

EDITORIAL

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Do we need more than one bronchial provocation test in order to diagnose asthma?

This editorial discusses the findings of the paper in this issue by E. Gade et al. [5] pp. 966–71.

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It is widely accepted that physicians need objective measurements on which to base their diagnosis of asthma and bronchial provocation tests are very useful in this respect [1–3]. These tests can be subdivided into direct and indirect [4]. The direct tests involve the administration of a provocative stimulus that causes airflow limitation predominately via a direct stimulatory effect on receptors present in airway smooth muscle. They include histamine and methacholine challenges. Indirect tests are thought to induce airway limitation by acting on cells other than smooth muscle cells, which upon stimulation, release mediators capable of inducing airway limitation. They include challenges with exercise, hyperpnoea, non-isotonic aerosols, and adenosine [4]. All these tests can be performed utilizing different protocols. There are thus numerous possible ways to perform a bronchial provocation test, which may confuse the clinician.

In the present issue of *Clinical and Experimental Allergy*, Gade and et al. [5] investigated how a direct and an indirect bronchial provocation test can affect each others' responses when the tests are performed on the same day, just one hour apart. They used methacholine challenge as the direct test with mannitol challenge as the indirect test, the latter test being one of the non-isotonic aerosol challenges. When the methacholine challenge was performed first, the response to the subsequent mannitol challenge was attenuated, in comparison with the situation where the response to mannitol was examined without any preceding challenge. On the contrary, the response to methacholine challenge was unaffected by a preceding mannitol challenge. This finding was somewhat surprising since refractoriness is a feature that is usually associated with indirect challenges. Therefore, this study is important and may even call into question the theory

about the division of bronchial provocation tests to direct and indirect. The authors concluded that these two bronchial provocation tests can be performed on the same day but that mannitol challenge should be performed before the methacholine challenge. However, from the clinical point of view, the question must be asked do we actually need more than one bronchial provocation test to diagnose asthma? Given the vast array of different ways to perform these tests this may further confuse the clinician.

Performing both a direct and an indirect test is often rationalized by their assumed different diagnostic profiles. Direct tests are considered suitable for excluding asthma, thanks to their high sensitivity and subsequent high negative predictive value. Indirect tests, in turn, are thought to be highly specific for asthma, and therefore suitable for confirming the diagnosis of asthma. This rationale was also used by Gade et al. [5]. However, these assumptions may not be correct and probably are based on the erroneous way to interpret bronchial responsiveness as a dichotomous, on–off phenomenon. This interpretation is especially problematic in direct bronchial challenges but also in indirect challenges [6].

Bronchial responsiveness to direct challenges is continuously and unimodally distributed within the population [7]. Asthmatic subjects tend to be located at the more hyperresponsive end of the spectrum while healthy subjects usually show mild or absent responsiveness. There is a considerable overlap in responsiveness between the groups and patients with various respiratory and cardiac disorders often lie within this overlapping zone [8]. Therefore, defining just one cut-off value for a positive response means that much information is lost. In most indirect challenges, healthy subjects are non-responsive even to maximal obtainable stimulus (e.g. exercise challenge) and therefore, the use of a single cut-off value is better rationalised. However, the indirect challenges also benefit from the continuous approach of the response [6].

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In direct challenges, the cut-off value for a positive response is usually set to produce a very high sensitivity to diagnose asthma. For example, if one utilizes the popular tidal breathing method, virtually all symptomatic asthmatic patients will respond to a histamine concentration of less than 8 mg/mL [9]. This very high sensitivity is achieved at the cost of low specificity because mild bronchial hyperresponsiveness is also present in many other disorders in addition to asthma, even in healthy subjects. However, if the cut-off value is lowered to 1 mg/mL, the specificity approaches 100%, close to that claimed by many indirect challenges. Naturally, this increase in specificity is achieved at the cost of sensitivity which then declines to less than 50%, a value comparable to the sensitivity of many indirect challenges when unselected asthmatic populations are investigated [6, 10–12]. Thus, by using flexible cut-off values for the positive response to a direct challenge it can be adjusted to act like an indirect challenge and therefore, it would seem that we do not need two different challenges in order to diagnose asthma.

There have not been many direct head-to-head comparisons conducted between direct and indirect challenges in populations similar to those clinicians encounter in their daily practice. In Finland, cold air, mannitol, and a dosimetric histamine challenge were performed in 37 steroid-naïve, recently diagnosed asthmatic patients with mild or atypical symptoms [11]. Because bronchial provocation tests are mainly used to confirm or exclude asthma in a situation where there is a high degree of uncertainty [3], this population is especially suitable for comparison of provocation tests. The sensitivity values were 24% for the cold air challenge, 51% for the mannitol challenge, and 81% for the histamine challenge when a cut-off value of 1.0 mg for PD₁₅ was used. However, if the cut-off value for the histamine challenge was reduced to 0.4 mg (a value that gives 100% specificity for this histamine challenge method [13]), the sensitivity decreased to 49% and the histamine and the mannitol challenges identified almost the same asthmatics. A recent large comparison between mannitol and methacholine challenge also pointed to an equivalent diagnostic accuracy in adult subjects [12]. However, in the children included in that study, the mannitol challenge showed better diagnostic accuracy than the methacholine challenge. Previous studies have also provided evidence for a superior diagnostic accuracy of indirect over direct challenges among children [14, 15].

Performing several diagnostic tests in a single patient also carries a statistical problem. Let us imagine that we perform 10 different asthma diagnostic tests on a completely healthy individual. Very possibly one of these tests would prove to be positive, by accident. Should we then regard this person as an asthmatic? The answer is naturally no since the absence of symptoms indicates the very low pre-test probability and the nine negative test results clearly overrule the one positive result. However, in

practice, clinicians often tend to overemphasize positive test results over the negative results. According to Bayes' theorem [16] the post-test probability after the first test is used to estimate the pre-test probability for the second test. In other words, if the first test is negative, the second test should be very clearly positive to be considered as a proof for asthma. Application of Bayes' theorem for a sequence of diagnostic tests presumes that the sensitivity and the specificity of every test is independent of the results of the other tests. This is usually not true, especially in case of bronchial provocation tests that measure more or less the same physiological mechanism of asthma. This further complicates the interpretation of the multiple test results and therefore, the clinician should be critical of recommendations for sequences of tests [16].

In conclusion, at present there is no need to perform more than one bronchial provocation test on a single patient if one wishes to diagnose asthma, and due to the statistical problems in the interpretation of a sequence of tests, this can even be misleading. One test is enough, and it should be carried out utilizing the highest possible quality control, with a full understanding about the continuous nature of bronchial responsiveness: the more severe the responsiveness, the greater the probability that asthma is present, and vice versa. The choice of the test can probably be made on the basis of feasibility in adult patients whereas in paediatric patients, indirect challenges may perform better than direct challenges.

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