

# Corticosteroids and Inhaled Salbutamol in Patients with Reversible Airway Obstruction Markedly Decrease the Incidence of Bronchospasm after Tracheal Intubation

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**Background:** In patients with bronchial hyperreactivity, airway instrumentation can evoke life-threatening bronchospasm. However, the best strategy for the prevention of bronchospasm has not been defined. Therefore, in a randomized, prospective, placebo-controlled study, the authors tested whether prophylaxis with either combined salbutamol-methylprednisolone or salbutamol alone (1) improves lung function and (2) prevents wheezing after intubation.

**Methods:** Thirty-one patients with partially reversible airway obstruction (airway resistance > 180%, forced expiratory volume in 1 s [FEV<sub>1</sub>] < 70% of predicted value, and FEV<sub>1</sub> increase > 10% after two puffs of salbutamol), who were naive to anti-obstructive treatment, were randomized to receive daily for 5 days either 3 × 2 puffs (0.2 mg) of salbutamol alone (n = 16) or salbutamol combined with methylprednisolone (40 mg/day orally) (n = 15). Lung function was evaluated daily. Another 10 patients received two puffs of salbutamol 10 min before anesthesia. In all patients, wheezing was assessed before and 5 min after tracheal intubation.

**Results:** Within 1 day, both salbutamol and salbutamol-methylprednisolone treatment significantly improved airway resistance (salbutamol, 4.3 ± 2.0 [SD] to 2.9 ± 1.3 mmHg · s · l<sup>-1</sup>; salbutamol-methylprednisolone, 5.5 ± 2.9 to 3.4 ± 1.7 mmHg · s · l<sup>-1</sup>) and FEV<sub>1</sub> (salbutamol, 1.79 ± 0.49 to 2.12 ± 0.61 l; salbutamol-methylprednisolone, 1.58 ± 0.66 to 2.04 ± 1.05 l) to a steady state, with no difference between groups. However, regardless of whether single-dose salbutamol preinduction or prolonged salbutamol treatment was used, most patients (8 of 10 and 7 of 9) experienced wheezing after intubation. In contrast, only one patient receiving additional methylprednisolone experienced wheezing (P = 0.0058).

**Conclusions:** Pretreatment with either salbutamol alone or salbutamol combined with methylprednisolone significantly and similarly improves lung function within 1 day. However, only combined salbutamol-methylprednisolone pretreatment decreases the incidence of wheezing after tracheal intubation. Therefore, in patients with bronchial hyperreactivity, preoperative treatment with combined corticosteroids and salbutamol mini-

mizes intubation-evoked bronchoconstriction much more effectively than the inhaled β<sub>2</sub>-sympathomimetic salbutamol alone.

IN patients with bronchial hyperreactivity, airway instrumentation by tracheal intubation may evoke life-threatening bronchospasm, perioperative complications, and prolonged intensive care treatment.<sup>1-6</sup> In particular, patients with active signs of obstructive airway disease are at a higher risk for perioperative complications.<sup>4</sup> Therefore, treatment in patients with previously undiagnosed bronchial hyperreactivity should intuitively be an important goal to improve lung function and to mitigate evoked bronchoconstriction. However, it is unknown which drugs should be used as first-line treatment, what the effects are, and how many days should elapse before anesthesia and surgery can proceed safely.

Unquestionably, within minutes, inhaled β<sub>2</sub>-adrenergic agonists improve lung function and can attenuate the bronchomotor response to tracheal intubation either in the awake state or during anesthesia when given before intubation.<sup>1,7-9</sup> When patients with severely exacerbated asthma were treated with three different regimens of intravenously administered β<sub>2</sub> agonists either with or without corticosteroids, only combined treatment improved forced expiratory volume in 1 s (FEV<sub>1</sub>) by 20% after 4 days of treatment.<sup>10</sup> However, whether a short preoperative course of corticosteroids in addition to inhaled β<sub>2</sub> agonists improves lung function or, possibly of greater importance, can diminish the bronchoconstrictor response to tracheal intubation is unknown.

Accordingly, we tested the null hypotheses that (1) a pretreatment course with oral methylprednisolone and inhaled salbutamol combined improves lung function only to the same extent as inhaled salbutamol alone, and (2) there is no difference in signs of bronchoconstriction evoked by intubation with these regimens compared with a single preintubation treatment with salbutamol.

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## Materials and Methods

### Patients

After gaining approval by the local ethics committee (Essen, Germany) and informed written consent, we enrolled in this randomized, double-blind, prospective study 41 inpatients (age, 61.7 ± 10.9 yr [SD]; 14 women, 27 men) scheduled to undergo surgery. All patients were newly diagnosed with reversible airway obstruction dur-

**Table 1. Baseline Clinical and Biometric Data of Patients with Reversible Airway Obstruction**

|  | Salbutamol                | Salbutamol-Methylprednisolone | Salbutamol Preinduction Only |
|--|---------------------------|-------------------------------|------------------------------|
| Enrolled patients, No.                       | 16 (9)                    | 15 (8)                        | 10                           |
| Male/female                                  | 12/4 (7/2)                | 10/5 (5/3)                    | 5/5                          |
| Age, yr                                      | 61.3 ± 7.2 (59.1 ± 9.1)   | 64.3 ± 10.5 (63.2 ± 10.7)     | 59.5 ± 15.2                  |
| Weight, kg                                   | 72.6 ± 12.6 (73.6 ± 16.3) | 72.9 ± 14.2 (74.3 ± 12.6)     | 71.9 ± 14.8                  |
| Height, cm                                   | 171.5 ± 7.1 (168.9 ± 6.7) | 171.3 ± 8.9 (171.6 ± 8.2)     | 167 ± 5.5                    |
| R <sub>aw</sub> , mmHg · s · l <sup>-1</sup> | 4.3 ± 2.0 (4.4 ± 2.1)     | 5.5 ± 2.9 (5.7 ± 3.4)         | 3.8 ± 1.4                    |
| R <sub>aw</sub> , % predicted                | 189 ± 13.6 (192 ± 15.1)   | 243 ± 129 (257 ± 118)         | 166 ± 60                     |
| FEV <sub>1</sub> , l                         | 1.79 ± 0.49 (1.82 ± 0.48) | 1.58 ± 0.66 (1.29 ± 0.64)     | 1.87 ± 0.39                  |
| FEV <sub>1</sub> , % predicted               | 60.3 ± 13.6 (58.6 ± 15.7) | 59.4 ± 28.9 (56.8 ± 31.3)     | 69.0 ± 11.3                  |
| VC, l  | 3.27 ± 0.67 (3.28 ± 0.50) | 2.91 ± 0.74 (2.77 ± 0.73)     | 2.84 ± 0.39                  |
| VC, % predicted                              | 81.2 ± 12.5 (79.8 ± 12.0) | 80.1 ± 16.2 (76.7 ± 9.5)      | 82.5 ± 9.2                   |

Data are presented as mean ± SD; data of patients undergoing general anesthesia are presented in parentheses.

FEV<sub>1</sub> = forced expiratory volume in 1 s; R<sub>aw</sub> = airway resistance; VC = vital capacity.

ing the preoperative investigations or were “noncompliant” patients who revealed during the investigation that they had received antiobstructive therapy once but had not received therapy for at least 1 month. All showed impaired lung function, *i.e.*, an airway resistance (R<sub>aw</sub>) greater than 180% of that predicted and a forced expiratory volume in 1 s (FEV<sub>1</sub>) less than 70% of that predicted (table 1). Furthermore, responsiveness of obstruction was indicated by an improvement of FEV<sub>1</sub> by more than 10% after two puffs (0.2 mg) of salbutamol.<sup>4,11</sup>

### Measurements

The same air-conditioned room was used for lung function testing, with humidity and room temperature (22° ± 1°C) unchanged, and for each patient, all measurements were performed at the same time of day (± 1 h). Lung function was measured using a body plethysmograph with an integrated spirometer (Jaeger, Würzburg, Germany). At the initial test, vital capacity (VC), FEV<sub>1</sub>, and R<sub>aw</sub> were assessed at baseline. When lung function testing revealed evidence of airway obstruction, the presence of reversible bronchoconstriction was confirmed in each patient by an increase in FEV<sub>1</sub> by more than 10% after administration of two puffs (0.2 mg) of salbutamol.

To assess bronchoconstriction in response to intubation, auscultation was always performed on either side of the chest at the fourth intercostal space (ICS) in the midaxillary line, the fifth ICS in the midclavicular line, and the second ICS in the parasternal line before intubation and 5 min after intubation. The presence of wheezing was determined by a simple *yes* or *no* score by a physician not involved in this study and blinded to the protocol. All patients were mechanically ventilated 10 times/min with a tidal volume of 10 ml/kg body weight and with an inspiratory flow of 40 l/min. Wheezing was defined as high pitched expiratory rhonchi<sup>12</sup> that were audible at at least three of six auscultation sites.

### Study Protocol

After initial pulmonary function testing to confirm the presence of reversible bronchoconstriction, patients were randomly allocated to receive in a double-blind fashion a 5-day treatment course with either combined salbutamol (two puffs [0.2 mg], 3 times/day) and methylprednisolone (40 mg orally) or salbutamol and oral placebo. Intake of medications was observed, and lung function tests were scheduled daily, unless the patients underwent surgery or were discharged without surgery for other reasons. Another 10 patients, serving as a control group, did not undergo any prolonged pretreatment and only received two physician-guided puffs of salbutamol before induction of general anesthesia on the day of surgery. Seven patients receiving salbutamol and seven receiving salbutamol-methylprednisolone treatment did not complete the full 5-day pretreatment for clinical reasons (discharge or more urgent surgery), but all underwent pretreatment and lung function tests for at least 3 days. Accordingly, the effects of intubation on the incidence of wheezing in these patients were not investigated. Induction of anesthesia was standardized using fentanyl (1.5 µg/kg), thiopental (5 mg/kg), and vecuronium (0.1 mg/kg), and auscultation for wheezing was performed before and 5 min after tracheal intubation by an assessor blinded to the specific treatment.

### Statistical Analysis

Data are presented as mean ± SD. We tested the *a priori* null hypotheses that (1) there is no change in values of variables (R<sub>aw</sub>, FEV<sub>1</sub>, VC) over the time of pretreatment between the two groups, and (2) there is no difference between groups with regard to wheezing after tracheal intubation. Hypotheses were tested by two-way repeated-measurement analysis of variance followed by *post hoc t* tests using the Bonferroni correction of the  $\alpha$  error (1) and the Fisher exact test (2). A null hypothesis was rejected with an  $\alpha$  error *P* value of less than 0.05/n.

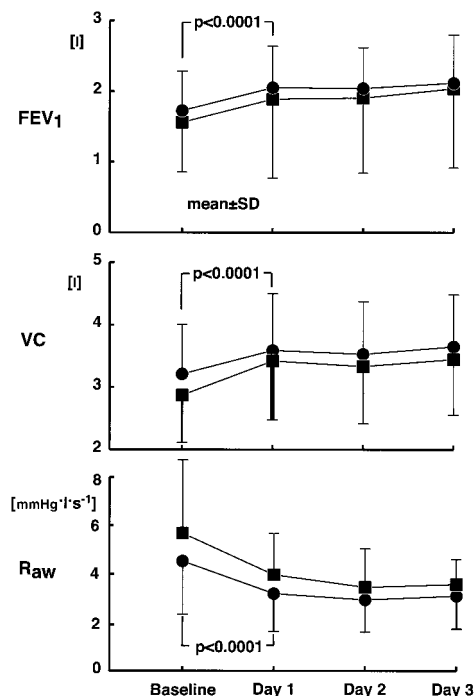


Fig. 1. Time course of forced expiratory volume in 1 s (FEV<sub>1</sub>), vital capacity (VC), and airway resistance (R<sub>aw</sub>) over 3 consecutive days for patients at baseline and after receiving salbutamol (circles) and for patients receiving combined salbutamol-methylprednisolone (squares). Pretreatment with either salbutamol alone or salbutamol combined with methylprednisolone significantly and similarly improved lung function after 1 day. No significant further improvement of lung function occurred over time.

## Results

### Lung Function during Salbutamol or Salbutamol-Corticosteroid Treatment

Forced expiratory volume in 1 s and VC increased significantly ( $P < 0.0001$ ) by approximately 23% and 15%, respectively, whereas R<sub>aw</sub> decreased by 36% in patients receiving salbutamol. Patients who also received methylprednisolone showed increases in FEV<sub>1</sub> and VC by 29% and 18%, respectively, whereas R<sub>aw</sub> decreased simultaneously by 42%. With pretreatment, most of the improvement occurred within 1 day, and no further statistically significant effects were detected thereafter, as shown in figure 1. Of note, there was no difference in the degree of measured improvement between treatments with combined salbutamol-methylprednisolone and salbutamol alone.

In patients receiving combined methylprednisolone and salbutamol ( $n = 15$ ), R<sub>aw</sub> decreased within 1 day, as well as in those receiving salbutamol alone ( $n = 16$ ), with no difference between groups ( $P = 0.2$ ). Although there was a significant difference ( $P = 0.0001$ ) between baseline and values on successive treatment days, no significant further improvement of lung function occurred over time beyond the first day of treatment.

Likewise, FEV<sub>1</sub> increased with both combined treatment and after salbutamol alone, with no difference between groups ( $P = 0.6$ ). Similarly, VC increased in patients receiving salbutamol-corticosteroid or salbutamol alone. Again, there was no difference between groups ( $P = 0.46$ ), and improvement reached an apparent plateau after 1 day of treatment (fig. 1).

### Incidence of Wheezing after Tracheal Intubation

We tested the incidence of wheezing in patients receiving two puffs of salbutamol before induction of anesthesia (control,  $n = 10$ ), in patients receiving salbutamol pretreatment alone for 5 days ( $n = 9$ ), and in those receiving methylprednisolone and salbutamol for 5 days ( $n = 8$ ). No patient in any group experienced wheezing before intubation. After tracheal intubation, there was a significant difference in the incidence of wheezing among the three groups tested ( $P = 0.0058$ ) (fig. 2). Of those patients receiving salbutamol-methylprednisolone combined, only a single patient of eight patients experienced wheezing after intubation, whereas seven of nine patients in the group with prolonged salbutamol pretreatment ( $P = 0.0152$ ) and eight of ten patients receiving a single dose of salbutamol preinduction experienced wheezing ( $P = 0.0152$ ). In fact, there was no difference between the prolonged and single-dose salbutamol pretreatment groups ( $P = 0.99$ ). Two patients in the group with prolonged salbutamol pretreatment and three patients in the group with single-dose salbutamol pretreatment required additional treatment for broncho-

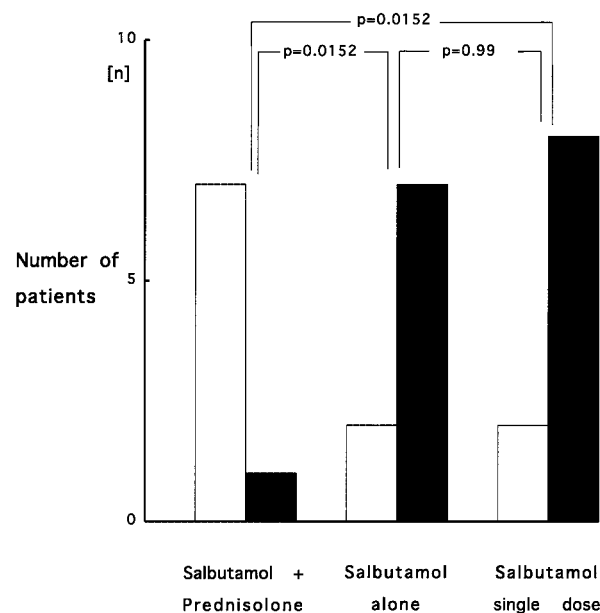


Fig. 2. Incidence of airway obstruction (wheezing) in patients after intubation when pretreated with salbutamol once and in patients pretreated for 5 days with either salbutamol alone or salbutamol combined with methylprednisolone. Only combined treatment with methylprednisolone and salbutamol significantly decreased the incidence of wheezing ( $P < 0.05$ ).

spasm. Therefore, wheezing occurred much more frequently in patients receiving salbutamol, regardless of whether they had received a pretreatment course or only a single dose of salbutamol, than in patients who received methylprednisolone.

## Discussion

In patients with hitherto untreated and partially reversible obstructive airway disease, within a day, salbutamol treatment markedly and significantly improved lung function, regardless of the combination with methylprednisolone. Both regimens improved lung function to a similar extent. In fact, despite improvement of lung function with salbutamol, the incidence of intubation-evoked bronchoconstriction was similar, regardless of whether salbutamol had been given only once or for several days before intubation. In contrast, only the addition of methylprednisolone to salbutamol pretreatment significantly decreased wheezing after intubation.

Patients with untreated bronchial obstruction and hyperreactivity are at higher risk for perioperative complications.<sup>4</sup> In fact, tracheal intubation in patients with obstructive airway disease can evoke life-threatening bronchospasm with asphyxia and persistent brain damage or death as shown by the closed claims study of the American Society of Anesthesiologists.<sup>3</sup> Several studies have suggested that patients with chronic obstructive pulmonary disease or asthma can benefit from preoperative treatment.<sup>7,13,14</sup> Nevertheless, how long a patient should be treated before undergoing airway instrumentation and surgery and whether this should include systemic corticosteroids is unknown. Even more important, there is no evidence showing that by preoperative therapy, improved lung function is associated with a lesser risk of bronchospasm after intubation. Accordingly, in a prospective, randomized, blinded fashion, we studied patients with hitherto untreated but pharmacologically partially reversible airway obstruction and assessed both the effect of added oral methylprednisolone on lung function over time and its effect on the reflex bronchoconstrictor response after the strong stimulus of tracheal intubation.

Patients were selected because of airway obstruction, which was untreated for at least 1 month, and a positive response after two puffs of salbutamol. Although some of our patients had not been diagnosed with obstructive airway disease before, most of the patients met the criteria for chronic obstructive pulmonary disease according to the British Thoracic Society's definition and the Global Initiative for Chronic Obstructive Lung Disease definition.<sup>15,16</sup> Diagnostic criteria for asthma include, in addition to a history or symptoms of allergic diathesis, the same values of airway obstruction but include total reversibility of airway obstruction.<sup>4,17</sup> Re-

versible airway obstruction has been defined differently by various authors. Although some consider a change in FEV<sub>1</sub> or VC by 10% to be clinically relevant,<sup>1</sup> others recommend a change by 15% after inhaled  $\beta$  agonists.<sup>18</sup> Because we included patients whose FEV<sub>1</sub> improved by more than 10% in response to salbutamol and because we observed mean changes of 20%, reversibility of obstruction was not only statistically significant but also clinically relevant. Therefore, most of our patients met the criteria for both chronic obstructive pulmonary disease and asthma, and can be defined as individuals with chronic obstructive pulmonary disease with a reactive component. However, the selection of the patients was based on lung function results and the reversibility of airway obstruction.

To account for potential variability of spirometric measurements, diurnal variation, or environmental influences, lung function tests were always performed at the same time of day in an air-conditioned room. Furthermore, FEV<sub>1</sub> and VC are known to have a low daily variability.<sup>11,19</sup> To assess the bronchoconstrictor response to intubation, all patients were examined in a standardized fashion. Of note, a change in lung sounds correlates with the degree of bronchial obstruction and a decrease of FEV<sub>1</sub> by 35–40% is required before wheezing can be detected in awake and spontaneously breathing patients.<sup>20,21</sup> In intubated patients, the same physical phenomenon can be expected because a passive expiration with a low tidal volume indicates even more narrowing of the bronchial system to produce wheezing than deep breaths in spontaneously breathing individuals. Because we detected a marked increase in wheezing in both the "fast-track" salbutamol group and patients with prolonged salbutamol treatment, a strong bronchoconstriction after intubation is evident even in the absence of quantitative measurements.

An important variable in our study is the choice of induction agents. Apparently, all induction agents have an effect on airway resistance. The effects on airway resistance of the drugs used have been found to be modest. Only in doses 20-fold higher than those used in our study did intravenous fentanyl result in a modest increase in airway resistance.<sup>22</sup> The clinical relevance of this effect can be regarded as negligible in our study design. The effects of barbiturates on airway resistance are discussed controversially. In the clinical range, the administration of thiopental may result in some constriction but at slightly higher doses even in bronchodilation.<sup>23,24</sup> However, we chose these drugs as induction agents because they do not reduce airway resistance by themselves, because we wanted to investigate the protective ability of preoperative treatment.<sup>6</sup>

Undoubtedly, inhaled  $\beta$ -adrenergic agonists can improve airway obstruction and lung function in anesthetized patients with a history of smoking, and a single treatment attenuates the response to intubation.<sup>7</sup> How-

ever, in volunteers with bronchial hyperreactivity undergoing awake fiberoptic intubation under local anesthesia, salbutamol pretreatment did not fully block the response to tracheal intubation.<sup>9</sup> In our anesthetized patients, the incidence of wheezing after intubation was high (80%), despite a single preinduction salbutamol treatment and also despite a prolonged course of inhalational salbutamol pretreatment. It is unlikely that this relates to underdosing because all inhalations were observed by a physician, excluding effects of poor patient compliance.

In general,  $\beta_2$ -adrenergic agonists can evoke hypokalemia and arrhythmias, which, in high doses, can lead to morbidity and mortality.<sup>25-28</sup> Therefore, with respect to tachycardia, some anesthesiologists hesitate to use  $\beta_2$ -adrenergic agonists in elderly patients, as in ours. However, with the choice of salbutamol, the use of a metered-dose inhaler, and a dose lower than eight puffs, adverse effects in general are hardly detectable, and major adverse effects are not expected.<sup>25-28</sup> Accordingly, the chosen dose of salbutamol used to test both for reversibility of bronchoconstriction and for treatment effects was large enough to provide effects but low enough to prevent toxicity.<sup>28,29</sup>

Corticosteroids can enhance the bronchodilatory effect of  $\beta_2$ -adrenergic receptor agonists. In addition to the direct effect of corticosteroids on smooth muscle, they increase the number of  $\beta_2$ -adrenergic receptors and their response to  $\beta_2$ -adrenergic receptor agonists.<sup>30</sup> However, whether short-term oral corticosteroid administration in addition to a  $\beta_2$ -adrenergic receptor agonist can attenuate the response to mechanically evoked airway irritation is unknown. Although inhalational steroids are believed to take weeks to months to attain their full effect, systemically administered corticoids may evoke this effect within 48 h. Accordingly, administration of glucocorticoids in dosages of 0.5-1 mg/kg orally is recommended.<sup>31,32</sup> On the other hand, systemic administration of corticosteroids before surgery may raise concerns about wound healing or postoperative infections. However, in a meta-analysis including 51 studies and 2,500 patients undergoing surgery, a high preoperative dose of methylprednisolone of 15-30 mg/kg was not associated with a significant increase in complication rate. The only significant finding was a decrease of pulmonary complications, mainly in trauma patients.<sup>33</sup> Furthermore, in 89 patients with asthma who were preoperatively treated with corticosteroids for 3-7 days, no increased incidence of postoperative infections or delayed wound healing was found.<sup>34</sup> In addition, of 68 patients treated with hydrocortisone (100 mg) injection every 8 h starting the night before surgery and continuing until resumption of oral medication, none of the patients had difficult wound healing or infection.<sup>35</sup> Hence, short-term corticosteroid administration is likely to have a low risk of adverse effects but, as we have shown, strongly atten-

uates reflex bronchoconstriction. Methylprednisolone was chosen because it yields higher lung parenchymal concentrations than cortisol and therefore is a preferred corticosteroid in systemic asthma treatment.<sup>32,36</sup>

At 24 h after initiation of treatment, lung function had already improved significantly and did not improve further, *i.e.*, apparently reaching a plateau regardless of treatment regimen. Additional treatment with methylprednisolone did not enhance the effect on lung function observed with salbutamol alone. However, only a single patient receiving methylprednisolone experienced wheezing after intubation, in contrast to the majority of patients pretreated with salbutamol alone. Accordingly, our data suggest that patients with reversible airway obstruction awaiting intubation benefit from a 5-day course of corticosteroids in addition to  $\beta_2$ -adrenergic therapy. This effect on evoked bronchoconstriction cannot be predicted by preoperative lung function measurements. These results match clinically with those of experiments in guinea pigs treated with dexamethasone ( $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  for 2 days), which resulted in both increased  $M_2$  muscarinic receptor function and decreased airway constriction to vagal nerve stimulation.<sup>37</sup>  $M_2$  receptors inhibit the release of acetylcholine from nerve endings, leading to smooth muscle constriction.<sup>37</sup> This mechanism is important in the context of reflex bronchoconstriction as a mechanism preventing excessive bronchoconstriction. With dexamethasone treatment, airway resistance improved after a pretreatment course of 2 days. Further investigation is needed to determine the shortest time necessary for effective pretreatment of patients with chronic obstructive disease with a reactive component.

In conclusion, salbutamol pretreatment for 5 days improves baseline lung function within 1 day, with no further improvement thereafter, but does not mitigate the bronchoconstrictor response to intubation compared with a single treatment just before intubation. In contrast, although additional administration of methylprednisolone does not increase the effects of salbutamol in improving lung function, it markedly decreased the incidence of wheezing and, hence, bronchospasm after tracheal intubation. Therefore, in patients with partially reversible airway obstruction who are naive to treatment, the addition of methylprednisolone to salbutamol is recommended for diminution of reflex bronchoconstriction evoked by tracheal intubation.

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