monotherapy for COPD has shown only limited benefit in some studies [3,4], while improvements in symptom control, lung function and all-cause mortality has been reported with the combination of ICS/LABA budesonide/formoterol [5-7] and fluticasone propionate/salmeterol [8]. Consequently, COPD guidelines (Global Initiative for Chronic Obstructive Lung Disease [GOLD]) include bronchodilator therapy as the primary treatment in COPD without mandating concomitant use of anti-inflammatory therapy [9].

Some concerns have existed in the past regarding the safety of LABAs in patients with airway disease, fueled by a meta-analysis conducted by Salpeter et al [10] that suggested there was a doubling of the risk of respiratory death in COPD with the use of a LABA compared with placebo. In a more recent meta-analysis, Rodrigo and coworkers [11] came to a different conclusion to those of Salpeter and colleagues [10], reporting no increased risk of mortality in COPD patients using LABAs. The difference in these findings may partly relate to differences in trial selection [10,11].

The objective of this study was to evaluate the efficacy and safety of two doses of the LABA formoterol, 4.5 and 9 μg twice daily (bid), in Japanese and European patients with COPD.

Methods

Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multinational (Japan, Romania, Russia and Ukraine) phase III study (Study code: D5122C00001; ClinicalTrials.gov identifier: NCT00628862) conducted at 65 centers in Japan and Europe. The study protocol was approved by the Institutional Review Board/Ethics Committee at all participating sites and the study was performed in accordance with the Declaration of Helsinki and the AstraZeneca policy on Bioethics and Human Biological Samples. All patients provided written informed consent prior to enrolment into the study.

The primary objective was to show that formoterol 4.5 and 9 μg bid for 12 weeks were superior to placebo in Japanese and European patients with COPD using forced expiratory volume in 1 second (FEV_1) 60-min post-dose as the primary outcome variable.

The study consisted of an enrolment period for withdrawal of pre-study medication, a 2-week run-in period and a 12-week treatment period. Clinic visits took place at baseline (on completion of the 2-week run-in period), and at weeks 4, 8, and 12 of the treatment period.

Study population

Male and female patients ≥ 40 years of age with a clinical diagnosis of COPD (post-bronchodilator FEV_1 < 80% of predicted normal, and post-bronchodilator FEV_1/forced vital capacity [FVC] < 70%) and current COPD symptoms were eligible for inclusion. Patients were also required to have a current or previous smoking history of ≥ 10 pack-years and a symptom score of at least 2 points (combination of breathlessness, cough, and/or night time awakenings due to symptoms; each assessed by the patients on a scale of 0-4 where 0 = no symptoms and 4 = severe symptoms) on at least 6 of the last 10 days of the run-in period.

Patients with a history and/or current clinical diagnosis of asthma were excluded from participating, as were those with a history and/or current clinical diagnosis of atopic disease such as allergic rhinitis. Additional exclusion criteria included use of an ICS within 4 weeks of the run-in period, COPD exacerbation requiring hospitalization and/or a course of antibiotics and/or systemic steroid therapy within 4 weeks of the run-in period, significant or unstable ischemic heart disease, or other relevant cardiovascular conditions, any other respiratory tract disorders or significant disease likely to place the patient at risk during the study.

Study treatments

Patients received inhaled formoterol 4.5 or 9 μg twice daily (bid) via Turbuhaler® or matching placebo for 12 weeks. Study treatments were taken at approximately the same time every morning and evening and immediately after measuring peak expiratory flow (PEF).

Salbutamol 100 μg/actuation via a pressurized metered-dose inhaler (pMDI) was available to relieve symptoms throughout the study period and patients could continue to take short-acting anticholinergics. Patients previously receiving long-acting anticholinergics were switched to short-acting anticholinergics at the start of the enrolment period. Glucocorticosteroid treatment was not permitted at any time during the study.

Outcomes

The primary outcome variable was change (ratio) from baseline to the end of treatment period in FEV_1 60-min post-dose. Secondary outcome variables included spirometry, diary variables, and assessment of health-related quality-of-life (HRQL). Spirometry endpoints were FVC 60-min post-dose, FEV_1 and FVC pre-dose and 5-min post-dose. Diary variables were morning and evening PEF, COPD symptom scores (night-time awakenings due to symptoms, breathlessness, and cough), and use of salbutamol as reliever medication (measured as inhalations/day). HRQL was assessed using the St George's Respiratory Questionnaire (SGRQ).

Safety and tolerability were assessed by evaluation of the nature, incidence and severity of adverse events, clinical laboratory variables including clinical chemistry,

hematology, and urinalysis, 12-lead electrocardiogram (ECG), blood pressure and pulse rate.

Statistical analyses

Sample size selection was based on clinical data derived from a published 6-month study [12]. With a two-sided test at level 0.05 and 176 patients per treatment group, the study was determined to have 80% power to detect a difference between the treatment groups of at least 0.06 L in the change from baseline FEV_1 value.

A last-observation-carried-forward (LOCF) approach was used to account for any missing week 6 data. The comparison of formoterol 4.5 and 9 μg bid with placebo was performed on the primary endpoint, mean change from baseline in FEV_1 60-min post-dose, using an analysis of covariance (ANCOVA) model including country and treatment as fixed factors and the baseline value as covariate. A two-sided 5% significance level was used and 95% confidence intervals (CIs) for the mean difference between each dose of formoterol and placebo were calculated. The multiplicity of statistical tests was adjusted by a "closed testing procedure" under which the null hypothesis that 9 μg bid was equal to placebo was tested; if this null hypothesis was rejected then the 4.5 μg bid dose versus placebo was tested.

As for FEV_1, the comparison of active treatments (formoterol 4.5 μg and 9 μg bid) with placebo for the secondary variables was performed using an ANCOVA model including country and treatment as fixed factors and the baseline value as covariate. The ANCOVA model used in the analysis was multiplicative. A two-sided 5% significance level was used and the "closed testing procedure" was applied.

The incidence of adverse events was calculated, and results from laboratory safety measurements, vital signs, and ECG, were analyzed primarily by means of descriptive statistics.

Results

A total of 613 patients were randomized to treatment (formoterol 4.5 μg bid n = 206; 9 μg bid n = 199; placebo n = 208); 539 (87.9%) patients were male; 324 (52.9%) patients were Japanese and 289 (47.1%) were European. The mean duration of COPD since diagnosis was 4.5 years (range 0-39 years), the mean post-bronchodilator FEV_1 was 51% of predicted normal, and the FEV_1/FVC was 46%. Of the 613 randomized patients, 563 patients completed the study (formoterol 4.5 μg bid n = 195; 9 μg bid n = 182; placebo n = 186) and 50 patients discontinued treatment (formoterol 4.5 μg bid n = 11; 9 μg bid n = 17; placebo n = 22); the flow of patients through the study and reasons for discontinuation are shown in Figure 1. There were no major differences in baseline characteristics between the three treatment groups (Table 1).

Disease-related treatment prior to enrolment included anticholinergics (55.5% of patients), inhaled selective β_2-agonists (49.1%), xanthines (18.6%), mucolytics (16.0%), inhaled β-agonists/other drugs for obstructive airway disease (10.8%) and systemic selective β_2-agonists (7.0%); these prior treatments were well balanced across the three treatment groups.

Efficacy

At the end of the treatment period, increases in FEV_1 60-min post-dose compared with baseline were significantly greater in the formoterol 4.5 and 9 μg bid groups (formoterol 4.5 μg: 112.6% of baseline; formoterol 9 μg: 113.4% of baseline; $p < 0.001$ for both groups) than in the placebo group (Table 2; Figure 2). No difference could be detected (0.7%) between the formoterol 4.5 μg and 9 μg bid groups (ratio of formoterol 9 μg vs. 4.5 μg 100.7%; $p = 0.643$)(Figure 2).

Significantly greater ($p < 0.05$) improvements in all of the secondary outcome measures (vs. baseline) were observed with the formoterol 4.5 and 9 μg bid groups compared with those seen in the placebo group (Tables 2 and 3). While both formoterol 4.5 and 9 μg bid significantly improved the SGRQ total score compared with placebo (-3.74 and -4.45, respectively; both $p \leq 0.001$), the proportion of patients with a clinically relevant improvement in SGRQ total score of > 4 units was statistically significantly greater for formoterol 9 μg bid vs. placebo (59.2% vs. 41.3%; $p < 0.001$) but not formoterol 4.5 μg bid vs. placebo (50.2% vs. 41.3%; $p = 0.0682$) (Figure 3). The difference between the two formoterol doses in the proportion of patients with an improvement in SGRQ total score of > 4 units approached statistical significance ($p = 0.0757$). A similar profile was observed when the SGRQ impact domain was evaluated separately (Figure 3).

Similarly, while both formoterol 4.5 and 9 μg bid significantly reduced the use of salbutamol as reliever medication compared with placebo (9 μg vs. placebo difference: -0.55, $p < 0.001$; 4.5 μg vs. placebo difference: -0.27, $p = 0.027$), the reduction observed in patients receiving formoterol 9 μg bid was significantly greater than that seen in those receiving 4.5 μg bid (9 μg vs. 4.5 μg difference: -0.27, $p = 0.029$) (Table 3; Figure 4).

Tolerability

Formoterol was well tolerated during 12 weeks' treatment; overall, 99 adverse events were reported by 69/206 (34%) patients receiving formoterol 4.5 μg bid, 87 adverse events by 63/199 (32%) patients receiving formoterol 9 μg bid and 100 adverse events by 69/208 (33%) patients receiving placebo. The majority of

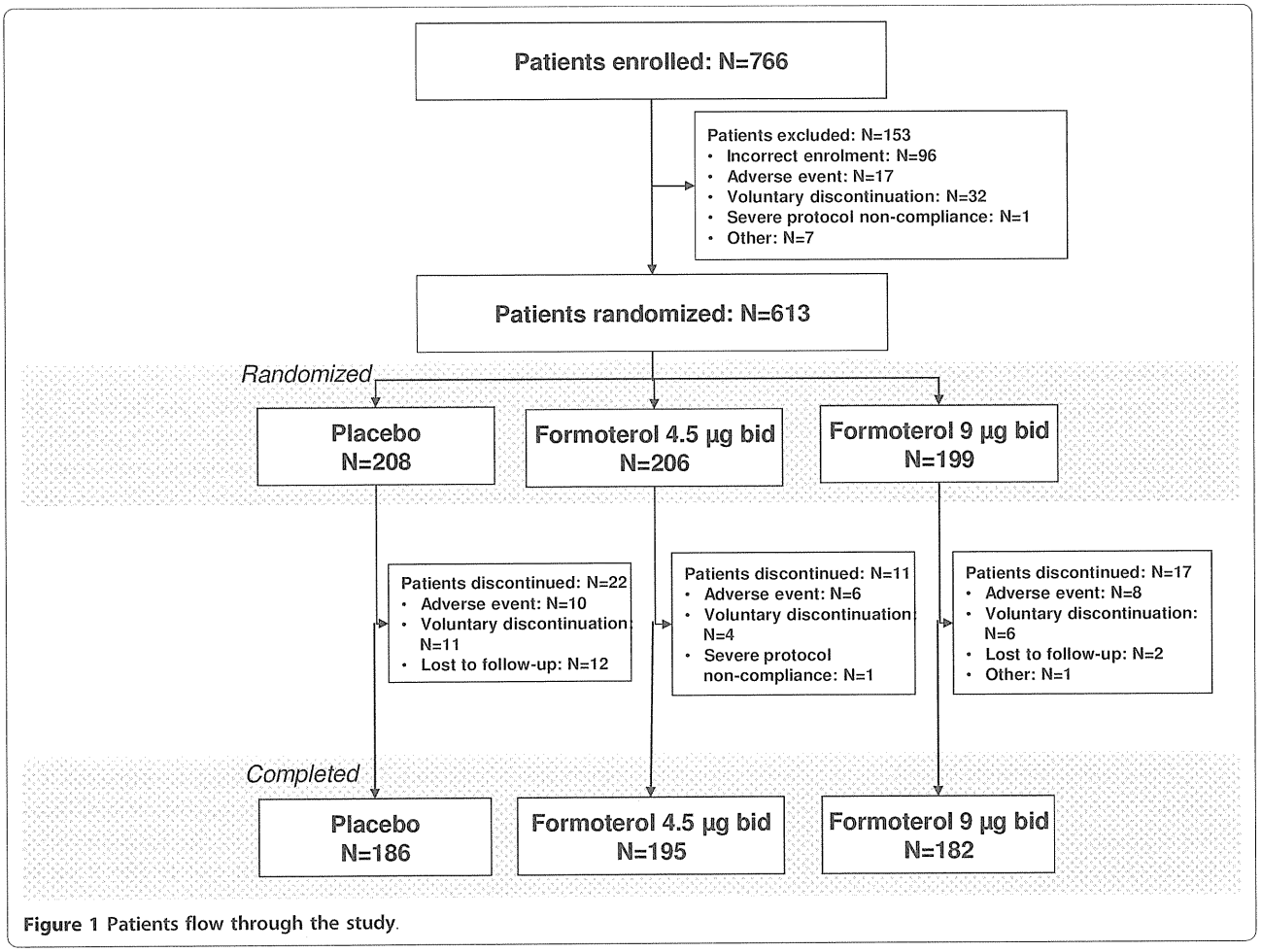

Figure 1 Patients flow through the study.

Table 1 Patients' baseline characteristics by treatment group at study entry (visit 2)

	Placebo	Formoterol 4.5 µg	Formoterol 9 µg
N	208	206	199
Mean age, years (range)	66.3 (40-86)	66.7 (41-85)	67.2 (44-88)
Patients ≥ 65 years, %	59.6%	64.6%	60.8%
Male, %	89.4%	88.8%	85.4%
Japanese/European, n (%)	110/98 (52.9%/47.1%)	106/100 (51.5%/48.5%)	108/91 (54.3%/45.7%)
Mean smoking pack years (range)	47.4 (10-152)	46.1 (10-150)	46.5 (11-175)
Mean duration of disease, years (range)	4.3 (0-25)	4.2 (0-39)	4.9 (0-34)
Mean FEV_1, L (range)[a]	1.37 (0.48-3.17)	1.30 (0.48-3.10)	1.30 (0.25-2.72)
Mean FEV_1, % of predicted normal (range)[a]	52.5 (16.6-83.7)	50.4 (22.0-79.4)	51.5 (9.3-79.5)
Patients with $FEV_1 \leq 50\%$, %	43.3%	50.5%	48.2%
Mean FEV_1/FVC ratio, % (range)[a]	45.6 (20.5-68.8)	44.6 (23.0-70.4)	46.5 (18.1-77.2)
Mean FEV_1 reversibility, % (range)	11.3 (-30.3-67.2)	10.5 (-17.9-61.6)	10.7 (-57.4-63.6)

[a]Pre-bronchodilator value.

Table 2 Mean values at baseline and post-treatment for spirometric and other parameters

	Placebo (n = 208)	Formoterol 4.5 μg (n = 206)	Formoterol 9 μg (n = 199)
60-min post-dose FEV_1, L			
Baseline	1.23	1.18	1.16
Post-treatment	1.25	1.33	1.31
Ratio to baseline (%)	101.3	112.6	113.4
Pre-dose FEV_1, L			
Baseline	1.23	1.18	1.16
Post-treatment	1.24	1.23	1.21
Ratio to baseline (%)	99.8	104.5	104.7
5-min post-dose FEV_1, L			
Baseline	1.23	1.18	1.16
Post-treatment	1.24	1.30	1.28
Ratio to baseline (%)	101.3	110.2	110.2
60-min post-dose FVC, L			
Baseline	2.77	2.71	2.61
Post-treatment	2.82	2.98	2.87
Ratio to baseline (%)	102.1	109.7	109.9
Pre-dose FVC, L			
Baseline	2.77	2.71	2.61
Post-treatment	2.80	2.81	2.70
Ratio to baseline (%)	100.7	103.6	103.4
5-min post-dose FVC, L			
Baseline	2.77	2.71	2.61
Post-treatment	2.80	2.94	2.84
Ratio to baseline (%)	101.6	108.5	108.9
Morning PEF, L/min			
Run-in	223.8	211.9	215.0
Treatment	227.6	228.1	233.5
Change from run-in	3.6	16.3	18.3
Evening PEF, L/min			
Run-in	233.8	221.4	221.9
Treatment	236.5	234.6	237.5
Change from run-in	2.4	13.2	15.8
Night-time awakening, score/day			
Run-in	0.73	0.66	0.83
Treatment	0.68	0.53	0.66
Change from run-in	-0.05	-0.13	-0.17
Breathlessness, score/day			
Run-in	1.65	1.51	1.72
Treatment	1.38	1.11	1.28
Change from run-in	-0.26	-0.41	-0.45
Cough, score/day			
Run-in	1.46	1.44	1.63
Treatment	1.26	1.11	1.21
Change from run-in	-0.20	-0.33	-0.41
Total symptom score			
Run-in	3.84	3.61	4.19
Treatment	3.32	2.75	3.14
Change from run-in	-0.51	-0.86	-1.04
Use of salbutamol, inhalations/day			
Run-in	1.86	2.09	2.40
Treatment	1.63	1.52	1.50
Change from run-in	-0.23	-0.60	-0.97
SGRQ total score			
Baseline	44.9	43.4	44.0
Last available score	42.9	38.2	38.2
Change from baseline	-2.0	-5.5	-6.4

adverse events were of mild or moderate intensity and the three treatment groups displayed similar patterns of adverse events (Table 4). The most frequently reported adverse events were nasopharyngitis, COPD exacerbation, and bronchitis complication.

Two deaths were reported in the formoterol 4.5 μg bid group, one as a result of acute sudden cardiopulmonary failure and the second due to unknown causes (this was in a 77-year-old male; cause of death was classified as respiratory standstill); neither was considered by the investigators to be related to study treatment. Serious adverse events were reported by 4 patients receiving formoterol 4.5 μg bid, 7 patients taking formoterol 9 μg bid and 4 patients on placebo. Six patients discontinued treatment due to adverse events in the formoterol 4.5 μg bid group, 8 patients discontinued in the 9 μg bid group and 10 discontinued in the placebo group.

There were no clinically significant changes in any of the three treatment groups in mean values over time for

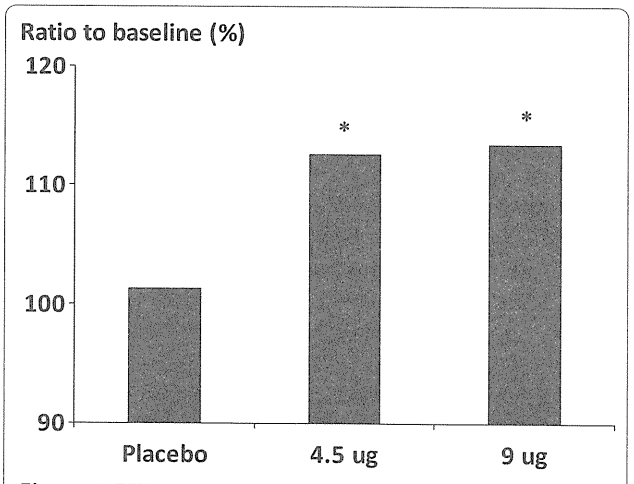

Figure 2 FEV_1 at 60-min post-dose in patients with COPD receiving formoterol or placebo; *p < 0.001 vs. placebo. FEV_1 at 60-min post-dose (ratio to baseline) in patients with COPD receiving formoterol 4.5 or 9 μg twice daily or placebo. *p < 0.001 vs. placebo.

Table 3 Differences between treatments (ratio for FEV_1 and FVC, absolute values for other variables) for spirometric and other parameters

Variable	9 μg vs. Placebo (p-value)	4.5 μg vs. Placebo (p-value)	9 μg vs. 4.5 μg (p-value)
60-min post-dose FEV_1, L	1.11 (< 0.001)	1.11 (< 0.001)	1.01 (0.643)
Pre-dose FEV_1, L	1.04 (0.002)	1.04 (0.002)	1.00 (0.955)
5-min post-dose FEV_1, L	1.09 (< 0.001)	1.09 (< 0.001)	1.00 (0.984)
60-min post-dose FVC, L	1.07 (< 0.001)	1.07 (< 0.001)	0.99 (0.642)
Pre-dose FVC, L	1.02 (0.135)	1.03 (0.026)	0.99 (0.483)
5-min post-dose FVC, L	1.07 (< 0.001)	1.07 (< 0.001)	1.00 (0.982)
Morning PEF, L/min	15.30 (< 0.001)	12.86 (< 0.001)	2.45 (0.360)
Evening PEF, L/min	13.78 (< 0.001)	10.85 (< 0.001)	2.93 (0.260)
Night-time awakening, score/day	-0.09 (0.038)	-0.10 (0.020)	0.01 (0.816)
Breathlessness, score/day	-0.17 (0.002)	-0.18 (0.001)	0.01 (0.822)
Cough, score/day	-0.13 (0.013)	-0.12 (0.023)	-0.01 (0.809)
Total symptom score	-0.41 (0.001)	-0.62 (0.001)	-0.25 (0.883)
Use of salbutamol, inhalations/day	-0.55 (< 0.001)	-0.27 (0.027)	-0.27 (0.029)
SGRQ total score	-4.45 (0.001)	-3.74 (0.001)	-0.71 (0.553)

ECG, pulse rate, blood pressure and any of the haematological, clinical chemistry and urinalysis variables.

Discussion

The results of the current study demonstrate that formoterol at doses of 4.5 μg and 9 μg bid is significantly more effective in improving lung function (FEV_1 60-min post-dose) in Japanese and European patients with COPD compared with placebo. The results of the secondary variables, both those related to lung function (for example, morning and evening PEF) and those related to daily diary card data (for example, COPD symptom score, and reliever medication use) and health-related quality-of-life (SGRQ total score) support the findings observed with the primary study endpoint. It is noteworthy that a clinically relevant benefit for formoterol 9 μg bid compared with 4.5 μg bid was demonstrated for the secondary endpoint of improved SGRQ

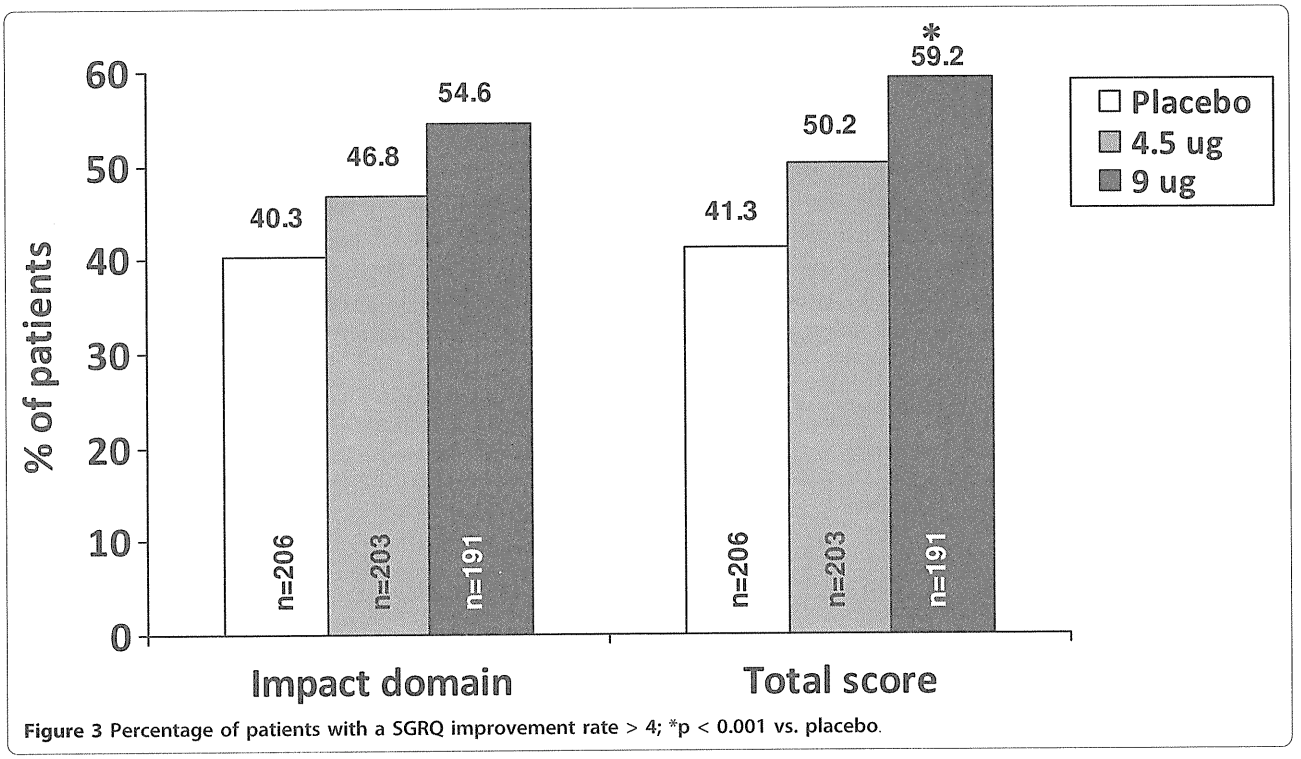

Figure 3 Percentage of patients with a SGRQ improvement rate > 4; *p < 0.001 vs. placebo.

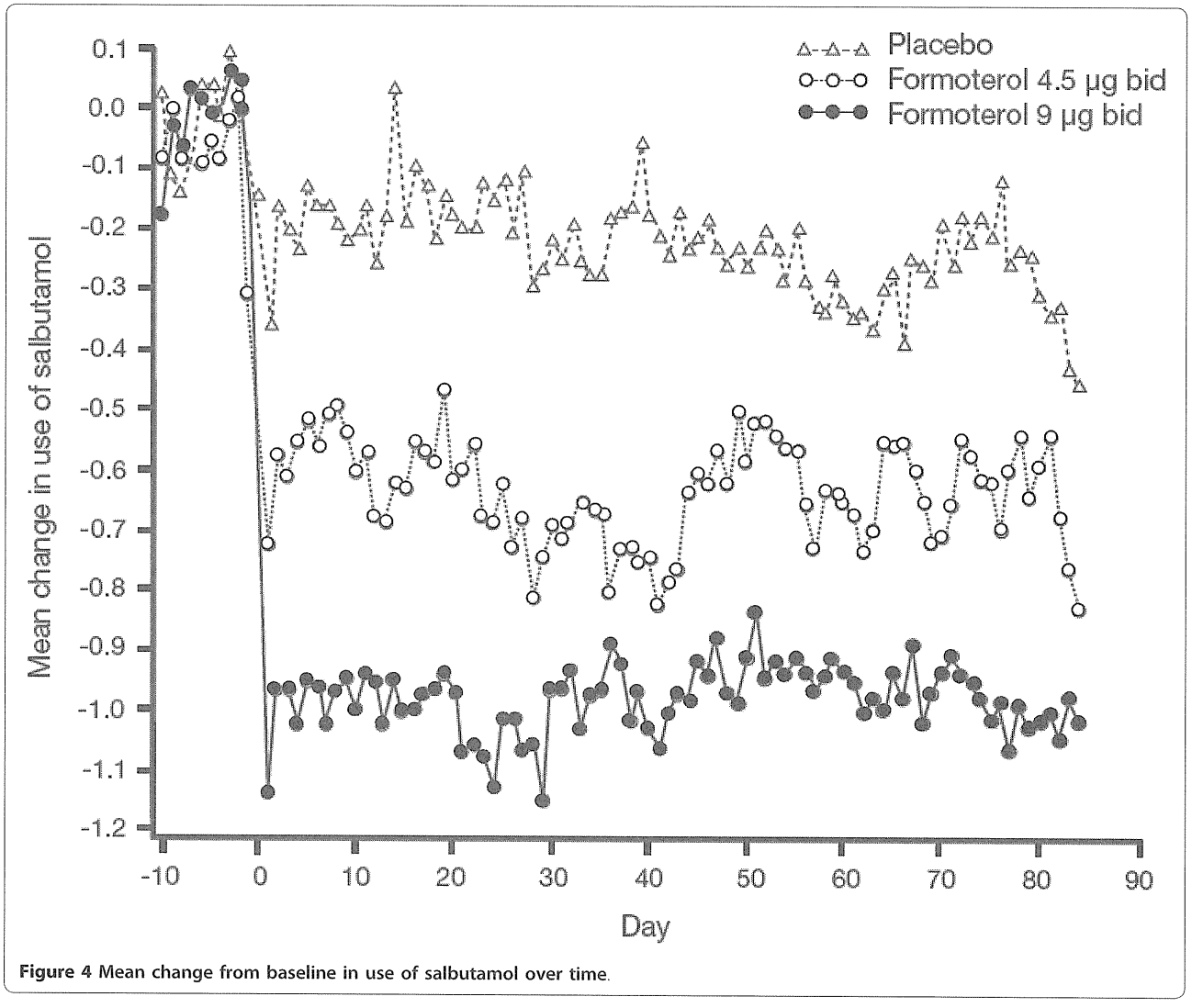

Figure 4 Mean change from baseline in use of salbutamol over time.

score and also a statistically significant improvement for formoterol 9 µg bid vs. 4.5 µg bid for use of reliever medication. The use of reliever medication was significantly lower in the formoterol 9 µg bid group compared with 4.5 µg bid, and the proportion of patients with a clinically relevant improvement in SGRQ total score of > 4 units [13] was statistically significantly greater for formoterol 9 µg bid vs. placebo but not formoterol 4.5 µg bid vs. placebo. While these results might not be that surprising, the additional reduction in reliever medication use and increase in the proportion of patients with a clinically relevant

Table 4 Adverse events with an incidence > 1

Adverse event, n (%)	Placebo (n = 208)	Formoterol 4.5 µg bid (n = 206)	Formoterol 9 µg bid (n = 199)
Nasopharyngitis	20 (9.6)	24 (11.7)	25 (12.6)
COPD exacerbation	17 (8.2)	10 (4.9)	8 (4.0)
Bronchitis complication	2 (1.0)	1 (0.5)	7 (3.5)
Pneumonia	0	2 (1.0)	3 (1.5)
Ill-defined disorder	2 (1.0)	2 (1.0)	1 (0.5)
Back pain	3 (1.4)	0	1 (0.5)
Dizziness	1 (0.5)	2 (1.0)	1 (0.5)
Glucose present in urine	2 (1.0)	2 (1.0)	0

improvement in SGRQ score might suggest that there is some additional benefit of formoterol 9 μg bid over 4.5 μg bid in this COPD patient population.

Both formoterol 4.5 and 9 μg bid for 12 weeks were well tolerated in Japanese and European patients with COPD. No clinically important safety differences between the formoterol 4.5 and 9 μg bid doses were observed. Concerns were raised regarding the ongoing safety of LABA therapy in patients with COPD following the publication of a meta-analysis of 22 studies of at least 3-month duration that suggested an increased risk of death with LABA therapy compared with placebo [10]. However, this analysis has been countered by a more recent meta-analysis which applied more rigorous study selection criteria and excluded studies with duplicate data; it also included studies of at least 1-month duration [11]. This latter meta-analysis found that LABAs reduced severe exacerbations compared with placebo (relative risk 0.78; 95% CI: 0.67-2.64) and that there was no significant difference between LABA and placebo with regard to the risk of respiratory death (relative risk 1.09; 95% CI: 0.45-2.64) [11]. The results of the current 12-week study are consistent with the latter meta-analysis; two deaths did occur in the study and although both patients had been randomized to formoterol 4.5 μg bid, neither death was considered to be related to study treatment.

Bronchodilator therapy represents the mainstay of treatment for patients with COPD. The place of LABA therapy as a bronchodilator for COPD has been revisited in recent years. LABA monotherapy is more commonly used in the management of COPD than it is in the management of asthma where LABA therapy is combined with concomitant ICS and is regarded with caution following the results of the Salmeterol Multicenter Asthma Research Trial [14], which demonstrated an increased risk of death in the salmeterol treatment arm. These data led to a black box warning being applied to both salmeterol and formoterol by the US Food and Drug Administration. Clinical studies have confirmed the efficacy of formoterol for bronchodilation in COPD in terms of improved lung function, symptoms, exacerbations, and HRQL [15-20]. Furthermore, formoterol has been shown to exert a faster onset of bronchodilatory effect compared with salmeterol in patients with COPD [21]. These data, combined with the results of the current study and the encouraging efficacy meta-analysis data described earlier [11], support the role of formoterol bronchodilator therapy in patients with COPD, with the potential caveat of excluding patients with an asthma component, as recommended in the current GOLD guidelines [9].

Conclusion

The results of the current study confirm that formoterol at doses of 4.5 and 9 μg bid is an effective and well tolerated first-line treatment option in the management of COPD, with additional benefits evident at the higher dose in terms of a reduced need for reliever medication and improved health-related quality-of-life.

List of abbreviations

ANCOVA: analysis of covariance; bid: twice daily; CI: confidence interval; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HRQL: health-related quality-of-life; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LOCF: last-observation-carried-forward; PEF: peak expiratory flow; pMDI: pressurized metered-dose inhaler; SGRQ: St George's Respiratory Questionnaire.

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Authors' contributions

MB and MI made significant contributions to the conception and design of the study. MB, HA, YF, MM, MN and MI made significant contributions to the acquisition of data, analysis and interpretation of data, and drafting of the manuscript. All authors read and approved the final manuscript.

Competing interests

Professor Miron Bogdan has received honoraria over the past year from Glaxo SmithKline, AstraZeneca, Pfizer and Actelion. These have not inappropriately influenced his work. Professor Bogdan has never received financial support from the tobacco industry. Professor Hisamichi Aizawa has served as a member of scientific advisory boards, received honoraria for lectures or research grants from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK and AstraZeneca KK. Professor Yoshinosuke Fukuchi has received honoraria for lectures from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK, Abbott Japan, Otsuka Pharmaceutical, and AstraZeneca KK. Professor Michiaki Mishima has served as a member of scientific advisory boards, received honoraria for lectures or research grants from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Pfizer Japan, MSD KK, Kyorin Pharmaceutical and AstraZeneca KK. Professor Masaharu Nishimura has served as a member of scientific advisory boards, received honoraria for lectures or research grants from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK, Abbott Japan, Pfizer Japan, MSD KK, Kyorin Pharmaceutical and AstraZeneca KK. Professor Masakazu Ichinose has served as a member of scientific advisory boards, received honoraria for lectures or research grants from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK, Abbott Japan and AstraZeneca KK.
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ORIGINAL ARTICLE

Immediate Noninvasive Ventilation May Improve Mortality in Patients With Hepatopulmonary Syndrome After Liver Transplantation

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Hepatopulmonary syndrome (HPS) is defined as hypoxemia induced by intrapulmonary vascular dilations associated with liver disease. Although liver transplantation (LT) is the only effective therapy established for severe HPS, patients with a partial pressure of arterial oxygen (PaO_2) less than 60 mm Hg have a poor prognosis. We treated a 4-year-old boy with HPS whose preoperative PaO_2 level was 48.8 mm Hg. After LT, he had persistent severe hypoxemia, although he was receiving high-flow oxygen. Noninvasive ventilation (NIV) was introduced, and his respiratory insufficiency promptly improved. Therefore, NIV therapy immediately after extubation following transplantation was administered to the next 4 consecutive HPS patients whose preoperative PaO_2 was less than 60 mm Hg. The NIV treatment of these 5 patients could have been responsible for preventing severe postoperative complications as well as reintubation and hospital death. NIV therapy for both pediatric and adult patients with severe HPS immediately after extubation might protect them from severe hypoxemia after transplantation and from complications necessitating reintubation and might improve their prognosis. *Liver Transpl 17:144-148, 2011.* © 2011 AASLD.

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Hepatopulmonary syndrome (HPS) is defined as a defect in arterial oxygenation induced by intrapulmonary vascular dilations associated with liver disease.[1] Previous studies have determined that HPS is an independent risk factor for long-term mortality in patients with cirrhosis.[2]

Orthotopic liver transplantation (OLT) is the only successful treatment for patients with HPS. However, the postoperative mortality rate of patients with severe hypoxemia before transplantation has been high.[3] Patients with a partial pressure of arterial oxygen (PaO_2) less than or equal to 60 mm Hg have been shown to have a poor prognosis after liver transplantation (LT), and a baseline PaO_2 less than or equal to 50 mm Hg has been associated with a poor survival rate, regardless of the decision to perform OLT.[2] Indeed, at

Abbreviations: $AaDO_2$, alveolar-arterial oxygen gradient; F_IO_2, fraction of inspired oxygen; HCV-LC, hepatitis C virus–related liver cirrhosis; HPS, hepatopulmonary syndrome; LDLT, living donor liver transplantation; LT, liver transplantation; NIV, noninvasive ventilation; OLT, orthotopic liver transplantation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; P_AO_2, partial pressure of alveolar oxygen; P_{atm}, atmospheric pressure; PH_2O, partial pressure of water vapor at body temperature; POD, postoperative day; SaO_2, arterial oxygen saturation; SpO_2, percutaneous oxygen saturation; ST, spontaneous/timed; *X*, leakage flow rate; *Y*, oxygen flow rate.

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TABLE 1. Preoperative Status of Five Cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	4	60	10	11	59
Sex	Male	Male	Female	Female	Male
Etiology	Biliary atresia	HCV-LC	Biliary atresia	Congenital absence of the portal vein	HCV-LC
Preoperative PaO_2 (mm Hg)	48.8	49.3	50	61.6 (2 L/minute by a nasal cannula)	57.5
Preoperative $AaDO_2$ (mm Hg)*	67.4	60.1	62.5	95.7†	58.0
Preoperative shunt ratio (%)	43.6	45	42.3	42	35.9
Child-Pugh class	A	C	A	A	C
Model for End-Stage Liver Disease score	9	17	10	11	17
LT date	July 2003	March 2005	December 2005	June 2006	October 2007
Blood group with graft	Identical	Identical	Identical	Compatible	Identical

*$AaDO_2$ ($PAO_2 - PaO_2$) = $F_IO_2(P_{atm} - PH_2O) - (PaCO_2/0.8) - PaO_2$.
†F_IO_2 for this case was determined to be 0.28.[12]

our institute, 6 of 14 patients with severe HPS (ie, patients with $PaO_2 < 60$ mm Hg, including 11 cases with $PaO_2 \leq 50$ mm Hg on room air) died in the hospital after living donor liver transplantation (LDLT).[4]

Noninvasive ventilation (NIV) is effective for respiratory insufficiency in many situations (eg, after organ transplantation).[5] However, there has been no previous report on the use of NIV after LT in patients with severe HPS.

Here we report the details of successful postoperative management with NIV treatment of 5 consecutive patients with severe HPS.

PATIENTS AND METHODS

Patients

From July 2003 to March 2009, 5 consecutive patients with severe HPS whose PaO_2 on room air was less than 60 mm Hg were under respiratory management with NIV during the perioperative period of LT. The preoperative status of these 5 patients is shown in Table 1. Although the use of NIV was unplanned in case 1, NIV was planned to be applied immediately after LDLT in the other 4 cases. However, 90 minutes passed before the introduction of NIV after extubation in case 3 because of a delay in medical orders. In case 4, the preoperative PaO_2 level was 61.6 mm Hg while the patient was receiving 2 L of oxygen per minute via a nasal cannula. Therefore, her PaO_2 level was presumed to be less than 50 mm Hg on room air because the fraction of inspired oxygen (F_IO_2) was presumed to be greater than 0.28 while she was receiving 2 L of oxygen per minute via the nasal cannula.[6] With the inclusion of case 4, PaO_2 in 4 of the 5 patients with HPS was less than or equal to 50 mm Hg while the patients were breathing room air. The preoperative shunt ratio, estimated with a technetium-99m macroaggregated albumin lung perfusion scan, was more than 40% in 4 of the 5 patients (Table 1).

After LT, the discontinuation of mechanical ventilation was considered under the following conditions, which were the same as those before the introduction of NIV treatment at our institution: (1) the patient was clinically stable, (2) the underlying disease and its complications had improved, (3) ventilator support was minimal (pressure support $\leq$ 6 cm H_2O and positive end-expiratory pressure $\leq$ 4 cm H_2O), and (4) spontaneous breathing was sufficient. When the patients were extubated, F_IO_2 of the ventilator settings ranged from 0.4 to 0.65, and the PaO_2/F_IO_2 ratio was greater than 100. The ethics committee of Kyoto University gave its approval for the protocol of this study.

Oxygen Therapy and NIV

For the estimation of F_IO_2 of oxygen therapy via a nasal cannula, face mask, or reservoir face mask, we calculated F_IO_2 with a previously published formula.[6] During NIV treatment, we used a full-face mask, a nasal mask (Resmed, North Ryde, New South Wales, Australia), or a nasal mask of pediatric size (Respironics, Murrysville, PA).

A bilevel positive airway pressure device (VPAP II ST-A, Resmed), supplemental oxygen, and a heated humidifier were used. At first, we used a full-face mask as an interface. After the mask had been secured, the level of support pressure, the expiratory positive airway pressure, and the amount of oxygen were progressively increased until the arterial oxygen saturation (SaO_2) was greater than 95%, and this was accompanied by decreased respiratory rates and/or reduced activity of accessory muscles for respiration, decreased paradoxical thoracoabdominal movement, and an improvement in the patient's respiratory discomfort. When NIV was being introduced, a doctor stayed at the bedside and observed the patient carefully while the SaO_2 levels and electrocardiogram were monitored. Throughout the first hour, the patient's condition was assessed repeatedly. To stabilize the patient's respiratory status, adjustments were made in NIV settings and oxygen.

TABLE 2. Initial Setting of NIV in Five Cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Mode	ST	ST	ST	ST	ST
Inspiratory positive airway pressure (cm H_2O)	5.6	11	8	11.2	8
Expiratory positive airway pressure (cm H_2O)	3.6	5	4	5.2	4
Respiratory rate (breaths/minute)	30	14	14	16	12
Amount of oxygen (L/minute)	15	15	12	15	8
Interface	Face mask	Face mask	Face mask	Face mask	Face mask

When NIV was initially applied, the goal was to continue its use as long as the patient could tolerate it or until it appeared to no longer be necessary. After the respiratory status was stabilized, some patients (cases 2 and 3) continued to use the nasal mask to avoid aspiration after vomiting. To prevent abdominal distension and vomiting, a gastric tube was inserted into the stomach on either the first or second day of NIV introduction in cases 2 to 5. When the SaO_2 levels were greater than 90% with the delivery of 5 L of oxygen per minute through a nasal cannula or mask, NIV was discontinued during awake periods, and the NIV settings (pressure and amount of oxygen) were gradually lowered. However, in case 3, NIV was discontinued while her SaO_2 levels were less than 90% but more than 85% because she insisted on stopping NIV as soon as possible.

To calculate F_IO_2 during NIV, we used the information supplied by the manufacturer and attached to the mask. With this information, F_IO_2 was determined from the following parameters: the leakage flow per minute from the mask at each pressure and the oxygen flow per minute during NIV. With X as the leakage flow rate and Y as the oxygen flow rate in this setting, F_IO_2 in this setting was calculated as follows:

$$F_IO_2 = [Y \times 1.0 + (X - Y) \times 0.21]/X$$

Whenever respiratory conditions deteriorated, invasive mechanical ventilation was applied. The predetermined criteria for reintubation were as follows: the failure to maintain an SaO_2 level less than 90% with F_IO_2 equal to or greater than 0.6, the development of conditions necessitating endotracheal intubation to protect the upper airway (seizure and severe hepatic coma), the development of copious tracheal secretions that could not be expectorated, an increase in the partial pressure of arterial carbon dioxide ($PaCO_2$) accompanied by a pH less than or equal to 7.30, and severe hemodynamic instability defined as a systolic blood pressure less than 70 mm Hg.

RESULTS

Case 1

Case 1 was a 4-year-old boy with biliary atresia. His preoperative PaO_2 level while he was breathing room air was 48.8 mm Hg, and his shunt ratio was 43.6% (Table 1). He underwent LDLT with an ABO-identical graft. On postoperative day (POD) 1, the patient was extubated. We could not keep his percutaneous oxygen saturation (SpO_2) greater than 90% even while he was inhaling high-flow oxygen (10 L/minute) with a reservoir face mask. We started NIV treatment on POD 9 (Table 2). After the introduction of NIV, within 6 hours, the PaO_2/F_IO_2 ratio and respiratory rate improved from 75.4 to 179.2 and from 45 to 34 breaths/minute, respectively (Table 3). On POD 12, NIV with oxygen was changed to the nocturnal use of NIV with oxygen and diurnal oxygen therapy. NIV was discontinued on POD 34, and oxygen therapy was stopped on POD 74. The patient was discharged from our hospital on POD 83 and remains alive.

Case 2

Case 2 was a 60-year-old man with hepatitis C virus–related liver cirrhosis (HCV-LC). His preoperative PaO_2 level while he was breathing room air was 49.3 mm Hg, and his shunt ratio was 45% (Table 1). After LDLT with an ABO-identical graft, extubation was executed on POD 2. Because of our experience with case 1, we started NIV immediately after extubation. We used NIV continuously all day, and his SpO_2 level was well controlled (Table 3). On POD 9, the patient received 1 hour of NIV 3 times per day because he refused to use NIV continuously. On POD 20, we were able to discontinue NIV, and the patient was discharged from our hospital on POD 33. He died 5 months after LDLT because of the rupture of a thoracic aortic aneurysm.

Case 3

Case 3 was a 10-year-old girl with biliary atresia. Because of her low PaO_2 level before transplantation, the patient started NIV with both face and nasal masks a few days before the operation. On POD 1, she was extubated. We introduced NIV 90 minutes after extubation, and her oxygenation improved (Table 3). From POD 12, the nocturnal use of NIV controlled her SpO_2 level well, but diurnally, severe hypoxemia with an elevated heart rate persisted despite the administration of high-flow oxygen with a reservoir face mask (Fig. 1). She wanted to discontinue NIV treatment on POD 89. However, her SpO_2 level was only 88% even

TABLE 3. Clinical Course of Five Cases

	Case 1	Case 2	Case 3	Case 4	Case 5
PaO_2/F_IO_2 before the operation	232.4	234.8	250.0	220.0*	273.8
PaO_2/F_IO_2 before extubation	101.2	107.8	138.5	186.7	289.0
Time from extubation to the introduction of NIV	8 days	Immediately	1.5 hours	Immediately	Immediately
PaO_2/F_IO_2 before NIV	75.4	107.8	73.6	186.7	289.0
PaO_2/F_IO_2 after NIV	179.2 (6 hours)	138.4 (4 hours)	177.9 (6 hours)	186.9 (3 hours)	252.9 (1 hour)
Respiratory rate before NIV (breaths/minute)	45	18	17	20	10
Respiratory rate 2 hours after NIV (breaths/minute)	34	22	15	18	14
Length of hospitalization (days)	98	33	105	51	119
Duration of NIV (days)	25	18	88	11	59
Duration of oxygen therapy (days)	74	33	171	41	63
SpO_2 on discharge (%)	99 (room air)	92 (room air)	88 (5 L/minute reservoir face mask)	97 (room air)	97 (room air)
Postoperative shunt ratio after LT (%)	14.7 (1 month)	34 (1 month)	16.5 (3 months)	7.6 (3 months)	26.0 (2 months)

*F_IO_2 for this case was determined to be 0.28.[12]

while she was breathing 5 L of oxygen per minute. She was discharged from our hospital on POD 95. Her oxygenation gradually improved over a long period, and her SpO_2 level stabilized at approximately 96% while she was breathing room air. Long-term oxygen therapy was discontinued after 171 days. She is alive, and her liver function and oxygenation have normalized.

Cases 4 and 5

Case 4 was an 11-year-old girl with congenital absence of the portal vein, and case 5 was a 59-year-old man with HCV-LC. After LDLT, both patients were extubated on POD 1, and NIV was introduced immediately. Their respiratory status stabilized, and they experienced no complications. They were discharged from our hospital and are alive.

All 5 patients with severe HPS were treated with NIV with the spontaneous/timed (ST) mode and could be discharged from the hospital after LT. After NIV was applied, the respiratory rate in case 1 improved. In contrast to case 1, the other 4 patients, who were started on NIV immediately or early after extubation, did not have severe tachypnea before extubation. These patients experienced no significant changes in their respiratory rates before and after NIV. Although case 1 had a bile leak, no other complications, including the necessity for reintubation, infection, or reoperation, were encountered in these patients. In addition, no severe complications such as pneumothorax, hypotension, or aspiration pneumonia related to the NIV treatment occurred among these 5 patients.

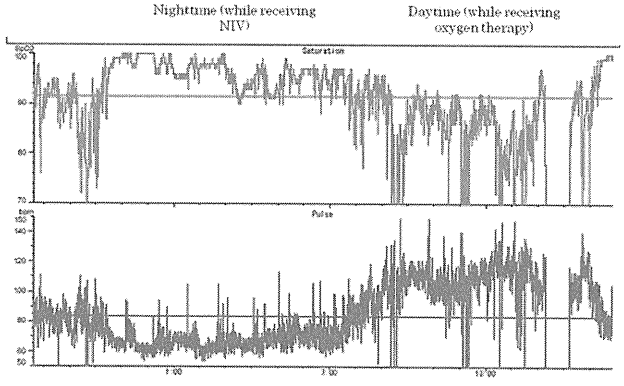

Figure 1. Changes in SpO_2 (top) and in the pulse rate (bottom) in a day. SpO_2 was higher when the patient was undergoing NIV therapy with oxygen at night than when the patient was receiving only oxygen therapy during the day. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

This is the first report showing the effectiveness of NIV treatment for hypoxemia in patients with severe HPS. The postoperative management of patients with severe HPS is said to be exceedingly difficult because HPS patients with severe hypoxemia manifest worsening of respiratory insufficiency after LT. The results of this study indicate that by controlling hypoxemia more effectively than the therapies used previously and by avoiding the need for reintubation without severe side effects, NIV after LT might improve the mortality rates of severe HPS patients.

The effectiveness of NIV in patients with acute respiratory failure after solid organ transplantation[5] and in the prevention of respiratory failure after extubation in high-risk patients[7] has been demonstrated. Feltracco et al.[8] reported the use of NIV in clinical practice (eg, as a tool facilitating early extubation and

as a prophylactic strategy for preventing postoperative pulmonary complications). However, that report did not examine the application of NIV for specific diseases as our study does.

Several factors are relevant to postoperative hypoxemia; these include intraoperative fluid overloading, atelectasis, and restrictive disorders due to abdominal distension and/or pleural effusion after transplantation. In addition, as a characteristic factor of hypoxemia in patients with HPS, absent or reduced pulmonary vascular tone with impaired hypoxic vasoconstriction due to HPS[9] may also contribute to postoperative hypoxemia. However, NIV could improve oxygenation despite the existence of these factors in these case series.

Recently, oxygen desaturation during sleep was reported in patients with HPS; the degree correlated with the severity of HPS.[10] NIV may prevent nocturnal hypoventilation and/or upper airway obstruction (eg, case 3; Fig. 1).

We previously reported on 21 HPS patients after LDLT in our hospital[4]; 14 had severe hypoxemia before LDLT. Although the LDLT surgical procedures and the management of infectious complications were unchanged between the 2 time periods, improvements in perioperative management, including surgical techniques, fluid management, and antibiotics, might have influenced the outcomes.

Although there was no serious ventilator-associated pneumonia resulting in hospital death in our previous studies, 11 of our 14 previous patients (78.6%) whose PaO_2 level before transplantation was less than 60 mm Hg developed serious postoperative infections, such as wound infections, sepsis derived from cholangitis, and intraperitoneal abscesses.[4,11] However, no postoperative infection occurred in the 5 cases shown here. We feel that the early improvement in oxygenation by NIV treatment might have prevented serious infectious complications in our patients.

Complications of NIV treatment such as severe skin rashes, eye irritation, gastric insufflation, and aspiration, which can necessitate the cessation of NIV treatment, were not apparent in our patients. When patients indicated discomfort from the mask or pressure, we decreased the usage time of NIV or changed to another type of mask.

This study has some limitations. First, the patient population was heterogeneous with respect to age and was small in number. The period between extubation and the introduction of NIV was also heterogeneous: NIV treatment began immediately after extubation in cases 2, 4, and 5 but not in cases 1 and 3. The PaO_2/F_IO_2 ratio before NIV in cases 1 and 3 decreased with respect to the ratio before extubation. Therefore, we propose that immediate (preventive) NIV after extubation would be more favorable in patients with severe HPS. According to Antonelli and Bello,[12] several studies have assessed the benefit of NIV in various weaning strategies, including the use of early extubation in patients who fail to meet standard extubation criteria (facilitation use), the avoidance of reintubation in patients who fail extubation (curative use), and the prevention of extubation failure in unselected and selected patients (preventive use). We propose that good results can be achieved by the preventive use of NIV in patients with HPS. However, it is impossible to determine the actual value of preventive NIV use for HPS patients without a prospective randomized trial.

In conclusion, although this study was not a randomized trial and the number of cases was small and heterogeneous, immediate NIV may possibly improve the prognosis in patients, both children and adults, with severe HPS without serious complications. We propose that this treatment be used for patients with severe HPS after LT because the control of consecutive severe hypoxemia after LT is one of the most important factors for the improvement of the prognosis of these patients.

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Impact of Exacerbations on Emphysema Progression in Chronic Obstructive Pulmonary Disease

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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

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-

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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 described 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.

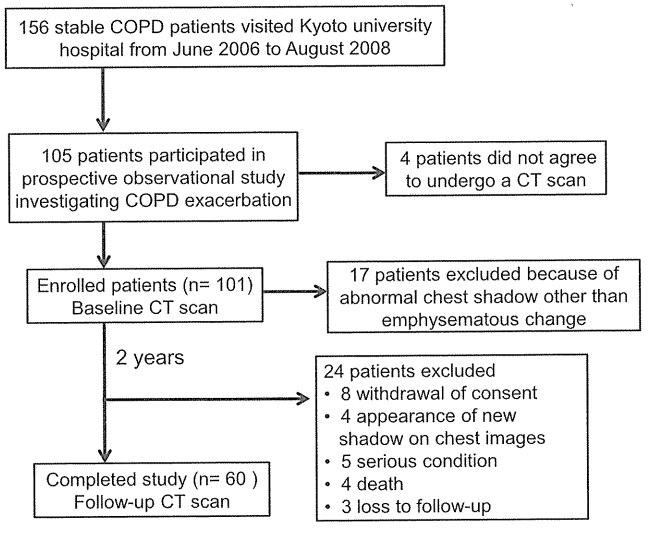

Figure 1. Patient disposition and reasons for exclusion. CT = computed tomography; COPD = chronic obstructive pulmonary disease.

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 FEV_1, $\%FEV_1$ (FEV_1 expressed as a percentage of the expected value), and ratio of diffusing capacity to alveolar ventilation (D_{LCO}/V_A) in both groups, but the degrees of decline were not significantly

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}/VA, ml/min/mm Hg/L: median (25th, 75th percentile)	2.67 (1.90, 3.25)

Definition of abbreviations: $\%FEV_1$, FEV_1 as a percentage of the predicted value; D_{LCO}/VA, ratio of diffusing capacity to alveolar ventilation.
n = 60 study patients.

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}/VA, 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: $\%FEV_1$, FEV_1 as a percentage of the predicted value; CT = computed tomography; D_{LCO}/VA, 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.

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 FEV_1, $\%FEV_1$, and D_{LCO}/VA, whereas changes in LAA% or D did not correlate with changes in FEV_1, $\%FEV_1$, or D_{LCO}/VA (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 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 ± 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

	Exacerbation (–)		Exacerbation (+)		
Parameter	Value	*P* Value (within Group)	Value	*P* Value (within Group)	*P* Value (between Groups)
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: $\%FEV_1$, FEV_1 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 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

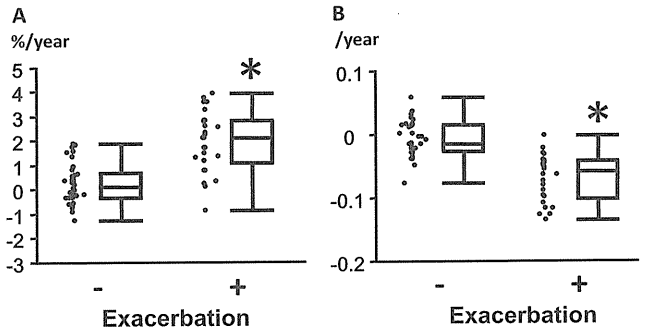

Figure 2. Change in (*A*) LAA% and (*B*) D in patients with and without a history of exacerbations (n = 26 and 34, respectively). *$P < 0.0001$ compared with patients without exacerbations. The *horizontal line* is the median value, the *box* is the interquartile range, and the *whiskers* indicate the 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.

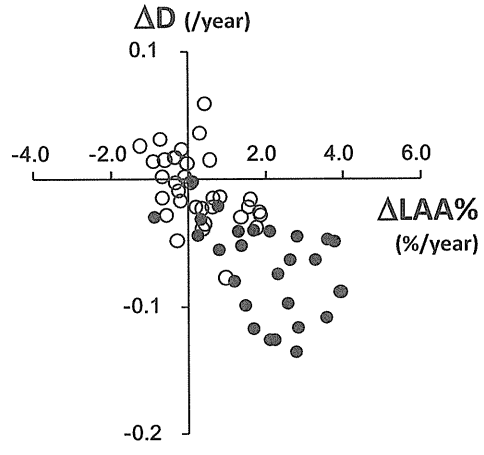

Figure 3. Relationship between changes in LAA% and D both in patients with and without a history of exacerbations. *Solid circles* and *open circles* show the change in patients with and without exacerbations, respectively. A significant correlation between an increase in LAA% and a decrease in D was 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

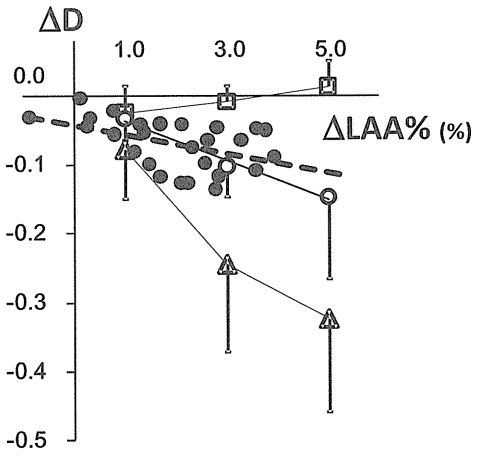

Figure 4. Change in LAA% and D obtained from model simulations and patients with a history of exacerbations. *Open squares* show mean values obtained by model A, which could not allow coalescence of preexisting LAAs. *Open circles* and *open triangles* show mean values obtained by model B15 and B30, 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 FEV_1, $\%FEV_1$, and D_{LCO}/V_A. These findings are consistent with our previous reports (3, 4), indicating that −960 HU was a reasonable threshold.

Although baseline FEV_1, $\%FEV_1$, and D_{LCO}/V_A correlated with baseline LAA% and D, changes in LAA% and D did not correlate with changes in FEV_1, $\%FEV_1$, and D_{LCO}/V_A. 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 FEV_1 and D_{LCO}/V_A 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, FEV_1 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 FEV_1 decline. It has been reported in the Framingham Offspring Cohort that FEV_1 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 FEV_1 (5), the present study found no significant difference in annual changes in FEV_1 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.

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