Assessment of bronchodilator response in children with asthma


ABSTRACT: The bronchodilator response (BDR) in forced expiratory volume in one second (FEV1) is routinely assessed to estimate the reversibility of airways obstruction. However, there is no consensus as to how the BDR should be expressed, and recommendations applying to children are lacking. Similarly, the relationship between BDR and nonspecific bronchial hyperresponsiveness to histamine (BHR) has not been elucidated.

These questions were addressed in 116 children, 7-16 yrs of age, with stable asthma after withdrawal of all pulmonary maintenance medication. Inclusion criteria were an initial FEV1, between 55–90% predicted, and/or FEV1, forced vital capacity (FVC) between 50–75%, as well as a fall in FEV1, of 20% or more when challenged with up to 150 μg histamine. The change in FEV1, (ΔFEV1) after inhalation of 800 μg salbutamol was expressed in four ways: as an absolute difference (ΔFEV1), as a percentage of predicted FEV1, (ΔFEV1,%pred) or initial FEV1, (ΔFEV1,%init), and as a percentage of the deficit in FEV1, (ΔFEV1,%(pred-init)). ΔFEV1,%init and ΔFEV1,%pred were not related to age and stature of the children; ΔFEV1,%(pred-init) was related to stature, whilst ΔFEV1,(l) was related to both age and stature. All indices correlated with initial FEV1, However, this is an artefact introduced by relating change to initial value, rather than to the mean of initial and final value. In fact, BDR, expressed as ΔFEV1,%pred, was only slightly greater in children with the lowest initial airway calibre (p<0.08), unlike ΔFEV1,%init. BDR was weakly related to BHR.

We conclude that the BDR in children is best expressed as ΔFEV1,%pred, because this is not dependent on age, stature and initial FEV1,. In addition, BDR should not be taken as a measure of bronchial responsiveness to bronchoconstricting stimuli.

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Assessment of responsiveness to a bronchodilator drug is a routine procedure both in clinical studies and in research [1]. In children and adults with asthma, the bronchodilator response (BDR) is often used to indicate the degree of reversibility, to aid in confirming the diagnosis, to select a population for a pharmacological study, and to evaluate a drug strategy [1-5]. In adults, it has also been used to distinguish subjects with asthma from those with chronic obstructive pulmonary disease (COPD), and in the follow-up of patients with COPD [1, 4-6]. However, there is no consensus in the literature as to how the bronchodilator response should be expressed, or what constitutes a significant response [2, 3, 5]. This is further complicated by the fact that the method of expressing a bronchodilator response depends on the objective of the test [5, 7]. These are the main reasons for the controversies and conflicting data in the literature on the diagnostic, therapeutic and prognostic value of a bronchodilator response [8].

BDR is usually assessed from the change in forced expiratory volume in one second (FEV1) after administration of a bronchodilator drug (ΔFEV1) Several different expressions: (ΔFEV1, in litres or as a percentage of either initial (ΔFEV1,%init) or predicted FEV1, (ΔFEV1,%pred), and also ΔFEV1, as a percentage of the deficit between predicted and initial value (ΔFEV1,%(pred-init)) [6], and different cut-off levels are used [3, 6, 9-12]. It has not been clearly stated what requirements an index of bronchodilator response should fulfill. Hence, when comparing children with different airway calibre, a
desired property of any index of bronchodilation is that it is not biased by initial airway calibre. In adults, it has been argued that using ΔFEV₁%(pred) has the disadvantage that it spuriously amplifies the recorded bronchodilator response in patients with a low FEV₁ [9], unlike ΔFEV₁(t) [11, 12], ΔFEV₁%pred [13, 14] and ΔFEV₁%(pred-init) [7]. In children, the interpretation is potentially compounded by the fact that ΔFEV₁ is related to body size and, hence, to lung volume, so that appropriate corrections need to be made. Therefore, when comparing children with different airway calibre, a desirable property of any index of bronchodilation is that it is not confounded by stature and age. Furthermore, as asthma is characterized by variable airways obstruction, another desirable feature is that the index is not dependent on initial airway calibre.

Most clinical studies on the interpretation of BDR are performed in adults, and data on asthmatic children are scarce. Therefore, we compared the properties of different expressions of BDR, in relation to their dependency on airway calibre, in a large sample of children with asthma. All patients were measured under standardized conditions, after withdrawal of all pulmonary maintenance medication.

A number of studies used bronchodilator response as an indicator of the degree of bronchial responsiveness [15, 16], or suggested that the assessment of BDR might be a useful guide to the presence of bronchial hyperresponsiveness (BHR) [17]. However, a scientific basis for this interchangeability is lacking [18]. Therefore, we also studied the relationship between BDR to salbutamol and BHR to histamine.

Patients

We used baseline data from a multicentre trial supported by the Dutch government [19]. The main goal of this trial was to compare the effect of long-term treatment with an inhaled bronchodilator (salbutamol, 200 µg t.i.d.) plus inhaled corticosteroid (budesonide, 200 µg t.i.d.) to that of long-term bronchodilator treatment alone.

One hundred and sixteen children with asthma, aged 7–16 yrs, were recruited from the paediatric out-patient clinics of three hospitals. Criteria for entering the study were a FEV₁ between 55–90% of predicted and/or a FEV₁/forced vital capacity (FVC) ratio between 50–75%, as well as the provocative dose of histamine causing a 20% fall in FEV₁ (PD₂₀ histamine) less than 150 µg (this being more than two standard deviations below the mean value in healthy children [20]). Children with other lung disease and/or concomitant major illness were excluded.

Informed consent was obtained from both the child and the parents, and the study was approved by the Medical Ethics Committees of the participating centres.

Methods

Baseline data were acquired at two visits, at an interval of two to four weeks [19]. For this report we only used data of the first baseline visit. Inhaled corticosteroids were tapered off, and were withheld for at least 2 weeks prior to the first baseline visit. Disodium cromoglycate was also stopped two weeks before the first baseline visit. The only drugs accepted were inhaled bronchodilators on demand, but these were withheld at least 8 h before measurement of ventilatory function. All measurements were performed during clinically stable periods; oral corticosteroid courses, if required, were finished at least 4 weeks before spirometry was performed.

Spirometry (FEV₁, FVC) was performed according to recommendations of the European Community for Coal and Steel [21] using water-sealed or dry rolling seal spirometer or pneumotachograph. FEV₁ and FVC manoeuvres were measured until 3 reproducible (less than 5% difference) recordings were obtained. Reference values of Zapletal et al. [22] were used.

Postbronchodilator FEV₁ was measured after inhalation of 800 µg salbutamol, in order to obtain near maximal bronchodilation [23]. Salbutamol was administered using a metered dose inhaler with a spacer (Volumatic®, Glaxo). One puff contained 200 µg salbutamol. While inspired slowly from functional residual capacity to total lung capacity, salbutamol was inhaled immediately after actuation. Subsequently, each breath was held for about 10 s before expiration. This was done four times and FEV₁ was recorded 20 min after the last dose of salbutamol.

Variability in FEV₁ was assessed from duplicate measurements in a subgroup of 78 children (two of the three centres). FEV₁ prior to bronchodilation was measured twice in these patients, with an interval of 10 min during which they remained seated.

Bronchial responsiveness to histamine was measured by inhalation of histamine diprophosphate in increasing dosages, according to a standardized protocol [24]. Histamine was nebulized with a DeVilbiss 646 nebulizer and a Rosenthal-French dosimeter. Inhaled doses were doubled at 5 min intervals from 2.5 up to 640 µg as a maximum. The effect of each dose was determined by measuring FEV₁ 3 min after each histamine administration. The PD₂₀ histamine was calculated using log-linear interpolation. Bronchial responsiveness to histamine and the bronchodilator response to salbutamol were assessed in each subject, at the same time of the day on separate days, with an interval of 1–7 days.

Statistical analysis

The bronchodilator induced change in FEV₁ was expressed in four different ways: 1) as the difference in litres (ΔFEV₁(t); 2) as a percentage of the predicted value (ΔFEV₁%(pred); 3) as a percentage of the initial value (ΔFEV₁%(init); and 4) as a percentage of the deficit in FEV₁ (ΔFEV₁%(pred-init)).

PD₂₀ values were logarithmically transformed to base 2, because this conveniently reflects the nature of the doubling doses. Distributions of variables were compared to standard normal distributions with the Kolmogorov-Smirnov (K/S) test [25]. The relationship between age,
Results

Clinical characteristics of the 116 children who entered the study are presented in Table 1. The distribution of initial FEV₁, post-bronchodilator FEV₁, ΔFEV₁, %pred, ΔFEV₁ (l) and ΔFEV₁ %init were all normal. The distribution of ΔFEV₁ % (pred−init) was positively skewed (that is, with a long tail to the right) (p<0.001). All distributions were continuous and unimodal.

The correlations between the indices of BDR and age, height, FEV₁ (l), FEV₁ %pred, and 3 logPD₂₀ are shown in Table 2. ΔFEV₁ %init, ΔFEV₁ %pred, ΔFEV₁ % (pred−init) were unrelated to the age of the children. Both ΔFEV₁ %init and ΔFEV₁ %pred were not related to the height, unlike ΔFEV₁ (l) and ΔFEV₁ % (pred−init). Highly significant negative correlations were found between FEV₁ %pred and ΔFEV₁ % (init) (fig. 1) and ΔFEV₁ % (pred−init) (fig. 2 and Table 2). Negative correlations between change and initial value may arise from regression to the mean, and be artificially introduced when a more or less constant numerator is divided by a denominator of varying magnitude; such spurious correlations disappear when the change is related to the mean of initial and final value. Negative correlations which persist imply that the bronchodilator response is largest in those with the lowest starting values [26]. The correlation disappeared when ΔFEV₁ %pred was related to the mean of pre- and postbronchodilator FEV₁ %pred (mean FEV₁ %pred) (table 2 and fig. 3). There was a significant correlation between ΔFEV₁ (l) and mean FEV₁ (l), (mean of value before and after bronchodilation) more strongly so between both ΔFEV₁ %init, ΔFEV₁ % (pred−init) and the mean FEV₁ %pred. The correlation between ΔFEV₁ (l) and mean FEV₁ (l) was removed after correction for age and height, as was also the case for the relationship between ΔFEV₁ %init and mean FEV₁ (l).

Table 1. - Patient characteristics of 86 boys and 30 girls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age yrs</th>
<th>Height cm</th>
<th>FEV₁ l</th>
<th>FEV₁ % pred</th>
<th>FVC l</th>
<th>FVC % pred</th>
<th>FEV₁/FVC</th>
<th>logPD₂₀ µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>11.0±1.9</td>
<td>147±12.5</td>
<td>1.7±0.45</td>
<td>75±13</td>
<td>2.5±0.67</td>
<td>92±13</td>
<td>70.9</td>
<td>4.02±1.49</td>
</tr>
</tbody>
</table>

Data are presented as mean±sd. FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PD₂₀: provocative dose of histamine producing a 20% fall in FEV₁.

Table 2. - Correlation coefficient between the indices of bronchodilator response and age, stature, initial FEV₁, mean of pre- and postbronchodilator FEV₁, and logPD₂₀ histamine

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔFEV₁ (l)</th>
<th>ΔFEV₁ %init</th>
<th>ΔFEV₁ %pred</th>
<th>ΔFEV₁ % (pred−init)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>0.44</td>
<td>0.14</td>
<td>0.11</td>
<td>-0.084</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.25</td>
<td>p=0.19</td>
</tr>
<tr>
<td>Height cm</td>
<td>0.47</td>
<td>0.07</td>
<td>0.04</td>
<td>-0.21</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.71</td>
<td>p=0.02</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>0.14</td>
<td>-0.38</td>
<td>-</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>p=0.14</td>
<td>p&lt;0.001</td>
<td></td>
<td>p=0.42</td>
</tr>
<tr>
<td>*Mean FEV₁ (l)</td>
<td>0.39</td>
<td>-0.13</td>
<td>-</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p=0.02</td>
<td></td>
<td>p=0.13</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>-</td>
<td>-0.69</td>
<td>-0.50</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>*Mean FEV₁ %pred</td>
<td>-</td>
<td>-0.42</td>
<td>-0.16</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.08</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>logPD₂₀ µg</td>
<td>-0.28</td>
<td>-0.30</td>
<td>-0.26</td>
<td>-0.07</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td>p=0.002</td>
<td>p=0.006</td>
<td>p=0.25</td>
</tr>
</tbody>
</table>

*: mean of the value before and after bronchodilation. FEV₁: forced expiratory volume in one second. The change in FEV₁ (ΔFEV₁) was expressed in four ways: as an absolute difference (ΔFEV₁ (l)), as a percentage of predicted FEV₁ (ΔFEV₁ %pred) or initial FEV₁ (ΔFEV₁ %init), and as a percentage of the deficit in FEV₁ (ΔFEV₁ % (pred−init)).
Fig. 1. - Relationship between bronchodilator response expressed as percentage of initial FEV₁ (%init) and initial FEV₁ % predicted. FEV₁: forced expiratory volume in one second.

Fig. 2. - Relationship between bronchodilator response expressed as percentage of predicted (ΔFEV₁ %pred) and initial FEV₁ % predicted. FEV₁: forced expiratory volume in one second.

The mean (sd) of differences of duplicate measurements in FEV₁ was -0.6% pred (3.5%); the upper 95% confidence limit was 7% pred. The mean (sd) day by day variation in FEV₁ was 7.9% pred (7.7%). There were no significant correlations between the day by day variation in FEV₁ and logPD₅₀ histamine (r=-0.13; p=0.20), ΔFEV₁ %pred (r=-0.05; p=0.65), ΔFEV₁ (%init) (r=0.04; p=0.72) and ΔFEV₁ (%init) (r=0.11; p=0.27).

Using commonly quoted cut-off levels for the expression of BDR, the percentage of "positive" responders was calculated (table 3) [1, 4, 10-12, 27].

**Table 3.** - Expressions of bronchodilator response in 116 children, with percentage of "positive" responses

<table>
<thead>
<tr>
<th>Index</th>
<th>Cut-off level</th>
<th>[Ref.]</th>
<th>&quot;significant&quot; responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFEV₁ %init</td>
<td>15</td>
<td>[4]</td>
<td>77 66</td>
</tr>
<tr>
<td>ΔFEV₁ (%init)</td>
<td>0.19</td>
<td>[11, 12]</td>
<td>92 79</td>
</tr>
<tr>
<td>ΔFEV₁ %pred</td>
<td>9</td>
<td>[10]</td>
<td>93 80</td>
</tr>
</tbody>
</table>

For abbreviations see legend to table 2.

ΔFEV₁ % (pred-init) showed values reaching infinity when initial FEV₁ %pred approached 100% (fig. 4).

Only weak correlations were observed between the indices of BDR and bronchial responsiveness to histamine (table 2).

**Discussion**

Measurement of the bronchodilator response is widely applied to assess the acutely reversible component of airways obstruction [1, 27]. However, there is no agreement on what constitutes a significant bronchodilator response [2]. This is partly explained by the lack of agreement on how to express the response to a bronchodilator drug [9, 28]. This prompted the present study, and the results suggest that in children the best way to
express bronchodilator response is the change in FEV₁ as a percentage of the predicted value.

Recently, a number of studies in adults have investigated the different ways of expressing a bronchodilator response [3, 7, 14]. These studies have shown that ΔFEV₁ (%init) is weakly or not related to the initial FEV₁ [9, 11-13, 29-31]. Thus, ΔFEV₁ (%pred yields a high value in patients with a low initial FEV₁, and a low value in those with a higher initial FEV₁ (fig. 1). This index erroneously suggests that those with a low FEV₁ are more responsive to a bronchodilator drug. In adults, this spurious conclusion can be circumvented by reporting the absolute rather than the percentage change [11, 12]. Another potential disadvantage of expressing the bronchodilator response relative to the initial value is that the latter is subject to change variability; hence, in the absence of any true change, the difference between two successive measurements is negatively correlated to the initial value [26]. On both accounts ΔFEV₁ (%init, in spite of its widespread use, is not an ideal index. A potential merit of ΔFEV₁ (%init, however, is that it reflects the greater clinical benefit on one and the same ΔFEV₁ in a patient with a poor initial than in one with a relatively normal baseline FEV₁. In adults, it has been advocated that the bronchodilator response be reported as an absolute change [11, 12], because this circumvents the above numerical problems. In children, we observed a significant correlation between ΔFEV₁ (t) and the mean of pre- and postbronchodilator value. This suggests that in children with mild asthma the improvement in FEV₁ was somewhat less than in those with moderately severe asthma; alternatively, in short children the absolute change is smaller than in tall children. Indeed, ΔFEV₁ (t) correlates both to height and age (table 2); after standardization for age and height (ΔFEV₁ (%pred) BDR was unrelated to the mean of pre- and postbronchodilator value (fig. 3). Therefore, in children ΔFEV₁ (t) is not to be recommended as an index for expressing the bronchodilator response.

In adults, it has been found that ΔFEV₁ (%pred-init), an index of the deficit in FEV₁ compared to the predicted value, was less dependent on the initial FEV₁, and more reproducible than the other indices of BDR [7]. Furthermore, a larger response to bronchodilators, expressed as ΔFEV₁ (%pred-init), was related to the outcome of patients with COPD [6]. However, the use of this index should be limited to patients with severe airflow obstruction, in whom the denominator (predicted-initial FEV₁) does not artificially inflate the response. As initial FEV₁ approaches the predicted value, this index of BDR gives progressively higher results, because the denominator approaches zero [14]. Therefore, in patients in whom FEV₁ is near the normal range, the spuriously inflated result mimics those of ΔFEV₁ (%init in patients with a poor initial FEV₁.

It has been suggested that ΔFEV₁ (%pred should be used as an index of bronchodilator response [10, 13, 14], as this would take into account confounding effects of height and sex. In keeping with this, we found that ΔFEV₁ (%pred was unrelated to age, height and sex (tables 2 and 3), desirable features which warrant its use in children. This index was not significantly related to the mean of pre- and postbronchodilator FEV₁ (%pred (table 2 and fig. 3). As in adults, the improvement in FEV₁ is only marginally larger in those with a lower than in those with a higher initial value [5, 14]. This is remarkable: airflow resistance is inversely related to the fourth power of airway diameter, so that for the same amount of smooth muscle relaxation one expects the improvement in FEV₁ to be most pronounced in asthmatic subjects with the severest airflow limitation. The dosage of inhaled salbutamol (800 µg) used in this study approached the therapeutic dosage to obtain (near) maximal bronchodilation [23]. However, there is residual airflow limitation; the mean FEV₁ after inhalation of 800 µg salbutamol was 92% of predicted in our study population; this is at least 10% below predicted normal, since healthy children also respond to bronchodilator drugs [10, 32, 33]. Thus, residual abnormality must be due to other geometric factors, such as hypertrophy and hyperplasia of mucus glands or smooth muscles, interstitial oedema, and thickening of the reticular lamina [34], which are not acutely influenced by smooth muscle relaxants.

For a bronchodilator response to be meaningful, it should exceed spontaneous variability, whilst a clinically unambiguous response should be greater than that obtained in healthy subjects. Published data on spontaneous variability in FEV₁ in children with asthma are lacking. In healthy school children (aged 12-15 yrs) in whom FEV₁ was measured on five consecutive days the mean±SD coefficient of variation of FEV₁ was 2.7±1.0% [35]; assuming a normal distribution the 95% confidence limit (CL) for spontaneous variability in FEV₁, is then 5.4%, or about 130 ml. In healthy children, the upper 95% CL of the bronchodilator response in FEV₁, has been reported as 9.0-11.0% [10, 32, 33]. In children with asthma, we found that the upper 95% CL for spontaneous variability in FEV₁, for duplicate measurements in 10 min was 7% pred. In healthy adults the upper 95% CL of the bronchodilator response in FEV₁, has been reported as 9.0-11.0% pred [10, 32, 33], and 7.7-10.5% of the initial value [220-315 ml] [10, 17, 31, 36]. In stable asthmatic adults the short-term variability in FEV₁, is similar to that in healthy subjects; the upper 95% CL of measurements repeated in 20 min was 190 ml [11, 12, 36]. In the present study, the proportion of children with a "positive" bronchodilator response differed according to the criteria applied (table 3). In our study the highest number of responders was found using ΔFEV₁ (%pred>9% [10] as a criterion, the lowest using ΔFEV₁ (%init >15% [27]. However, the distribution of BDR is unimodal [10], with large overlap between subjects with [14], and without asthma [10, 37]. Therefore, a reliable cut-off level designating "positive" BDR cannot be determined.

Both bronchial hyperresponsiveness and an increase in FEV₁ in response to bronchodilators are important characteristics of asthma [1, 28]. Therefore, it is tempting to regard the two phenomena as highly correlated, and several studies have used the response to bronchodilators as an indicator of BHR [15, 16]. We found only a weak association between the level of BHR and the bronchodilator response to salbutamol (table 2). Studies on the relationship between BHR and BDR have yielded
conflicting results; some found a correlation [38], others did not [18, 39]. There are some important differences in the mechanisms underlying both phenomena [38]. Numerous patients with irreversible airflow obstruction exhibit considerable bronchoconstrictor responses [40], while healthy subjects without BHR may reveal a marked BDR. The observation that the increase in FEV₁ after inhalation of anticholinergics and beta-agonists is usually comparable, whereas the protective effect of anticholinergics on a bronchoconstrictor response is less than is the case for beta-agonists [41], is further evidence for different pathophysiologica mechanisms. Finally, the bronchodilator effect persists longer than the protective effect against bronchoconstrictor stimuli [42]. Thus, there is both observational and pathophysiologica evidence against interchanging bronchial responsiveness to histamine and a bronchodilator response to salbutamol.

In summary, we conclude that in children with asthma, expressing the change in FEV₁ relative to the initial value has the drawback that assessing what is a clinically significant response becomes dependent on the initial value of FEV₁; overlooking this feature leads to erroneous conclusions about the degree of bronchodilator responsiveness. In children, the absolute change in FEV₁ related to stature and age, but this can be remedied by expressing the response to bronchodilator drugs as a percentage of the predicted FEV₁. On both accounts AFEV₁ %pred is recommended for use in children; a similar recommendation has been made for adults [14]. Furthermore, we conclude that the correlation between bronchodilator response and bronchial responsiveness to histamine is weak, and that a bronchodilator response should not be used as a measure of bronchial hyper-responsiveness.

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