Total reversibility testing as indicator of the clinical efficacy of formoterol in COPD

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Summary. Rationale: The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend bronchodilator reversibility testing to guide treatment decisions. This study evaluated the relationship between the change in forced expiratory volume in 1 s (FEV\textsubscript{1}) with salbutamol or formoterol and the clinical effects of a 4-week formoterol (Foradil\textsuperscript{a}) treatment.

Methods: At Visit 1, patients (n = 448) with stable chronic obstructive pulmonary disease took an FEV\textsubscript{1} reversibility test using 200\textsuperscript{mg} salbutamol via a metered dose inhaler. At Visit 2 (Day 0), an FEV\textsubscript{1} reversibility test was performed using formoterol via a dry-powder inhaler (Aerolizer\textsuperscript{a}). Patients then received formoterol 12\textsuperscript{mg} twice daily until Visit 3 (Day 21–30), when a further formoterol FEV\textsubscript{1} reversibility test was performed. Clinical parameters included FEV\textsubscript{1}, symptom questionnaires and rescue medication use.

Results: There was no significant relationship between the immediate change in FEV\textsubscript{1} with salbutamol and the absolute change from baseline in FEV\textsubscript{1}, symptom scores or rescue medication use after a 4-week formoterol treatment. Relative immediate change in FEV\textsubscript{1} with formoterol was correlated with change in rescue medication use (P = 0.02) and FEV\textsubscript{1} at Visit 3 (P < 0.001). Total reversibility in FEV\textsubscript{1} with formoterol (post-dose Visit 3–pre-dose Visit 2) was correlated with all treatment efficacy variables (P < 0.01).

Conclusions: Immediate salbutamol reversibility testing, as performed under these study conditions, failed to predict the clinical efficacy of formoterol. Total reversibility after 4 weeks of formoterol treatment may be a better predictor of clinical benefits of long-term bronchodilator therapy.

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Introduction

Bronchodilators are central to the symptomatic management of chronic obstructive pulmonary disease (COPD), recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,\(^1\) and may be prescribed on an as-needed or regular basis. The choice of bronchodilator treatment is generally based on the physician’s assessment of the patient’s response to short-acting \(\beta_2\)-agonists. The GOLD guidelines recommend the use of bronchodilator reversibility testing for COPD diagnosis and as a guide to treatment decisions. Several definitions of partially reversible COPD are used, e.g. that of the American Thoracic Society (ATS) \((\geq 15\% \text{ increase in baseline forced expiratory volume in } 1 \text{ s (FEV}_1\text{) within 15–30 min of inhaling salbutamol})\) and that of the European Respiratory Society (ERS)/Société de Pneumologie de Langue Française \((\geq 12\% \text{ increase in predicted FEV}_1\text{ and } \geq 200 \text{ mL increase after salbutamol inhalation})\).\(^2–^4\) While reversibility testing is recommended in the guidelines, it is generally acknowledged, however, that patients who do not show a significant FEV\(_1\) response to a bronchodilator reversibility test may still benefit symptomatically from bronchodilator treatment (ATS, GOLD, etc.).

In addition, reversibility tests in COPD have low reproducibility as the FEV\(_1\) response can vary depending on the drug used and the method of inspiratory manoeuvre preceding the test.\(^5–^7\) A number of studies have shown that reversibility testing with short-acting \(\beta_2\)-agonists may not be the most accurate means of predicting the efficacy of long-acting \(\beta_2\)-agonist treatment.\(^8–^10\) For example, Cazzola et al.\(^5\) found that reversibility to salbutamol was not an accurate means of predicting bronchodilation after salmeterol treatment. Likewise, Mahler\(^11\) showed improvements in lung function and reductions in the severity of dyspnoea with both salmeterol and ipratropium, in a subgroup of patients who exhibited irreversibility to salbutamol.

There is currently a need for a standardised reversibility test, which can be used to predict the clinical benefit of long-term bronchodilator treatment. The aim of this study was to evaluate the relationship between reversibility tests using salbutamol or formoterol and the clinical effect of a 4-week treatment with formoterol.

Materials and methods

Patients

All patients were aged \(\geq 40\) years, with stable COPD according to ATS criteria (1995). They were to be current or previous smokers (\(>20\) pack-years) with an FEV\(_1\) of \(<70\%\) of predicted and an FEV\(_1\)/FVC of \(<88\%\) or \(<89\%\) of predicted value in men and women, respectively. Patients were excluded if they had a history of asthma, other clinically significant disease or respiratory tract infection, or had been hospitalised for a COPD exacerbation in the month prior to the study or during the preliminary period. Patients receiving non-potassium-sparing diuretics, \(\beta\)-blockers, quinidine or quinidine-like antiarrhythmics, tricyclic antidepressants, serotonin reuptake inhibitors, or monoamine oxidase inhibitors were also ineligible for enrolment. Bronchodilator treatments were stopped before Visit 1 according to the following scheme. Short-acting \(\beta_2\)-agonists were stopped 6 h prior to Visit 1; anticholinergics, long-acting \(\beta_2\)-agonists, fixed combinations of short-acting anticholinergic and \(\beta_2\)-agonist were stopped 12 h prior to Visit 1; and theophylline and other xanthine derivatives were stopped 36 h prior to Visit 1. Treatment with concomitant inhaled or nasal corticosteroids was allowed if patients were on a stabilised regimen. However, patients who had received systemic corticosteroids or fixed combinations of inhaled long-acting \(\beta_2\)-agonist and corticosteroid within the previous month or who required long-term oxygen treatment were excluded.

Written informed consent was provided by all enrolled subjects and the study was conducted in accordance with the latest revisions to the Declaration of Helsinki and with local ethics committee approval.

Study design

This was a multicentre open-label study, which included three visits. At Visit 1 (Day –30 to –14), patients were assessed for eligibility and underwent a reversibility test with FEV\(_1\) measurements before and 15–30 min after salbutamol 200 \(\mu\)g delivered via a pressurised metered-dose inhaler (100 \(\mu\)g/puff; Ventoline\(^8\), GlaxoSmithKline, Marly-le-Roi, France). Patients were also issued with study self-assessment diaries to record COPD symptoms, rescue medication use and morning pre-dose peak expiratory flow (PEF; measured using a standard Mini-Wright peak flow meter). According to a symptom questionnaire already used in previous studies,\(^12,13\) patients scored the following six symptoms on a four-point scale (0 = best to 3 = worst) up to a maximum of 18 per day: ability to perform usual daily activity, breathlessness over the past 24 h, waking at night due to respiratory...
symptoms, breathlessness on rising, cough, and sputum production. Between Visits 1 and 2, the only bronchodilator allowed was on-demand salbutamol. At Visit 2 (Day 0), a reversibility test was carried out with FEV1 measurements before and 15–30 min after formoterol 12 μg delivered via a dry-powder inhaler (Foradil®, Aerolizer®, Novartis Pharma, Basel, Switzerland). The single dose of 12 μg of formoterol was selected because it induces a maximal bronchodilation similar to that of 200 μg of salbutamol,14,15 which is the dose generally used for reversibility testing in clinical practice.8,16,17

Patients then received formoterol 12 μg twice daily (b.i.d.) between Visits 2 and 3 (minimum duration 21 days, maximum duration 30 days). No other bronchodilator treatment was allowed, except on-demand salbutamol. At Visit 3, an FEV1 reversibility test was performed before and 15–30 min after inhalation of formoterol 12 μg. Bronchodilator reversibility tests were performed at the same time of day at each visit.

Definitions and efficacy variables

All spirometry assessments were performed in triplicate with the highest values being used for analysis. Spirometers were calibrated before each visit. FEV1 reversibility data were presented as both the absolute difference (absolute change in FEV1 in L) and the relative changes (in percentage of the baseline value and in percentage of the predicted value). For the total FEV1 reversibility test, the difference between the pre-dose measurement at Visit 2 and the post-dose measurement at Visit 3 was calculated. In contrast to the total reversibility test, standard reversibility test measured at each visit was termed immediate reversibility test. The primary efficacy variable was the relationship between immediate change in FEV1 with salbutamol at Visit 1 and the efficacy variables (change in baseline FEV1, PEF, symptom scores and rescue medication use) following the 4-week formoterol treatment. Secondary efficacy variables included the relationship between immediate (Visit 2) or total (Visit 3) change in FEV1 with formoterol and the efficacy variables of the 4-week formoterol treatment, and the relationship between immediate change in FEV1 with salbutamol (Visit 1) and formoterol (Visit 2) and total change in FEV1 with formoterol (Visit 3).

Statistical analyses

Reversibility tests and clinical and spirometric efficacy variables at each visit were recorded using descriptive statistics and graphical representations (mean values are presented ± standard deviation unless otherwise specified). The Wilcoxon’s rank signed test was used to assess the change in efficacy variables from the previous visit, and the McNemar test was used to compare the reversibility tests at Visits 1 and 2 and total reversibility with regard to ATS and ERS criteria. Calculation of correlation coefficients and linear regression modelling were used to explore the relationship between reversibility and efficacy variables.

All included patients were taken into account in the safety analysis. Reversibility tests and clinical and spirometric efficacy variables were described for all patients with valid baseline reversibility and a measure of efficacy at Visit 3. Patients with relative reversibility of FEV1 at baseline of more than ±30% were excluded from the efficacy analysis to prevent the inclusion of COPD patients with associated asthma.

Results

A total of 448 patients were enrolled in the study from 262 private practice pulmonologists. Twenty-eight patients (6.3%) discontinued from the study prematurely, the main reasons being loss of contact (2.0% [9/448]), adverse events (AEs) (1.6% [7/448]), patients no longer met the protocol criteria (1.1% [5/448]) and withdrawal of consent (0.9% [4/448]). Thirty-four (7.6%) patients were excluded from the per-protocol population due to relative reversibility of FEV1 of more than ±30%. Patient demographics and baseline spirometry values are shown in Table 1. The majority of patients had moderate Stage II (58.0%) or severe Stage III COPD (32.4%) according to the GOLD definition.

The breakdown of patients receiving long-term bronchodilator treatment before the start of the study were as follows: fixed combination of salbutamol and ipratropium bromide (22.3%), fixed combination of fenoterol and ipratropium bromide (15.8%), salmeterol (8.5%), theophylline (3.8%), ipratropium bromide (2.0%), oxitropium bromide (0.4%), and short-acting β2-agonists (43.3%). Inhaled corticosteroids were used by 48.0% of patients during the study.

Reversibility tests

The mean FEV1 absolute values (± SD) observed before and after bronchodilator at each visit are shown in Table 2 and the mean values of reversibility in FEV1 at each visit are presented in Fig. 1.
The mean (±SD) immediate absolute change in FEV₁ after administration of 200 μg salbutamol was 0.15 ± 0.13 L (relative reversibility: 10.2 ± 9.0% of baseline value, 5.1 ± 4.6% of predicted value). At Visit 2, the mean (±SD) immediate absolute change in FEV₁ after administration of 12 μg formoterol was 0.16 ± 0.16 L (relative change: 12.0 ± 14.0% of baseline value, 5.5 ± 5.4% of predicted value), and at Visit 3, 0.12 ± 0.19 L (relative change: 8.8 ± 12.8% of baseline value, 4.3 ± 6.8% of predicted value). The total reversibility test with formoterol (difference between the pre-dose measurement at Visit 2 and the post-dose measurement at Visit 3) showed a change in FEV₁ of 0.21 ± 0.26 L (relative change: 16.5 ± 19.9% of baseline value, 7.5 ± 9.1% of predicted value). A significantly greater number of patients met the ATS criterion for reversible COPD with the total formoterol reversibility test than with the immediate salbutamol reversibility test (48.2% and 32.2%, respectively, \( P = 0.008 \)). A similar difference was observed with the ERS criterion with 52.4% of patients meeting the criterion with the total formoterol reversibility test compared with 34.5% with the immediate salbutamol reversibility test \( (P < 0.001) \). The percentage of ATS/ERS reversible patients was also significantly greater with the immediate formoterol reversibility test (34.3% and 38.1%) than with the immediate salbutamol reversibility test \( (P < 0.001) \).

**Clinical efficacy variables**

The efficacy variables after the 4-week formoterol treatment are shown in Table 3. Formoterol

<table>
<thead>
<tr>
<th>Visit 1 (salbutamol 200 μg)</th>
<th>Before bronchodilator</th>
<th>After bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.54 (0.49)</td>
<td>1.71 (0.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 2 (formoterol 12 μg)</th>
<th>Before bronchodilator</th>
<th>After bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.55 (0.56)</td>
<td>1.71 (0.57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visit 3 (formoterol 12 μg after a 4-week treatment)</th>
<th>Before bronchodilator</th>
<th>After bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.62 (0.56)</td>
<td>1.76 (0.59)</td>
</tr>
</tbody>
</table>
treatment resulted in significant improvements from baseline in daily symptom scores, rescue medication use, PEF and baseline FEV₁ (all \( P < 0.01 \)).

**Reversibility–efficacy correlations**

**Primary efficacy endpoints**
There was no significant relationship between immediate change in FEV₁ with salbutamol and the absolute change from baseline in FEV₁ after the 4-week formoterol treatment (Fig. 2). Similarly, no significant relationship was found between immediate change in FEV₁ with salbutamol (either absolute or relative) and symptom scores, rescue medication use or PEF after the 4-week formoterol treatment (Table 4).

**Secondary efficacy endpoints**
The correlations between change in FEV₁ with formoterol and each of the efficacy variables are shown in Table 4. Relative immediate change in FEV₁ with formoterol significantly correlated with change in rescue medication use (\( P = 0.02 \)) and in baseline FEV₁ (\( P < 0.001 \)), but not with symptoms or PEF. In contrast, relative total change in FEV₁ with formoterol significantly correlated with all the treatment efficacy variables. Absolute total change in FEV₁ with formoterol was also significantly correlated with change in symptoms, PEF and baseline FEV₁.

**Safety and tolerability**
Formoterol was generally well tolerated. At least one AE was experienced by 16.7% patients (75/448) and 2.9% of patients (13/448) experienced an AE suspected to be drug related. Class effects for \( \beta_2 \)-agonists included muscle cramps (0.7%, three patients), tremor (0.4%, two patients), palpitations (0.2%, one patient) and headache (0.2%, one patient). Five patients (1.1%) withdrew because of one or more AEs suspected to be drug related.

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**Figure 1** Mean reversibility in FEV₁ at Visits 1 (after salbutamol), 2 and 3 (after formoterol) and total reversibility (difference post-dose FEV₁ at Visit 3–baseline FEV₁ at Visit 2) expressed in (a) absolute value (L), (b) percentage of baseline value, and (c) percentage of predicted value.

**Table 3** Changes in efficacy variables (per protocol population).

<table>
<thead>
<tr>
<th>Efficacy variable (mean±SD)</th>
<th>Baseline</th>
<th>After 4-weeks formoterol treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily symptom score (0–18 scale)</td>
<td>4.56±2.88</td>
<td>Difference (-0.83±2.21^\dagger)</td>
</tr>
<tr>
<td>Number of puffs/day of salbutamol</td>
<td>2.3±2.4</td>
<td>Difference (-1.3±1.9^\dagger)</td>
</tr>
<tr>
<td>Peak expiratory flow rate (L/min)</td>
<td>298.9±98.0</td>
<td>Difference (+28.3±38.2^\dagger)</td>
</tr>
<tr>
<td>Baseline FEV₁ measured at Visits 2 and 3 (L)</td>
<td>1.54±0.53</td>
<td>Difference (-0.09±0.24^\dagger)</td>
</tr>
</tbody>
</table>

\dagger standard deviation; and FEV₁, forced expiratory volume in 1s.

\dagger Statistically significant change (\( P < 0.01 \) Wilcoxon’s signed rank test).
(fine tremor in two patients; sensation of malaise in one patient; palpitations in two patients; dyspnoea in one patient; nervousness in one patient). Eight severe AEs occurred (1.8%): seven of these events were not suspected to be drug related (cancer in three patients; bronchospasm in one; infection in one; accidental thoracic trauma in one; death due to a sudden cardiorespiratory arrest of unknown cause in a 75-year-old patient) and one event was suspected to be drug related (patient with known coronary heart disease hospitalised for severe angina, without myocardial infarct).

Table 4  Correlation coefficients (P-values) between the absolute and relative (in % of baseline value) changes in forced expiratory volume in 1 s (FEV₁) with salbutamol and formoterol and the changes in efficacy variables following a 4-week formoterol treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate change in FEV₁ with salbutamol</td>
</tr>
<tr>
<td></td>
<td>Absolute</td>
</tr>
<tr>
<td>↓ Symptoms</td>
<td>-0.018</td>
</tr>
<tr>
<td></td>
<td>(P = 0.73)</td>
</tr>
<tr>
<td>↓ Rescue salbutamol</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>(P = 0.74)</td>
</tr>
<tr>
<td>↑ PEF</td>
<td>-0.040</td>
</tr>
<tr>
<td></td>
<td>(P = 0.45)</td>
</tr>
<tr>
<td>↑ Baseline FEV₁</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>(P = 0.31)</td>
</tr>
</tbody>
</table>

P-values are related to the test of null Pearson correlation coefficient.
FEV₁, forced expiratory volume in 1 s.

Figure 2  Relationship between the relative immediate change in FEV₁ with salbutamol and the absolute change in the baseline FEV₁ after a 4-week formoterol treatment.

Discussion
The GOLD guidelines state that bronchodilator reversibility testing may be performed at the time of diagnosis of COPD to help rule out a diagnosis of asthma, to establish a patient’s best attainable lung function, to gauge prognosis, and to assess potential response to treatment. They go on, however, to acknowledge the day-to-day variability of the response, the arbitrariness of the values used to define a significant response, and the fact that patients who do not show a significant response to
the test may benefit symptomatically from long-term bronchodilator therapy. Further doubts as to the diagnostic and prognostic value of the procedure were raised in two recent publications. The analysis of data from two studies showed convincingly that the failure to demonstrate a response to a single bronchodilator challenge did not predict either a lack of subsequent bronchodilator response, or improvements in other variables such as symptom relief and quality of life with regular use of bronchodilator therapy. Similar findings have been reported in earlier studies. In the present study, we have confirmed that, in patients with stable COPD, immediate reversibility testing with salbutamol is not useful to predict whether a patient will benefit from a 4-week period of treatment with formoterol, in terms either of lung function or symptomatically.

Our study assessed the predictive value of single reversibility testing using the bronchodilator formoterol. This agent is suitable for use in such a test because of its rapid onset of action, demonstrably similar to that of salbutamol in COPD patients. Furthermore, formoterol is a full agonist at the $\beta_2$-adrenoceptor, allowing a maximal bronchodilator response to be attained. In addition, there is some evidence to suggest that the response to formoterol is less affected by the genetic polymorphisms in the $\beta_2$-adrenoceptor that may lead to variability in the bronchodilator response to salbutamol.

In this study, we used two methods to assess the predictive value of reversibility testing using formoterol. First, we compared the effects of a single test with the clinical and objective responses observed during 4 weeks of formoterol treatment (immediate reversibility test). Immediate reversibility test proved to be predictive of the 4-week improvement in lung function but did not correlate with the improvement in clinical symptoms. The second method was to assess reversibility as the difference between the baseline value (pre-bronchodilator) and the value obtained post-bronchodilator when the test was repeated following the short course of treatment with formoterol (total reversibility test). In contrast, total reversibility test (expressed in absolute values or as percentage change) was significantly correlated with both lung function and clinical improvements. The test is therefore likely to prove relevant for long-term improvements in exercise capacity and quality of life, which are largely impacted by the symptoms of COPD. Furthermore, the total reversibility test identified significantly more patients who met the ATS/ERS criteria for reversibility than did the single test using salbutamol. Other studies evaluating reversibility and other lung function parameters have administered treatments on an open-label basis. As the main objective was to evaluate the correlation between reversibility tests and clinical parameters, and not to compare the efficacy of salbutamol and formoterol, the open-label design of this study is unlikely to have introduced any bias.

The test of total reversibility could be readily incorporated into the routine assessment and management of COPD patients. In practice, we would recommend that baseline spirometry be performed at the initial assessment, before beginning formoterol treatment, with a second spirometry performed after at least 1 month of treatment with the same agent, using one capsule of formoterol 12 $\mu$g from the patient’s own treatment. The total reversibility test could help the physician to confirm the clinical improvement reported by the patient and provide relevant information to guide decisions on further treatment. In addition, the use of this test to assess reversibility will enable the adequate identification of potentially eligible (reversible) patients who stand to benefit from long-term bronchodilator therapy.

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**References**


