Cough and Sputum Production Are Associated With Frequent Exacerbations and Hospitalizations in COPD Subjects*

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Background: **Epidemiologic studies indicate that chronic cough and sputum production are associated with increased mortality and disease progression in COPD subjects. Our objective was to identify features associated with chronic cough and sputum production in COPD subjects.**
Methods: **Cross-sectional analysis of data were obtained in a multicenter (17 university hospitals in France) cohort of COPD patients. The cohort comprised 433 COPD subjects (65 ± 11 years; FEV_1, 50 ± 20% predicted). Subjects with (n = 321) and without (n = 112) chronic cough and sputum production were compared.**
Results: **No significant difference was observed between groups for age, FEV_1, body mass index, and comorbidities. Subjects with chronic cough and sputum production had increased total mean numbers of exacerbations per patient per year (2.20 ± 2.20 vs 0.97 ± 1.19, respectively; $p < 0.0001$), moderate exacerbations (1.80 ± 2.07 vs 0.66 ± 0.85, respectively; $p < 0.0001$), and severe exacerbations requiring hospitalizations (0.43 ± 0.95 vs 0.22 ± 0.56, respectively; $p < 0.02$). The total number of exacerbations per patient per year was the only variable independently associated with chronic cough and sputum production. Frequent exacerbations (two or more per patient per year) occurred in 55% vs 22% of subjects, respectively, with and without chronic cough and sputum production ($p < 0.0001$). Chronic cough and sputum production and decreased FEV_1 were independently associated with an increased risk of frequent exacerbations and frequent hospitalizations.**
Conclusions: **Chronic cough and sputum production are associated with frequent COPD exacerbations, including severe exacerbations requiring hospitalizations.**
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Key words: airway mucus; chronic bronchitis; COPD; COPD exacerbations

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; OR = odds ratio

Both chronic cough and sputum production and not fully reversible airflow limitation, which defines COPD, are associated with cigarette smoking.[1] However, chronic cough and sputum production are present only in a subset of patients with COPD,[1,2] and their impact on the natural history of COPD has long been a debate.[3] Early studies[4] reported that chronic cough and sputum production were unrelated to loss in lung function in patients with mild COPD. Subsequently, Vestbo et al[5] reported that chronic cough and sputum production were associated with disease progression (*ie*, FEV_1 decline) in subjects with COPD. Several investigators[1,6,7] further reported that chronic cough and sputum production were associated with premature death in subjects with COPD. Although these studies suggest that chronic cough and sputum production are important manifestations in COPD subjects, available

data[3] mostly are based on epidemiologic studies. Because such studies do not allow for precise patient phenotyping, the clinical features associated with chronic cough and sputum production in COPD subjects remain to be established.

The present study examined the hypothesis that chronic cough and sputum production are associated with distinct clinical features in COPD patients. We performed a cross-sectional analysis of data collected prospectively in a large cohort of patients with a secured diagnosis of COPD. Subjects were recruited in 17 university hospitals throughout France. Detailed phenotypic characterization of the subjects allowed us to determine the clinical manifestations associated with chronic cough and sputum production among them.

Methods and Materials

Study Design

A cross-sectional analysis of a cohort of COPD patients recruited between January 2005 and May 2007 was performed. The subjects were recruited from 17 pulmonary units in university hospitals located throughout France. Respiratory physicians prospectively recruited subjects with a secured diagnosis of COPD who were in stable condition (*ie*, no history of exacerbation requiring medical treatment for the previous 4 weeks). The diagnosis of COPD was based on the presence of a postbronchodilator FEV_1/FVC ratio $< 70\%$, as recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 guidelines.[8] Patients with a main diagnosis of bronchiectasis, asthma, or any significant respiratory diseases were excluded. Subjects with chronic cough and sputum production, and an FEV_1/FVC ratio $> 70\%$ (former GOLD stage 0) also were recruited in the cohort but were excluded from the analyses. The study was approved by the Ethics Committee of Versailles (France), and all subjects provided informed written consent.

Data Collection

A standardized questionnaire was used that covered demographic data; pulmonary risk factors (*eg*, current or past tobacco smoking); comorbidities; and COPD characteristics, including symptoms, date of diagnosis, forced spirometry, and therapy with the patient in stable condition. Chronic cough and sputum production were considered to be present when subjects answered the following question affirmatively: "Did you cough up phlegm (in the morning or during the day) for at least 3 months each year during the past two years?"[9]

Pulmonary function tests were performed according to international standards,[10] and predicted values were calculated using the European Community for Steel and Coal[11] reference values. The severity of COPD in subjects who were in stable condition was evaluated according to GOLD spirometric classification based on postbronchodilator FEV_1.[8] Stages were defined as follows: stage I, $FEV_1 \geq 80\%$ predicted; stage II, $FEV_1 \geq 50\%$ and $< 80\%$ predicted; stage III, $FEV_1 \geq 30\%$ and $< 50\%$ predicted; and stage IV, $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure.[8]

The number of acute exacerbations of COPD during the previous year were determined according to each subject's self-reported events for mild and moderate exacerbations. For severe exacerbations, data were obtained from medical records. Exacerbations were defined as short-term and sustained changes in the subject's baseline dyspnea, cough, and/or sputum that warrant changes in regular medication.[8] The severity of COPD exacerbations was classified based on health-care resource utilization[12], as follows: a self-managed exacerbation was considered to be mild; a moderate exacerbation was defined as an exacerbation requiring medical assistance (without the need for hospitalization or an emergency unit admission) and/or the use of antibiotics or systemic steroids; and a severe exacerbation was as an exacerbation requiring hospitalization. We found that subjects in this cohort had a median of 1 exacerbation per patient per year (minimum number, 0 exacerbation per patient per year; maximum number, 12 exacerbations per patient per year). Thus, COPD subjects with frequent exacerbations were defined as those who experienced at least two exacerbations during the previous year.[13] We also defined frequent moderate exacerbations (*ie*, requiring medical assistance and/or the use of antibiotics or systemic steroids two or more times per patient per year) and frequent severe exacerbations (*ie*, requiring two or more hospitalizations per patient per year).

Statistical Analysis

Quantitative variables are reported as the mean ± SD or as the median (minimum to maximum); qualitative variables are reported as percentages. Differences in demographic and clinical characteristics between subjects with and without chronic cough and sputum production were analyzed using *t* tests (for continuous variables) and χ^2 tests (for qualitative variables). The data obtained on exacerbation numbers in subjects with and without chronic cough and sputum production were not normally distributed and were analyzed using the nonparametric Mann-Whitney test. All variables associated with chronic cough and sputum production with $p < 0.20$ in univariate analysis were computed in a multivariate logistic regression model to identify factors inde-

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pendently associated with this phenotypic characteristic. Because we found that chronic cough and sputum production were associated with frequent exacerbations during the previous year, we examined whether this association was independent of known risk factors for frequent exacerbations. Thus, we performed a second multivariate logistic regression analysis that included potential predictors of frequent COPD exacerbations, including current smoking, FEV_1 percent predicted, cardiovascular comorbidities, and chronic cough and sputum production. A p value < 0.05 was considered statistically significant. Analyses were performed using a statistical software package (SAS, version 9.1; SAS Institute; Cary, NC).

Results

Description of the Study Cohort

Data were collected on 502 subjects; 23 subjects were excluded from the analyses because spirometry results showed a postbronchodilator $FEV_1/FVC > 70\%$ (former GOLD stage 0). Additionally, 46 subjects were excluded from the analyses because the presence or absence of chronic cough and sputum production had not been recorded accurately. These 46 subjects were not statistically different from the other subjects for age, gender, smoking habits, FEV_1, or exacerbations (data not shown). Thus, the analyses were performed for the remaining 433 subjects.

The clinical characteristics of the subjects are shown in Table 1. Most subjects were ex-smokers (current smokers, 25%), and only 12 subjects (2.8%) had never smoked. One third of these 433 subjects were classified as being in GOLD stage IV, and half were in GOLD stage III or IV. Further, 18% of the subjects were treated with long-term oxygen therapy. The mean (± SD) number of exacerbations was 1.88 ± 2.06 per patient per year (median, 1 exacerbation per patient per year; range, 0 to 12 exacerbations per patient per year).

Long-acting bronchodilators (*ie*, long-acting β_2-agonist [LABA] or inhaled corticosteroid [ICS]/LABA and/or tiotropium) were prescribed for 70% of subjects in GOLD stage I and II, 85% of subjects in GOLD stage III, and 96% of subjects in GOLD stage IV. All subjects were prescribed short-acting bronchodilators.

Table 1—*Characteristics of COPD Subjects According to the Presence of Chronic Cough and Sputum Production

Characteristics	All (n = 433)	Chronic Cough and Sputum Production (n = 321)	No Cough and Sputum Production (n = 112)	p Value
Female gender	21	19	21	0.53
Age, yr	65 ± 11	64 ± 11	66 ± 11	0.08
Current smokers	25	28	18	0.03†
Duration of smoking,‡ yr	37 ± 12	37 ± 11	37 ± 12	0.85
Smoking, pack-yr	46 ± 29	47 ± 29	44 ± 29	0.39
FEV_1				
L	1.39 ± 0.61	1.36 ± 0.57	1.47 ± 0.69	0.10
% predicted	50.4 ± 19.7	49.9 ± 19.9	52.4 ± 19.2	0.24
FVC, L	2.74 ± 0.92	2.74 ± 0.86	2.75 ± 1.04	0.91
GOLD stages				0.09
I	7	7	6	
II	42	40	49	
III	18	20	11	
IV	33	33	34	
Body mass index, kg/m^2	25.2 ± 5.2	25.2 ± 5.4	25.0 ± 4.6	0.65
Specific comorbidities				
Congestive heart failure	12.9	13.9	9.6	0.25
Coronary artery disease	14.9	16.3	10.6	0.15
Diabetes mellitus	12.0	13.2	8.6	0.20
Hypertension	35.0	33.4	39.6	0.24
At least one cardiovascular comorbidity§	22.6	24.3	17.5	0.15
Inhaled therapy				
LABAs	52	51	56	0.34
ICSs/LABAs	18	19	14	0.26
ICSs‖	52	53	50	0.58
Tiotropium	11	12	8	0.26
Home oxygen therapy	16	16	18	0.62
All exacerbations/patient/yr	1.88 ± 2.06	2.20 ± 2.20	0.97 ± 1.19	< 0.0001†

*Data are presented as mean ± SD or %, unless otherwise indicated.
†Value is significant.
‡Only 12 subjects were never-smokers.
§At least one cardiovascular comorbidity is defined by the presence of congestive heart failure and/or coronary artery disease.
‖ICSs (outside of fixed associations) were associated with long-acting bronchodilators in all cases.

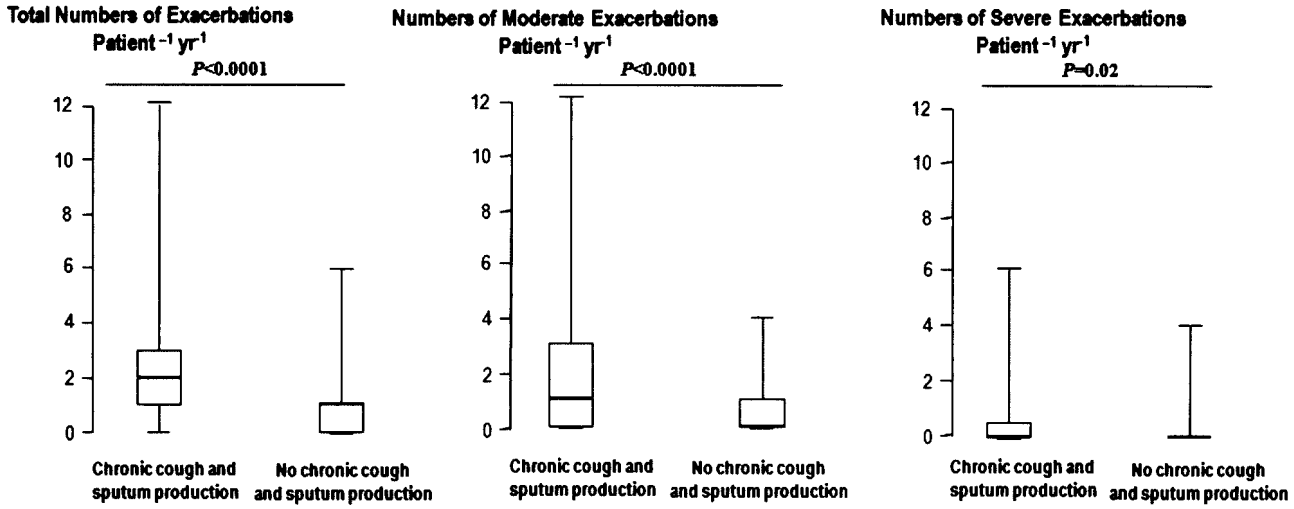

FIGURE 1. Number of exacerbations were compared in subjects with or without chronic cough and sputum production during the previous year. *Left*: total number of exacerbations per patient per year. *Center*: number of moderate exacerbations per patient per year. *Right*: number of severe exacerbations per patient per year. Each box plot comprises five horizontal lines that display the 10th, 25th, 50th, 75th, and 90th percentiles of the variable.

Association of Chronic Cough and Sputum Production With Other Phenotypic Manifestations

Chronic cough and sputum production was found in 321 of 433 (74.1%) of the subjects. Current smoking was significantly more prominent in subjects with chronic cough and sputum production (28% vs 18%, respectively; $p < 0.03$) [Table 1]. No significant difference was observed between subjects with and without chronic cough and sputum production for age, cumulative duration of tobacco smoking, FEV_1, body mass index, and cardiovascular comorbidities. Similarly, no significant difference was found for maintenance inhaled therapy (*ie*, LABA, fixed combinations of ICS/LABA, ICS, and tiotropium) between the subject groups.

Among subjects with chronic cough and sputum production, only 22% reported no exacerbation during the previous year, whereas 42% of the subjects without chronic cough and sputum production reported no exacerbations ($p < 0.0001$). Subjects with chronic cough and sputum production had experienced twice as many exacerbations as subjects with no chronic cough and sputum production ($p < 0.0001$) [Table 1 and Fig 1, *left*]. Furthermore, subjects who reported chronic cough and sputum production had increased numbers of moderate exacerbations ($p < 0.0001$) [Fig 1, *center*] and severe exacerbations ($p < 0.02$) [Fig 1, *right*]. In multivariate logistic regression analysis, the number of exacerbations during the previous year was the only variable independently associated with the presence of chronic cough and sputum production (odds ratio [OR], 1.55; $p < 0.0001$) [Table 2].

Frequent Exacerbations in COPD Subjects With and Without Chronic Cough and Sputum Production

Frequent exacerbations (two or more exacerbations per patient per year) occurred in 55% of subjects with chronic cough and sputum production but only in 22% of subjects without chronic cough and sputum production ($p < 0.0001$) [Fig 2, *left*]. Similarly, subjects reporting chronic cough and sputum production were more likely to have experienced two or more moderate

Table 2—*Multivariate Logistic Regression With Chronic Cough and Sputum Production as Dependent Variable**

Dependent Variables	β ± SE	Estimated OR	95% CI	p Value
Age	−0.01 ± 0.01	0.99	0.96–1.01	0.31
Current smoking	−0.26 ± 0.16	0.60	0.32–1.12	0.11
FEV_1 % predicted	−0.20 ± 0.22	0.82	0.54–1.25	0.36
At least one cardiovascular comorbidity	−0.22 ± 0.16	0.65	0.35–1.21	0.17
All exacerbations/patient/yr	0.44 ± 0.10	1.55	1.28–1.87	< 0.0001†

*Variables included in the analysis were those associated with chronic cough and sputum production with a p value <0.20. β = estimated coefficient; CI = confidence interval.
†Value is significant.

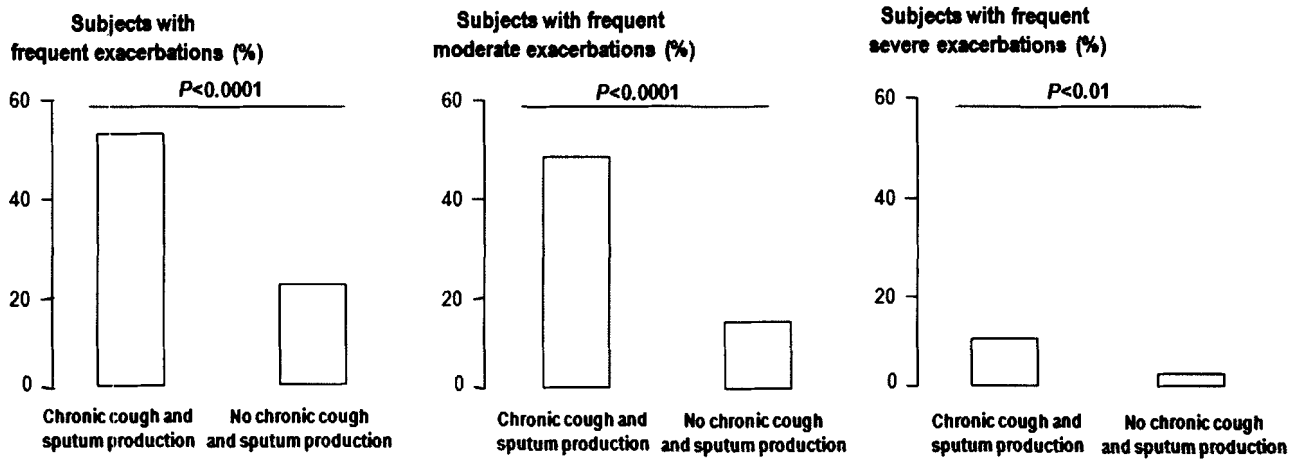

FIGURE 2. Percentages of frequent exacerbations among COPD subjects with or without chronic cough and sputum production. *Left*: percentage of subjects with frequent exacerbations (defined as two or more exacerbations per patient per year) were determined in subjects with (n = 321) and without (n = 112) chronic cough and sputum production. Similarly, percentages of subjects with frequent (*ie*, two or more) moderate exacerbations (*center*) and severe exacerbations (*right*) were determined. Results are expressed as percentage of the number of subjects in each group.

exacerbations per patient per year ($p < 0.0001$) [Fig 2, *center*] and two or more severe exacerbations per patient per year ($p < 0.01$) [Fig 2, *right*].

We used a logistic regression model to examine whether chronic cough and sputum production were associated with frequent exacerbations independently of other factors known to be associated with frequent COPD exacerbations. In this model, we included postbronchodilator FEV_1 (percent predicted), current tobacco smoking status, age, and the presence of at least one cardiovascular comorbidity (*eg*, congestive heart failure and/or coronary artery disease).[14] Factors independently associated with frequent exacerbations were a decrease in FEV_1 and the presence of chronic cough and sputum production (Table 3). Similarly, a decrease in FEV_1 and the presence of chronic cough and sputum production were independently associated with increased frequent moderate and frequent severe exacerbations.

Table 3—*Multivariate Logistic Regression With Frequent Exacerbations (Two or More per Patient per Year) as Dependent Variable

Variables	β ± SE	Estimated OR	95% CI	p Value
All exacerbations				
Age	−0.00 ± 0.01	0.99	0.98–1.02	0.85
FEV_1 % predicted (10-unit OR)†	−0.02 ± 0.01	1.21	1.09–1.35	0.0006‡
Current smoking	0.17 ± 0.14	1.42	0.84–2.40	0.19
At least one cardiovascular comorbidity	0.10 ± 0.13	1.21	0.72–2.02	0.47
Chronic cough and sputum production	0.71 ± 0.14	4.15	2.43–7.08	< 0.0001‡
Moderate exacerbations				
Age	−0.00 ± 0.01	0.99	0.97–1.02	0.60
FEV_1 % predicted (10-unit OR)†	−0.02 ± 0.00	1.20	1.07–1.34	0.001‡
Current smoking	0.12 ± 0.13	1.27	0.75–2.16	0.37
At least one cardiovascular comorbidity	−0.01 ± 0.13	1.00	0.59–1.67	0.97
Chronic cough and sputum production	0.77 ± 0.15	4.65	2.54–8.48	< 0.0001‡
Severe exacerbations				
Age	0.03 ± 0.02	1.02	0.98–1.07	0.80
FEV_1 % predicted (10-unit OR)†	−0.05 ± 0.01	1.75	1.36–2.26	<0.0001‡
Current smoking	0.13 ± 0.22	1.29	0.53–3.16	0.57
At least one cardiovascular comorbidity	0.14 ± 0.21	1.34	0.58–3.10	0.49
Chronic cough and sputum production	0.70 ± 0.31	4.08	1.18–14.09	0.03‡

*Variables included in the analysis were those previously described as being associated with frequent exacerbations. See Table 2 for abbreviations not used in the text.

†OR per each 10% decrease in FEV_1.

‡Value is significant.

Discussion

Studying a large cohort of COPD subjects, we found that the number of exacerbations during the previous year was the only independent factor linked to chronic cough and sputum production. In addition, chronic cough and sputum production were associated with frequent exacerbations, including moderate and severe exacerbations. Importantly, the association between chronic cough and sputum production and frequent exacerbations was independent of other known risk factors for frequent exacerbations,[14] including FEV_1, age, cardiovascular comorbidities, and current smoking. These results indicate a strong relationship between chronic cough and sputum production and frequent exacerbations in COPD subjects.

This study has important strengths. We studied a large group of COPD subjects (n = 433) in a multicenter cohort in France. The diagnosis of COPD was secured on international criteria,[8] and a standardized questionnaire was used, allowing for detailed phenotypic characterization of the subjects. All physicians participating in the study were respiratory specialists involved in the care of COPD patients, thereby increasing the accuracy of COPD diagnosis and the quality of patient phenotyping. However, we recognize some limitations. The subjects were recruited from university hospitals and may represent a specific population of COPD. Exacerbation severity was evaluated according to health-care utilization criteria.[12] Although this classification is appropriate for France, health-care utilization for COPD patients may vary among countries, depending on access; thus, substantial difficulty could exist in the standardization of such a definition.[13] Data were obtained cross-sectionally, and the numbers of exacerbations and their degree of severity were determined according to medical records and patient recollections. Seemungal et al.[15] found that about 50% of acute exacerbations of COPD are not reported by patients. Thus, the exacerbations were more likely to be underestimated than overestimated in the present study. Importantly, all variables related to exacerbation frequency, including markers of severe exacerbations (*ie*, hospitalization), which were evaluated objectively based on medical records, also showed associations with chronic cough and sputum production, further reinforcing our findings on exacerbation numbers.

Chronic cough and sputum production were reported more often in our cohort (74%) than in previous studies.[2,16] For example, Kanner et al[2] reported that chronic cough and sputum production were present in 35% of subjects with mild COPD (mean FEV_1, 78 ± 9% predicted); however, in the Copenhagen City Heart Study, Vestbo and Lange[16] found that productive cough was present in about 10% of subjects with mild COPD and in about 40% of subjects with more advanced disease. In this latter group of subjects, results were obtained in only 33 patients.[16] These data suggest that the frequency of chronic cough and sputum production increases with disease severity. It is suggested by our group that the sampling of a population may affect the prevalence of chronic cough and sputum production. Because our cohort was recruited in university hospitals and was biased toward severe cases, we assume that this finding could explain the high numbers of patients with this phenotype.

We used the classic clinical definition of chronic cough and sputum production,[9] whereas in a previous report, Miravitlles et al[17] defined chronic mucus hypersecretion as the emission of > 1 cup (30 mL) of sputum daily. These authors reported that chronic mucus hypersecretion was present in 40 to 52% of COPD subjects (mean FEV_1, 50% predicted). Thus, differences in the definition of chronic cough and sputum production also may account for some of the difference in the prevalence of these symptoms among COPD subjects. On the other hand, it is extremely difficult to assess this phenotype objectively, and one should rely on patients' perception and recall.

How do these results add to our current knowledge of the relationship between chronic cough and sputum production and COPD exacerbations? Seemungal et al[15] recorded daily symptoms prospectively for 1 year in a cohort of 70 patients with COPD. About half of the exacerbations remained unreported (median, three exacerbations per year, including reported and unreported exacerbations). These authors found that daily cough and sputum was associated with frequent exacerbations (three or more exacerbations per year; OR, 1.34). The severity of exacerbations was not described.[15] In a cross-sectional study of a cohort of general practitioner-diagnosed COPD subjects, Miravitlles et al[17] reported an association between chronic mucus hypersecretion and the presence of two or more exacerbations during the previous year (OR, 1.54). However, about 20% of their subjects were never-smokers, raising the possibility that these subjects had other obstructive lung diseases. In the present study, we report an association between chronic cough and sputum production and frequent COPD exacerbations, including moderate exacerbations (*ie*, requiring medical assistance) and severe exacerbations (*ie*, requiring hospitalization), in a large cohort of well-characterized COPD subjects.

Chronic cough and sputum production are associated with increased overall mortality in subjects with or without airflow obstruction.[7] In the present study, congestive heart failure and coronary artery disease

seemed more prevalent among subjects with chronic cough and sputum production, although these findings were not statistically different. We speculate that cardiovascular comorbidities may play roles in the increased mortality observed in subjects with chronic cough and sputum production. This hypothesis will require further investigation.

In the present study, the number of exacerbations during the previous year was the only independent factor linked to chronic cough and sputum production, and chronic cough and sputum production were independently associated with frequent exacerbations. The presence of frequent exacerbations may in itself favor the chronic cough and sputum phenotype. The increase in cough and sputum production that occurs during an acute exacerbation may persist for several weeks after the onset of the exacerbation, and recovery often is incomplete.[18,19] The persistence of such bronchitic symptoms may be related to the persistence of an inflammatory process in the airways of patients with frequent exacerbations. Bhowmik et al[20] reported that COPD subjects with frequent exacerbations have increased sputum concentrations of interleukin-6 and interleukin-8 compared with COPD subjects with fewer exacerbations. Furthermore, a similar increase in sputum eosinophils was found in COPD subjects during acute exacerbations,[21] especially in exacerbations related to viral infection or viral/bacterial coinfection,[22] and in stable COPD subjects with chronic cough and sputum production,[23] which can be of importance to sustain our clinical findings. Alternatively, chronic mucus hypersecretion may facilitate lower airway infection and COPD exacerbations. Prescott et al[24] reported that chronic cough and sputum production in COPD subjects were significant predictors of death from pulmonary infections but not of noninfectious death. Because chronic cough and sputum production are believed to originate from inflammatory mechanisms in proximal airways, it is speculated that retrograde aspiration may lead to mucus obstruction in small airways, an important prognosis factor among COPD subjects.[25,26] Regardless of the biological mechanisms, our data suggest an association between chronic cough and sputum production and frequent exacerbations of COPD.

Conclusions

Our data suggest that chronic cough and sputum production are closely associated with the occurrence of COPD exacerbations, including severe exacerbations. Interestingly, longitudinal studies[16,27] have shown that chronic cough and sputum production may not be a stable feature. Although current therapies are not known to affect chronic cough and sputum production, we suggest that therapeutic interventions targeting chronic cough and sputum production may be useful. Because frequent COPD exacerbations are associated with a high morbidity and mortality[13] and heavy use of health-care resources,[14,28] we suggest that COPD patients with chronic cough and sputum production may represent a target population for whom specific therapeutic interventions should be developed.

Appendix

The members of the Initiatives Bronchopneumopathie Chronique Obstructive (BPCO) Scientific Committee are as follows: Graziella Brinchault-Rabin (Rennes); Pierre-Régis Burgel (Paris, Cochin); Denis Caillaud (Clermont-Ferrand); Philippe Carré (Carcassonne); Pascal Chanez and Christophe Pinet (Marseille); Ari Chaouat (Vandoeuvre les Nancy); Isabelle Court-Fortune (Saint-Etienne); Antoine Cuvelier (Rouen); Roger Escamilla (Toulouse); Chantal Raherison (Bordeaux); Christophe Gut-Robert and Christophe Leroyer (Brest); Gilles Gebrak (Paris); Romain Kessler (Strasbourg); Franck Lemoigne and Cecile Peirera (Nice); Pascale Nesme-Meyer (Lyon); Thierry Perez and Isabelle Tillie-Leblond (Lille); Christophe Perrin (Cannes); and Nicolas Roche (Paris, Hôtel Dieu).

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