Effect of a β₂-Agonist (Broxaterol) on Respiratory Muscle Strength and Endurance in Patients with COPD with Irreversible Airway Obstruction*

Stefano Nava, M.D.; Paola Crotti, M.Sc.; Giovanni Gurrieri, M.D.; Claudio Fracchia, M.D.; and Ciro Rampulla, M.D.

The effect of broxaterol, a new β₂-agonist, on respiratory muscle endurance and strength was studied in a double-blind, placebo-controlled, randomized crossover clinical trial in 16 patients with chronic obstructive pulmonary disease (COPD) with irreversible airway obstruction (FEV₁ = 57.1 percent of predicted). One patient withdrew from the study because of acute respiratory exacerbation. Inspiratory muscle strength was assessed by maximal inspiratory pressure (MIP) and endurance time was determined as the length of time a subject could breathe against inspiratory resistance (target mouth pressure = 70 percent of MIP, VT/Tot = 0.4). Broxaterol (B) or placebo (P) was given orally for seven days at the dose of 0.5 mg three times a day with a washout period of 72 h between study treatments. Measurements were performed before administration of B or P and 2 h (six patients) or 8 h (nine patients) after the end of each treatment. No significant changes in FEV₁ or FRC were observed after B or P suggesting that diaphragmatic length was maintained constant with each treatment. The MIP did not significantly change, while endurance time increased after B in the patients tested at 2 h (from 234.8 ± 48.1 s to 254.0 ± 48.0 s, p < 0.05) and at 8 h (from 187.2 ± 31.1 s to 258.2 ± 40.4 s, p < 0.005). No changes were observed after P. Minute ventilation, airway occlusion pressure (P0.1), integrated electromyographic activities of the diaphragm (Edi), and intercostal parasternals (Eic) (normalized to the value obtained during MIP) showed no change during the endurance run with different treatments. We conclude that in a group of COPD patients with irreversible airway obstruction, B significantly improves respiratory muscle endurance, and that this does not arise as a result of an effect on neuromuscular drive or pulmonary mechanics, but may be mediated by peripheral factors.

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*From the Pneumology Division of Centro Medico di Riabilitazione di Montecasino Fondazione Clinica del Lavoro, Pavia, and Zambon Research SPE, Bresso, Milano, Italy.

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Reprint requests: Dr. Gurrieri, c/o Zambon Research SPE, Via Lillo del Duca 10, Bresso (MI), Italy 20019

It has been suggested that patients with chronic obstructive pulmonary disease (COPD) may develop respiratory muscle fatigue during acute exacerbations or even develop long-term respiratory muscle fatigue by long-term breathing against high loads. Recognition of pulmonary pump failure will have important therapeutic implications; rest is the recognized treatment for fatigue of other skeletal muscles, but this is still controversial for the diaphragm and the other respiratory muscles.

Pharmacologic intervention is an alternative therapeutic approach, both in reducing the respiratory preload, by removing the airway obstruction, and in directly enhancing respiratory muscle contractility. Methylxanthines have been extensively evaluated; however, studies in both animals and humans are still controversial regarding their effectiveness in improving diaphragmatic strength or in preventing fatigue. Catecholamines and β₂-agonists have been reported to influence skeletal muscle contractility in vitro and in vivo, but their action on respiratory muscle is not completely understood. Isoproterenol has been shown to improve inotropism of the fatigued canine diaphragm, but is refractory in hypercapnic depression of diaphragmatic contractility. Terbutaline and fenoterol have been shown to increase the contractility of the fatigued diaphragm in dogs, but they have no effect on the nonfatigued muscle. Salbutamol has failed to show any significant effect in both conditions. On the other hand, a newly synthesized β₂-agonist, broxaterol, seems to improve the strength of the fresh canine diaphragm at low stimulation frequencies and to promote recovery from muscle fatigue. Nevertheless, the small number of studies performed in humans is controversial. Terbutaline has been shown to have a small, nonsignificant effect on respiratory muscle contractility in normocapnic COPD patients. In a group of normal humans, Javaheri et al. reported no significant effect of salbutamol on the strength of the nonfatigued diaphragm and on its endurance time. More recently, two studies carried out in the same population showed that fenoterol enhances inspiratory muscle endurance.
time. This parameter is very important in COPD patients, since a reduction in this time is consistent with the development of acute or even "incipient" fatigue.

The aim of the present study was to investigate the effect of broxaterol on both respiratory muscle endurance and maximal force in a group of COPD patients with irreversible airway obstruction. We chose this particular population since a direct effect of a β2-agonist on inspiratory muscle endurance could be masked by the bronchodilating property of these drugs that may improve muscular efficiency by reducing the loads against which the patients breathe. Broxaterol, or 1-(3-bromo-5-isoxazolyl)-2-(tert-butyl amino) ethanol hydrochloride (synthesized and developed by Zambon Research Spa, Bresso, Italy), is a new β2-agonist, which is structurally different from other β2-agonist drugs, having the 3-bromo-isoxazolic ring substituted for the aromatic nucleus. The bronchodilating activity of oral or inhaled broxaterol is similar to that of salbutamol.24,25

MATERIALS AND METHODS

Sixteen COPD inpatients, with a FEV1, reduction >20 percent of the predicted values, were enrolled after giving an oral consent. All were in stable condition and were admitted to the study only if they showed no response (<5 percent change from baseline values) in static and dynamic lung volumes after administration of salbutamol (400 μg) in different tests performed on two consecutive days. After the first set of measurements, one of the patients (No. 2) withdrew from the study, since he suffered from an acute respiratory exacerbation. Table 1 illustrates the clinical characteristics of the group at enrollment. Six patients in treatment with slow-release theophylline and three under therapy with inhaled β2-agonists were asked to stop the use of these drugs, 72 h and 24 h, respectively, prior to being screened for bronchodilator response and when they were admitted to the study.

Study Design

The study was carried out as a randomized double-blind, placebo-controlled crossover trial. Patient compliance was monitored by pill counts and by ensuring that all patients had taken the medication the morning before the tests. After baseline evaluation of pulmonary function tests, respiratory muscle strength and endurance, and P0.1 (control measurements), eligible patients were randomly assigned to receive either 0.5 mg of broxaterol three times daily for one week or comparably administered placebo tablets. Treatment effects were assessed 2 h after the last dose in six patients and after 8 h in the remaining nine patients, to evaluate the possible persistence of the drug effect over time. After a 72-h washout period, new baseline measurements (endurance time and maximal inspiratory pressure [MIP]) were repeated in each patient (second control measurements) and the patients were then crossed over to the alternative one-week treatment, followed by assessment of treatment effects.

Measurements

Static and dynamic lung volumes were measured using body plethysmography (Jaeger, Wurzburg, Germany). Respiratory muscle strength was assessed by the mouth MIP recorded at functional residual capacity (FRC) using a tube-type mouthpiece with a small hole. Each patient performed a minimum of five MIP maneuvers, with at least a 1-min interval between efforts, until two acceptable values, not differing more than 5 percent from each other, were obtained. The MIP generated was recorded on a strip chart recorder; this enabled elimination of maneuvers performed incorrectly (ie, plateau not maintained for more than 1.5 s, sharp peaks).

Respiratory muscle endurance was assessed using a fatigue run protocol. Each patient performed two or three practice runs, the best of which was chosen as baseline value. Tidal volume (VT) was obtained by integration from a calibrated pneumotachograph (Fleish No. 3). With a mouthpiece in place and noseclip on, patients were asked to breathe. Mouth pressure (Pm) was recorded by a differential pressure transducer (Honeywell, Freeport, IL, ± 250 cm H2O) and displayed on an oscilloscope. After five minutes of spontaneous breathing, an inspiratory device (a tube with an adjustable orifice) was added to the system, so that the inspiratory resistance could be set for a Pm equal to 70 percent of the baseline value of MIP. A two-way valve allowed subjects to exhale without resistance. Respiratory rate was maintained constant for all endurance runs (20 breaths/minute), as well as as cycle TVTOT (0.4). To achieve the respiratory pattern and target pressure, a square wave was drawn on an oscilloscope in front of the patients. Patients were requested to maintain that pattern as long as they could and were verbally encouraged throughout the run. Fatigue time was expressed as the moment at which the patient could not maintain the target pressure for four consecutive breaths. Thereafter an MIP starting from FRC was measured immediately. Integrated diaphragmatic (Edi) and intercostal parasternal (Eic) electromyograms (EMGs) were also monitored during fatiguing run. Edi was obtained in five subjects using both esophageal and surface electrodes, while in the others it was only recorded with surface electrodes. A Swan-Ganz pacing catheter, mounted at the tip, with a balloon, was used as an esophageal electrode; it was inserted into the stomach, where it was inflated and subsequently anchored to the gastroesophageal junction when a good and reproducible signal-to-noise ratio during MIP was obtained. Surface EMG was recorded by electrocardiographic electrodes applied to the skin over the sixth and seventh intercostal spaces close to the costal border. Eic was obtained by surface electrodes placed on the second right intercostal space close to the sternum. The EMGs were filtered (20-Hz to 1,000-Hz band-pass), full-wave rectified, and then integrated using a filter (Pynter) with a time constant of 0.03 s.

In ten subjects, rib cage and abdominal displacements were

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recorded during the runs by means of inductive plethysmography. Rib cage band was placed at the level of the axilla, while the abdominal one was positioned just above the umbilicus. Calibration was performed with the isovolume maneuver in the sitting position. Respiration was used to check if, during ventilation, the two compartments were or were not in phase and if paradoxical breathing was present.

Before and during each run, we measured the airway pressure generated 100 ms after the start of inspiration against a closed system (P0.1) as described by Witheral et al. by a gauge placed at the level of the mouthpiece and connected to a pressure transducer (Honeywell, Freeport, Ill., ±50 cm H2O). Signals were recorded on a strip chart recorder and then measured. Three to five P0.1 determinations were obtained for each patient during quiet breathing, and at least two measurements were recorded immediately before the end of the run. The averages of the values obtained during spontaneous breathing and at endurance time limit were considered for data analysis.

In the last six subjects, arterialized blood gases from the ear lobe were withdrawn before the fatiguing run and immediately after the end of the fatiguing run. They were analyzed by blood gas analyzer (ABL 300 Radiometer, Copenhagen, Denmark).

Venous blood sample was withdrawn in three subjects, 2 and 8 h after the last drug administration before endurance run, in order to measure plasma broxaterol. A specific radioimmunoassay method for measurement of broxaterol in plasma and urine was developed by Zambon Research Spa.

Data Analysis

All the EMGs, Pm, Vt, rib cage, and abdomen displacement were continuously recorded on a strip chart recorder (Battaglia and Rangoni, Casalecchio di Reno, Italy). The Pm was analyzed using peak amplitude obtained from immediately preceding baseline, and the integrated EMGs were measured as millimeter deflection from baseline and then expressed as percentage of the maximum obtained during the MIP maneuver. All calculated values are expressed as mean and standard deviation (±SD). Analysis of variance was used for statistical analysis of data. The comparison was performed between the baseline (control measurements) and 2 or 8 h after the end of the first treatment and between the second baseline (second control measurements) and 2 or 8 h after the end of the second treatment. Correlations between FRC and endurance time values were analyzed using Pearson’s correlation coefficient. A p value <0.05 was chosen as the threshold of a statistically significant difference (two-tailed test).

**Results**

**Endurance Time**

All the values in this section are presented considering only the 15 subjects who were able to complete the whole study. Figure 1 illustrates endurance time, as mean and individual values, before and after a week of administration of the two treatments, at 2 (A group) and 8 (B group) h after the last administration. No significant difference was found between the two controls and between control and placebo. Broxaterol induced a significant increase compared with placebo in endurance time both in group A (from 234.8 ± 48.9 s to 284.0 ± 48.0 s, p <0.05) and group B (from 187.2 ± 31.06 s to 258.2 ± 40.41 s, p <0.005).

**Respiratory Muscle Pressure**

No significant difference was shown in MIP after administration of the two treatments (Fig 2). On completion of fatiguing runs, MIP significantly decreased (p <0.001) to a mean value of 72.6 ± 4.6 percent of prerun measurements.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21638/ on 05/31/2017)

**Figure 1.** Changes in the time of endurance 2 (top panel) and 8 (bottom panel) h from last oral administration of broxaterol or placebo. Data are expressed as individual values and as mean ± SD.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21638/ on 05/31/2017)

**Figure 2.** Changes in respiratory muscle strength 2 (top panel) and 8 (bottom panel) h from last oral administration of broxaterol or placebo. Data are expressed as individual values and as mean ± SD.
Pulmonary Function Tests

Mean FEV₁ at enrollment was 57.07 ± 18.68 percent of predicted values, and FRC was 136.0 ± 28.18 percent of predicted. As shown in Figure 3, since the patients chosen had irreversible airway obstruction, neither broxaterol nor placebo produced any significant change in static and dynamic lung volumes. However, even though mean values did not change, variations occurred when data were expressed as individual values. Since even relatively small changes in lung volumes (especially FRC) could determine important changes in the diaphragm length-tension relationship, Figure 4 shows correlation of the delta variation from baseline of FRC and endurance time. The low r value (0.06) obtained indicates that in this study, there was no relationship between the small changes in FRC and time required to develop respiratory muscle fatigue.

EMG Changes

As shown in Table 2, the mean integrated inspiratory EMG values for the diaphragm, expressed as a percentage of the values obtained during an MIP maneuver, show a small increase toward the end of the fatiguing run compared with the value recorded at the beginning, both for broxaterol and placebo. Toward the end of the run, all patients reached an EMG amplitude equal or very close to the value recorded during a maximal inspiratory maneuver. In five of the patients we compared the Edi activity as recorded by surface electrodes and by esophageal electrodes during one of the fatiguing runs. A good correlation (r = 0.98) was found between the two methods. Edi increased progressively during the fatiguing run, always reaching the greater values at time limit.

Ventilatory Response and P0.1 Changes

During spontaneous breathing, before the beginning of the test, the mean values for minute ventilation were 14.7 ± 3.2 L/min, 14.8 ± 3.7 L/min, and 15.0 ± 3.7 L/min for control, broxaterol, and placebo, respectively. Since during fatiguing runs, the pattern of breathing was imposed, the increase in minute ventilation was similar and constant throughout the test in the three conditions (25.8 ± 7.3 L/min, 25.1 ± 7.4 L/min, and 24.0 ± 5.5 L/min at the end of fatiguing run for control, broxaterol, and placebo, respectively).

During spontaneous breathing only one patient showed asynchronous thoracoabdominal motion, as assessed by Respirtrace, while in all but one, we observed asynchronous movements usually toward the end of the endurance runs. Synchronous breathing

![Figure 3. Dynamic and static lung volumes, as absolute values, at control and after placebo or broxaterol administration.](image)

![Figure 4. Relationship between changes in functional residual capacity (FRC) and changes in endurance time after broxaterol administration. As indicated by the very low r value, no correlation was found between the two parameters.](image)

| Table 2—Integrated Diaphragmatic (Edi) and Intercostal Parasternal (Eic) Electromyograms during Fatigue Runs |
|-----------------|-------------|---------|-----------|-------------|
|                 | Broxaterol |         | Placebo   |             |
|                 | Edi         | Eic     | Edi       | Eic         |
| Begin run, %    | 76.0 ± 8.9  | 50.1 ± 11.6 | 77.0 ± 9.9 | 48.4 ± 11.5 |
| 50% time of endurance, % | 93.2 ± 9.6 | 71.3 ± 14.6 | 95.1 ± 13.1 | 70.5 ± 12.8 |
| End run, %      | 91.1 ± 13.5 | 93.6 ± 12.4 | 93.8 ± 9.5 | 89.3 ± 16.1 |
was defined as simultaneous in-phase motion of the rib cage and abdomen during ventilation. Asynchronous breathing was identified as waveforms showing out-of-phase rib cage and abdomen movement during ventilation.

Respiratory drive from central nervous system centers as indirectly assessed by PaO₂ showed a marked increase (p<0.001) from spontaneous breathing to values recorded at the end of fatiguing runs. However, as illustrated in Figure 5, no significant difference was found either in spontaneous breathing or at the end of the endurance runs after placebo or broxaterol long-term administration.

Blood Gas Changes

As shown in Table 3, in six patients in whom blood gases were monitored, PaCO₂ decreased at the end of the endurance runs. Conversely, PaO₂ showed an increase at fatigue time, this being more marked, even though not significantly, after broxaterol.

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Broxaterol Plasma Concentrations

In three subjects in whom plasma broxaterol was measured, it was found that broxaterol concentrations 2 h after oral administration ranged from 1.38 ng/ml to 1.03 ng/ml, and 8 h after from 0.08 ng/ml to 0.05 ng/ml.

Adverse Events

Tremors or muscle twitching were reported in four patients during broxaterol administration and in two with placebo, while two patients complained of heartburn during placebo and broxaterol treatment, respectively.

Discussion

In the present study we provide evidence that broxaterol significantly improves endurance time of the respiratory muscle during fatigue, induced acutely by inspiratory resistive loads in patients with COPD. Conversely, broxaterol has little effect on the maximal strength of the respiratory muscle. Our data suggest that the potentiating action of broxaterol on endurance time may be mediated by peripheral factors.

Study Controls

A major problem in comparing different fatiguing runs in the same patients concerns several variables that have to be maintained constant. In particular, the length and the geometry of the diaphragm and other respiratory muscle may be altered by many factors that could influence their action and strength. Since our patients had irreversible airway obstruction, lung volumes did not significantly change with treatment, excluding an important variation of the position of the diaphragm in its length-tension curve. Furthermore minute ventilation, respiratory rate, inspiratory time, and the tension-time index (Pm/MIP × Ti/Tot) were kept constant during endurance runs. These controls indicate that in our study the experimental conditions
did not change with time. Different levels of hypoxia or hypercapnia could also interfere with diaphragmatic contractility, decreasing the inotropic effect of the muscle. In our study, these problems were avoided since the level of ventilation during loaded breathing was set to a high level that resulted in a decrease in PaCO₂, while PaO₂ increased, albeit differently depending on the treatment.

Site of Fatigue

When admitted to the study, our patients with COPD did not show any direct sign of acute or incipient respiratory muscle fatigue (decrease in maximal static pressure) or fatiguing pattern of breathing (tachypnea, use of neck inspiratory muscles, and asynchronous or paradoxic movements of chest wall and abdomen) as recently defined by Rochester. Inspiratory loading breathing led to the development of signs of acute respiratory muscle fatigue, evidenced by the significant decrease in MIP at the end of the runs and indirectly by the progressive change in the thoracoabdominal motion that shifted from synchronous to asynchronous in all patients.

There are two recognized components of muscle fatigue. Central factors are thought to reduce the central neural drive, while peripheral factors seem to impair the neuromuscular coupling. In this study, the EMGs of the diaphragm or intercostal parasternals did not decrease during any of the fatiguing runs, clearly demonstrating that the decrease in Pm/Edi was not due to a diminution in Edi or Eic. In all patients, Edi reached an amplitude equal or very close to the value achieved during the MIP maneuver, usually toward the end of the run. This suggests that since recruitment was nearly maximal, no motivational factors have to be taken into account when considering time limit. In keeping with data of Breslin et al., Eic progressively increased during the fatiguing run. In fact, the authors demonstrated that during loaded breathing, accessory muscle recruitment is an important contributor to the maintenance of ventilation and the pattern of breathing. Furthermore P0.1 was similar between treatments, both during spontaneous breathing and during fatiguing conditions, excluding any effect of broxaterol on the neural drive.

We can therefore suppose that peripheral factors are probably major contributors to the development of fatigue in this study.

Mechanism of Action of Broxaterol

In the present study, we did not directly investigate the mechanisms of action of broxaterol; it is known from several studies that certain β₂-agonists can have inotropic effects on the fatigued diaphragm. These studies suggested that the effects could be due to an extra release of Ca in the sarcoplasmic reticulum. Suzuki et al. have demonstrated that the release of Ca is probably caused by a drug-induced stimulation of the Ca pump, since it is not mediated via adenosine 3',5'-cyclic monophosphate (cAMP). Other mechanisms of action may be involved, such as the effect on the electrogenic Na-K transport and on the metabolism of glycogen.

Since our patients did not show any sign of respiratory muscle fatigue at enrollment, the lack of improvement in MIP after broxaterol is in agreement with previous studies on the contractile properties of unfatigued muscles, done both in animals and humans. It is known that β₂-agonists have two different modes of actions on slow- and fast-twitch muscle fibers, both of which are present in the diaphragm. In nonfatigued slow-twitch muscles, β₂-agonists decrease twitch duration and amplitude; they act in an opposite fashion in nonfatigued fast-twitch fibers. Therefore, it may be possible that the competing mechanism results in no effect on the inotropic characteristics of the nonfatigued muscle. It has been shown, however, that β₂-agonists have an increased inotropic effect on the fast-twitch fibers of the fatigued diaphragm, while the inhibitory effect on slow-twitch fibers is not potentiated after fatigue, resulting in a net augmentation of diaphragm contractility. This mechanism may therefore explain the prolongation of the endurance time observed in our patients during fatiguing run.

Other important actions of β₂-agonists arise from their cardiovascular effect. The rate of development of respiratory muscle fatigue largely depends on the balance between the level of respiratory muscle blood flow and the metabolic demands of these muscles. Pathologic factors that alter blood flow, such as hypoperfusion, alteration in length, and increase in work of breathing (as during fatiguing inspiratory resistive loads) may influence this balance and enhance the rate of development of muscle fatigue. Subsequently it has been demonstrated that increased perfusion in itself may improve force generation of the diaphragm in vivo. Goodman and Gilman reported that sympathomimetic amines increase blood flow to the skeletal muscles; since the smooth muscle of blood vessels supplying skeletal muscles is full of β₂-receptors, their activation causes vasodilatation. There is no direct evidence from this study that blood flow increased after broxaterol administration. During the fatiguing run, after broxaterol, however, PaO₂ showed a marked, though not significant, increase; this did not happen after placebo. The lack of a statistically significant difference may be a result of the small sample size, since p value was equal to 0.062. It may then be suggested that broxaterol improves muscular efficiency (respiratory muscle work/respiratory muscle oxygen consumption). This may be mediated by changes in muscle perfusion (i.e, increased cardiac output, decreased vascular resistance) that could eliminate the
accumulation of metabolites developed during diaphragmatic fatigue, such as hydrogen or inorganic phosphate, that have been reported to decrease force-generating capacity and alter Ca sensitivity. A possible effect of broxaterol on respiratory muscle blood flow could, on the whole, be masked during normal breathing conditions, since blood flow to the diaphragm and other respiratory muscles has been shown to dramatically increase only in peculiar conditions such as loaded breathing. This may explain why broxaterol did not induce an increase in the force of the nonfatigued muscle.

The scanty data available in literature concerning the effect of β₂-agonists on endurance time in humans are controversial. Javaheri et al showed no improvement after salbutamol administration, while two preliminary reports indicated that fenoterol improved the endurance property of the diaphragm. Moreover, all of these studies were performed in normal subjects, while our study was conducted in patients with COPD.

We observed no difference in changes in endurance time in the patients, studied at different times after last drug administration. It is known from the literature and also confirmed by our results that the blood level of broxaterol is high 2 h after the last administration by long-term oral route; on the contrary, only small amounts of the drug are present after 8 h. It has already been shown that, following long-term oral administration, broxaterol shows a persistent bronchodilating effect even when plasma concentrations are low. This may suggest that plasma concentration of unchanged broxaterol in these patients does not completely reflect the kinetics of the pharmacologic activity, as already shown for other drugs such as ibopamine.

Limitations of the Study

One possible limitation of the present study is that it relies on the use of surface electrodes to record diaphragmatic electrical activity; this method may be criticized because of the possible contamination of other muscles such as the intercostals or the abdominal muscles. However, since the EMG signal recorded from an esophageal electrode is not affected by contamination, the good agreement observed between surface and esophageal EMG in the five subjects in whom both were measured demonstrated that surface electrodes, at least in this study, adequately record diaphragmatic electrical activity.

The patients enrolled in this study had moderate airway obstruction (FEV₁ = 57 percent of predicted) without signs of acute or incipient respiratory muscle fatigue. One may hypothesize that patients with more severe COPD, who are more prone to respiratory muscle fatigue, may respond in a different manner to broxaterol. However, this was not the case with patients 1, 15, and 16, who had a greater degree of airway obstruction compared with the rest of the group (see Table 1).

Finally, the possibility of patients being aware of taking broxaterol due to side effects cannot be excluded. However, few patients experienced typical effects of β₂-agonists even during placebo administration.

Conclusions

In summary, the present study demonstrates how a new β₂-agonist, broxaterol, enhances the endurance time of respiratory muscles in patients with COPD with irreversible airway obstruction. We also confirm the hypothesis that β₂-agonists do not improve the contractility of the nonfatigued respiratory muscle. These findings are important from a clinical point of view since β₂-agonists may be used together with traditional treatments to prevent the occurrence of pulmonary pump failure in patients with moderate COPD. Further studies are needed to investigate the role of β₂-agonists in more severe COPD in patients who exhibit signs of acute or incipient fatigue.

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