

# Bronchiectasis, Exacerbation Indices, and Inflammation in Chronic Obstructive Pulmonary Disease

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**Relationships between high-resolution computed tomography (HRCT) findings in chronic obstructive pulmonary disease (COPD) and bacterial colonization, airway inflammation, or exacerbation indices are unknown. Fifty-four patients with COPD (mean [SD]: age, 69 [7] years; FEV<sub>1</sub>, 0.96 [0.33] L; FEV<sub>1</sub> [percent predicted], 38.1 [13.9]%; FEV<sub>1</sub>/forced vital capacity [percent predicted], 40.9 [11.8]%; arterial partial pressure of oxygen, 8.77 [1.11] kPa; history of smoking, 50.5 [33.5] smoking pack-years) underwent HRCT scans of the chest to quantify the presence and extent of bronchiectasis or emphysema. Exacerbation indices were determined from diary cards over 2 years. Quantitative sputum bacteriology and cytokine measurements were performed. Twenty-seven of 54 patients (50%) had bronchiectasis on HRCT, most frequently in the lower lobes (18 of 54, 33.3%). Patients with bronchiectasis had higher levels of airway inflammatory cytokines ( $p = 0.001$ ). Lower lobe bronchiectasis was associated with lower airway bacterial colonization ( $p = 0.004$ ), higher sputum interleukin-8 levels ( $p = 0.001$ ), and longer symptom recovery time at exacerbation ( $p = 0.001$ ). No relationship was seen between exacerbation frequency and HRCT changes. Evidence of moderate lower lobe bronchiectasis on HRCT is common in COPD and is associated with more severe COPD exacerbations, lower airway bacterial colonization, and increased sputum inflammatory markers.**

**Keywords:** bronchiectasis; chronic obstructive pulmonary disease; computed tomography scanning; exacerbation; inflammation

Patients with chronic obstructive pulmonary disease (COPD) are prone to exacerbations, which account for significant morbidity and mortality and are a key determinant of health-related quality of life (1). There is considerable heterogeneity in the character, frequency, and time course of COPD exacerbations, which cannot be accounted for solely on the basis of degrees of airway obstruction or disease severity. Mechanisms governing the natural history of COPD exacerbations remain poorly understood.

Lower airway bacterial colonization is a common clinical finding in COPD (2) and is increasingly recognized as an independent stimulus to airway inflammation (3). We have shown that lower airway bacterial colonization can modulate the character and frequency of COPD exacerbations (4). In addition, we have demonstrated that patients with frequent exacerbations have higher levels of induced sputum interleukin (IL)-6 and IL-8 in the stable state compared with those with infrequent

exacerbations (5), suggesting the presence of heightened airway inflammation in this patient group. Symptoms of daily cough and sputum production have been shown to be factors predictive of frequent COPD exacerbations (1), and one study reported that 29% of patients with COPD who developed an exacerbation in primary care were found to have some bronchiectatic changes when evaluated by computed tomography scanning (6). The implications of this finding are unknown, and the role of undiagnosed bronchiectasis in influencing relationships between exacerbation frequency, lower airway bacterial colonization, and airway inflammation in COPD has not been examined.

This study was designed to evaluate the prevalence and extent of bronchiectasis and emphysema on high-resolution computed tomography (HRCT) scanning in a well characterized group of stable patients with moderate to severe COPD, and to relate this to the presence of lower airway bacterial colonization, levels of airway inflammatory markers, exacerbation frequency, severity, and time course. Sputum samples were obtained from patients monitored in the East London COPD Study. These patients completed daily diary cards for changes in symptoms and peak flow and reported exacerbations to the study team as previously described (7). A validated exacerbation frequency was calculated for each patient and this was related to the detection of bronchiectasis and emphysema on HRCT in the stable state. Stable daily symptoms, symptoms at exacerbation, and recovery from exacerbations were also examined with reference to the distribution and severity of HRCT findings. Some of the results of this study have previously been reported in the form of abstracts (8–11).

## METHODS

### Study Subjects

Fifty-four stable patients with moderate to severe COPD were recruited as volunteers from those being monitored in the East London COPD Study, which is a prospective cohort-based study of COPD exacerbations. Patients in the study were recruited on a sequential basis from the outpatient department of the London Chest Hospital, and were representative of patients with moderate to severe COPD in the United Kingdom who are referred from primary care to secondary care because of increasing disability due to COPD. Patients gave informed consent to undergo CT scanning and ethics approval was obtained from the East London and City Health Authority Research Ethics Committee. See the online supplement for additional details on these methods.

COPD was defined as an FEV<sub>1</sub> of less than 70% predicted for age and height,  $\beta_2$ -agonist reversibility on predicted FEV<sub>1</sub> of less than 15% and/or 200 ml, with an FEV<sub>1</sub>/FVC ratio of less than 70%. Patients with previously diagnosed or clinically evident bronchiectasis or other significant respiratory disease were excluded. Subjects were recruited when stable, without any evidence of an exacerbation for at least 6 weeks. Baseline measurements were made of height, weight, FEV<sub>1</sub>, FVC, and peak expiratory flow rate by rolling seal spirometer (SensorMedics, Yorba Linda, CA). Pulmonary diffusion was measured by single-breath carbon monoxide/helium diffusion (Pulmolab 501; Morgan Medical, Ferraris, UK). Arterialized ear lobe blood gases were analyzed for arterial oxygen and carbon dioxide partial pressures (12).

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### Sputum Sampling

Stable patients attended the research clinic in the morning. Patients and diary cards were examined to confirm the absence of an exacerbation over the preceding 6 weeks, as defined by our previously validated criteria (7). If no spontaneous sputum sample was available, sputum induction was performed with a DeVilbiss UltraNeb 2000 nebulizer (DeVilbiss Healthcare, Somerset, PA) with 3% saline as described previously (13). See the online supplement for additional details on this procedure. Fifteen of the sputum samples obtained have been used for an analysis of the relationship between bacterial load and FEV<sub>1</sub> decline in COPD (14).

At this clinic visit an appointment was also made to attend for an HRCT scan of the chest at a later date. Patients were asked to inform the study team if they developed symptoms of an exacerbation before or on the date of this scan, in which case it was rebooked for a period 6 weeks after this exacerbation.

### Sputum Examination

Sputum samples were examined as soon as possible, within 2 hours of collection. The sample was separated from contaminating saliva, one-third was taken for quantitative bacterial culture, and the remainder was processed according to previously published methods (13). See the online supplement for additional details on these methods. Sputum levels of IL-6 and IL-8 were measured by ELISA (R&D Systems Europe, Abingdon, UK).

### Quantitative Identification of Bacteria

Sputum samples were processed by application of sputolysin (Sputasol; Unipath, Hampshire, UK) and cultured on appropriate media according to previously described protocols (4, 15). See the online supplement for additional details on these methods.

All estimations of inflammatory mediators and bacterial colonization were performed by observers blind to the clinical characteristics of the patients in the study.

### HRCT Scans

**Assessment of bronchiectasis.** CT scans were performed from December 2000 to August 2001, using a HiSpeed ZX/i scanner (GE Medical Systems, Milwaukee, WI). High-resolution images were obtained in full inspiration at 1-mm collimation at 1-cm intervals from the apices to the lung bases. The CT scans were interpreted for the presence of bronchiectasis by two radiologists experienced in the interpretation of HRCT (I.V. and R.H.R.) and blinded to the patient's clinical grouping or microbiological status. The presence of bronchiectasis was based on the following criteria: nontapering bronchus with internal diameter 110% or greater than the adjacent pulmonary artery or the presence of visible bronchi within 1 cm of the costal pleural surface or adjacent to the mediastinal pleural surface. Bronchiectasis was scored in each lobe by consensus, using the grading system proposed by Smith and coworkers (16) as follows: 0 if no bronchiectasis was present; 1 if less than 25% of bronchi were bronchiectatic; 2 if 25–49% of the bronchi were bronchiectatic; 3 if 50–74% of the bronchi were bronchiectatic; and 4 if 75% or more of the bronchi were bronchiectatic. The lingula was graded as a separate lobe, resulting in a maximum score of 24 per patient. Previous studies have shown that more than 50% of healthy volunteers may have at least one dilated bronchus on HRCT (17). A similar finding was reported in 53% of normal subjects at altitude (18), a change likely to be driven by hypoxia, and elderly patients may also have a higher normal ratio of bronchus to artery (19). Therefore only patients with a total bronchiectasis score of 2 or more were considered to have changes consistent with clinically significant disease for the purposes of this study. Patients with a score of 0 or 1 (less than 25% of bronchiectatic bronchi in one lobe) were considered "normal." Study subjects were categorized in this way for calculations of bronchiectasis prevalence and comparisons of other parameters.

**Assessment of emphysema.** Emphysema was quantitatively assessed by determining the area of both lungs, measuring less than –950 Hounsfield units (HU) (20) at 4 levels, including 5 cm above the carina, the carina, 5 cm below the carina, and 2 cm above the highest hemidiaphragm. For each lung at each level the total area, emphysematous area less than –950 HU, and mean lung density were assessed with

standard CT software (GE Medical Systems). At each level the percentage of emphysematous lung was calculated. The overall degree of each patient's emphysema was expressed as a percentage of the total lung area assessed.

### COPD Exacerbations

All patients maintained daily diary cards on which they recorded their indoor peak expiratory flow rate measured with a Mini-Wright peak flow meter (Clement Clarke International, Harlow, UK) after their morning medication. Patients also noted any appearance or increase in intensity of "major" symptoms (dyspnea, sputum purulence, and sputum amount) or "minor" symptoms (nasal discharge/congestion, wheeze, sore throat, and cough) over their chronic (stable) symptoms on their diary cards. Throughout the study patients were seen every 3 months for diary card review and spirometry. A member of the study team saw patients within 48 hours of the detection of deterioration in symptoms and the diagnosis of an exacerbation was confirmed in each case. Exacerbations were identified according to defined criteria of any two major symptoms or one major and one minor symptom, as described above, on two consecutive days, the first of which was taken as the day of onset of exacerbation (1, 7). Exacerbation numbers were calculated from diary cards for a moving 24-month period of follow-up, encompassing 1 year before and 1 year after each study patient's CT scan, and covered the period from December 1999 to August 2002. The sum of the major and minor symptoms listed above gave a daily exacerbation symptom count. The difference in symptom count between exacerbation onset and a baseline, taken as the mean over Days 14 to 8 preceding onset, was calculated. Exacerbation recovery was the time from onset for a 3-day moving average of the symptom count to equal or become less than the baseline. The time to recovery of symptoms was taken as an indicator of exacerbation severity.

### Statistical Analysis

Normally distributed data were summarized as means (SD) and skewed data were summarized as medians (interquartile range, IQR). Continuous variables with normal distributions were compared by *t* test (two-tailed, unpaired) whereas those with nonnormal distributions were compared by the Mann-Whitney U test or Wilcoxon signed ranks test as appropriate. Sputum cytokine levels and total bacterial counts were correlated by Spearman rank correlation. The median exacerbation frequency for this group was 2.54 per patient per year, in agreement with previously published results (1), and this was taken as the cutoff point to identify patients as either frequent or infrequent exacerbators. Median values of exacerbation severity (based on the time to recovery of symptoms), over the moving 24-month period referred to above, were computed for each patient. Generalized linear models, which allowed for their Poisson-shaped distribution, were used to assess the relationship between the distribution and extent of bronchiectasis and exacerbation indices. Data analysis was performed in SPSS for Windows version 11 for STATA 5.0 (SPSS Inc., Chicago, IL).

## RESULTS

### Patients

At the time of recruitment for the present study there were 79 patients in total being monitored in the East London COPD Study, of which 54 were willing to undergo sputum sampling and a CT scan of the chest. Table 1 shows the baseline physiological characteristics of the 54 patients studied. Twenty-seven (50%) were daily sputum producers, 16 (29.6%) were current smokers, and 51 (94%) were taking inhaled steroids at a median (IQR) beclomethasone equivalent dosage of 1.25 (0.8–2.0) mg/day. We have compared the baseline characteristics of these study subjects with those who did not undergo CT scans, and there was no statistically significant difference between the two groups with respect to FEV<sub>1</sub>, FVC, or any other physiological parameter. Subjects in the present study had been prospectively monitored for a median (IQR) 1,197 (804–1,941) days at the start of CT scanning in December 2000.

**TABLE 1. BASELINE PHYSIOLOGICAL CHARACTERISTICS OF PATIENTS STUDIED**

Number	54 (36 M, 18 F)
Age, yr (range)	69.04 (48–83)
FEV <sub>1</sub> , L	0.96 (0.33)
FEV <sub>1</sub> , % predicted	38.10 (13.9)
FEV <sub>1</sub> , % reversibility	9.10 (12.0)
FVC, L	2.40 (0.73)
FEV <sub>1</sub> /FVC, % predicted	40.90 (11.8)
T <sub>LCO</sub> , % predicted	55 (18.7)
V <sub>A</sub> , ml	4,772 (1,237)
K <sub>CO</sub> , % predicted	70 (26.5)
Pa <sub>O<sub>2</sub></sub> , kPa	8.77 (1.11)
Pa <sub>CO<sub>2</sub></sub> , kPa	5.94 (1.02)
Pack-years of smoking	50.5 (33.5)
Daily inhaled steroids,* mg; median (IQR)	1.25 (0.8–2.0)
Daily sputum producers, number (%)	27 (50)
Exacerbations, median per year	2.54

Definition of abbreviations: F = female; IQR = interquartile range; M = male; T<sub>LCO</sub> = transfer factor; V<sub>A</sub> = alveolar volume.

All data are quoted as means (SD) except as noted otherwise.

\* Daily inhaled steroid dose was normalized per steroid potency and represents beclomethasone equivalent dose.

Table 2 compares the physiological characteristics of the frequent (n = 27) and infrequent (n = 27) exacerbators; the two groups were similar except, of course, in the number of exacerbations per year (p < 0.001).

Forty-four patients underwent CT scanning within a median (interquartile range, IQR) 10.5 (4–32.5) days of stable sputum sampling. Ten patients developed exacerbations before or on the day of CT scanning, resulting in deferral of the scan to a date at least 6 weeks later. For these 10 patients the median (IQR) number of days between sputum sampling and CT scanning was 66.5 (52.7–95.2) days.

The median (IQR) time from the last exacerbation to the time of CT scanning was 65 (45–92) days. The median (IQR) time to recovery of peak flow after the last exacerbation was 5 (1–15) days, and the median time to recovery of symptoms was 12 (6–16.5) days.

## Exacerbations

A median of 672 (558–724) days of diary card data were analyzed for patients included in the study. Two hundred fifty exacerbations were documented over the study period of which 15, in 11 patients, required hospital admission. Of reported exacerbations, 84.7% were treated with oral antibiotics and 55.3% were treated with oral prednisolone.

## HRCT Scans

**Bronchiectasis scores.** Twenty-seven of 54 patients (50%) had significant detectable bronchiectasis (a total bronchiectasis score of  $\geq 2$ ) on HRCT. The total bronchiectasis scores are shown in Figure 1. See the online supplement for additional detail on the individual results for each study subject (Table 1). Of those in whom bronchiectasis was detected, the median score was 3 (range, 2–14). In this group, 8 of 27 (29.6%) had a cumulative upper lobe score of  $\geq 2$  (range, 2–5), 8 of 27 (29.6%) had a cumulative middle lobe/lingular score of  $\geq 2$  (range, 2–5), and 18 of 27 (66.7%) had a cumulative lower lobe score of  $\geq 2$  (range, 2–8), that is, bronchiectasis was most frequently detected in the lower lobes.

The total bronchiectasis score was inversely related to Pa<sub>O<sub>2</sub></sub>, that is, was higher with worsening hypoxemia ( $\rho = -0.299$ , p = 0.03). No relationship was seen between the total bronchiectasis score and stable respiratory symptoms or spirometric measurements.

**Emphysema scores.** The median (IQR) total emphysema score was 15.6% (13.6) with a range from 1.24 to 51.5%.

The total emphysema score was inversely related to the FEV<sub>1</sub> ( $\rho = -0.3$ , p = 0.027), the FEV<sub>1</sub>% predicted ( $\rho = -0.34$ , p = 0.012), and the FEV<sub>1</sub>/FVC ratio ( $\rho = -0.426$ , p = 0.001). Higher emphysema score was also related to lower K<sub>CO</sub> ( $\rho = -0.365$ , p = 0.021). No relationship was seen between emphysema scores and chronic stable daily symptoms, pack-years of smoking (p = 0.19), current smoking (p = 0.66), or other physiological parameters.

## Bacterial Isolates

Fifty-two sputum samples were obtained from patients in the stable state, of which 43 (82.7%) were spontaneous and 9 (17.3%) were induced samples. Twenty-eight of 52 (53.8%) sputum

**TABLE 2. BASELINE PHYSIOLOGICAL CHARACTERISTICS OF PATIENTS GROUPED BY EXACERBATION FREQUENCY**

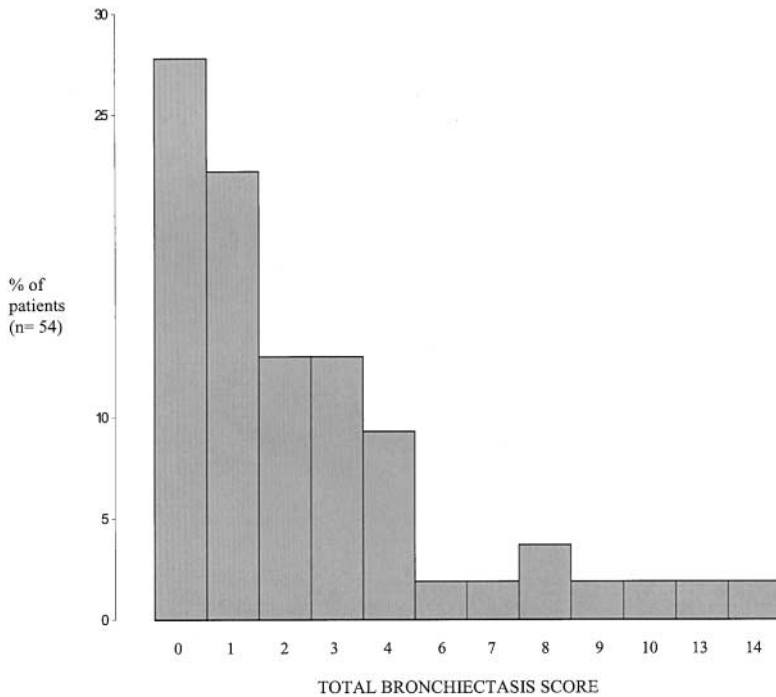
Parameter	Exacerbation Frequency	
	< 2.54/yr (n = 27)	> 2.54/yr (n = 27)
Age, yr	70.50 (7.04)	67.70 (6.93)
FEV <sub>1</sub> , L	1.03 (0.32)	0.89 (0.33)
FEV <sub>1</sub> , % predicted	40.70 (13.4)	36.10 (14.2)
FEV <sub>1</sub> /FVC, % predicted	40.52 (9.3)	41.10 (14.2)
T <sub>LCO</sub> , % predicted	57 (16.7)	54 (20.4)
V <sub>A</sub> , ml	4,724 (1,342)	4,806 (1,183)
K <sub>CO</sub> , % predicted	77 (29.5)	65 (23.4)
Pa <sub>O<sub>2</sub></sub> , kPa	8.80 (0.92)	8.75 (1.30)
Pack-years of smoking	48.00 (29.2)	51.60 (37.6)
Daily inhaled steroids, mg; median (IQR)	1.0 (0.5–2.0)	1.6 (1.0–2.0)
Daily sputum producers, %	13	14
Daily dyspnea, %	23	22
Percentage with LABC, %	25	29
Exacerbations per year, median (IQR)	1.5 (1.0)	4.2 (2.6)*
Total bronchiectasis score, median	2.0	1.0
Total emphysema score, %; median	15.3	15.6

Definition of abbreviations: LABC = lower airway bacterial colonization; for other abbreviations see Table 1.

All data are quoted as means (SD) except as noted otherwise.

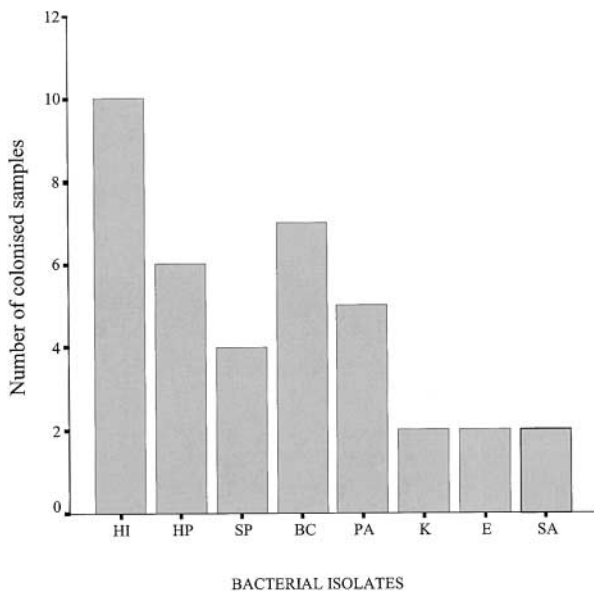
No significant difference was found in any parameter other than, of course, exacerbations per year.

\* p < 0.001.



**Figure 1.** Total bronchiectasis scores: 27 of 54 patients (50%) had significant detectable bronchiectasis (a total bronchiectasis score of 2 or more) on high-resolution CT scanning.

samples yielded a positive culture of one or more potentially pathogenic microorganisms as previously defined (3). Pathogens recovered included *Haemophilus influenzae* (10 of 28, or 35.7%), *Branhamella catarrhalis* (7 of 28, or 25%), *Haemophilus parainfluenzae* (6 of 28, or 21.4%), *Pseudomonas aeruginosa* (5 of 28, or 17.9%), *Streptococcus pneumoniae* (4 of 28, or 14.3%), *Klebsiella* species (2 of 28, or 7.1%), *Staphylococcus aureus* (2 of 28, or 7.1%), and *Enterobacter* species (2 of 28, or 7.1%). These are shown in Figure 2. Eight of the 28 colonized patients



**Figure 2.** Potential pathogens isolated in 52 sputum samples. BC = *Branhamella catarrhalis*; E = *Enterobacter* species; HI = *Haemophilus influenzae*; HP = *Haemophilus parainfluenzae*; K = *Klebsiella* species; PA = *Pseudomonas aeruginosa*; SA = *Staphylococcus aureus*; SP = *Streptococcus pneumoniae*.

(28.6%) were colonized by multiple organisms. “Nonspecific growth” was defined as the isolation of nonpotentially pathogenic microorganisms, which are not usually involved in respiratory infections in immunocompetent hosts (*Streptococcus viridans* group, *Neisseria* species, *Corynebacterium* species, and coagulase-negative staphylococci) (21).

Sputum IL-8 levels were higher in samples colonized by a potentially pathogenic microorganism than in those with a finding of nonspecific growth (median [IQR]: IL-8 [pg/ml], 4,598 [2,404–5,581] and 3,343 [1,808–4,538], respectively;  $p = 0.026$ ) and were related to the total bacterial count ( $p = 0.417$ ,  $p = 0.03$ ) in colonized samples. The total bacterial count was higher with worsening hypoxemia ( $p = -0.288$ ,  $p = 0.04$ ).

#### Bacterial Colonization, Airway Inflammation, and HRCT Findings

**Prevalence of bronchiectasis and airway inflammation.** Subjects with significant detectable bronchiectasis (total score of 2 or more) exhibited higher levels of airway inflammation than those with a score of 0 or 1 (Table 3). The median (IQR) sputum IL-8 level (pg/ml) in patients with significant bronchiectasis was 3,939 (3,173–5,528) versus 3,897 (1,772–4,733) in those without ( $p = 0.001$ ). The median (IQR) IL-6 level (pg/ml) in patients with significant bronchiectasis was 113.2 (20.1–218.9) versus 50.2 (13.6–213) in those without ( $p = 0.001$ ).

**Distribution of bronchiectasis and lower airway bacterial colonization.** A specific relationship was seen between the extent of bronchiectasis in the lower lobes and the presence of lower airway bacterial colonization. Subjects were categorized, as for the total bronchiectasis scores, into those patients with a total lower lobe score of 0 or 1 ( $n = 36$  of 54, or 66.7%) and those with a total lower lobe score of 2 or more (18 of 54, or 33.3%). Lower lobe bronchiectasis was related to percentage colonization by a potentially pathogenic microorganism ( $\chi^2$ ,  $p = 0.004$ ; odds ratio, 7; 95% confidence intervals, 1.47–37.9; Figure 3) and to percentage colonization by *Haemophilus influenzae* ( $\chi^2$ ,  $p = 0.041$ ). Levels of airway inflammatory markers were also higher in patients with significant lower lobe bronchiectasis

**TABLE 3. RELATIONSHIP BETWEEN THE PRESENCE OF BRONCHIECTASIS ON HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCANNING AND AIRWAY INFLAMMATORY CYTOKINE LEVELS**

Parameter*	Total Bronchiectasis Score		p Value†
	0 or 1 (n = 27)	≥ 2 (n = 27)	
Stable sputum IL-8 level, pg/ml	3,897 (1,772–4,733)	3,939 (3,173–5,528)	0.001
Stable sputum IL-6 level, pg/ml	50.2 (13.6–213)	113.2 (20.1–218.9)	0.001

Definition of abbreviation: IL = interleukin.

Study subjects were divided into those patients with a total bronchiectasis score of 0 or 1 and those with a total score of 2 or more (n = 27 of 54, or 50% in each group).

\* Values for airway inflammatory cytokine levels indicate medians (IQR).

† Poisson regression.

(Table 4). The median (IQR) sputum IL-8 level (pg/ml) in those patients with a lower lobe bronchiectasis score of 2 or more was 4,681 (3,258–5,785) and in those with a score of 1 or less it was 3,614 (1,929–4,663) (p = 0.001). The median (IQR) sputum IL-6 level (pg/ml) in patients with a lower lobe bronchiectasis score of 2 or more was 96.2 (13.6–178) and in those with a score of 1 or less it was 62.6 (19.1–219) (p = 0.03). These relationships were not seen when similar categories were applied to the degree of upper or middle lobe bronchiectasis.

No relationship was seen between the degree of emphysema on HRCT and bacterial colonization or airway inflammation.

#### Relationships with Exacerbation Indices

##### *Distribution/extent of bronchiectasis and exacerbation severity.*

A specific relationship was seen between exacerbation severity, as assessed by the time to recovery of symptoms, and the extent of bronchiectasis in the lower lobes. Patients with a lower lobe bronchiectasis score of 2 or more took longer to recover from their symptoms after an exacerbation than did patients with a lower lobe score of 1 or less. The median time to recovery was 12 versus 10 days in each group, respectively (p = 0.001; Table 4). These relationships were not seen when similar categories were applied to the degree of upper or middle lobe bronchiectasis.

No difference was seen in the proportions of exacerbations treated with oral prednisolone between patients with and without significant lower lobe bronchiectasis (p = 0.193, Poisson regression).

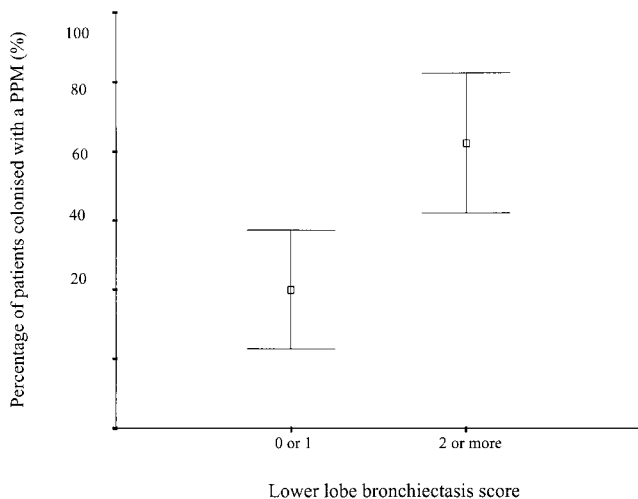
**Bronchiectasis and exacerbation frequency.** The total or lower lobe bronchiectasis scores were not related to exacerbation frequency or number. The number of exacerbations experienced by patients per year was related to the sputum IL-6 level (p = 0.017, Poisson regression), as previously reported (5).

**Emphysema scores and exacerbation indices.** Patients with a higher emphysema score had a reduced incidence of symptoms of increased sputum volume (p = 0.001), wheeze (p = 0.015), or sore throat (p = 0.038) at exacerbation. No relationships were seen between emphysema scores and other indices of exacerbation severity or exacerbation frequency.

## DISCUSSION

This study was designed to evaluate structural changes in bronchiectasis seen on HRCT scanning in patients with moderate to severe COPD, and to relate these to a number of clinical parameters, including indices of exacerbation frequency and severity, airway inflammatory markers, and the presence of lower airway bacterial colonization. Fifty percent of these patients had evidence of significant radiologic bronchiectasis, with HRCT changes being seen most frequently in the lower lobes. The presence of bronchiectasis was associated with increased airway inflammation, as measured by sputum levels of IL-6 and IL-8, but was not related to exacerbation frequency. The extent of bronchiectasis in the lower lobes was related to percentage colonization by a potential pathogen in the lower airway, increased airway inflammatory markers, and longer time to symptom recovery at exacerbation.

A number of previous studies have examined relationships between structural changes seen on HRCT scanning and functional or physiological parameters in COPD, notably in the context of  $\alpha$ -1-antitrypsin disease (22, 23). It is not known, however, whether morphologic changes in the airways or lung parenchyma in usual COPD in the stable state can be related to the number or severity of exacerbations experienced by patients, or to levels of airway inflammation. Recurrent COPD exacerbations are associated with a heightened airway inflammatory burden, and with the presence of lower airway bacterial colonization (4, 5), which in turn has been shown to be an independent stimulus to airway inflammation in COPD (24–28). In addition, we have found that lower airway bacterial colonization in the stable state is associated with increased symptom counts and sputum purulence at exacerbation (4). The possible role of unrecognized bronchiectasis in orchestrating such relationships in COPD has not been previously assessed.



**Figure 3.** Relationship between the extent of lower lobe bronchiectasis and colonization by a potentially pathogenic microorganism (PPM) with 95% confidence intervals, p = 0.004, odds ratio = 7.0. Subjects were categorized, as for the total bronchiectasis scores, into those patients with a total lower lobe score of 0 or 1 (n = 36 of 54, or 66.7%) and those with a total lower lobe score of 2 or more (n = 18 of 54, or 33.3%).

**TABLE 4. RELATIONSHIP BETWEEN THE EXTENT OF LOWER LOBE BRONCHIECTASIS ON HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCANNING AND LEVELS OF AIRWAY INFLAMMATORY MARKERS AND EXACERBATION SEVERITY AS ASSESSED BY MEDIAN TIME TO RECOVERY OF SYMPTOMS**

Parameter	Lower Lobe Bronchiectasis Score		p Value*
	0 or 1 (n = 36)	≥ 2 (n = 18)	
Stable sputum IL-8 level,† pg/ml	3,614 (1,929–4,663)	4,681 (3,258–5,785)	0.001
Stable sputum IL-6 level,† pg/ml	62.6 (19.1–219)	96.2 (13.6–178)	0.03
Time to recovery of symptoms after exacerbation, d	10	12	0.001

Study subjects were divided into those patients with a total lower lobe score of 0 or 1 (n = 36/54 or 66.7%) and those with a total lower lobe score of 2 or more (18/54 or 33.3%).

\* Poisson regression.

† Values for airway inflammatory cytokine levels indicate medians (IQR).

The present study examined a well characterized group of hospital outpatients with moderate to severe COPD. HRCT scans of the chest were performed on patients in the stable state and the extent of bronchiectasis and emphysema was quantified. Patients filled in daily diary cards for peak flow and symptoms over 2 years and were seen every 3 months for spirometry and diary card review. Exacerbations were validated clinically within 48 hours of onset and from diary cards according to our previously defined criteria (7). By these means we were able to carefully examine relationships between HRCT findings, the frequency and severity of exacerbations, stable levels of airway inflammation, and bacterial colonization.

HRCT is now accepted as the imaging modality of choice for the evaluation of bronchiectasis (29–38) and emphysema (39, 40). Thin-section CT has been shown to have discriminatory value in obstructive lung disease (41). However, there is no consensus to date on the role of HRCT in quantifying the structural changes of bronchiectasis in patients with COPD, and its use may have had a number of limitations in the present study. Previous studies of HRCT scanning in patients with clinical bronchiectasis (42, 43), and one study of patients with cystic fibrosis (44), found significantly higher mean bronchiectasis scores than those seen in our cohort. The sensitivity and specificity of bronchiectasis detection by HRCT may therefore have been lower in our group of patients with COPD, who had a relatively smaller burden of disease than subjects in other studies (45). The extent of bronchiectasis has been shown to be negatively correlated with FEV<sub>1</sub>% predicted (16), suggesting that in patients with COPD bronchiectasis may develop in the presence of progressive airway obstruction. We found no relationship between the bronchiectasis score and spirometric measurements; however, this may have been due to the narrow spread of FEV<sub>1</sub>, as all our patients had relatively severe COPD with a mean (SD) FEV<sub>1</sub>% predicted of 38.1 (13.9)%. This would also explain the relatively high prevalence of bronchiectasis found in our study. Comparison with a control group of subjects without COPD would have allowed a more detailed assessment of the accuracy of HRCT to score bronchiectasis or emphysema in our patients with COPD. In view of the range of FEV<sub>1</sub> of our study subjects, the conclusions of this study are limited to patients with moderate to severe COPD.

An important finding in this study was the relationship between the detection of radiologic bronchiectasis on HRCT and more severe COPD exacerbations, as assessed by time to symptom recovery. We have previously shown that exacerbation severity in COPD can be related to this parameter (7). The extent of lower lobe bronchiectasis was also related in this study to the presence of lower airway bacterial colonization. The presence of bacteria in the lower airway in COPD implies a breach of

host defense mechanisms, which fuels a vicious cycle of structural damage, loss of epithelial cell integrity (46), impaired mucociliary clearance (47), and mucus hypersecretion (48). This results in further mucosal injury and inflammation, which could thereby provide the mechanism for longer and more severe COPD exacerbations. The correlation between total bronchiectasis score and PaO<sub>2</sub> also suggests that an imbalance between alveolar ventilation and pulmonary perfusion could be a complementary mechanism contributing to lower airway bacterial colonization in COPD. The findings of this study therefore demonstrate that radiologic evidence of structural damage in the COPD airway, which may be driven in part by lower airway bacterial colonization, may have important clinical implications. These findings could also explain why antibiotics have been shown to be of limited efficacy in modifying outcome measures in studies of COPD exacerbations (49). The presence of these CT changes may provide a means of identifying those patients with COPD who are at risk of more severe COPD exacerbations.

In this study the emphysema score was associated with a lower incidence of increased sputum purulence, sore throat, or wheeze at exacerbation. The extent of radiologic emphysema has been shown to be related to physiological correlates such as airway obstruction, as found in this study, as well as measures of health status (22) and numbers of leukocytes in the small airways (50). However, little is known about relationships with exacerbation indices or symptoms. These findings suggest that the character of exacerbations may differ in COPD depending on the distribution of the pathophysiological abnormalities within the lung, with exacerbations associated with purulent sputum occurring more in the context of large airway damage and remodeling, as opposed to parenchymal disease. This requires confirmation in larger studies.

No relationship was seen in this study between radiologic evidence of bronchiectasis or emphysema and exacerbation frequency. It is possible that the study was underpowered for detecting this relationship. However, we have previously shown that a significant proportion of exacerbations in our cohort of patients with COPD have a viral etiology, most commonly human rhinovirus infection (51). Little information is available on how viruses and bacteria may interact in the COPD airway, and it is likely that mechanisms governing exacerbation frequency in COPD are multifactorial.

There are a number of possible reasons why bronchiectasis was detected most frequently in the lower lobes in this study. In a previous study of patients with chronic purulent sputum production (52) a predominantly lower lobe distribution of bronchiectasis was found in subjects with impaired mucociliary clearance, one of the impaired host defense mechanisms seen in COPD. In addition, in a study of patients with bronchiectasis of known

etiologies (53), a lower lobe distribution was most often seen in patients with a history of childhood viral infections, a suggested risk factor for COPD. It is possible that multiple physiological and pathologic alterations, including damaged mucociliary transport, localized or diffuse peripheral obliteration of the bronchial tree or lung tissue scarring act in concert in COPD, in the context of an already disrupted lung parenchyma, to produce the structural changes of bronchiectasis seen on HRCT. Further longitudinal studies are now required to establish criteria for the detection of these structural changes and their significance in COPD, and how they may relate to the natural history of this condition.

Clinical history and examination correlate poorly with HRCT features, with patients with bronchiectasis often being clinically indistinguishable from other study subjects (6, 16). A high prevalence of bronchiectasis has been demonstrated in an unselected group of patients with a primary care diagnosis of COPD (6), and studies of patients with  $\alpha$ -1-antitrypsin disease have suggested that bronchiectasis may be present either concomitantly (54) or before the development of emphysema (55, 56). The  $\alpha$ -1-antitrypsin status of our patients was not routinely ascertained, and none had clinical evidence of bronchiectasis on recruitment. However, it is possible that some of these patients had bronchiectasis and then developed COPD with emphysema in addition to this at a later date. Only 50% of our patients with COPD reported daily cough and sputum production, and no relationship was seen in this study between these symptoms and bronchiectasis scores, suggesting that the HRCT findings in our patients were likely to represent subclinical changes. Our findings therefore suggest that while HRCT continues to be an infrequently used tool in the assessment of COPD, subclinical bronchiectasis, which may nevertheless have important implications for some patients, is likely to remain undiagnosed.

In summary, this study has shown a high prevalence of radiologic bronchiectasis in a group of patients with moderate to severe COPD without clinical signs of this condition. Patients with moderate lower lobe bronchiectasis experienced more severe exacerbations, were more likely to exhibit lower airway bacterial colonization, and had heightened levels of airway inflammation. This suggests that HRCT scanning may be useful in identifying particular subgroups of patients with moderate to severe COPD, who are prone to more severe exacerbations and to the increased morbidity associated with these. Moreover, this study provides further evidence linking the presence of lower airway bacterial colonization, and related structural airway changes, to important clinical parameters in COPD.

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