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RESEARCH ARTICLE

# Effect of a $\beta_2$-Adrenoceptor Agonist and an Anticholinergic Drug on Respiratory Patterns and Dyspnea Sensation in Patients with COPD

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## Abstract

**Background and aim:** The standard treatment of patients with COPD comprises $\beta_2$-agonists and anticholinergics. Both drugs exert similar effects in terms of bronchodilation but in the clinical use we observed that some patients reported a stable degree or even an increase of dyspnea after the administration of $\beta_2$-agonists compared to anticholinergics. We hypothesized that $\beta_2$-agonists might favor an additional change in breathing pattern leading to increased minute volume and respiratory rate, and thereby a smaller reduction of dyspnea compared to anticholinergics.

**Methods:** Nineteen patients with moderate to severe COPD were evaluated in a placebo-controlled, randomized, double-blinded, triple-crossover design comprising four visits. We evaluated changes in respiratory rate, tidal volume, lung function and dyspnea before and after administration of fenoterol, oxitropium and placebo.

**Results:** The changes in respiratory patterns were not statistically significant and showed large variability. Despite this there were overall tendencies. Respiratory rate increased after fenoterol and decreased after oxitropium and placebo, while tidal volume increased after fenoterol and decreased after oxitropium and placebo. Overall, the perceived reduction of dyspnea, however, was similar after fenoterol and oxitropium.

**Conclusion:** The data did not indicate a homogeneous and stable pattern over all patients. Although the observed changes were not statistically significant, they pointed towards the hypothesis underlying this study. It may be that in single patients with COPD indeed the beneficial effect of $\beta_2$-agonists is partially counteracted by an adverse change in breathing pattern. We believe that this possibility is worth of clinical attention.

## Introduction

According to clinical experience, patients with moderate to severe COPD benefit from appropriately chosen doses of $\beta_2$- adrenoceptor agonists in a similar manner as from anticholinergic drugs. This can be verified for the changes of lung function in forced expiration and inspiration [1], whether it is also reflected in spontaneous breathing patterns has not been clarified.

In the clinical use of both types of drug, we sometimes had the impression that there are, however, differences with regard to dyspnea. Some patients reported a non-improvement or even worsening of dyspnea after the inhalation of $\beta_2$-agonists compared to anticholinergics, despite a response in terms of spirometric lung function. Although these observations were not systematic and might have been prone to observation bias, it seemed worthwhile to consider pathophysiological mechanisms that could mediate a different sensation of dyspnea despite similar functional effects. To us, the discrepancy seemed to occur primarily in moderate to severe COPD, despite the fact that both types of drugs are also effective in asthma [2].

Indeed, the phenomenon of increased dyspnea after administration of $\beta_2$-agonists has been examined previously. Initially it was attributed to dyspnea caused by oxygen deficiency, as blood gas analysis indicated a decrease of $PaO_2$ in some patients. It was suggested that this occurs due to increases in cardiac output [3] or in-

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trapulmonary shunt [4]. This seemed to be a plausible explanation, although the relationship between blood $PaO_2$ and perceived dyspnea is known to be not particularly close. However, later studies using inhaled fenoterol did not confirm measurable alterations in cardiac output [5].

Since dynamic hyperinflation is known to be related to dyspnea, there may be alterative explanations via mechanical factors that are active in severe COPD and related to both dynamic hyperinflation and increased respiratory work [6,7]. Even at rest patients may breathe at their respiratory limit, and one might argue that even a slight increase in respiratory rate or tidal volume would be sufficient to increase the perceived dyspnea and thus to abolish some of the benefits of the drug. $\beta_2$- agonists are certainly candidates for such adverse responses because of their spectrum of side effects.

In a study on the protective effects of various drugs on airway responses to hypertonic saline inhalation [8], additional body plethysmographic measurements (not contained in the publication) in some patients seemed to indicate a positive bronchodilator response to salbutamol but also an increase of respiratory work. As respiratory work depends on both obstruction and breathing pattern, this was suggestive of an increase of minute volume after fenoterol, in line with a worsening of dyspnea in the visual analog scale.

To address this question, breathing pattern and dyspnea after inhalation of equivalent doses of fenoterol and oxitropium which elicit similar spirometric effects [2] could be analyzed in a non-invasive setting. We hypothesized that in patients with COPD, as an adverse effect, a $\beta_2$- agonist might provoke a change of breathing pattern by raising minute volume and respiratory rate. This could counteract the bronchodilator effect, leading to a smaller reduction of dyspnea compared to an anticholinergic that does not affect the breathing pattern in the same manner. This difference would occur despite similar functional effects.

## Material and Methods

### Patients

Twenty-one patients with stable, moderate to severe chronic obstructive pulmonary disease (NHLBI-GOLD 2005) were included, and 19 patients finished the study. One patient discontinued the study because of appendicitis, and the recordings of one patient were lost due to a computer failure. Thus, 19 patients were evaluated. The mean (± SD) Forced Expiratory Volume in 1 second ($FEV_1$) amounted to 1.15 (± 0.4) liters corresponding to 38.3 (± 8.6)% predicted; the mean Forced Inspiratory Volume in 1 second ($FIV_1$) was 3.20 (± 0.94) liters, and Forced Vital Capacity (FVC) was 2.84 (± 0.92) liters. The disease was considered as stable if there was no exacerbation within the last 21 days. Other inclusion criteria were an age of 40-75 years and a smoking history of ≥ 10 pack-years. Exclusion criteria were the presence of other lung diseases than COPD (in particular asthma), alpha-1-deficiency and significant heart disease (> NYHA II).

Prior to each visit patients had to withdraw their medication: Short-acting $\beta_2$-agonists ≥ 8 h, long-acting $\beta_2$-agonists ≥ 24 h, short-acting anticholinergics ≥ 8 h, leukotriene receptor antagonists ≥ 3 d. Inhaled corticosteroids were allowed, as well as long-acting anticholinergics (tiotropium) to guarantee the stability of the clinical state, as it turned out not to be feasible to withdraw these drugs. To standardize the patient's history, an administration 6 h prior to the measurements was requested in those patients who took the drug regularly. All other medication was taken as usual. Patients were not allowed to alter their medication during the study. Informed consent was obtained from all patients and the study was approved by the appropriate Ethics Committee.

### Assessments

Lung function was assessed using an electronic spirometer (Masterlab CareFusion, Höchberg, Germany) and quantified by $FEV_1$ and FVC, as well as $FIV_1$, Inspiratory Vital Capacity (IVC), Intrathoracic Gas Volume (ITGV), Residual Volume (RV) and Total Lung Capacity (TLC) [9,10]. At visit 1 a body plethysmograph with integrated assessment of single-breath diffusion capacity ($TL_{CO}$) was used (Masterlab CareFusion, Höchberg, Germany) [11]. Blood gas analysis was done using the analyzer Ciba Corning 278, (Fernwald, Germany).

We considered it important to choose a non-invasive method of recording the breathing pattern which did not disturb the patients [12]. Thus a method for recording respiratory rate and tidal volume was chosen which is established in sleep medicine, is no burden for the patient and does not need specific compliance (Respitrace device, Alice IV-Non invasive Monitoring Systems, North Bay Village, Florida, USA) [13-15]. Two elastic straps were wrapped around the patient's chest and abdomen and fixed with tapes to avoid changes of position. These straps were expanded during inspiration and returned to their initial length during expiration. The change in length was calibrated (see below), recorded and electronically stored.

To evaluate the initial dyspnea, the modified Borg scale was used at the beginning of visits 2-4 (see below) [16-18]. Patients were asked to relate their present dyspnea to a value between 0 (= not at all/just perceptible) to 10 (maximum). To assess changes in dyspnea after the measurement periods of 45 min duration, the visual analog scale was used. This comprised a 200 mm line, zero being located in the middle and the left end of the scale (-100) being related to maximum deterioration, the right end (+100) to maximum improvement.

The VAS scale was used as it is known to capture changes of dyspnea better than a repeated assessment of the Borg scale.

### Study protocol

The study followed a placebo-controlled, randomized, triple-crossover, double-blind, double-dummy design and included four visits. The first visit was used to characterize the patients, while at visits 2, 3 and 4 medications were given in random order. Patients received either 2 puffs of fenoterol (200 µg) and 2 puffs of oxitropium placebo, or 2 puffs of oxitropium bromide (0.2 mg) and 2 puffs of fenoterol placebo, or 2 puffs each of fenoterol and oxitropium placebo per Metered-Dose Inhaler (MDI). The double-dummy design was chosen in order to account for the different flavors of the propellants. The time interval between these visits was at least one day, but no more than 4 days.

The first visit included the assessment of clinical history, physical examination, blood gas analysis, spirometry, body plethysmography and single-breath diffusing capacity for carbon monoxide ($TL_{CO}$), as well as explanation of the study to the patient. Inclusion and exclusion criteria were checked and patients gave their consent.

At the beginning of the three following visits, patients were interviewed regarding changes in dyspnea or medication, signs of exacerbation, and unscheduled visits to physicians. The present state of dyspnea at rest was quantified by the Borg scale, and lung function was assessed by spirometry. The subsequent continuous recording of respiratory rate and tidal volume was performed in a neutrally designed room equipped with a patient bed. The neutral design was chosen to avoid influences on the patient's mood, as mood is known to influence breathing pattern. During the measurements patients were allowed to read newspapers or to listen to music but not exciting one.

The following measurements were conducted in a half-sitting (45°) relaxed position. First, the Respitrace-System was connected to the patient and volumetrically calibrated using 4-5 deep breaths to a spirometer. During the following 45 min baseline data were collected. Patients were asked not to fall asleep and to avoid extensive movements. Immediately afterwards they quantified the change in dyspnea via VAS. This was followed by a further determination of lung function and blood gases to detect changes relative to the initial value.

Then the patients received two MDI containing the randomized study medication; one of these one always contained a matched placebo (see above). Immediately after inhalation of the study medication the second measurement period of 45 min duration was started. After this patients again quantified changes in dyspnea via VAS, followed by another measurement of lung function and blood gas analysis. This sequence of measurements was identically performed for all three crossover arms of the drug administration.

### Data analysis

Mean values as well as Standard Deviations (SD) and Standard Errors (SEM) were computed to describe the results, either the variability of data or the reliability of mean values. The Respitrace data were expressed as number of breaths and mean tidal volume per 5 min. To reduce the scatter and the number of data points, ANOVA analyses were also performed with the data averaged over 15-min periods, thus representing 3 data points before and 3 data points after drug administration. Minute volume could be derived from tidal volume and breathing frequency.

The different conditions were compared to each other using repeated-measures Analysis of Variance (ANOVA) in appropriate designs, either with or without interaction terms. Changes of breathing pattern and dyspnea caused by fenoterol could be detected by comparing placebo and fenoterol visit, and changes caused by oxitropium bromide by comparing the placebo and oxitropium visit. Differences between the effects of the two active drugs could be investigated by comparing the fenoterol and oxitropium visit.

## Results

The 19 patients (6 m, 13 f) whose data were evaluated had a mean (± SD) age of 65.9 ± 6.5 years, number of pack-years of 57 ± 15 pack-years, and diagnosed duration of the disease of 12.8 ± 5.7 years. All patients took short-acting $\beta_2$- agonists on demand. None of them had a long-term oxygen therapy. Further characteristics are given in Table 1.

### Lung function response

In terms of $FEV_1$, fenoterol induced an improvement by 8.1 ± 17.5 and 7.9 ± 11.6% relative to the values assessed immediately before and after, respectively, the first resting period. The corresponding changes for oxitropium bromide were 8.2 ± 16.6 and 12.3 ± 18.5%, those for placebo -2.5 ± 6.7 and -3.1 ± 6.7%. The bronchodilator effects of fenoterol were statistically significantly different from zero for $FEV_1$ and FVC, the effects of oxitropium for $FEV_1$, FVC and IVC ($p < 0.05$ each). The changes observed after placebo were not significant. The effects of fenoterol and oxitropium did not significantly differ from each other in any of the lung function measures.

### Changes in tidal volume

The results are shown in Figure 1 and Table 1. The evaluation of tidal volumes showed a slight mean decrease by 50 ml in the baseline measurement (45 min average after versus 45 min average before) of the placebo visit. A similar effect was observed after 200 µg fenoterol, while after inhalation of 0.2 mg oxitropium

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**Table 1:** Changes in breathing pattern and dyspnea.

| **Tidal Volume [ml]** | **Baseline (1st) Period** | | | **Intervention (2nd) Period** | | |
|---|---|---|---|---|---|---|
| **Interval (min)** | **0-15 Mean (SD/SEM)** | **15-30 Mean (SD/SEM)** | **30-45 Mean (SD/SEM)** | **0-15 Mean (SD/SEM)** | **15-30 Mean (SD/SEM)** | **30-45 Mean (SD/SEM)** |
| Fenoterol | 503 (183/42) | 482 (175/40) | 460 (152/35) | 505 (185/43) | 493 (195/45) | 461 (198/45) |
| Oxitropium | 584 (234/54) | 531 (151/35) | 509 (158/36) | 560 (248/57) | 529 (232/53) | 529 (237/54) |
| Placebo | 593 (235/54) | 568 (189/43) | 536 (172/40) | 596 (173/40) | 569 (173/40) | 527 (154/35) |
| **Respiratory Rate (per 5 min)** | **Baseline (1st) Period** | | | **Intervention (2nd) Period** | | |
| **Interval (min)** | **0-15 Mean (SD/SEM)** | **15-30 Mean (SD/SEM)** | **30-45 Mean (SD/SEM)** | **0-15 Mean (SD/SEM)** | **15-30 Mean (SD/SEM)** | **30-45 Mean (SD/SEM)** |
| Fenoterol | 89 (31/7) | 86 (31/7) | 89 (28/6) | 88 (30/7) | 88 (30/7) | 91 (27/6) |
| Oxitropium | 90 (28/7) | 91 (29/7) | 89 (29/7) | 90 (31/7) | 89 (28/6) | 87 (27/6) |
| Placebo | 89 (29/7) | 90 (28/6) | 88 (27/6) | 89 (28/6) | 90 (29/7) | 91 (26/6) |
| **Minute Volume [l]** | **Baseline (1st) Period** | | | **Intervention (2nd) Period** | | |
| **Interval (min)** | **0-15 Mean (SD/SEM)** | **15-30 Mean (SD/SEM)** | **30-45 Mean (SD/SEM)** | **0-15 Mean (SD/SEM)** | **15-30 Mean (SD/SEM)** | **30-45 Mean (SD/SEM)** |
| Fenoterol | 8.5 (3.6/0.8) | 7.8 (3.4/0.7) | 7.8 (2.9/0.7) | 8.8 (4.2/1.0) | 8.3 (3.4/0.8) | 8.4 (3.7/0.9) |
| Oxitropium | 10.1 (4.2/1.0) | 9.5 (3.6/0.8) | 8.9 (3.6/0.8) | 9.5 (4.5/1.0) | 9.0 (4.1/1.0) | 8.8 (3.8/0.9) |
| Placebo | 10.1 (4.0/0.9) | 10.1 (4.3/1.0) | 9.2 (3.5/0.8) | 10.3 (3.7/0.9) | 10.0 (3.9/0.9) | 9.5 (3.7/0.9) |
| | | | | | | |
| **Fenoterol Visit** | | **Mean** | **SD** | **Median** | **Maximum** | **Minimum** |
| Borg Scale | | 3.0 | 1.2 | 3 | 5 | 1 |
| VAS after Baseline Period | | 6.1 | 19.3 | 0 | 83 | 0 |
| VAS after Intervention Period | | 12.1 | 19.2 | 0 | 61 | -13 |
| Total VAS (both periods) | | 18.2 | 25.4 | 12 | 83 | -13 |
| **Oxitropium Visit** | | | | | | |
| Borg Scale | | 2.9 | 0.9 | 3 | 5 | 1 |
| VAS after Baseline Period | | 6.3 | 18.1 | 0 | 72 | 0 |
| VAS after Intervention Period | | 11.1 | 19.4 | 0 | 64 | 0 |
| Total VAS (both periods) | | 17.5 | 28.6 | 0 | 100 | 0 |
| **Placebo Visit** | | | | | | |
| Borg Scale | | 2.8 | 0.9 | 3 | 5 | 1 |
| VAS after Baseline Period | | 5.6 | 17.8 | 0 | 71 | -13 |
| VAS after Intervention Period | | 4.1 | 18.7 | 0 | 47 | -33 |
| Total VAS (both periods) | | 9.7 | 27.8 | 0 | 71 | -37 |

The upper part of the table shows mean values, standard deviations and standard errors of breathing frequency, tidal volume and minute volume in the three 15-min periods before and after administration of each of the three study medications. The lower part shows the statistical characteristics of the Borg scale, measured at the beginning of each visit and of the Visual Analog Scale (VAS) measured after the 45-minute baseline period and after the 45-minute intervention period, i.e. after medication. SD: Standard Deviation; SEM: Standard Error of the Mean; min: Minutes; l: Liter; ml: Milliliter; VAS: Visual Analog Scale.

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there was an increase by 150 ml. In the placebo visit the tidal volume decreased during baseline measurement and after inhalation in a similar manner.

### Changes in respiratory rate

Figure 1 describes the results of the Respitrace measurements in 9, 5-minute-intervals for changes of respiratory rate after inhalation of fenoterol, oxitropium and placebo. It shows a mild decrease of respiratory rate in the first 5-minute-interval of the baseline measurement. However after inhalation of 200 µg fenoterol the respiratory rate increased again to its primary value (Figure 1 and Table 1).

In the baseline measurement of the oxitropium-visit, the respiratory rate decreased about 2 breaths per minute. This is equivalent to the trend after inhalation of 0.2 mg of oxitropium (Figure 1 and Table 1).

In the placebo-visit the respiratory rate also decreased about 2 breaths per minute. After inhalation of placebo, the respiratory rate increased more than 4 breaths/minute (Figure 1 and Table 1).

### Changes in minute volume

The observed changes in minute volume are shown in Table 1. The analysis of the values showed no statistically significant differences.

### Dyspnea

Table 1 also shows the results of the Borg Scale at the beginning of each visit. The data were analyzed by repeated-measures variance analysis (ANOVA). The differences were not statistically different between medications. To evaluate possible differences between VAS values recorded after the 45-min baseline period, data

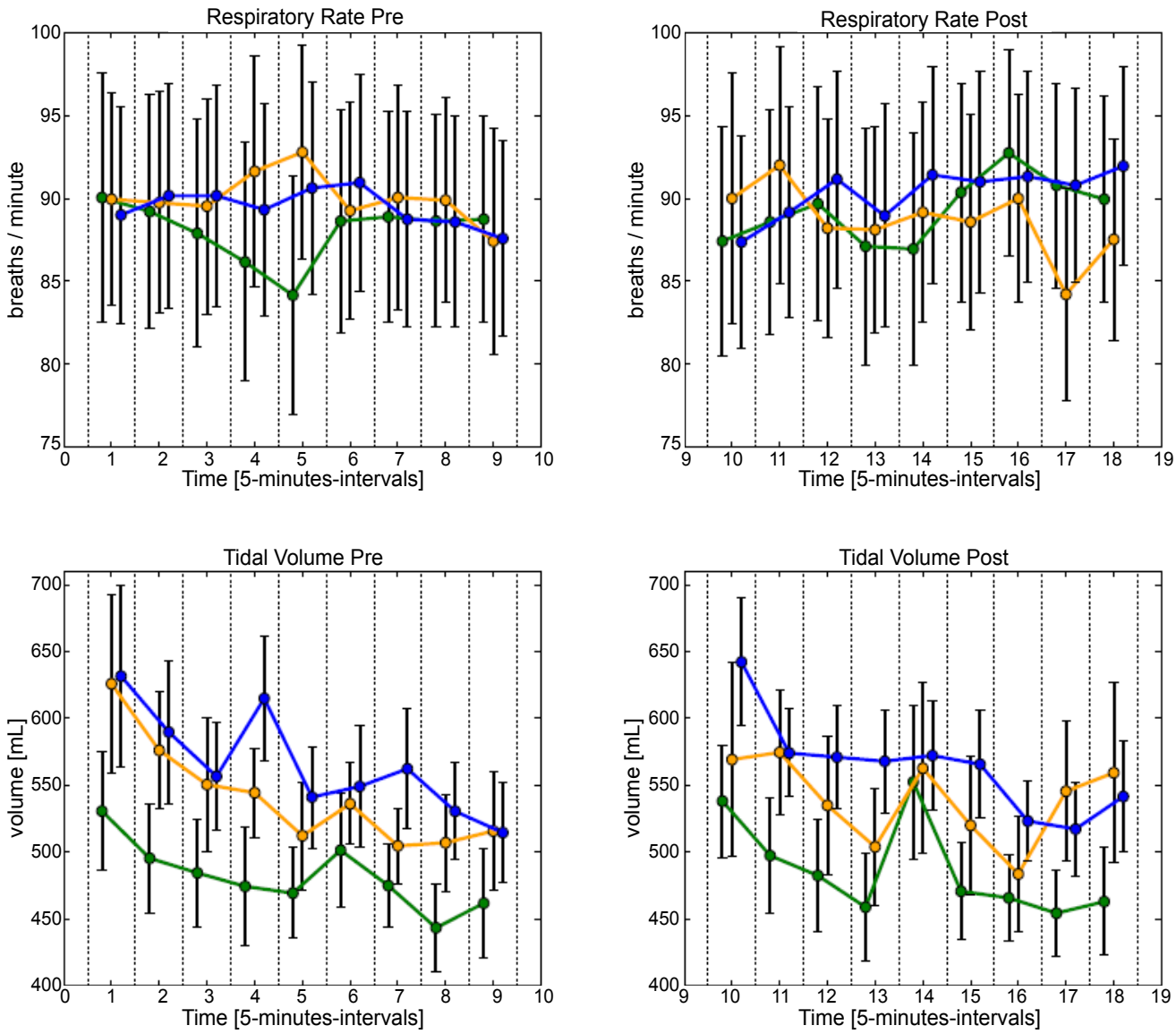


**Figure 1:** Time course of respiratory rate and tidal volume.

Graphical presentation of tidal volume and respiratory rate (mean values and Standard Error of the Mean (SEM)) during baseline measurement and 45 minutes after treatment with fenoterol, shown as average of 5-min intervals. Fenoterol: Green, Oxitropium: Yellow, Placebo: Blue. Data points have been slightly shifted against each other with regard to the time axis in order to increase their visibility.

were compared by Friedman's ANOVA (Table 1). The respective differences were also not significantly different between study days. Similarly, the VAS scale was also used to assess the changes in dyspnea after the 45-min intervention period, i.e. after drug administration (Table 1). Again, the analysis did not indicate statistical significance. The lack of effects was also reflected in the lack of correlation of Borg and VAS results with either lung function data or data on the respiratory pattern.

## Discussion

The present study was conducted to compare possible effects of a $\beta_2$-agonist and an anticholinergic drug on breathing pattern and dyspnea at rest in patients with moderate to severe COPD. The hypothesis was that fenoterol, relative to oxitropium, could alter the breathing pattern in a way which partially counteracted the improvement of lung function by increasing respiratory work and dynamic hyperinflation, thus raising dyspnea [19]. There were no significant differences between the effects of the two drugs, but there was a tendency towards such differences, as reflected in an increase of tidal volume and a decrease of respiratory rate after inhalation of oxitropium, in contrast to fenoterol or placebo. However, despite the efforts undertaken to obtain recordings that were stable over time, the variability of measurements was high so that statistically significant conclusions could not be drawn. Moreover, there was no difference in the reported dyspnea.

The doses of the drugs compared corresponded to those commonly used, i.e. 200 µg of fenoterol and 0.2 mg of oxitropium bromide. In designing the study it seemed secondary to which extent these drugs were or are still in use, as we aimed to assess actions exerted by the type of drug, however in established doses. When assessing the breathing of patients at rest, we took special care not to disturb the spontaneous pattern by using a mouthpiece or by a non-standardized, busy environment. We also chose observation periods of 45 min duration before and after drug administration as these seemed long enough to observe a potential effect but short enough to be acceptable by the patients without too great chance to fall asleep.

The fact that we did not observe a worsening of dyspnea after inhalation of fenoterol compared to oxitropium, at least in terms of the VAS scale, might have been due to the limited resolution of such scales in the absence of exercise. However, when preparing the study, physical exercise of the patients did not seem feasible as it would have been very likely that the dyspnea due to increased ventilation would dominate all potential changes due to potential changes in the breathing pattern elicited by the drugs. Such changes are likely to become apparent only at rest when there are no other factors influencing the breathing pattern. Within this study it was also not possible to test whether very mild exercise (slow walking) would have been useful to induce greater changes in dyspnea without abolishing potential effects of the drugs on the breathing pattern.

It cannot be excluded that the results were influenced by previous treatment with other drugs, in particular the long-acting anticholinergic tiotropium or corticosteroids. We were forced to allow this medication in our setting to ensure a clinically stable state of the patients. The interval between the routine administration of tiotropium and measurements was only 6 hours. However, this concerned only 3 patients; a subgroup analysis of these three patients was not meaningful, and the results were apparently unchanged after tentative exclusion of these. Baseline values of lung function and Borg scale showed no statistical differences between the visits, thus baseline conditions were comparable between medications.

The lung function measurements used were non-invasive, and all patients were accustomed to the respective maneuvers. Thus lasting effects on breathing pattern are unlikely. However, there might have been an effect of blood gas analysis as some of the patients felt unpleasant with the procedure. We included blood gas analysis instead of the determination of oxygen saturation owing to its higher sensitivity. Retrospectively, oxygen saturation probably would have been preferable.

The consistent improvement of dyspnea after the first 45-min measurement period might have been due to the fact that the patients felt comfortable over all the time. In the second 45-min period, i.e. after inhalation of the drug, the change in dyspnea was much greater after administration of fenoterol or oxitropium than after placebo or within the first 45-min period. This underlined that even in the absence of exercise the medication indeed caused a reduction in dyspnea. The differences in dyspnea between fenoterol and oxitropium, however, were insignificant. The bronchodilatory effect of fenoterol was statistically different for $FEV_1$ and FVC, the effect of oxitropium was significant for $FEV_1$, FVC and IVC but we do not believe that this difference was relevant for our results. Surprisingly, the- rather variable- data on breathing patterns did not indicate any significant relationship between individual respiratory patterns and perceived dyspnea after administration of the drugs.

On average, the decrease of tidal volume after administration of placebo corresponded to a reduction of dyspnea, despite the lack of correlation of individual values. First, patients who initially showed an elevated tidal volume calmed down, the tidal volume and respiratory work decreased and resulted in decreased dyspnea. Second, on average, respiratory rate seemed to be associated with dyspnea after the administration of fenoterol. These findings might support our hypothesis. This might be relevant, as the monitoring of the respiratory rate was far more robust than that of tidal volume, as the recording in most cases is not critically affected by dislocation of the straps.

The comparison of average respiratory rates after administration of fenoterol versus oxitropium also showed patterns compatible with our hypothesis. Certainly, this result must be handled with care because it might be due to the small number of subjects in view of unexpectedly large variability. Possibly, a subgroup study of patients with clinically known discrepancy between changes of dyspnea and lung function after inhalation of $\beta_2$-agonists would be helpful. However, within the framework of our study it was not possible to recruit a sufficient number of these patients in finite time.

Data evaluation was complicated by artefacts in the Respitrace measurement that increased short-time variability. This primarily affected the assessment of tidal volume, as the numerical values could be influenced by dislocations of the straps after calibration. The so-called Respi-Shirt would have been an alternative for our measurements but it was not available to us. It allows the measurement of respiratory rate and tidal volume by several sensors built into a tight shirt instead of measurement with only two straps. Possibly this method results in lower rates of sensor dislocation leading to higher accuracy of volume determination. However, a significant improvement in the measurement of respiratory rate is not to be expected from this, as the evaluation by counting respiratory excursions was not markedly affected by dislocations or other artefacts. Further, an evaluation of lung volumes by electrical impedance tomography may show increased accuracy but this methods bears other difficulties when applied over a longer time period [20,21]. A further source of error could have been that patients might have performed the "calibration-breaths" in an either more abdominal or thoracic breathing mode compared with their regular breathing.

## Conclusion

The present data did not show statistically significant differential effects on dyspnea and lung function of a $\beta_2$-agonist and an anticholinergic drug. Despite the limitations and difficulties described, we found changes in breathing patterns that pointed at least towards the hypothesis underlying the study, i.e. that part of the beneficial effect on dyspnea of a $\beta_2$-agonist might be cancelled through concomitant changes in breathing pattern, as compared to an anticholiniergic drug. Based on this and in view of the known variability of individual disease and side-effect patterns we believe that it is still worthwhile to keep in mind this possibility in clinical assessments if one encounters patients reporting only minor reductions in dyspnea after a $\beta_2$-agonist despite a response in terms of lung function.

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## Conflict of Interest

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