



# Relief of dyspnoea by $\beta_2$ -agonists after methacholine-induced bronchoconstriction

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## KEYWORDS

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**Summary** Virtually all asthma patients use bronchodilators. Formoterol and salbutamol have a rapid onset of bronchodilating effect, whereas salmeterol acts slower. We studied the onset of improvement of dyspnoea sensation after inhalation with these bronchodilators and placebo to reverse a methacholine-induced bronchoconstriction as a model for an acute asthma attack.

Seventeen patients with asthma completed this randomised, double-blind, crossover, double-dummy study. On 4 test days, forced expiratory volume in 1 s (FEV<sub>1</sub>) and Borg score were recorded and patients were challenged with methacholine until FEV<sub>1</sub> fell with  $\geq 30\%$  of baseline value. Thereafter, formoterol 12  $\mu\text{g}$  via Turbuhaler<sup>®</sup>, salbutamol 50  $\mu\text{g}$  via Turbuhaler<sup>®</sup>, salmeterol 50  $\mu\text{g}$  via Diskhaler<sup>™</sup>, or placebo was inhaled. FEV<sub>1</sub> and Borg scores were assessed during the following 60 min.

The first sensed improvement of Borg score was significantly ( $P < 0.05$ ) faster achieved with formoterol (geometric mean (Gmean) (range) 1.5 (1–40) min) and salbutamol 1.8 (1–10) min than with salmeterol 4.5 (1–30) min and placebo 3.4 (1–40) min.

The Borg score returned significantly faster to the baseline value with formoterol, salbutamol, and salmeterol (Gmean time 13.8 (1–75), 13.4 (1–60), and 18.0 (1–75) min, respectively) than with placebo (33.6 (1–75) min).

Formoterol and salbutamol act significantly faster than salmeterol in relieving dyspnoea induced by methacholine-induced bronchoconstriction, in patients with asthma.

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**Abbreviations:** FEV<sub>1</sub>, Force expiratory volume in 1s; Gmean, Geometric Mean; min, minutes; PC<sub>20</sub>, The provocative concentration of methacholine to induce a 20% fall in FEV<sub>1</sub>; *sd*, standard deviation; T, Timepoint

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## Introduction

Asthma is characterised by episodes of acute bronchoconstriction which are clinically perceived as dyspnoea.<sup>1</sup> There is considerable evidence that dyspnoea has a pronounced effect on a patient's quality of life.<sup>2</sup> It is even postulated that dyspnoea is the most important symptom to drive patients to consult their general practitioner for relief of symptoms.<sup>3</sup>

Patients' adherence to therapy enhances when confidence in medication increases.<sup>4</sup> This confidence may be gained by the subjective relief of asthma symptoms like dyspnoea. Long-acting  $\beta_2$ -agonists, like the long-acting formoterol and salmeterol, are being used in the maintenance treatment of asthma,<sup>5,6</sup> while  $\beta_2$ -agonists like formoterol, salbutamol, and terbutaline with their rapid bronchodilating effect<sup>7</sup> are used as add-on therapy. Though the fast effect on airway smooth muscle relaxation is well documented, yet it is unknown whether they provide a rapid improvement in dyspnoea sensation as well. Therefore, we investigated the onset of improvement of dyspnoea after inhalation of formoterol, salbutamol, in comparison with placebo in a model of an acute asthma attack, with methacholine-induced moderate to severe bronchoconstriction.

## Methods

This study is a post-hoc analysis of an earlier study which investigated the bronchodilating effect (forced expiratory volume in 1 s—FEV<sub>1</sub>) of  $\beta_2$ -agonists in reversing a methacholine-induced bronchoconstriction<sup>7</sup> in 21 asthmatic patients. The present report analyses the effect on Borg scores, which was simultaneously recorded for safety reasons.

Patients with stable asthma were invited to participate in this randomised, double-blind, double-dummy, placebo controlled, crossover study to assess effect of salmeterol (Serevent™ Diskhaler™ 50 µg, GlaxoSmithKline, Zeist, The Netherlands), formoterol (Oxis® Turbuhaler® 12 µg, AstraZeneca, Lund, Sweden), salbutamol (50 µg Turbuhaler® AstraZeneca, Lund Sweden) or placebo (Turbuhaler® or Diskhaler™; provided by AstraZeneca, Lund Sweden). Inclusion criteria were an age between 18 and 45 years, an FEV<sub>1</sub> > 1.5 l and > 60% predicted,<sup>8</sup> a provocative concentration of methacholine causing a fall in FEV<sub>1</sub> ≥ 20% (PC<sub>20</sub> methacholine) ≤ 8 mg ml<sup>-1</sup> and a fall in FEV<sub>1</sub> > 30% upon continuation of the test, and no concomitant diseases or conditions that might interfere with the study. Patients had to be able to use Turbuhaler® and Diskhaler™ according to the instructions of the manufacturer. The Medical Ethics Committee of the Martini Hospital, Groningen, approved the study. All patients gave written informed consent before the start of the study.

The methacholine provocation test was performed as described previously.<sup>7</sup> In short, patients inhaled increasing concentrations of methacholine

0.125–64 mg ml<sup>-1</sup> during a period of 2 min until a fall in FEV<sub>1</sub> of ≥ 30% was reached. During and after the test, the Borg score was also measured at the same time points as when the FEV<sub>1</sub> was assessed. Immediately after reaching a fall in FEV<sub>1</sub> ≥ 30%, study medication was inhaled ( $T = 0$  min). Subsequently, FEV<sub>1</sub> and Borg score were assessed at 1, 3, 5, 10, 15, 20, 25, 30, 40, 50, and 60 min.

The FEV<sub>1</sub> was recorded with a daily calibrated dry spirometer (Schiller SP-100; Schiller, Vaar, Switzerland). Dyspnoea was assessed by the modified Borg score.<sup>9</sup> Patients were shown a large written printed explanation of the score ratings and were asked to rate their shortness of breath on a scale of 0–10, with 0 = nothing and 10 = maximal.

## Statistical analysis

The primary endpoint of this post-hoc analysis was the time from inhalation of the study drug (i.e. end of provocation test,  $T = 0$ ) to sense the first improvement of Borg score. This time point is considered to be the onset of relief of dyspnoea. A secondary parameter was the time needed to return to the pre-provocation Borg score. In those cases where the Borg score did not return to the pre-methacholine values, the recovery time was arbitrarily set at 75 min. Other parameters analysed were FEV<sub>1</sub> at the time of onset of relief of dyspnoea (as percentage change from the  $T = 0$  value), and the FEV<sub>1</sub> at the time when Borg score returned to pre-methacholine value (as percentage change from the pre-methacholine baseline). Data on recovery times are presented as geometric means (Gmean) because of the non-normal distribution.

The Wilcoxon Signed Rank test is used to compare treatments. A  $P$ -value ≤ 0.05 is considered statistically significant.

## Results

Twenty-one patients were enrolled. Two patients were withdrawn because of unstable asthma; one patient did not attend agreed visits while another failed to achieve a fall of at least 30% after methacholine challenge. The remaining 17 patients completed the four test days. The demographic data of these patients are shown in Table 1. Baseline conditions prior to inhalation of study medication, i.e. FEV<sub>1</sub>, Borg scores, and PC<sub>20</sub> values were comparable on all study days, except for the methacholine-induced fall in FEV<sub>1</sub>, which was largest before the administration of formoterol

(Table 2). The methacholine-induced increase in Borg score and the decrease in FEV<sub>1</sub>, faded away gradually in all treatment arms (Fig. 1), though not complete within 60 min after placebo.

**Table 1** Patients demographics.

Male, <i>n</i> (%)	5 (29)
Mean age, years (range)	30 (18–41)
Mean FEV <sub>1</sub> , L (range)	3.29 (2.09–5.17)
Mean FEV <sub>1</sub> , % predicted normal (range)	96 (73–122)
Gmean PC <sub>20</sub> , mg ml <sup>-1</sup> (range)	0.70 (0.06–5.00)
Inhaled steroid use, <i>n</i> (%)	15 (88)
β <sub>2</sub> -agonist reliever use, <i>n</i> (%)	17 (100)

Gmean = geometric mean; PC<sub>20</sub> provocative concentration of methacholine causing a forced expiratory flow in 1 s (FEV<sub>1</sub>) to fall by 20%.

### Time to onset of first improvement in Borg score

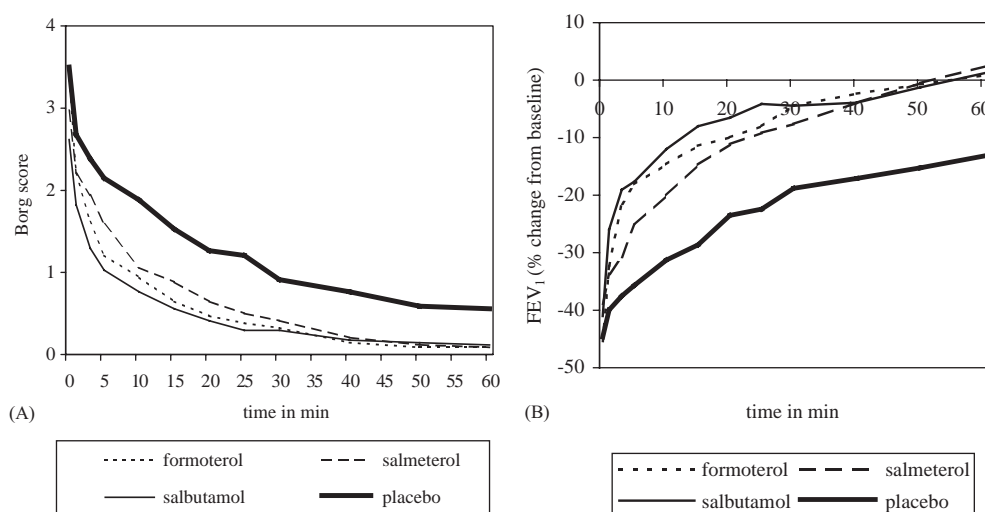
Within 2 min after inhalation of formoterol and salbutamol, an improvement in Borg score was reported. Gmean time (range) values of the first sensed improvement were 1.5 (1–40) min for formoterol, 1.7 (1–10) min for salbutamol, 4.5 (1–30) min for salmeterol and 3.4 (1–40) min for placebo. The onset of effect of formoterol and salbutamol both differed significantly from placebo (both  $P \leq 0.05$ ) and salmeterol (both  $P \leq 0.01$ ; Fig. 2). Salmeterol did not differ from placebo.

At the moment of the first sensed improvement, FEV<sub>1</sub> values had improved as well, but were still below pre-methacholine baseline. FEV<sub>1</sub> had improved with mean (standard deviation (sd)) 15.9 (11.9)%, 18.4 (10.24)%, 13.9 (12.4)% and 10.6 (7.6)% after formoterol, salbutamol, salmeterol, and placebo, respectively. The differences between the four treatments were not significant.

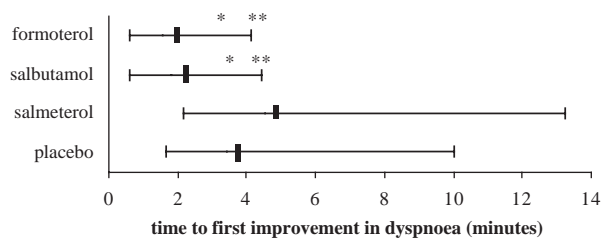
**Table 2** Baseline conditions on each study day (*n* = 17).

	FEV <sub>1</sub> (l)	% Decrease in FEV <sub>1</sub> from pre-methacholine	Borg score after methacholine provocation (units)	PC <sub>20</sub> (mg ml <sup>-1</sup> )
Formoterol	3.3 ± 0.8	45.4 ± 11.7	3 (1–9)	1.1 (0.4–7.0)
Salbutamol	3.3 ± 0.8	41.2 ± 8.8	2 (0.5–8)	0.8 (0.3–4.3)
Salmeterol	3.2 ± 0.8	38.9 ± 0.8	2 (0.5–9)	0.9 (0.3–8.3)
Placebo	3.2 ± 0.9	44.7 ± 11.2	3 (0.5–9)	1.0 (0.3–7.2)

Data are mean ± sd except Borg score: median (range) and PC<sub>20</sub>: Gmean (range). PC<sub>20</sub> provocative concentration of methacholine causing a forced expiratory flow in 1 s (FEV<sub>1</sub>) to fall by 20%.



**Figure 1** Borg score (A) and FEV<sub>1</sub> (as percentage change from baseline); (B) during the first 60 min following inhalation of study medication after methacholine-induced bronchoconstriction.

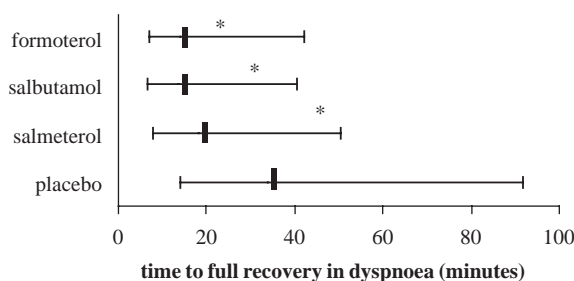


**Figure 2** Gmean and 95% confidence interval for the time to the first sensed improvement of Borg score following inhalation of study medication after methacholine-induced bronchoconstriction. \* $P \leq 0.05$  versus placebo; \*\* $P \leq 0.01$  versus salmeterol.

### Time to return to baseline Borg score

After placebo treatment, it lasted approximately half an hour before the effects of methacholine on dyspnoea were completely gone, after active treatments the recovery went faster. The Gmean (range) values for the recovery time were 13.8 (1–75) min for formoterol, 13.4 (1–60) min for salbutamol, 18.0 (1–75) min for salmeterol, and 33.6 (1–75) min for placebo. The values were significantly different between placebo and all active treatments ( $P \leq 0.001$ ), yet not between active treatments (Fig. 3).

The Borg score did not return to pre-methacholine values in 3 of 17 cases after inhalation of formoterol, 0/17 after salbutamol, 1/17 after salmeterol and 7/17 cases after inhalation of placebo. At the moment that the Borg score had returned to its baseline value, mean FEV<sub>1</sub> values were still lower than at the beginning of the test. The remaining % falls in FEV<sub>1</sub> on the formoterol, salbutamol, salmeterol, and placebo test days were 10.1 (7.6)%, 10.5 (12.5)%, 10.8 (11.4)%, and 15.8 (15.1)%, respectively below pre-methacholine baseline values.



**Figure 3** Gmean with 95% confidence interval for the recovery time of Borg score to return to baseline value following inhalation of study medication after methacholine-induced bronchoconstriction. \* $P \leq 0.001$  versus placebo.

### Discussion

This post-hoc analysis shows that the onset of relief of dyspnoea, measured by the modified Borg score, is significantly faster achieved with inhalation of the rapidly acting  $\beta_2$ -receptor agonists formoterol and salbutamol than with salmeterol or placebo. Thus, the rapid bronchodilating effects of formoterol and salbutamol are perceived by patients as well.

After inhalation of both placebo and salmeterol, the first moment that the patients sense an improvement of dyspnoea occurs at 5 min. Thus, it takes 4–5 min before the methacholine starts to fade away. The onset of dyspnoea relief with salmeterol does not differ significantly from that after placebo and is therefore too slow to be accurately perceived by patients in the present model. The complete recovery of methacholine-induced dyspnoea with salmeterol is detected after a mean of 18 min after inhalation, not significantly slower than with formoterol and salbutamol, but significantly faster than with placebo. We conclude that rapidly acting bronchodilators formoterol and salbutamol not only provide rapid bronchodilation<sup>7</sup> but a rapidly sensed onset of relief of dyspnoea as well.

Different methods have been applied to assess the perception of dyspnoea, for instance the Visual analogue scale<sup>10,11</sup> and modified Borg score.<sup>9,12,13</sup> We have used the modified Borg score to determine the perception of dyspnoea, because Borg scale scores have been found to be better reproducible than outcomes of the Visual Analogue Scale.<sup>9</sup> Moreover, Borg scores are easy to measure, easily understood, and mimic closely real-life situations, when people use semantics to describe the perception of dyspnoea. The magnitude of modified Borg scores (between 0 and 10) gives an estimate of the severity of perceived dyspnoea<sup>14</sup> and in analogy of the visual analogue score represents the individually assessed inconvenience of asthma symptoms during provocation tests.<sup>11</sup> For this reason, we did not present the absolute levels of Borg scores in calculating the onset of the perception of improvement of dyspnoea, but primarily the individually assessed time points when the Borg scores improved in each individual patient. The latter represents more accurately the individual patient's ability to subjectively perceive clinically relevant effects, in line with objective changes in lung function.<sup>11</sup>

After the first timepoint when the Borg score had returned to baseline values, some bronchoconstriction remained. This is not an unexpected finding as in earlier studies using methacholine-induced

bronchoconstriction, approximately a 10% fall in FEV<sub>1</sub> is the minimal difference which is perceived in patients with asthma<sup>12</sup>

When methacholine is applied to induce bronchoconstriction, the induced bronchoconstriction is solely due to airway smooth muscle cells contraction. Therefore, we believe that methacholine-induced bronchoconstriction is a proper model to investigate the bronchodilating effects of  $\beta_2$ -agonists by reversing the airway smooth muscle contraction that accompanies an acute spontaneous asthma attack.

In summary, a single inhalation of formoterol and salbutamol induce a relief of dyspnoea within 2 min, in methacholine-induced bronchoconstriction as a model to induce dyspnoea in patients with asthma. The onset of dyspnoea relief provided by salmeterol could not be determined in this model since the spontaneous recovery of dyspnoea occurred at the same time as with placebo. Notwithstanding the observed faster onset of dyspnoea relief with formoterol and salbutamol, complete recovery of induced dyspnoea was always obtained more rapidly with all three  $\beta_2$ -agonists in comparison with placebo.

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