspire to the same extent at the entry and follow-up scan could skew the lung density (45). We measured total lung volume to estimate the influence of inspiration level, using all CT images of the lung. As shown in Table 3, there were no significant changes in these lung volumes within patients. The degrees of changes were not different between patients with and without exacerbations. In stepwise multivariate regression analysis (Table 4), exacerbations contributed to changes in LAA% ($R^2 = 0.41$) or D ($R^2 = 0.48$) independent of changes in lung volume and baseline CT parameters of emphysema. In addition, it is interesting that in these analyses, changes in CT-derived lung volume contributed to changes in LAA% ($R^2 = 0.10$), but not to changes in D. The change in lung volume did not correlate with the change in D not only in the patients with exacerbations, but also in those without exacerbations (Figure E2). These indicate that changes in D in the longitudinal study could be less influenced by the level of inspiration at CT scanning than changes in LAA%.

This study used one scanner to avoid the effects of inter-scanner errors, and we routinely calibrated the equipment using air and water phantoms as in our previous longitudinal study (26). Moreover, CT numbers were corrected in all images using air densities sampled from the intrathoracic trachea of each subject to eliminate the influence of X-ray tube aging. CT numbers in intrathoracic organs could be influenced by the chest wall. Extracorporeal air density might be used to see differences in CT numbers among different CT scanners. However, we used intrathoracic tracheal air density because

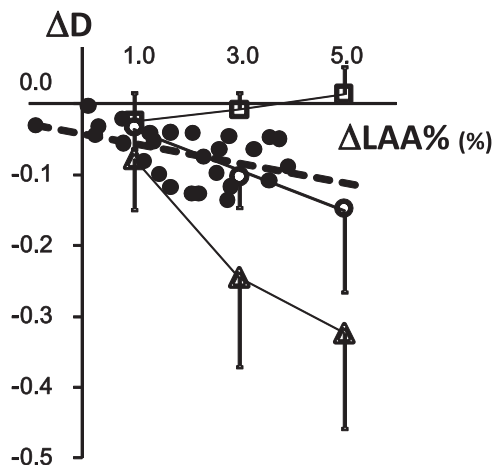


Figure 4. Change in LAA% and D obtained from model simulations and patients with a history of exacerbations. *Open squares* show mean values obtained by model A, which could not allow coalescence of preexisting LAAs. *Open circles* and *open triangles* show mean values obtained by model B15 and B30, respectively, which caused coalescence of LAAs at different rates (15 or 30%). *Error bars* represent the SD. $n = 8$ per each model. *Solid circles* show original data from patients with a history of exacerbations. The *dotted line* represents the regression line.

the reference should be as close to the target tissue as possible (46) and interscanner variability was not a problem in this study. When we measured LAA% using CT images with a slice thickness of 2 mm in the previous studies (3, 4, 24, 25), the threshold between LAA and normal lung area was defined as -960 Hounsfield units (HU) because the mean -2 standard deviation (SD) of the CT number in the volunteer lungs was approximately -960 HU (47). As a different slice thickness (0.5 mm) might influence the threshold value and data, we calculated LAA% using three threshold values, -910 , -930 , and -960 HU, to ensure that similar differences of changes in LAA% between patients with and without exacerbations could be detected. When -960 HU was used as the threshold, the baseline LAA% significantly correlated with FEV₁, %FEV₁, and DL_{CO}/VA. These findings are consistent with our previous reports (3, 4), indicating that -960 HU was a reasonable threshold.

Although baseline FEV₁, %FEV₁, and DL_{CO}/VA correlated with baseline LAA% and D, changes in LAA% and D did not correlate with changes in FEV₁, %FEV₁, and DL_{CO}/VA. This might have been because in addition to the extent of emphysema, other factors such as airway remodeling influenced the change in lung function. Moreover, the association of LAA% and D with FEV₁ and DL_{CO}/VA at study entry was thought to reflect long-term lung inflammatory response and destruction. A 2-year observational period might have been too short to detect correlations of changes in these parameters.

In patients without exacerbations, FEV₁ was significantly decreased after the 2-year follow-up, although LAA% was not changed (Table 3). It should be noted that not only the extent of emphysema or airway remodeling, but also aging itself, might influence the FEV₁ decline. It has been reported in the Framingham Offspring Cohort that FEV₁ decreases by about 20 ml/year even in healthy never-smokers (48).

There are several limitations to the present study. First, the sample size is small. Second, the observational period of 2 years is not long. However, as we performed a single-center study and used only one scanner, the instability of CT scanners was less problematic than in multicenter studies. In addition, exacerbations were prospectively recorded by at least two respiratory

physicians who were unaware of CT data. These advantages were thought sufficient to overcome the small sample size and length of observational period. Third, although frequent exacerbations have been reported to be associated with a decline in FEV₁ (5), the present study found no significant difference in annual changes in FEV₁ between the two groups. Additional medications used, such as tiotropium or fluticasone/salmeterol, might make it difficult to detect any differences. Fourth, many exacerbations were treated in the outpatient setting, and few exacerbations required hospitalization (Table E1). We could not assess how the severity of exacerbations would affect the extent of emphysema progression. This should be investigated in future studies. Fifth, because the size of the lung CT voxel could be larger than that of an alveolus and one voxel could not be completely filled with lung tissue, changing from a normal density voxel to a low-attenuation voxel may not strictly correspond to the pathological change of emphysema progression. However, it is well known that LAAs in CT images closely correlate with the extent of pathological emphysema (10–12). We previously demonstrated that D is greatly related to the fractal dimension of the alveolar tissue structure in the lung specimen (4). We thus assume that our methodology can unveil the features of emphysema progression.

In conclusion, emphysema progression assessed by CT was greater in patients with a history of exacerbations than in those without. Both increases in LAA% and decreases in D were found, suggesting that exacerbations are associated with the coalescence of neighboring preexisting LAAs. Hence, the management of exacerbations is important to prevent further emphysema progression.

Author Disclosure: N.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.M. and T.H. received support from the Grant-in-Aid Program. T.O., K.T., S.M., D.K., and E.O. do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. Y.H. and M.M. received support from the Grant-in-Aid Program.

Acknowledgment: The authors thank Akane Haruna, Megumi Kudo, Hirofumi Kiyokawa, and Tamaki Takahashi for assistance with data collection, and Koji Koizumi and Ryuzo Tanaka for technical assistance. The authors also thank Associate Professor Tatsuro Ishizaki and Professor Takeo Nakayama in the Department of Health Informatics at the Kyoto University School of Public Health for help with the statistical analyses.

References

1. Roisin RR. Global strategy for diagnosis, management, and prevention of COPD updated 2009. Available from: <http://www.goldcopd.com>
2. American Thoracic Society. The definition of emphysema: report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases Workshop. *Am Rev Respir Dis* 1985;132:182–185.
3. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, Itoh H, Pare PD, Hogg JC, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. *Am J Respir Crit Care Med* 2000;162:1102–1108.
4. Mishima M, Hirai T, Itoh H, Nakano Y, Sakai H, Muro S, Nishimura K, Oku Y, Chin K, Ohi M, et al. Complexity of terminal airspace geometry assessed by lung computed tomography in normal subjects and patients with chronic obstructive pulmonary disease. *Proc Natl Acad Sci USA* 1999;96:8829–8834.
5. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–852.
6. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–1422.
7. Miravittles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, Vereza H, Murio C, Ros F, Vidal R. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax* 2004;59:387–395.
8. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in

- patients with chronic obstructive pulmonary disease. *Thorax* 2005;60:925–931.
9. Wouters EF. The burden of COPD in the Netherlands: results from the Confronting COPD Survey. *Respir Med* 2003;97:S51–S59.
 10. Muller NL, Staples CA, Miller RR, Abboud RT. “Density mask”: an objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782–787.
 11. Sakai N, Mishima M, Nishimura K, Itoh H, Kuno K. An automated method to assess the distribution of low attenuation areas on chest CT scans in chronic pulmonary emphysema patients. *Chest* 1994;106:1319–1325.
 12. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;152:653–657.
 13. Madani A, Zanen J, de Maertelaer V, Gevenois PA. Pulmonary emphysema: objective quantification at multi-detector row CT: comparison with macroscopic and microscopic morphometry. *Radiology* 2006;238:1036–1043.
 14. Madani A, Van Muylem A, de Maertelaer V, Zanen J, Gevenois PA. Pulmonary emphysema: size distribution of emphysematous spaces on multidetector CT images—comparison with macroscopic and microscopic morphometry. *Radiology* 2008;248:1036–1041.
 15. Dirksen A, Piitulainen E, Parr DG, Deng C, Wencker M, Shaker SB, Stockley RA. Exploring the role of CT densitometry: a randomised study of augmentation therapy in α_1 -antitrypsin deficiency. *Eur Respir J* 2009;33:1345–1353.
 16. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, Hirai T, Niimi A, Nishimura K, Chin K, *et al.* CT scan findings of emphysema predict mortality in COPD. *Chest* 2010;138:635–640.
 17. Mandelbrot B. The fractal geometry of nature. New York: Freeman; 1983.
 18. McNamee JE. Fractal perspectives in pulmonary physiology. *J Appl Physiol* 1991;71:1–8.
 19. Suki B. Fluctuations and power laws in pulmonary physiology. *Am J Respir Crit Care Med* 2002;166:133–137.
 20. Sato A, Hirai T, Imura A, Kita N, Iwano A, Muro S, Nabeshima Y, Suki B, Mishima M. Morphological mechanism of the development of pulmonary emphysema in *klotho* mice. *Proc Natl Acad Sci USA* 2007;104:2361–2365.
 21. Terada K, Muro S, Ohara T, Kudo M, Ogawa E, Hoshino Y, Hirai T, Niimi A, Chin K, Mishima M. Abnormal swallowing reflex and COPD exacerbations. *Chest* 2010;137:326–332.
 22. Terada K, Muro S, Ohara T, Haruna A, Marumo S, Kudo M, Ogawa E, Hoshino Y, Hirai T, Niimi A, *et al.* Cough-reflex sensitivity to inhaled capsaicin in COPD associated with increased exacerbation frequency. *Respirology* 2009;14:1151–1155.
 23. Terada K, Muro S, Sato S, Ohara T, Haruna A, Marumo S, Kinose D, Ogawa E, Hoshino Y, Niimi A, *et al.* Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. *Thorax* 2008;63:951–955.
 24. Ogawa E, Nakano Y, Ohara T, Muro S, Hirai T, Sato S, Sakai H, Tsukino M, Kinose D, Nishioka M, *et al.* Body mass index in male patients with COPD: correlation with low attenuation areas on CT. *Thorax* 2009;64:20–25.
 25. Ohara T, Hirai T, Muro S, Haruna A, Terada K, Kinose D, Marumo S, Ogawa E, Hoshino Y, Niimi A, *et al.* Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. *Chest* 2008;134:1244–1249.
 26. Ohara T, Hirai T, Sato S, Terada K, Kinose D, Haruna A, Marumo S, Nishioka M, Ogawa E, Nakano Y, *et al.* Longitudinal study of airway dimensions in chronic obstructive pulmonary disease using computed tomography. *Respirology* 2008;13:372–378.
 27. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173:1114–1121.
 28. Mercer PF, Shute JK, Bhowmik A, Donaldson GC, Wedzicha JA, Warner JA. MMP-9, TIMP-1 and inflammatory cells in sputum from COPD patients during exacerbation. *Respir Res* 2005;6:151.
 29. Drost EM, Skwarski KM, Sauleda J, Soler N, Roca J, Agusti A, MacNee W. Oxidative stress and airway inflammation in severe exacerbations of COPD. *Thorax* 2005;60:293–300.
 30. Qiu Y, Zhu J, Bandi V, Atmar RL, Hattotuwa K, Guntupalli KK, Jeffery PK. Biopsy neutrophilia, neutrophil chemokine and receptor gene expression in severe exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;168:968–975.
 31. Mitsunobu F, Ashida K, Hosaki Y, Tsugeno H, Okamoto M, Nishida K, Takata S, Yokoi T, Mishima M, Tanizaki Y. Complexity of terminal airspace geometry assessed by computed tomography in asthma. *Am J Respir Crit Care Med* 2003;167:411–417.
 32. Coxson HO, Whittall KP, Nakano Y, Rogers RM, Sciruba FC, Keenan RJ, Hogg JC. Selection of patients for lung volume reduction surgery using a power law analysis of the computed tomographic scan. *Thorax* 2003;58:510–514.
 33. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, DeCamp MM, Benditt J, Sciruba F, Make B, *et al.* Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am J Respir Crit Care Med* 2006;173:1326–1334.
 34. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet* 1999;354:456–460.
 35. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996;154:407–412.
 36. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA; Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999;340:1941–1947.
 37. Stockley RA, O’Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000;117:1638–1645.
 38. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–1554.
 39. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
 40. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest* 2004;125:2011–2020.
 41. Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M, Merino M, Perez J, Lima J. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 2006;61:189–195.
 42. Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Willits LR, Yates JC, Vestbo J. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH Study results. *Eur Respir J* 2009;34:641–647.
 43. Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, Reznick RH, Wedzicha JA. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:400–407.
 44. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128–1138.
 45. Coxson HO, Mayo J, Lam S, Santyr G, Parraga G, Sin DD. New and current clinical imaging techniques to study chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:588–597.
 46. Boden SD, Goodenough DJ, Stockham CD, Jacobs E, Dina T, Allman RM. Precise measurement of vertebral bone density using computed tomography without the use of an external reference phantom. *J Digit Imaging* 1989;2:31–38.
 47. Mishima M, Hirai T, Jin Z, Oku Y, Sakai N, Nakano Y, Sakai H, Chin K, Ohi M, Kawakami K, *et al.* Standardization of low attenuation area versus total lung area in chest X-ray CT as an indicator of chronic pulmonary emphysema. *Front Med Biol Eng* 1997;8:79–86.
 48. Kohansal R, Martinez-Cambor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham Offspring Cohort. *Am J Respir Crit Care Med* 2009;180:3–10.