Immediate bronchodilator response in FEV1 as a diagnostic criterion for adult asthma

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Not enough data exist to differentiate adult asthma patients from healthy subjects by ΔFEV1BDR
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ABSTRACT Asthma is characterised by variable and reversible expiratory airflow limitations. Thus, it is logical to use the change in forced expiratory volume in 1 s (FEV_1) in response to a bronchodilator (ΔFEV_1BDR) as a diagnostic tool; increases of ⩾12% and ⩾200 mL from the baseline FEV_1 are commonly used values. We aimed to evaluate the historical development of diagnostic cut-off levels for the ΔFEV_1BDR for adults and the evidence behind these recommendations.

We searched for studies from the reference lists of all the main statements, reports and guidelines concerning the interpretation of spirometry and diagnostics for asthma and conducted a literature search.

A limited amount of evidence regarding the ΔFEV_1BDR in healthy populations was found, and even fewer patient studies were found. In healthy persons, the upper 95th percentile for the absolute ΔFEV_1BDR ranges between 240 mL and 320 mL, the relative ΔFEV_1BDR calculated from the initial FEV_1 ranges from 5.9% to 13.3% and the ΔFEV_1BDR calculated from the predicted FEV_1 ranges from 8.7% to 11.6%. However, the absolute and percentage ΔFEV_1BDR values calculated from the initial FEV_1 are dependent on age, sex, height and the degree of airway obstruction. Thus, the use of the ΔFEV_1BDR calculated from the predicted FEV_1 might be more appropriate.

Not enough data exist to assess the sensitivity of any of the cut-off levels for the ΔFEV_1BDR to differentiate asthma patients from healthy subjects. Further studies in newly diagnosed asthma patients are needed.

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Introduction

Obstructive lung diseases are defined as conditions in which airflow in the airways is decreased. Airflow obstruction can be fixed, as in chronic obstructive pulmonary disease (COPD), or variable, as in asthma. The diagnosis of asthma has generally been based on a long-term history of typical symptoms. In addition, objective lung function measurements have been recommended [1, 2]. Significant reversibility of airway obstruction after inhalation of bronchodilator medication has been the main objective hallmark of asthma for decades [3–6]. The Global Initiative for Asthma (GINA) report prefers spirometry with a reversibility test as the first test if the patient's history or examination is suggestive of asthma [6].

An increase in forced expiratory volume in 1 s (FEV_1) after inhalation of 200–400 µg of salbutamol or the equivalent (ΔFEV_1BDR) is considered significant if it is ⩾12% and ⩾200 mL when compared with the initial FEV_1 [3, 5]. Hopp and Pasha [7] reviewed the paediatric literature regarding normal and abnormal improvements in FEV_1 after administration of a bronchodilator. They found only a limited number of studies; the majority of them supported that a 9–10% improvement in FEV_1 could be clinically relevant. In contrast to previous assumptions that asthma is a disease that begins during childhood, recent studies have shown that most new asthma patients are diagnosed as adults [8, 9]. Adult-onset asthma is less often atopic, and the role of disease-modifying factors, such as obesity, smoking, environmental exposures and comorbidities, is substantial [10–12].

Much of our knowledge on the nature and management of asthma is based on studies using a significant ΔFEV_1BDR as a diagnostic criterion for diagnosing patients with asthma. The evidence behind the use of a bronchodilator response (BDR) to diagnose asthma in adults has not been reviewed. Differential diagnostics between asthma and COPD (or asthma–COPD overlap) and the choice of appropriate reference values and how they are used (*e.g.* % predicted *versus* lower limit of normal) are not covered by this review. We evaluated the evidence behind the quantifiable improvement in FEV_1 after administration of short-acting bronchodilator as a significant change or as a diagnostic method in adult asthma.

Methods

Theoretical considerations for the use of the ΔFEV1BDR as a diagnostic tool in asthma

Asthma is defined as "a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" [6]. Thus, it is logical to use the ΔFEV_1BDR as a diagnostic tool. However, to determine the appropriate cut-off points, their specificity and sensitivity, and the clinical value of a BDR to diagnose asthma, we consider that data regarding the following facts are necessary. 1) Values of ΔFEV_1BDR >95th percentile in the healthy population are often considered abnormal. However, it is important to notice that this cut-off only separates "healthy" from "abnormal", *i.e.* it does not state that those with abnormal values have the specific disease of asthma rather than any other disease; 2) to obtain the sensitivity of the cut-off values for asthma diagnostics and to evaluate the overlap between healthy individuals and patients with asthma, the ΔFEV_1BDR should be studied in therapy-naïve patients with asthma diagnosed by the gold standard method. As there is no gold standard method to diagnose asthma, we considered a combination of history and symptoms, other lung function measurements and evaluation by an asthma specialist as the appropriate standard; 3) in adults, other significant lung diseases (*e.g.* COPD, bronchiectasis and fibrosis) may cause obstruction and/or reduction in volume or flow parameters. To obtain the specificity of the cut-off values for asthma, the ΔFEV_1BDR in other therapy-naïve relevant patient groups (as diagnosed by the gold standards specific to those diseases) should be studied. This allows evaluation of the specificity of a certain ΔFEV_1BDR for diagnosing asthma.

To determine how well the ΔFEV_1BDR has been characterised as a diagnostic tool for asthma, we searched the reference lists of all the main statements, reports and guidelines on the interpretation of spirometry and management of asthma. Most of them were published by the American Thoracic Society, European Respiratory Society, British Thoracic Society, National Heart, Lung, and Blood Institute and GINA (supplementary table S1). We conducted a literature search in PubMed (keywords: asthma, bronchodilator response, FEV_1). A common recommendation when assessing the ΔFEV_1BDR is to perform spirometry before and after inhaled administration of 200–400 µg of salbutamol or the equivalent [5, 6]. Thus, we concentrated on the evidence obtained by measuring responses to a short-acting β_2-agonist. However, when appropriate, spontaneous variability or placebo responses may be mentioned. There is no consensus on the most reliable way to calculate and express the ΔFEV_1BDR. The three most commonly used methods are 1) absolute volume change (mL or L); 2) ΔFEV_1 % of the initial FEV_1, and 3) ΔFEV_1 % of the predicted FEV_1, all after bronchodilator administration (table 1). Other ways to measure the ΔFEV_1BDR exist [19, 20], but as they are rarely used, they are not discussed in this review.

TABLE 1 Three most common methods to calculate the immediate forced expiratory volume in 1 s (FEV_1) in response to a bronchodilator discussed in the recommendations, reports and guidelines for asthma and spirometry measurements

	Unit	Calculation formula	Recommendation
Absolute volume change[#] (ΔFEV_1)	Litres (L) or millilitres (mL)	post-bronchodilator FEV_1 – initial FEV_1	ATS 1991 [3], ERS 1993 [4], ATS/ERS 2005 [5], GINA 2002–2007 [6], BTS/SIGN 2008–2016 [13], NICE 2017 [14]
ΔFEV_1 % of the initial FEV_1	Percentage (%)	(post-bronchodilator FEV_1-initial FEV_1)/ initial FEV_1 × 100	ACCP 1974 [15], Intermountain Thoracic Society 1984 [16], ATS 1991 [3], ATS/ERS 2005 [5], NHLBI 2007 [17], GINA 2002–2017 [6], BTS/SIGN 2008–2016 [13], NICE 2017 [14]
ΔFEV_1 % predicted[¶]	Percentage (%)	(post-bronchodilator FEV_1 – initial FEV_1)/ predicted FEV_1 × 100	ERS 1993 [4], NHLBI 2007 [17], GPIAG 2009 [18]

ATS: American Thoracic Society; ERS: European Respiratory Society; GINA: Global Initiative for Asthma; BTS: British Thoracic Society; SIGN: Scottish Intercollegiate Guidelines Network; NICE: National Institute for Health and Care Excellence; ACCP: American College of Chest Physicians; NHLBI: National Heart, Lung, and Blood Institute; GPIAG: General Practice Airways Group. [#]: absolute volume change is usually combined with the percentage change cut-off. Only in BTS/SIGN guidelines was a single cut-off value based on the absolute change used as a criterion. [¶]: can also be expressed as post-bronchodilator FEV_1% pred – pre-bronchodilator FEV_1% predicted.

Results

Description of the BDR and historically suggested cut-off values

The historical development of the description and cut-off values for the immediate FEV_1BDR in the recommendations, reports and guidelines on adult asthma or spirometry measurement are presented and briefly discussed in the supplementary material (table S1).

Determination of the upper normal limit of the ΔFEV_1BDR in healthy adults

The main population-based studies on the ΔFEV_1BDR are presented in supplementary table S2.

In larger (>200 persons) population-based samples of healthy subjects, the upper 95th percentiles of the absolute ΔFEV_1BDR range between 240 mL and 320 mL; the ΔFEV_1% of the initial FEV_1 range between 5.9% and 13.3%; and the ΔFEV_1% of the predicted FEV_1 range between 8.7% and 11.6% (table S2). However, the obtained absolute and ΔFEV_1% of the initial FEV_1 were dependent on sex, age, height and initial values, phenomena that were less significant with the ΔFEV_1% of the predicted FEV_1 [22–25].

Studies on the short-term variability in FEV_1

Patients with asthma have been proposed to have greater variability in FEV_1 and less variability in the forced vital capacity (FVC) response to a bronchodilator than those with asthma–COPD overlap or COPD [24].

If the ΔFEV_1BDR is considered a diagnostic marker, the response should be larger than natural short-term (*e.g.* 20 min) variability in the FEV_1 between two measurements or the response of FEV_1 to a placebo inhaler. In a study group of patients with heterogeneous airway obstructions (n=40) who were referred for pulmonary function evaluation, the FEV_1 response was first measured compared to a placebo and then to an active bronchodilator [26]. Following placebo inhalation, the upper 95% confidence limit of the absolute ΔFEV_1BDR was 178 mL and the ΔFEV_1% of the initial FEV_1 was 12.3%. After that, a larger group of similar patients (n=40+32) received a bronchodilator. Among this latter group of patients who received an active bronchodilator, 42% and 39% of the subjects reached the upper 95th percentile limits of placebo-induced ΔFEV_1% of the initial FEV_1 and absolute ΔFEV_1, respectively [26]. Another study evaluated patients with airway obstruction [27]. Patients were divided to three groups according to their initial FEV_1 levels: 0.5–1.0 L (n=72), 1.15–2.40 L (n=51) and 2.45–4.70 L (n=27) [26]. The natural short-term variability (two measurements within a 20-min interval) in FEV_1 did not differ between these groups. The upper limit of the 95% confidence interval of the absolute variability was 160 mL, and this was not related to sex, smoking status or age. Thereafter, patients with an increase ⩾160 mL in FEV_1BDR were classified as responders, the proportion of which increased significantly with an increasing initial FEV_1. Then, the ΔFEV_1% of the initial FEV_1 after bronchodilator administration was measured and two cut-off levels (10% and 15%) were used. When using the 10% criterion, the proportion of responders in all three groups with different degrees of initial FEV_1 was similar, and in many patients, the increase in FEV_1 was indistinguishable from natural variability. However, the criterion of 15% more often selected those with a low initial FEV_1 [27]. These two studies [26, 27] in patients with airway obstructions suggest that the ΔFEV_1BDR is generally larger than the natural variability or response to placebo, but the sensitivity of

these cut-off levels may be low, and if cut-off levels that are too low are used, the response may be indistinguishable from natural variability.

Sensitivity of the immediate BDR as a diagnostic marker in asthma

To evaluate the sensitivity of the obtained cut-off points for asthma diagnostics and to evaluate the overlap between healthy subjects and patients with asthma, the ΔFEV$_1$BDR should be studied in therapy-naïve patients without or with regular bronchodilator therapy and asthma diagnosed by the gold standard methodology. We were not able to find any such studies. Few small asthma studies with unclear diagnostic criteria and therapies (total n=289) were found and suggested that the mean values of the absolute ΔFEV$_1$BDR varied between 274 mL and 550 mL; the ΔFEV$_1$ calculated from the initial FEV$_1$ varied between 13.7% and 25.9%; and the ΔFEV$_1$ calculated from the predicted FEV$_1$ varied between 7.8% and 21.8% (table S3). In a very recently published study including patients with airway obstruction who were subsequently diagnosed with asthma (diagnostic criteria unknown), the results fall in to the ranges mentioned above [28].

In an Australian population-based cohort study (n=4002, age ⩾18 years), the prevalence of current doctor-diagnosed asthma was 9.4% (n=380) [29]. The prevalence of a positive ΔFEV$_1$BDR was assessed in four ways: the ΔFEV$_1$% of the initial FEV$_1$ was either ⩾12% or ⩾15%; the ΔFEV$_1$% of the predicted FEV$_1$ was ⩾9%; or the absolute ΔFEV$_1$BDR was ⩾400 mL. In current asthma patients (current asthma therapy not withdrawn) and not-current asthma patients, at least one of the criteria for a significant BDR was fulfilled in 6.7% and 1.3% of patients, respectively (ΔFEV$_1$BDR ⩾400 mL) and 17.9% and 4.5% of patients, respectively (ΔFEV$_1$% of predicted FEV$_1$ ⩾9.0%). This suggests that the sensitivities of these criteria are low, at least in patients currently on asthma therapy and that all of these criteria may misclassify patients. A ΔFEV$_1$ ⩾9% pred identified nearly all patients who were classified by the standard criteria (ΔFEV$_1$BDR ⩾12% or ⩾15% or ⩾400 mL). Furthermore, this study revealed that these four ΔFEV$_1$BDR criteria detect quite different subjects, which may have implications for clinical practice. For example, if the ΔFEV$_1$BDR ⩾400 mL was the only significant response, most subjects were young males aged <35 years. The standard criteria for the ΔFEV$_1$% of the initial FEV$_1$ ⩾12% or ⩾15% were biased towards detecting younger subjects. Thus, the authors suggest a need for age-specific cut-offs when using these criteria [29]. The use of the ΔFEV$_1$% of the predicted FEV$_1$ has been proposed to eliminate this age-related problem [4]. However, even the criterion of the ΔFEV$_1$% of the predicted FEV$_1$ ⩾9% missed 6% of patients identified as having a ΔFEV$_1$BDR ⩾400 mL [29].

Discussion

Asthma affects a vast number of adults. Most patients are diagnosed with asthma as adults [8, 9], remission is rare [30, 31] and the majority of patients are not well controlled [31]. Adult asthma is a lifelong burden; thus, the diagnosis should be made carefully and objectively [1], and if possible, before starting treatment to avoid a misdiagnosis [32]. The diagnosis of asthma has been based on the medical history, typical symptoms and reversibility of airway obstruction measured most often by the ΔFEV$_1$BDR. A cut-off value of 12% for the ΔFEV$_1$% of the initial FEV$_1$BDR has been used as a categorical diagnostic test. However, the current evaluation of guidelines and the evidence behind their recommendations indicates that even though there is some agreement regarding the upper 95th percentile of the ΔFEV$_1$BDR in healthy persons, the current method of expressing the ΔFEV$_1$BDR (absolute and percentage calculated from the initial FEV$_1$) may not be optimal. Furthermore, there is a lack of data to assess the sensitivity and specificity of any of the ΔFEV$_1$BDR cut-off points used in the diagnosis of asthma, and the amount of overlap in the ΔFEV$_1$BDR between patients with asthma and healthy subjects or those with other lung diseases is not known.

The latest British asthma guidelines state that there is no definitive evidence on the most appropriate choice of algorithm for making a diagnosis of asthma in clinical settings [13]. However, the traditional cut-off of ΔFEV$_1$% of the initial FEV$_1$ ⩾12% with volume increase of ⩾200 mL has been used since 1991 [3] and is still regarded as strongly suggestive of asthma, although some COPD patients meet the same criterion [13]. In the recent National Institute for Health and Care Excellence document, the same thresholds for a positive ΔFEV$_1$BDR test are recommended, even though they are not diagnostic for asthma alone [14]. In the current GINA report, many methods to confirm variable expiratory airflow limitations are mentioned, one of which is a ΔFEV$_1$BDR of >12% and >200 mL from the initial level (greater confidence if the ΔFEV$_1$ is >15% and >400 mL) [6].

In five population-based studies, where the possibility of obstructive disease was ruled out (nonsmokers and no questionnaire-based asthma or other lung disease) [21–25], the mean and median ΔFEV$_1$% of the initial FEV$_1$BDR were between 1.8% and 3.4%. The upper 95th percentiles for the absolute ΔFEV$_1$BDR varied between 240 mL and 320 mL, and the ΔFEV$_1$% of the initial FEV$_1$ varied between 5.9% and 13.3%.

In four of these studies, the upper 95th percentiles for the ΔFEV1% of the predicted FEV1 were calculated, and the variation between the reported values was smaller, ranging between 8.7% and 11.6% [21, 22, 24, 25]. Recently, Quanjer *et al.* [24] proposed that this problem (ΔFEV1% of the initial FEV1 being dependent on age and sex) might be avoided by using the change in the z-score for the FEV1 for evaluating a BDR. However, the data obtained from healthy persons (cut-off points described earlier) differentiate between a normal and abnormal ΔFEV1BDR, but not necessarily between healthy subjects and those with a specific disease (*e.g.* asthma) or between subjects with different diseases.

There is still lack of consensus regarding how to express and measure the ΔFEV1BDR. Different methods of measuring the ΔFEV1BDR may identify different kinds of patients [29]. Until now, the most commonly used method was the absolute volume of the ΔFEV1BDR and the ΔFEV1% of the initial FEV1. However, studies from the late 1960s to the 1990s show that the ΔFEV1% of the initial FEV1 can be biased [19, 21, 33, 34]. One of the first reports of standardisation of lung function testing [4] showed that a more reliable estimate of the ΔFEV1BDR can be obtained when the improvement in the FEV1 and/or FVC is both >12% predicted and >200 mL. In addition, there are some preliminary data to suggest that this approach may allow better discrimination between patients with asthma and COPD, even though the patient populations are not well characterised [34, 35]. Recent large population-based studies have also supported the use of the ΔFEV1% pred [22, 24, 25, 36] or the change in the z-score, the latter also eliminating the effect of age [24]. In addition, a FVCBDR may be more relevant than a FEV1BDR, especially in older subjects if they have severe airway obstruction [24].

For a practising clinician, it is important to know the sensitivity and specificity of the diagnostic test in use. To obtain the sensitivity of the recommended ΔFEV1BDR cut-off points for asthma diagnostics and to evaluate the overlap between healthy subjects and patients with asthma, the ΔFEV1BDR should be studied in therapy-naïve patients with asthma diagnosed by the gold standard methodology or, if such a method does not exist, by other relevant methods. However, the guidelines on the role of the ΔFEV1BDR for diagnosing asthma are not based on studies of therapy-naïve newly diagnosed adult patients with asthma to assess the sensitivity of this test for diagnosing asthma. If asthma patients were included in these studies, there was lack of information regarding the age of asthma onset, duration of the disease, atopic status or previous anti-inflammatory medication treatment [19, 28, 33, 34, 37, 38]. Thus, the sensitivity of the ΔFEV1BDR as a diagnostic tool for asthma remains unknown. The ΔFEV1BDR may not be a very sensitive tool for the confirmation of current asthma, as 82% of patients with current asthma (lacking detailed information) did not demonstrate a significant ΔFEV1BDR, even though 29% of them had moderate-to-severe respiratory symptoms [29]. Thus, the ΔFEV1BDR is an imperfect tool for screening for asthma among the general population. A Danish study [39] involving mainly atopic young adults whose inhaled corticosteroids were not withdrawn suggested that the sensitivity of the ΔFEV1BDR (>12% and >200 mL) as a diagnostic marker may not be very high (13% positive). Instead, the specificity (93%) appeared to be high for the diagnosis of asthma *versus* no asthma. The authors propose that different diagnostic methods including peak flow follow-up and provocation tests should be combined to diagnose asthma objectively and reliably [39]. However, the use of a combination of diagnostic tests does not reduce the need for knowledge on the accuracy, sensitivity and specificity of the cut-off-points. In future studies, it will be crucial to elucidate how the diagnosis is made and whether the patients are treatment-naïve or not. Currently, many confounding basic factors and missing data make it difficult to compare and interpret the results of the ΔFEV1BDR studies performed so far for application in clinical practice.

Taken together, we conclude that in population-based studies in healthy persons, the upper 95th percentile of the absolute ΔFEV1BDR varied between 240 mL and 320 mL, and that of the ΔFEV1% of the initial FEV1 varied between 5.9% and 13.3%. In four population-based studies, the ΔFEV1% of the predicted FEV1 was measured, and the results varied less, from 8.7% to 11.6%. Several studies prefer expressing a BDR as the ΔFEV1% of the predicted FEV1 or the change in the z-score to overcome the influence of age, sex, height and level of obstruction on the appropriate cut-off value. There are no relevant published data to assess the sensitivity or specificity of any cut-off level of the ΔFEV1BDR for diagnosing asthma or for the differential diagnosis of other lung diseases. Further studies involving treatment-naïve patients with a new asthma diagnosis or suspicion of asthma are needed to assess the actual properties of BDRs as asthma diagnostics and for differentiating between obstructive pulmonary diseases and their phenotypes.

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