Risk factors of readmission to hospital for a COPD exacerbation: a prospective study

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Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are a leading cause of admission to hospital among men in many countries, although the factors causing exacerbations are largely unknown. The association between readmission for a COPD exacerbation and a wide range of modifiable potential risk factors, after adjusting for sociodemographic and clinical factors, has been assessed.

Methods: Three hundred and forty patients with COPD recruited during an admission for an exacerbation in four tertiary hospitals in the Barcelona area of Spain were followed for a mean period of 1.1 years. Information on potential risk factors, including clinical and functional status, medical care and prescriptions, medication adherence, lifestyle, health status, and social support, was collected at the recruitment admission. A Cox’s proportional hazards model was used to obtain independent relative risks of readmission for COPD.

Results: During the follow-up period 63% of patients were readmitted at least once, and 29% died. The final multivariate model showed the following risk (or protective) factors: >3 admissions for COPD in the year before recruitment (hazard ratio (HR)=1.66, 95% CI 1.16 to 2.39), forced expiratory volume in 1 second (FEV1) percentage predicted (0.97, 95% CI 0.96 to 0.99), oxygen tension (0.88, 95% CI 0.79 to 0.98), higher levels of usual physical activity (0.54, 95% CI 0.34 to 0.86), and taking anticholinergic drugs (1.81, 95% CI 0.79 to 0.98). Exposure to passive smoking was also related to an increased risk of readmission with COPD after adjustment for clinical factors (1.63, 95% CI 1.04 to 2.57) but did not remain in the final model.

Conclusions: This is the first study to show a strong association between usual physical activity and reduced risk of readmission to hospital with COPD, which is potentially relevant for rehabilitation and other therapeutic strategies.
approved the protocol and written informed consent was obtained from all patients.

Information about factors potentially related to COPD exacerbations was obtained by an extensive bibliographic search that has been described elsewhere.1 A large number of potential risk factors—including variables related to clinical status, characteristics of medical care, medical prescriptions, adherence to medication, lifestyle, quality of life, and social support—was identified and has been reported elsewhere.1 All the variables were considered in the analysis.

During the recruitment hospital admission, patients were asked to complete a questionnaire. Most of the questionnaire content was obtained from previously validated instruments, while some questions were developed and pilot tested. Questions for usual physical activity were adapted from the Spanish validation15 of the Minnesota Leisure Time Physical Activity Questionnaire, a measure of physical activity in the general population.16 Each specific activity was assigned an intensity unit based on their rate of energy expenditure expressed as metabolic equivalent task (METs), the ratio of work metabolic rate to resting metabolic rate.17 The energy expenditure in physical activity was then expressed as the total activity metabolic index per day in kcal/day, taking into account the intensity code for each physical activity, the number of times that this activity was performed in a usual day, and the average time spent in each session. In addition, weight, height and tricipital skinfold thickness were measured. Sputum samples were collected during the first 48 hours after admission and processed within an hour, accepting only those considered suitable for culture according to their rate of energy expenditure.

Follow up

Six (1.7%) of the 346 patients recruited did not survive the recruitment admission; 340 patients were therefore followed from the day of discharge after the recruitment admission until 1 May 1999 or the day of death, if earlier. There were no losses to follow up as all patients were either contacted for telephone interview, registered as dead in the mortality registry, or visited in the outpatient clinics or hospitalised after 1 May 1999.

Information on readmissions during the follow up period was obtained from the Minimum Basic Dataset (CMBD), a national administrative database that is monitored to high quality standards.18 The primary study outcome was the time to readmission for a COPD exacerbation. All admissions with a main or secondary diagnosis fulfilling any of the following code combinations (according to the International Classification of Diseases, 9th revision) were recorded as a COPD exacerbation: (1) 490–496 (COPD group), 480–486 (pneumonia), 487 (influenza), or 518.81 (respiratory failure) as the main diagnosis; (2) 428 (cardiac failure) as the main diagnosis if 518.81 or 491.21 was the main diagnosis; (2) 428 (cardiac failure) as the main diagnosis if 518.81 or 491.21 was the main diagnosis; (3) any other respiratory problems (011 (tuberculosis), 466 (acute bronchitis), 500–505 (pneumoniosis), 277.6 (deficit α-antitrypsin)) as the main diagnosis if 518.81 or 491.21 was the secondary diagnosis. Criteria of the expert consensus of the American Thoracic Society19 were used to define such combinations.

Vital status was ascertained through a telephone interview with patients or their proxies and a record linkage with the Catalonia mortality registry for the years 1997–1999.
without admission in the year before recruitment, a lower percentage predicted FEV₁, and a lower P<sub>O₂</sub>, were independently related to a higher risk of re-admission for COPD, whereas having had >3 COPD admissions in the year before recruitment, living alone, pneumococcal vaccination, nutritional status, and LTOT were also associated with a higher risk of readmission for COPD but did not achieve statistical significance. None of the remaining factors (socioeconomic status, living alone, pneumococcal vaccination, nutritional status, adherence to medication, comorbidity, or bacterial infection at baseline) was significantly associated with readmission.

In a final multivariate model, a high level of usual physical activity was associated with a 46% reduction in the risk of a readmission for COPD, whereas having had >3 COPD admissions in the year before recruitment, a lower percentage predicted FEV₁, a lower level of P<sub>O₂</sub>, being a former smoker exposed to passive smoking, influenza vaccination, respiratory rehabilitation, and LTOT were also associated with a higher risk of readmission for COPD but did not achieve statistical significance. None of the remaining factors (socioeconomic status, living alone, pneumococcal vaccination, nutritional status, adherence to medication, comorbidity, or bacterial infection at baseline) was significantly associated with readmission.
DISCUSSION

To our knowledge, this is the first study to show that patients with COPD who perform a relatively high level of physical activity in their daily life have a substantially reduced risk of readmission due to exacerbation. Since the third of patients with COPD who reported an activity equivalent to walking ≥60 minutes a day had a reduction in risk of readmission to hospital of almost 50%, this is potentially relevant. Moreover, the association did not change when adjusted for COPD severity, nutritional status factors, or respiratory rehabilitation. Such results are in agreement with the increased risk of COPD admission associated with a limited 6 minute walking test reported in a previous group of COPD patients,[25] both studies suggesting that conditioned patients have a lower risk of COPD admission which is independent of the way conditioning is evaluated. Because our finding has not been reported previously, its mechanism can only be speculated. One possible explanation is that exercise leads to a better conditioned cardiovascular system[26] that would adapt better to the increase in oxygen intake in respiratory muscles that occurs during a COPD exacerbation.[27] In addition, a programme of endurance training can reduce exercise induced lactic acidosis and improve the oxidative capacity of the muscles in patients with moderate to severe COPD,[28] suggesting that such muscles would be more able to tolerate a COPD exacerbation than untrained muscles. We found no relationship between physical activity and rehabilitation or nutritional status, which suggests that physical activity in this population depends on other factors. The extent to which these results may have relevance for rehabilitation programmes[29] or clinical practice[30] is not yet clear.

Several factors related to medical care or prescriptions—such as being controlled by a pulmonologist, taking anticholinergics or oral corticosteroids—were associated with a higher risk of readmission for COPD in the adjusted clinical model, contrary to what had been expected. Similar results were also found in the previous case-control EFRAM study,[11] although they were more evident in the follow up analysis. We consider that a previous COPD admission may play a role of “confounding by indication”, a term used when the confounder represents a perceived high risk or poor prognosis that results in an indication for treatment.[31] In our study, having had previous admissions fulfils the two conditions necessary to qualify as a confounder. Firstly, patients who had had a previous COPD admission at recruitment (82%) had a higher prevalence of prescriptions of anticholinergics or oral corticosteroids than those who had never had a COPD admission (18%). Secondly, having had a previous admission (independ-
Longitudinal data can be analysed in different ways and, in our Cox analysis, repeated admissions in the same subject were not taken into account. However, very similar parameter estimates were obtained when repeated admissions were included in a Poisson regression model. Such consistency was expected since Poisson regression can be seen as a special case of a proportional hazards model with a constant baseline hazard.21

Patients who died without a readmission were excluded, a decision that could have introduced a degree of survival bias. However, these patients constituted a small proportion (8%) of the total and only showed slight differences in age and BMI. Moreover, when they were included in the analysis by combining death and readmission as the outcome variable, the same risk factors for COPD readmission were obtained and estimates did not change substantially (data available from the authors).

Patients included in our study were mostly men with a mean age of 69 years, mean percentage predicted FEV1 of 36%, and probably elsewhere, with the exception of the male predominance. Generalisation of our results should be restricted to COPD in this stage of the disease since patients in earlier or advanced stages may differ substantially. Another potential problem in the method of recruitment is that some readmissions during the follow up period may not really be new exacerbations but a relapse of the previous one. In order to avoid this the analysis was repeated, excluding those patients whose readmission occurred within 14 days of the previous discharge (n=38), and very similar results were obtained (data available from the authors).

This is the first study to show a strong association between usual physical activity and reduced risk of COPD readmission which is potentially relevant for rehabilitation and other therapeutic strategies. Overall, the analysis yielded results which were consistent with the previous case-control approach—that is, the association of COPD admission with a relapse of the previous exacerbation of severe chronic obstructive lung disease. Am J Respir Crit Care Med 1996; 154:959–67.

REFERENCES
LUNG ALERT

Leukotriene receptors are overexpressed in aspirin sensitive asthmatics


Patients with aspirin sensitivity, asthma, and nasal polyps exhibit increased synthesis of cysteinyl leukotrienes—both basally and in response to exogenous aspirin—and increased responsiveness to inhaled cysteinyl leukotrienes, in contrast to patients with aspirin tolerant asthma. The authors hypothesised that the latter effect reflects overexpression of the cysteinyl leukotriene receptor CysLT1.

Nasal biopsy specimens were obtained from 22 aspirin sensitive and 12 aspirin tolerant patients with chronic rhinosinusitis and nasal polyposis. The absolute number (and percentage of CD45+ leucocytes) of cells expressing the CysLT1 (but not LTB4) receptor was increased in the aspirin sensitive group, despite no overall difference in numbers of leucocytes. Subsequently, nasal application of lysine aspirin to aspirin sensitive patients caused a reduction in the percentage of CD45+ leucocytes expressing the CysLT1 receptor compared with placebo.

This study raises intriguing questions about the pathogenesis of aspirin sensitive syndromes, providing evidence for overexpression of the CysLT1 receptor in addition to increased leukotriene production. This overexpression is reduced by aspirin desensitisation. Further studies are warranted of leukotriene antagonists and aspirin desensitisation in patients with nasal polyposis with aspirin sensitivity. Variation in the response to leukotriene antagonists may well be related to differences in CysLT expression in inflammatory cells in the upper and lower airway.

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