

# Impairment of small airways in COPD patients with frequent exacerbations and effects of treatment with tiotropium

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**Abstract:** Disease exacerbations are an important aspect of COPD, because they affect its course and are associated with higher lung function decline. On the other hand, data obtained by biopsies have demonstrated that the progression of COPD is related to an increasing impairment of small airways. We sought to evaluate the small airway impairment (FEF<sub>25–75</sub>) in two groups of COPD patients (each group had 37 subjects) in relation to the frequency of exacerbations and the effectiveness of treatment with tiotropium bromide on the small airway impairment. The mean number of exacerbations was 3.6/year and 1.38/year in frequent and in infrequent exacerbators, respectively ( $p < 0.001$ ). The mean value of FEF<sub>25–75</sub> at baseline was 624 mL and 865 mL in frequent and in infrequent exacerbators respectively ( $p = 0.002$ ). The changes in respiratory parameters versus baseline showed increases in mean FEV<sub>1</sub>, FVC, and FEF<sub>25–75</sub> in both groups but only the increase in FEF<sub>25–75</sub> in frequent exacerbators was statistically significant ( $p = 0.013$ ). During the 3-month period of the study the mean number of exacerbations was 0.66 in frequent and 0.12 in infrequent exacerbators. These findings indicate that COPD patients with frequent exacerbations have a higher impairment of small airways. Treatment with tiotropium in COPD subjects with frequent exacerbations proved to be effective in improving small airway impairment.

**Keywords:** COPD, exacerbations, small airways, FEF<sub>25–75</sub>, tiotropium

## Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem. It is characterized by a progressive impairment of lung function (Barnes 2000) and leads to inability and mortality, which are projected to increase their burden in future (Murray and Lopez 1997). This makes the treatment strategies for COPD very important, currently stated as mainly smoking cessation, drug therapy, and pulmonary rehabilitation (Sutherland and Cherniak 2004).

An important aspect of COPD is the exacerbations, which occur regardless of the stage of disease according to GOLD classification (Pauwels et al 2004; Rabe et al 2007), and is currently defined as “... a sustained worsening of the patient’s symptoms from his or her usual stable state that is beyond normal day to day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum color. The change in these symptoms often necessitates a change in medication.” (The National Collaborating Centre for Chronic Conditions 2004).

Exacerbations clearly affect the course of the disease, since their frequency is related to lung function decline (Donaldson et al 2002). In particular, data obtained by biopsies demonstrated that the progression of COPD is associated with an increasing impairment of small airways which is strongly related to infiltration of inflammatory cells in airways walls and accumulation of exudate in the lumen (Hogg et al 2004).

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Tiotropium bromide, a second-generation anticholinergic agent, showed a favorable influence on the rate of exacerbations in COPD patients (Brusasco et al 2003).

We sought to evaluate 1) the small airway impairment in COPD patients with frequent or infrequent exacerbations and 2) the effect of treatment with tiotropium bromide on small airway impairment.

## Methods

### Patients

Seventy-six subjects referred to the Unit of Pulmonary Rehabilitation of the ICP Hospital in Milan were included in the study. To be included, patients had to be in a stable condition, free from exacerbations for at least 2 months, classified in GOLD stage 2–4 according to FEV<sub>1</sub> values, and on treatment only with inhaled drugs such as long-acting beta2-agonists (LABA) or inhaled corticosteroids (IC), plus short acting beta2-agonists (SABA) as needed. The patients were divided according to the frequency of exacerbations: patients with more than 2 exacerbations per year formed group A; patients with up to 2 exacerbations per year formed group B. In all patients, treatment with tiotropium, at the currently recommended dose of 18 µg once daily, was added. For drugs already used, the inhalation technique was optimized by employing spacer devices, if they had not been already introduced. Patients initiating treatment with tiotropium were trained to use the dry powder inhaler device.

Pulmonary function was measured at baseline and after 3 months of treatment. Patients were instructed to recognize and report any exacerbation during the study.

### Pulmonary function

The FEV<sub>1</sub>, the FVC, the expiratory flows at low volumes (FEF<sub>25</sub>, 50, and 75), the FRC, and the residual volume (RV) were measured by an automated pulmonary function testing center (6200 Autobox DL, Sensor Medics, Yorba Linda, CA, USA) in accordance with recognized standards (American Thoracic Society 1995). Variables were measured at baseline and after the 3-month treatment. Prior to measurement SABA were discontinued for at least 8 hours, LABA and IC for at least 12 hours, and, at the second measurement, tiotropium for 24 hours.

### Statistical analysis

Differences in the number of exacerbations and in pulmonary function in relation to the intervention in patients in groups A and B were analyzed by the Mann Whitney U test, setting a p value lower than 0.05 as significant.

## Results

Two out of the 76 patients included in the study did not perform the second plethysmography (1 in group A and 1 in group B) and were not considered in the analysis. Table 1 shows the characteristics of the 74 patients, 37 in each group.

The mean number of exacerbations was  $3.6 \pm 0.64$ /year in group A and  $1.38 \pm 0.59$ /year in group B ( $p < 0.001$ ). The baseline mean value of FEF<sub>25–75</sub> was  $624 \pm 418$  mL in group A and  $865 \pm 372$  mL in group B ( $p = 0.002$ ).

Changes in each respiratory parameter versus baseline are reported in Table 2. There were increases in mean FEV<sub>1</sub>, FVC, and FEF<sub>25–75</sub> in both groups, but only the increase in FEF<sub>25–75</sub> in group A was statistically significant ( $p = 0.013$ ).

During the 3-month study period the mean number of exacerbations was  $0.66 \pm 0.18$  in group A and  $0.12 \pm 0.05$  in group B.

## Discussion

Exacerbations are a serious concern in COPD. They represent an important cause of hospitalization and mortality and consume great medical resources (Garcia-Aymerich et al 2001; Rabe et al 2003). Frequent exacerbations are associated with a higher lung function decline. A longitudinal study with a 4-year follow-up reported that COPD patients with frequent exacerbations (median rate of 4.2/year) had a higher decline of FEV<sub>1</sub> (especially in persistent smokers) than those with infrequent exacerbation (median rate of 1.9 per year): FEV<sub>1</sub> decline was 40 mL/year versus 32 mL/year in patients with frequent and infrequent exacerbations, respectively (Donaldson et al 2002). This confirmed the results of a previous study on COPD patients with exacerbations, which showed a higher FEV<sub>1</sub> decline in current smokers than in ex-smokers (Kanner et al 2001) and draws the attention to the importance of the underlying damage to the airways.

**Table 1** Characteristics of patients at inclusion

Group	A	B
Gender	22 males, 15 females	23 males, 14 females
Mean age (range)	71.7 years (55–85)	72.1 years (56–88)
Mean duration of COPD	13.8 years	12.3 years
Active smoking history	29/37	31/37
Use of IC	30/37	27/37
Use of LABA	20/37	23/37
Mean FEV <sub>1</sub> (mL)	1191 ± 185	1249 ± 373
Mean FVC (mL)	2212 ± 803	2433 ± 649

**Abbreviations:** IC, inhaled corticosteroids; LABA, long-acting beta2-agonists.

**Table 2** Changes in respiratory parameters after treatment with tiotropium

Group	A	B
Baseline mean FEV <sub>1</sub> (mL)	1191 ± 185	1249 ± 373
Mean FEV <sub>1</sub> after tiotropium	1236 ± 201	1423 ± 411
Baseline mean FVC (mL)	2212 ± 803	2433 ± 649
Mean FVC after tiotropium	2284 ± 780	2587 ± 671
Baseline FEF <sub>25-75</sub> (mL)	624 ± 418	865 ± 372
FEF <sub>25-75</sub> after tiotropium	892 ± 497	1012 ± 438

A significant advance in the knowledge of the kind of damage in COPD was achieved by the study of Hogg et al. These authors investigated the progression of the disease in different COPD stages by means of lung biopsies. They found that the grade of wall thickness of the small airways, resulting from infiltration of inflammatory cells and structural changes, was correlated with disease severity, as assessed by FEV<sub>1</sub> values (Hogg et al 2004). It is somewhat surprising that, following such observation, measurement of small airway parameters in COPD patients has been almost overlooked.

We designed the present study to investigate the changes in small airway obstruction in patients with COPD with frequent or infrequent exacerbations undergoing treatment with tiotropium. We chose tiotropium because of its effectiveness, which was clearly demonstrated by a Cochrane meta-analysis (Barr et al 2005), by its ability to reduce the number of exacerbations (Brusasco et al 2003), and by its capacity to improve pulmonary function (Casaburi et al 2000; Cazzola et al 2005; Incorvaia et al 2007) including small airway parameters (Incorvaia et al 2007). In particular, such effects had already been detected after short-term treatment and are likely to be linked to the ability of the drug to reach the deeper airways and to interact with muscarinic receptors, particularly with those positioned in the smooth muscle of small airways (Barnes 1993). The efficiency of the specific dry powder inhaler device may possibly help patient performance in such effects (Dahl et al 2003).

Our findings indicate that frequent exacerbators have significantly lower FEF<sub>25-75</sub> (the main functional parameter of small airways) values compared to infrequent exacerbators. The mean number of exacerbations was  $3.6 \pm 0.64$ /year in frequent and  $1.38 \pm 0.59$ /year in infrequent exacerbators, data comparable to those reported by Donaldson et al in the study on association between lung function decline and frequent exacerbations (Donaldson et al 2002). Treatment with tiotropium improved pulmonary function parameters, including FEV<sub>1</sub>, FVC, and FEF<sub>25-75</sub>, but only the increase in FEF<sub>25-75</sub> mean value in frequent exacerbators was statistically

significant. Otherwise these subjects had a significantly lower mean baseline value, indicating a more severe impairment in small airways, compared with infrequent exacerbators. Both groups showed a decrease in rate of exacerbations during the 3-month study period. We planned such a trial duration because as our patients were undergoing pulmonary rehabilitation we needed to avoid possible bias on exacerbations by this treatment, as observed in a previous study (Riario-Sforza et al 2005). On the other hand, the ability of tiotropium to reduce the rate of COPD exacerbations has already been reported in a 6-month, multicenter, controlled study, which detected a significantly lower number of exacerbations in tiotropium than in placebo-treated patients (Brusasco et al 2003). The nature of such an effect is not easy to explain, since tiotropium is a bronchodilating and not an anti-inflammatory agent, as are IC, which is known to reduce exacerbations (Phua and Macintyre 2007). A recent study evaluated the effect of tiotropium on inflammatory markers in sputum and in serum and on exacerbations in COPD: a 52% reduction in exacerbation frequency was observed, compared with no significant change in inflammatory markers (Powrie et al 2007).

Our study, conducted on patients already treated with IC, who received tiotropium as an additional agent, showed that tiotropium may further reduce the number of exacerbations. Still, the major observation of the present study is that COPD patients with frequent exacerbations have a higher impairment of small airways, as assessed by measurement of their functional parameter FEF<sub>25-75</sub>, and that treatment with tiotropium can significantly improve this parameter.

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