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Bronchodilator responsiveness: interpret with caution

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Bronchodilator responsiveness (BDR) is widely considered to be a key diagnostic criterion for asthma, and is used to differentiate asthma from chronic obstructive pulmonary disease (COPD). Currently, the threshold of a 12% increase in FEV₁ from baseline following inhaled salbutamol, with at least a 200 ml increase in absolute terms, is recommended as a response indicative of asthma,¹ although recent British guidelines recognise the poor discriminatory function of this criterion.² Thus, despite this criterion being commonly used in clinical practice, there is uncertainty regarding its clinical utility, in particular its ability to differentiate asthma from COPD, or indeed, normal subjects.

One approach to enable a better understanding of the clinical utility of BDR is to determine the worldwide distribution of

BDR in health and disease, which has been undertaken by Tan and colleagues, and reported in *Thorax*.³ The authors report BDR in terms of change in FEV₁ and FVC following 200 µg of salbutamol delivered by metered dose inhaler via a spacer, in around 10 000 adults aged 40 years and older from 14 countries in North America, Europe, Asia and Africa who participated in the Burden of Obstructive Lung Disease study. The Burden of Obstructive Lung Disease methodology is robust and has many strengths, not the least of which is its multi-national nature and the central review of all spirometry, which increases confidence in the reliability of the lung function values obtained. The results of this study are, therefore, likely to be unbiased, and precise estimates of the populations described. The authors report that the most reliable metric of BDR was the change in FEV₁ relative to predicted FEV₁ (Δ FEV₁p). In healthy non-smokers, the threshold or upper limit of normality for Δ FEV₁p was 10% without heterogeneity across populations. The authors also report the more commonly used measure of change in FEV₁ from baseline, and give a threshold of 12%.

The values reported are consistent with the current ATS/ERS Task Force cut-offs for defining a clinically significant bronchodilator response.⁴ The authors propose that this strengthens the applicability of this measure for global interpretation of bronchodilator testing on the basis that values above this cut-off are beyond 95% of the distribution of healthy individuals and, as such, can be considered 'abnormal,' thus reflecting the presence of disease.

Although it is also proposed that such a cut-off discriminates healthy subjects from obstructed individuals, this unfortunately is not the case. Further analysis of their data indicates that BDR discriminates poorly between healthy subjects and individuals with airflow obstruction regardless of comorbid asthma (FEV₁/FVC <0.7, FEV₁ % predicted <80%). The authors found that BDR was consistent with a Gaussian (normal) distribution. The mean (SD) values for BDR expressed as Δ FEV₁p in healthy individuals was 2.6% (4.8) and 4.2% (5.7) in obstructed individuals. The Gaussian distribution gives the proportion of those above the cut-off of 10% as 6.1% (healthy), and 15.4% (obstructed). For healthy versus obstructed, the sensitivity was 15.4%, specificity 93.9%, likelihood ratio test positive 2.5, and test negative 0.9. These values, particularly for likelihood ratio negative, are not consistent with a good discriminatory test. Values for likelihood ratio positive and negative that are considered to represent clinically relevant changes in post-test probabilities of disease are 5 and 0.2, respectively.

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Likewise, in individuals with obstruction, the proposed cut-off levels discriminate poorly between self-reported asthma and COPD. When BDR was expressed as change in FEV₁ from baseline, the mean (SD) value was 7.7% (11.0) in COPD and, by calculation, 11.9% (14.1) in self-reported asthma. The Gaussian distribution gives the proportion of those above the cut-off of 12%, the value recommended for use in clinical practice to diagnose asthma,¹ as 34.8% in COPD and 49.7% in self-reported asthma. This is consistent with studies which have shown that there is a large overlap of individual BDR in patient subgroups of asthma and COPD, despite significant differences in mean response.^{5–7} Among those with airflow obstruction, and considering self-reported asthma versus COPD, using a 12% change from baseline as the cut-off value, the sensitivity for asthma was 49.7%, specificity 65.2%, likelihood ratio test positive 1.4, and test negative 0.8. Selection of other cut-off levels is unlikely to improve performance because of the considerable overlap in the levels of BDR between COPD and asthma. However, it would be possible for the authors to construct ROC curves to determine the sensitivity and specificity of different cut-off values to address this question.

Another desirable characteristic for diagnostic tests is repeatability when measured over time. From the Lung Health Survey, it was reported that there is substantial annual variability of BDR.⁸ Similarly, large within-subject variability of BDR was observed in the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study in which about 50% of patients with moderate to severe COPD changed responder status between study visits.⁹ Therefore, BDR is a poorly repeatable characteristic of individual patients with airways obstruction.

BDR has also been widely used to assess potential treatment response. However, the lack of an acute BDR does not preclude subsequent benefit from maintenance inhaled long-acting bronchodilator therapy.¹⁰

These findings have implications not only for diagnosis but also in the generalisability of randomised controlled trials (RCTs) on which both guidelines and clinical practice are based. The understandable desire to have objective criteria governing the selection of trial participants leads to the unintended consequence that the results of such trials have limited generalisability to the majority of patients with airways disease. Most asthma RCTs require subjects to have BDR of at least 15% increase in FEV₁ from baseline, and COPD RCTs require subjects to have <10% increase in FEV₁. In a random population, these criteria alone result in around 76% of adults with asthma and 29% of adults with COPD being ineligible for the major RCTs on which their management has been based.^{11 12}

In conclusion, there is considerable overlap in BDR in health and disease, and between asthma and COPD. It has recently been argued that 'spirometry is an essential tool in patient evaluation, but dangerous for disease diagnosis, and the term, COPD, should only be used in the appropriate clinical (diagnostic) context'.¹³ Similarly, we would propose that BDR testing is interpreted with caution, and that it is considered in its clinical context because a large proportion of patients with asthma and COPD will have values within the healthy range.

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