Evaluation of bronchodilator response in patients with airway obstruction

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The aim of this study was to define the most useful index of expressing bronchodilator response and to distinguish between asthma and COPD.

A prospective study was carried out of bronchodilator response in 142 asthmatics and 58 COPD patients in a university hospital.

Reversibility was expressed as: 1. absolute change (Δabs); 2. % of initial (Δ%init); 3. % of predicted (Δ%pred) and 4. % of maximum possible response (Δ%max). Dependence on forced expirations volume in 1 sec (FEV1) as % of predicted and sensitivity and specificity for diagnosis of asthma were established.

A relationship between Δabs and initial FEV1 was not found in asthma (Δabs vs. % initial FEV1, r=0.07) or COPD (r=0.02). Δ%pred did not show a correlation in asthma (r=0.10) or COPD (r=0.06). Δ%init was dependent on the baseline value in asthma (r=0.38, P<0.001) but not in COPD (r=0.18, P=n.s.). Δmax was dependent in both. The combination of best sensitivity and specificity to separate asthma and COPD was obtained with Δabs (0.4 or 0.6%). The worst specificity for asthma diagnosis was obtained with Δ%init (30%). The best likelihood ratios were obtained with Δabs and Δ%pred and the worst likelihood ratio with Δ%init.

Δ%init is not recommended as an index for differential diagnosis between asthma and COPD; 2) Δ%init overscores bronchodilator response in patients with low FEV1. The independence of each bronchodilator response index should be verified in clinical trials for each selected sample.

Introduction

The measurement of spirometric data before and after inhaling a bronchodilator is a commonly ordered pulmonary function test in clinical and research settings. Despite its well-known limitations, it is one of the most useful criteria for asthma diagnosis. Additionally, most clinical trials define ‘reversible’ vs. ‘non-reversible’ airway obstruction depending on bronchodilator response, which theoretically determines homogeneous study samples. However, there are no uniformly accepted criteria for defining a ‘significant’ response (1,2). Questions to answer are: 1. which spirometric indices should be considered to evaluate response (forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), forced expiratory flow between 25 and 75% of FVC (FEF25-75) and FEV1/FVC); 2. which is the best way to express change after inhaling a bronchodilator (absolute change, percentage of initial FEV1, percentage of predicted FEV1, percentage of maximal possible response)?

and 3. what amount of change should be considered a positive response?

Although a percentage of the initial FEV1 value is not either a part of the definition of bronchodilator response for international societies nor universally accepted, it is a very common means of expression. An increase in FEV1 >15% was the most popular definition of a positive bronchodilator response found in a review of the asthma and chronic obstructive pulmonary disease (COPD) literature and some medical settings (3). However, this criterion has recently been challenged due to an inadequate ability to separate diagnostically asthma and COPD patients (4) and mainly because of the generation of a much greater proportion of responsive patients (probably false) among patients with very low initial FEV1 (5–7). On the other hand, expressing change as an absolute value (for instance, 200 ml) may theoretically require values impossible to achieve for patients with very low FEV1, thus creating a falsely high proportion of non-responsive tests. Choosing one or the other criterion may result in a different classification of a relevant number of patients (5).

These difficulties have provoked increasing interest in exploring other ways to express bronchodilator response (8,9). The characteristics of an ideal index should be maximal independence of the pre-bronchodilator FEV1 value, greatest power to discriminate asthma and COPD...
and the reproducibility of bronchodilator response. We have examined the different ways of expressing bronchodilator response in patients with previously known disease (asthma and COPD) in order to define their dependence on initial FEV₁ and their efficacy to separate patients with asthma from patients with COPD.

Material and Methods

Two hundred patients with airway obstruction were studied during a routine visit in our chest clinic (142 asthmatics, 58 COPD). They were included in the study if they had a previously diagnosed airway obstructive disease and a present baseline spirometry with a FEV₁/FVC relationship 1.64 or below the predicted value or lower. All COPD patients showed FEV₁ values lower than 70% of predicted value. To test the power of each index to discriminate between COPD and asthma patients, a comparison was performed studying the subgroup of asthmatics with FEV₁ lower than 55% of predicted value (n=61) in order to match COPD and asthma patients for baseline lung function. Patients with other chronic respiratory diseases (occupational lung disorder, bronchiectasis, interstitial lung disease, tuberculosis and cancer), previous thoracic surgery, heart failure or any other condition able to interfere with an adequate expiratory manoeuvre or a correct classification of asthma or COPD were excluded. A standardized history of respiratory symptoms was obtained. Patients were classified as asthmatics when they reported attacks of breathlessness and wheeze according ATS criteria and were classified as asthmatics when they reported attacks of breathlessness and wheeze according ATS criteria and were classified as asthmatics. To avoid misclassification, a history of cough with sputum. To avoid misclassification, a history of symptoms since childhood or adolescence, 2. symptomatic-free periods of longer than 3 months, 3. spontaneous variations of FEV₁ during the year of over 20% of baseline value; 4. a histamine challenge test with a PC₂₀ < 8 mg ml⁻¹.

Patients were classified as COPD when they were heavy smokers and patients with history suggesting COPD but who were not smokers were not included, even though a small group of asthmatics can be smokers and a few COPD patients are not ex-smokers. Patients not clearly classified as one or the other group were not included. Patients under current treatment with systemic steroids were excluded. All patients with asthma were receiving inhaled steroids and bronchodilators following international stepwise guidelines. COPD patients were not receiving inhaled steroids but only regular treatment with inhaled bronchodilators and theophylline during symptomatic periods.

All spirometric tests were performed in the seated position by the same two technicians according to standardized guidelines. Calibration was checked every day. Patients were requested to abstain from inhaled steroids, theophylline and bronchodilators for at least 12 h before the study. FEV₁ and FVC were assessed at least three times with a dry wedge bellows spirometer (Vitalograph, London, U.K.). The data from the flow-volume curves with the highest sum of FVC and FEV₁ were used for calculations. The FEV₁ was measured before and 20 min after inhalation of 200 µg salbutamol from a metered dose inhaler (Glaxo, Argentina). The bronchodilator (Bd) response of each patient was expressed in four different ways: 1. absolute change (dabs): FEV₁ post – FEV₁ pre-Bd; 2. percentage of initial FEV₁ (A%init): (FEV₁ post-Bd – FEV₁ pre-Bd)/FEV₁ pre-Bd x 100; 3. percentage of predicted FEV₁ (A%pred): (FEV₁ post-Bd – FEV₁ pre-Bd/predicted FEV₁) x 100; and 4. percentage of maximal possible response (A%max): (FEV₁ post-Bd – FEV₁ pre-Bd)/(predicted FEV₁ – FEV₁ pre-Bd) x 100. All negative changes were classed as zero.

In order to investigate the dependence of each index on baseline FEV₁, linear regression analysis of the bronchodilator response was applied, taking the Pearson correlation coefficient as a measure of the extent of the relationship. The two-tailed t-test for unpaired samples was applied to compare group means.

The sensitivity and specificity of a bronchodilator response to salbutamol in separating patients with asthma and COPD were calculated applying most commonly published values (dabs 200 ml, A%init 15%) or values derived from confidence intervals previously obtained in studies with placebo in our pulmonary function laboratory (A% pred 9%, A%max 50%) (10). The predictive value for a positive test [true positives/(true positives + false positives)] and the predictive value for a negative test [true negatives/(true negatives + false negatives)] were calculated on the basis of an arbitrarily chosen clinical pre-test probability of asthma of 30 and 70%. The likelihood ratio (sensitivity/1 – specificity), which reflects the ability of a test to discriminate between subjects with asthma or COPD was also calculated for each index (11). For this analysis, two different samples were studied: 1. the whole sample of asthmatics vs. COPD and 2. the sample of asthmatics with FEV₁ lower than 55% of predicted value vs. COPD.

Results

Of the 200 patients, 142 were classed as asthmatic (mean age 55.4 ± 19.0 years, 68 women) and 58 as COPD (mean age 67.3 ± 7.0 years, 12 women). Baseline FEV₁ in asthma patients was 1.57 ± 0.76 l (59.4 ± 19.1% of predicted) and in patients with COPD 1.01 ± 0.34 l (39.7 ± 14.7% of predicted). CVF was 2.59 ± 0.87 l (80.6 ± 20.2% of predicted) in asthmatics and 1.23 ± 0.55 l (60.2 ± 13.7% of predicted) in COPD. Of the COPD patients 23% were current smokers and 77% ex-smokers (63.3 ± 36.5 pack years). Sixty-one asthmatic patients showed an FEV₁ lower than 55% of predicted (mean FEV₁ 41.9 ± 8.7%).

RELATIONSHIP BETWEEN BASELINE FEV₁ AND BRONCHODILATOR RESPONSE

There was no relationship between dabs and pre-Bd FEV₁ either in asthmatics or in COPD. Changes expressed as
Table 1. Correlation coefficient (r) for asthma and COPD vs. absolute FEV₁ and FEV₁ % predicted

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vs. baseline FEV₁ (absolute value)</td>
<td>vs. baseline FEV₁ (% of predicted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFFV₁ absolute</td>
<td>P = 0.14, n.s.</td>
<td>P = 0.17</td>
<td>P = 0.07</td>
<td>P = n.s.</td>
</tr>
<tr>
<td>Δ% FEV₁ initial</td>
<td>0.26 &lt; 0.005</td>
<td>0.18 n.s.</td>
<td>0.38 &lt; 0.001</td>
<td>0.18 n.s.</td>
</tr>
<tr>
<td>Δ% FEV₁ predicted</td>
<td>0.06 n.s.</td>
<td>0.06 n.s.</td>
<td>0.10 n.s.</td>
<td>0.06 n.s.</td>
</tr>
<tr>
<td>Δ% maximal possible</td>
<td>0.07 n.s.</td>
<td>0.42 &lt; 0.001</td>
<td>0.22 &lt; 0.001</td>
<td>0.27 &lt; 0.01</td>
</tr>
</tbody>
</table>

Asthma, n = 142; COPD, n = 58.

n.s., not significant; bold type indicates significant difference.

Δ%red, did not show correlation with pre-Bd FEV₁ in asthmatics or in COPD (Table 1).

On the other hand, the bronchodilating response expressed as a percentage of the initial value was dependent on pre-Bd FEV₁ in asthmatics, although not in COPD. Bronchodilator responsiveness expressed as a percentage of the maximal possible response tends to infinity when pre-Bd FEV₁ is equal or higher than predicted, therefore it cannot be calculated in these situations. The correlation coefficient was calculated excluding such cases, although the scattering of Δ%max was very important. Δ%max was dependent on pre-Bd FEV₁ as % predicted in asthmatics and COPD (Table 1). When the sample was considered as a whole (asthma + COPD) (n = 200), Δabs (r = 0.03, P = n.s.) (Fig. 1) and Δ%pred (r = 0.02, P = n.s.) (Fig. 2) were still independent of pre-Bd FEV₁. However, Δ%init (r = 0.37, P < 0.001) (Fig. 3) and Δ%max (r = 0.22, P < 0.005) were dependent on the pre-Bd FEV₁ value.

BRONCHODILATOR RESPONSE IN PATIENTS WITH ASTHMA AND COPD

Bronchodilator response was significantly different between asthmatics and COPD when expressed as Δabs (asthma 0.31 ± 0.22 vs. COPD 0.16 ± 0.14; P < 0.001) or Δ% pred (asthma 12.0 ± 7.9 vs. 6.29 ± 5.1%; P < 0.001). Change expressed as Δ%init or Δ%max was not different between both groups of patients (Table 2, Fig. 4). However, if only patients with reduced FEV₁ (lower than 55% of predicted) were considered, all indices reached statistical significance in separating asthma and COPD (Table 2, Fig. 4).

Bronchodilator response did not show a sensitivity higher than 85% to establish asthma diagnosis for any index. The lowest specificity was obtained with Δ%init (50.0%) (Table 3). When predictive values for a positive and negative test were calculated on the basis of an arbitrarily chosen clinical pre-test probability of asthma of 30 and 70%, the best predictive values for a positive test were obtained with Δabs (50.5 and 84.8%) and Δ% pred (49.2 and 84.1%), while the lowest predictive value for a positive test (39.4 and 78.0%) was obtained with Δ%init. Even with a high predictive value for a positive test,
FIG. 3. Relationship between pre-Bd FEV₁ as a percentage of predicted value and Δabs in the whole population (asthma + COPD). Dependence on the degree of baseline airflow obstruction was not found (r = 0.03, P = n.s.; y = 2.9212x + 53.899).

The highest likelihood ratios (2.23 and 2.03); much higher than values for Δ%init (1.28). If only those asthmatics with lower FEV₁ values were considered (to match the patients for baseline lung function), the results were not notably different.

A subgroup of 8 (5.6%) patients were classed as bronchodilator-responsive when applying Δ%pred but as non-responsive when applying Δ%init (Δ% pred > 9%, Δ%init < 15%). When these patients were compared with the opposite situation (non-responsive on applying Δ%pred but responsive on applying Δ% init: n = 12, i.e. 8.4% of patients), they showed a higher pre-Bd FEV₁ (78.6 ± 14.7 vs. 37.1 ± 8.1 % predicted, P = <0.001). No COPD patient was classed as responsive by only Δ%pred > 9%, because all such patients showed a corresponding Δ% init of >15%. However, 10 patients (17.2%) who were classified as non-responsive according to Δ%pred < 9% showed Δ%init > 15%.

### Table 2. Response to bronchodilator: comparison between patients with asthma and COPD

<table>
<thead>
<tr>
<th>Patients with FEV₁ lower than 55% of predicted</th>
<th>Asthma</th>
<th>COPD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFEV₁ abs (%)</td>
<td>0.32 ± 0.20</td>
<td>0.16 ± 0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ% FEV₁ init (%)</td>
<td>26.5 ± 14.6</td>
<td>16.9 ± 14.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Δ% FEV₁ pred (%)</td>
<td>13.2 ± 7.9</td>
<td>6.29 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ% max (%)</td>
<td>23.5 ± 15.3</td>
<td>2.95 ± 3.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**FIG. 4.** Distribution of bronchodilator response in asthma (♂) and COPD (♀) expressed by different indices (patients with FEV₁ below 55% of predicted). Bronchodilator response as: (a) absolute change; (b) % of possible maximum; (c) % of baseline FEV₁; and (d) % predicted.
TABLE 3. Response to bronchodilator: sensitivity and specificity of different indices in patients with FEVi <55% (asthma: n=61)

<table>
<thead>
<tr>
<th>Index</th>
<th>Cut-off level</th>
<th>True responsive</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabs</td>
<td>200 ml</td>
<td>43</td>
<td>70.4%</td>
<td>70.6%</td>
</tr>
<tr>
<td>d%init</td>
<td>15%</td>
<td>52</td>
<td>85.2%</td>
<td>50.0%</td>
</tr>
<tr>
<td>dabs + d% init</td>
<td>42</td>
<td>68.8%</td>
<td>70.6%</td>
<td></td>
</tr>
<tr>
<td>d%pred</td>
<td>9%</td>
<td>41</td>
<td>67.2%</td>
<td>70.6%</td>
</tr>
<tr>
<td>A% max</td>
<td>50%</td>
<td>4</td>
<td>6.5%</td>
<td>98.2%</td>
</tr>
</tbody>
</table>

Bold type indicates significant difference.

TABLE 4. Response to bronchodilator: predictive values for a positive and negative test for patients with FEVi lower than 55% (asthma: n=61)

<table>
<thead>
<tr>
<th>Pre-test probability of asthma 30%</th>
<th>Pre-test probability of asthma 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
<td>PV for a positive test (%)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>dabs</td>
<td>50.5</td>
</tr>
<tr>
<td>d%init</td>
<td>39.4</td>
</tr>
<tr>
<td>dabs + d% init</td>
<td>48.1</td>
</tr>
<tr>
<td>d%pred</td>
<td>49.2</td>
</tr>
<tr>
<td>A% max</td>
<td>75.5</td>
</tr>
</tbody>
</table>

The clinical usefulness of each index is highly dependent on clinical pre-test probability of asthma. A%init shows the worst results of predictive values for a positive or negative test in most circumstances. In patients with high clinical pre-test, the presence of a positive response expressed as A%max may be a very specific diagnostic index. Bold type indicates significant difference.

Discussion

This study demonstrates that expressing bronchodilator response in one of the most popular ways (increase in FEVi as a percentage of baseline FEVi) has important disadvantages: it is strongly dependent on the pre-bronchodilator FEVi, does not reveal significant differences between asthma and COPD patients and shows the weakest power to discriminate between these two conditions.

In order to define reversibility to bronchodilator, three factors should be considered: 1. which will be the applied indices? (FEVi, FVC, FEF25-75?); 2. which will be the chosen way of expressing this response? and 3. which will be the cut-off limits to define a positive response?

Firstly, FEVi was better than other commonly used tests for evaluating bronchodilating drugs (5,12). Secondly, the cut-off limits of a positive response may be defined from studies using patient samples to determine confidence intervals for spontaneous variability (13) or placebo response (10,14), or may be calculated from the response to bronchodilator in normal subjects (15). Taking into account that the distribution of bronchodilator response in any of those populations is continuous and unimodal, any definition of the 'cut-off' level for a positive response will be arbitrary. The chosen values for this study were derived from confidence intervals for response to placebo obtained at our pulmonary function laboratory (10), which are similar to currently published values (1,16).

Finally, if the two most commonly used indices for expressing response (dabs and d%init) are analysed, it seems obvious that a change of 200 ml may be a small variation in a baseline FEVi of 2.5 l (<10%), while it may be almost impossible to achieve for a very low baseline FEVi, e.g. 0.4 l (50%). At the same time, a change of 15% in initial value may be a very low value in the second example (60 ml), with equivocal clinical significance and even the possibility of under-resolution of the spirometry equipment. The number of patients classed differently according to the different criteria is not small (12% of asthmatics in a study population) (5) and is important in defining which index is more accurate.

An index with a greater independence of baseline FEVi increases the comparability between different subjects and also between tests with different baseline FEVi in the same subject (5,17). According to our results in patients with asthma, only dabs and d%pred were independent of pre-Bd FEVi, while in COPD patients only A%max showed a strong dependence on the baseline FEVi value. These results in COPD patients contrast with data obtained by Dompeling et al. (17), where A%init was very dependent on...
There was a disagreement regarding the bronchodilator response in patients with airway obstruction. The higher homogeneity of our sample (and heterogeneity of results) shows the influence of population pre-Bd FEVi. Differences in patient selection may explain characteristics on diagnosis and severity of airway disease. Perhaps the smaller number, n = 58 vs. 111) may be the pre-Bd FEVi is consistently observed. Nevertheless, the heterogeneity of results shows the influence of population characteristics on diagnosis and severity of airway disease.

This fact is remarkably relevant when defining bronchodilator response in clinical trials or in patients in different clinical situations. If an inclusion criterion is a predictor of bronchodilator response expressed as A%init (which is very common) (18,19) this will select patients with a more severe pre-bronchodilator airway obstruction. On the other hand, if the sample is composed of more severely affected patients, the response to bronchodilator as a percentage of initial value will be magnified due to the chosen criterion. Similarly, the response to any bronchodilator in a patient who has experienced great change in his or her baseline FEVi may be falsely interpreted as different. This potential error would be avoided if response were expressed as Dabs. Finally, in light of the strong dependence of A%init, the prognostic significance of bronchodilator responsiveness in COPD patients should be reconsidered. A worse prognosis for patients with higher reversibility (expressed as A%init) has been reported (20,21). However, is this really the influence of reversibility or solely due to the selection of more severe patients who show a greater response when expressed as D%init (22).

It is remarkable that several different studies which have analyzed the dependence of bronchodilator response on pre-bronchodilator values, while in accord over the strong dependence of D%init, show very different results regarding other methods of expressing reversibility (Table 5). Obviously, the composition of the sample is critical in determining such relationships. This is very important in designing clinical trials and the chosen method of expressing bronchodilator response should be assessed in that particular sample to exclude dependence on baseline FEV1.

When advantages of Dabs and A%pred in separating positive and negative responses are clear, the prognostic significance of these indices in evaluating the long-term outcome has not been assessed.

Reversibility with a bronchodilator is also a criterion for differential diagnosis between asthma and COPD. Even when inflammation and not bronchodilator response distinguishes between the two disorders, the degree of bronchial responsiveness is a commonly used criterion to separate asthma and COPD in clinical practice and inclusion in clinical trials. In this study, none of the indices resulted in a good differentiation between the two disorders. This is in agreement with previous studies, indicating that up to 23% of asthmatics showed a non-responsive bronchodilator as a percentage of initial value. Published studies disagree considerably over the strong influence of reversibility or solely due to the selection of more severe patients who show a greater response when expressed as D%init (22).

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test probabilities. This emphasizes that, in a clinical setting, the occurrence of a negative test does not exclude the presence of asthma, even when a better diagnosis may be obtained by ΔFeV₀ or Δ%pred.

We conclude that: 1. in clinical practice Δ%init is a poor diagnostic tool to differentiate asthma from COPD; 2. in patients with a previously known diagnosis, Δ%init overestimates the response to bronchodilator in subjects with very low baseline FEV₁; and 3. in clinical trials studying reversibility, the chosen index should be assessed to exclude dependence on the initial FEV₁. The expression which correlates best with clinical improvement after long-term treatment has not yet been defined, therefore the inclusion of different indices for expressing bronchodilator response in clinical trials studying the effects of long-term inhalational therapy would be extremely useful.

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References