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IMMEDIATE BRONCHODILATOR RESPONSE IN FEV_1 AS A DIAGNOSTIC CRITERION FOR ADULT ASTHMA

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Take home message: Not enough data exist to differentiate adult asthma patients from healthy subjects by ΔFEV_1BDR.

Abstract

BACKGROUND: Asthma is characterized by variable and reversible expiratory airflow limitations. Thus, it is logical to use the change in 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.

AIM: To evaluate the historical development of diagnostic cut-off levels for the ΔFEV_1BDR for adults and the evidence behind these recommendations.

METHODS: 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.

RESULTS: 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 and 320 mL, for the relative ΔFEV_1BDR calculated from the initial FEV_1 ranges from 5.9-13.3%, and for the ΔFEV_1BDR calculated from the predicted FEV_1 ranges from 8.7-11.6%. 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.

CONCLUSIONS: 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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Keywords: Asthma, adult, adult-onset, FEV_1, bronchodilator response, bronchodilators, diagnostic, salbutamol, COPD

Abbreviations:

ATS	American Thoracic Society
BDR	Bronchodilator response
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
$\Delta FEV_1 BDR$	Change in forced expiratory volume in 1 second as a response to a bronchodilator
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid
NHLBI	National Heart, Lung and Blood Institute
NICE	National Institute for Health and Care Excellence

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Introduction

Obstructive lung diseases are defined as conditions in which the 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 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 coworkers [7] have recently 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 also 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 short-acting bronchodilator administration as a significant change or as a diagnostic method in adult asthma.

Methods

Theoretical considerations for the use of the ΔFEV_1BDR as a diagnostic tool in asthma.

Asthma is defined as "*a heterogeneous disease, usually characterized 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. **What is normal?** Values of ΔFEV_1BDR higher than the 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. **What is the sensitivity**? 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. **What is the specificity**? 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 characterized 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 American Thoracic Society (ATS), European Respiratory Society (ERS), British Thoracic Society (BTS), National Heart, Lung and Blood Institute (NHLBI) and GINA (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 [13,14], but as they are rarely used, they were not discussed in this review.

Table 1. Three most common methods to calculate the immediate FEV_1 BDR discussed in the recommendations, reports and guidelines for asthma and spirometry measurements

	Unit	Calculation formula	Recommended in the following documents
Absolute volume change (ΔFEV_1)	litres (L) or millilitres (mL)	$postbd\ FEV1 - initial\ FEV1$	ATS 1991 [3], ERS 1993 [4], ATS/ERS 2005 [5], GINA 2002-2017 [6], BTS/SIGN 2008-2016 [15], NICE 2015 [16]*
ΔFEV_1 % of the initial FEV_1	Percentage (%)	$\frac{postbd\ FEV1 - initial\ FEV1}{initial\ FEV1} * 100$	ACCP 1974 [17], Intermountain Thoracic Society 1984 [18], ATS 1991 [3], ATS/ERS 2005 [5], NHLBI 2007 [19], GINA 2002-2017 [6], BTS/SIGN 2008-2016 [15]
ΔFEV_1 % of the predicted FEV_1**	Percentage (%)	$\frac{postbd\ FEV1 - initial\ FEV1}{predicted\ FEV1} * 100$	ERS 1993 [4], NHLBI 2007 [19], GPIAG 2009 [20]

postbd = post-bronchodilator, FEV_1= forced expiratory volume in 1 second
ATS=American Thoracic Society, ACCP=American College of Chest Physicians, ERS=European Respiratory Society, GINA=Global Initiative for Asthma, BTS/SIGN= British Thoracic Society/Scottish Intercollegiate Guidelines Network, NICE=National Institute for Health and Care Excellence, GPIAG=General Practice Airways Group
*The 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 the percent predicted FEV_1 after bronchodilator administration minus the percent predicted FEV_1 before bronchodilator administration

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_1 BDR in the recommendations, reports and guidelines on adult asthma or spirometry measurement are presented and briefly discussed in the online supplement (Table S1).

Determination of the upper normal limit of the ΔFEV_1BDR in healthy adults (Table S2)

The main population-based studies on the ΔFEV_1BDR are presented in online 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 and 320 mL, of the ΔFEV_1% of the *initial* FEV_1 range between 5.9% and 13.3%, and of 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 which were less significant with the ΔFEV_1% of the *predicted* FEV_1 [21,22,24,25].

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 FVC BDR than those with asthma-COPD overlap or COPD [24].

If the ΔFEV_1 in response to bronchodilator administration 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 heterogenous airway obstructions (n=40) who were referred for pulmonary function evaluations, 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 by 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_1 after bronchodilator administration 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_1BDR 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_1BDR varied between 274 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 varies 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=4,002, age ≥18 years), the prevalence of current doctor-diagnosed asthma was 9.4% (n=380) [29]. The prevalence of a positive ΔFEV_1BDR 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_1BDR 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 1.4% of

patients, respectively, ($\Delta FEV_1BDR \geq 400$ mL) and to 17.9% and 4.5% of patients, respectively ($\Delta FEV_1\%$ of *predicted* $FEV_1 \geq 9.0\%$). 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 $\Delta FEV_1 \geq 9\%$ of the *predicted* value identified nearly all patients who were classified by the standard criteria ($\Delta FEV_1BDR \geq 12\%$ or $\geq 15\%$ or ≥ 400 mL). Furthermore, this study revealed that these four ΔFEV_1BDR criteria detect quite different subjects, which may have implications for clinical practice. For example, if the $\Delta FEV_1BDR \geq 400$ mL was the only significant response, most subjects were young males aged <35 years. The standard criteria for the $\Delta FEV_1\%$ of the *initial* $FEV_1 \geq 12\%$ or $\geq 15\%$ 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 $\Delta FEV_1\%$ of the *predicted* FEV_1 has been proposed to eliminate this age-related problem [4]. However, even the criterion of the $\Delta FEV_1\%$ of the *predicted* $FEV_1 \geq 9\%$ missed 6% of patients identified as having a $\Delta FEV_1BDR \geq 400$ 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 life-long 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_1BDR. A cut-off value of 12% for the $\Delta FEV_1\%$ of the *initial* FEV_1 after bronchodilator administration 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_1BDR in healthy persons, the current method of expressing the ΔFEV_1BDR (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_1BDR cut-off points used in the diagnosis of asthma, and the amount of overlap in the ΔFEV_1BDR 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 [15]. However, the traditional cut-off of $\Delta FEV_1\%$ 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 [15]. In the recent NICE document, the same thresholds for a positive ΔFEV_1BDR test are recommended, even though they are not diagnostic for asthma alone [16]. In the current GINA report, many methods to confirm variable expiratory airflow limitations are mentioned, one of which is a ΔFEV_1BDR of >12% and >200 mL from the initial level (greater confidence if the ΔFEV_1 >15% and >400 mL) [6].

In five population-based studies, where the possibility of obstructive disease was ruled out (non-smokers and no questionnaire-based asthma or other lung disease) [21-25], the mean and median $\Delta FEV_1\%$ of the *initial* FEV_1 after bronchodilator administration were between 1.8% and 3.4%. The upper 95th percentiles for the absolute ΔFEV_1BDR varied between 240 and 320 ml, and the $\Delta FEV_1\%$ of the *initial* FEV_1 varied between 5.9% and 13.3%. In four of these studies, the upper 95th percentiles for the $\Delta FEV_1\%$ of the *predicted* FEV_1 were calculated, and the variation between the reported values was smaller, ranging between 8.7% and 11.6% [21,22,24,25]. Recently, Quanjer and coworkers [24] proposed that this problem ($\Delta FEV_1\%$ of the *initial* FEV_1 being dependent on age and sex) might be avoided by using the change in the *z* score for the FEV_1 for evaluating a BDR. However, the data obtained from healthy persons (cut-off points described above) differentiate between a normal and abnormal ΔFEV_1BDR 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 ΔFEV_1BDR. Different methods of measuring the ΔFEV_1BDR may identify different kinds of patients [29]. Until now, the most commonly used method was the absolute volume of the ΔFEV_1BDR and the $\Delta FEV_1\%$ of the *initial* FEV_1. However, studies from the late 1960s to 1990s show that the $\Delta FEV_1\%$ of the *initial* FEV_1 can be biased [13,21,33,34]. One of the first reports of standardization of lung function testing [4] showed that a more reliable estimate of the ΔFEV_1BDR can be obtained when the improvement in the FEV_1 and/or FVC is both larger than 12% calculated from the *predicted* value and exceeds 200 mL. There are also 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 characterized [34,35]. Recent large population-based studies have also supported the use of the $\Delta FEV_1\%$ of the *predicted* FEV_1 [22,24,25,36] or the change in the z score, the latter also eliminating

the effect of age [24]. In addition, a BDR in the FVC may be more relevant than a BDR in the FEV_1, 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 ΔFEV_1BDR cut-off points for asthma diagnostics and to evaluate the overlap between healthy subjects and patients with asthma, the ΔFEV_1BDR 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 ΔFEV_1BDR 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 [13,28,33,34,37,38]. Thus, the sensitivity of the ΔFEV_1BDR as a diagnostic tool for asthma remains unknown. The ΔFEV_1BDR 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 ΔFEV_1BDR even though 29% of them had at least mild-to moderate symptoms [29]. Thus, the ΔFEV_1BDR is an imperfect tool for screening for asthma among the general population. A recent real-life Danish study [39] involving mainly atopic young adults whose ICSs were not withdrawn suggested that the sensitivity of the ΔFEV_1BDR (>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 objectively and reliably diagnose asthma [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 ΔFEV_1BDR 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 ΔFEV_1BDR varied between 240 and 320 mL and that of the ΔFEV_1% of the *initial* FEV_1 varied between 5.9% and 13.3%. In four population-based studies, the ΔFEV_1% of the *predicted* FEV_1 was measured, and the results varied less, from 8.7% to 11.6%. Several studies prefer expressing a BDR as the ΔFEV_1% of

the *predicted* FEV_1 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 ΔFEV_1BDR 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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