

EDITORIAL

Clinical & Experimental Allergy

Utility of inhaled allergen challenge in clinical diagnosis and management of asthma: What never? Well, hardly ever!

This editorial discusses the findings in the paper by Fernández et al [7] pp. 649–656.

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Controlled inhalation challenge of sensitized asthmatic subjects with allergen extract can lead to rapid airway narrowing within minutes, termed the early asthmatic response (EAR), which in around 50% will be followed by a late asthmatic response (LAR) at 3–8 h together with an increase in non-specific airway hyperresponsiveness (AHR) to agents such as methacholine or histamine. The first description of allergen challenge in asthma was by Charles Blackley in 1873 [1], while the LAR was described by Herxheimer in the 1950s [2] and associated increases in AHR was described by the Hamilton group [3]. Allergen challenge has proved to be an invaluable tool for research in mechanisms of asthma both in human volunteers and in animal models, and is widely used for assessment of new therapeutic agents [4]. In a review in 1975, Pepys suggested that allergen challenge was useful to confirm both diagnosis of asthma and sensitization to the test agent, although he commented that the EAR correlated closely with clinical history and skin prick (not intradermal) test (SPT) results [5]. Now that we have well-characterized allergen extracts for SPT, and can measure specific IgE to allergen extracts and component major allergens, does it still have any clinical utility and if so when might it be useful?

A report of the EAACI subcommittee on bronchial provocation tests (BPT) with allergens in 1997 stated that 'BPT continues to be used in the aetiological diagnosis of asthma because skin tests and *in vitro* tests may not always reflect the allergic situation at the bronchial level'

[6]. However the report also stated that indications for BPT in diagnosis in asthma were not clear. Possible uses of BPT in clinical management of asthma might be as follows:

1. If there remains doubt about the relevance of an allergen to asthma symptoms after careful history, assessment of allergen sensitization, and lung function tests.
2. Where allergen specific intervention is considered: allergen avoidance or immunotherapy.
3. Confirmation of the relevance of occupational exposure to asthma symptoms.

Does BPT with allergen add anything to diagnosis? In this issue of Clinical and Experimental Allergy, Fernandez et al. [7] report on a retrospective study of 74 asthmatic patients who underwent BPT to *Alternaria alternata* in their hospital. They show that allergen sensitization as detected by positive SPT (> 5.5 mm weal diameter) and specific IgE of > 16 kU_A/L predicted a positive BPT with up to 99% accuracy. Interestingly, even though the asthmatics studied were selected on the basis of sensitization to *A. alternata*, for 26 this was on the basis of a positive intradermal test with negative SPT. Of these 26, only one had a positive BPT to *A. alternata*, suggesting that intradermal tests were not helpful in diagnosis. The findings are in agreement with their own results for cat allergen [8] showing that using a cut-off value for specific IgE can predict accurately the likelihood of a positive BPT to allergen (at least by EAR), although in that study they found intradermal testing more predictive than SPT. This is analogous to described cut-offs for predicting clinically relevant food sensitization for example to peanut and milk allergens [9, 10]. In the case of asthma, it has been suggested that bronchial sensitivity (dose of allergen producing a positive BPT) is not closely related to skin, conjunctival or nasal reactivity [11], but is more closely linked to non-specific AHR. Indeed Cockcroft et al. [12] produced a formula for predicting bronchial reactivity

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based on specific IgE and AHR measured by histamine or methacholine. It seems reasonable to assume that almost all asthmatics with non-specific AHR will have a positive BPT to an allergen if they are sensitized above a certain threshold (as measured by SPT or serum-specific IgE).

Although guidelines are published for performing inhaled allergen challenge in asthmatics, the procedure is laborious and expensive, requires expertise and is subject to variation in allergen extracts, few of which are licensed for clinical use [6]. False-positive BPT are reported for people, with rhinitis and atopic dermatitis, although others suggest that this problem can be avoided by dose selection [6]. Most reports of use of BPT for diagnosis concentrate on the EAR; although, the LAR and associated increase in AHR relate more to severity of asthma [6, 13] and may respond more to interventions such as immunotherapy [6, 14]. These are more time consuming to measure, and many centres (as described by Fernandez and colleagues) give oral or inhaled corticosteroids after the EAR to prevent LAR and increased AHR. How well does BPT predict clinical symptoms of asthma on allergen exposure? There are few studies correlating BPT with natural exposure. Arvidsson et al. [15] studied 62 patients with symptoms of asthma on cat exposure, positive SPT and specific IgE to cat with both BPT and environmental exposure. All 62 had a positive BPT by EAR, and 37 during environmental challenge, while for LAR the corresponding figures were 29 and 21 with 65% consistency for the LAR. How accurately the EAR predicts clinical symptoms in patients without a clear history or with multiple allergen sensitization is not known. The significance of a positive BPT may vary from allergen to allergen and it is important to bear in mind that allergen extracts used in challenge studies are not the form of allergen seen 'in the wild'. In a study of ragweed allergic subjects, inhaled challenge with whole pollen grains did not produce EAR in any of the subjects whereas pollen fragments produced an EAR in six of seven subjects tested [16]. The relation between pollen and *A. alternata*-induced asthma and climatic conditions, which fragment pollen grains and mould spores is well documented in 'thunderstorm asthma' [17].

In their article Fernandez et al. [7] comment on the safety of BPT using allergen. They state that in their unit allergen challenges have been performed for over 20 years without safety concerns. This may be so in large centres with considerable experience using standardized well-characterized extracts. However, the procedure still carries some risk, particularly of exacerbating asthma if insufficient attention is paid to patient selection, the LAR and increased AHR. If used it should be restricted to experienced specialist centres following agreed guidelines [6].

In addition to accurate measurement of specific IgE in serum, assays are now available to measure IgE to specific allergen molecules such as Der p 1, in what has been termed component resolved diagnosis (CRD) [18]. This is an emerging field, but early indications are that sensitization to certain components may predict clinical patterns of disease. For example, sensitization to the major olive pollen allergen, Ole e 1, is associated with seasonal rhinitis, whereas sensitization to Ole e 10 is associated with asthma [19]. Thus CRD may give clinically relevant information and may further reduce the need for *in vivo* testing such as BPT. Recombinant or purified allergens have been used in a research context, but are not yet routinely available for allergen challenge, nor is it yet feasible to measure the exact allergen composition of allergen extracts used in BPT.

Is allergen challenge BPT helpful in selecting which allergens should be given by immunotherapy or recommended for allergen avoidance? Given the data from Fernandez and colleagues, it seems that most decisions can be based on clinical history and IgE sensitisation (by SPT or serum IgE to whole allergen extracts or components) and that very rarely will BPT add useful information. This is particularly so if immunotherapy is restricted to a few allergens as currently recommended [20].

An area where BPT has been used in diagnosis is to confirm clinical suspicion of the role of occupational exposure in asthma symptoms. However here too, evidence suggests that history and detection of specific IgE is often sufficient. For example in baker's asthma, a study of 107 bakers with work-related symptoms of rhinitis and/or asthma, serum specific IgE cut-offs of 2.32 kU/L for wheat flour and 9.64 kU/L for rye flour gave 100% positive predictive value for BPT [21]. Similar findings are reported with other protein allergens, although BPT may be required for metal salts and other chemical sensitizers.

Why might allergen challenge be positive where skin tests or serum IgE is negative? Explanations may be local bronchial mucosal IgE production or isolated T cell-mediated LAR [22, 23]. There is insufficient published data to know the prevalence of such patients, who one might conjecture to have relatively mild disease (in the absence of systemic sensitization), and it is unknown whether allergen specific interventions would be effective in treatment.

Is allergen challenge BPT ever useful clinically? As history, together with specific IgE measurements, SPTs and possibly CRD, together with confirmation of asthma (and AHR by histamine or methacholine challenge) are predictive in almost every case the answer would seem to echo Gilbert and Sullivan in HMS Pinafore: 'What never? Well, hardly ever!'

References

- 1 Blackley CH. *Experimental studies on the course and nature of catarrhus aestivus (hay fever or hay asthma)*. London: Bailliere, Findal and Cox, 1873.
- 2 Herxhimer H. The late bronchial reaction in induced asthma. *Int Arch Allergy Appl Immunol* 1952; 3:323–8.
- 3 Cartier A, Thomson NC, Frith PA, Roberts R, Hargreave FE. Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. *J Allergy Clin Immunol* 1982; 70:170–7.
- 4 O'Byrne P, Gauvreau GM, Brannan JD. Provoked models of asthma: what have we learnt? *Clin Exp Allergy* 2009; 39:181–92.
- 5 Pepys J. New tests to assess lung function. Inhalation challenge tests in asthma. *N Engl J Med* 1975; 293:758–9.
- 6 Melillo G, Bonini S, Cocco G *et al.* Provocation tests with allergens. *Allergy* 1997; 52 (Suppl. 35):5–36.
- 7 Fernandez C, Bevilacqua E, Fernandez N *et al.* Asthma related to alternaria sensitization: an analysis of skin tests and serum-specific IgE efficiency based on the bronchial provocation test. *Clin Exp Allergy* 2011; 41:649–656.
- 8 Fernández C, Cárdenas R, Martín D *et al.* Analysis of skin testing and serum-specific immunoglobulin E to predict airway reactivity to cat allergens. *Clin Exp Allergy* 2007; 37:391–9.
- 9 Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005; 115:1291–6.
- 10 Hamilton RG. Clinical laboratory assessment of immediate-type hypersensitivity. *J Allergy Clin Immunol* 2010; 125:S284–96.
- 11 Mosbech H, Dirksen A, Madsen F, Stahl Skov P, Weeke B. House dust mite asthma. Correlation between allergen sensitivity in various organs. *Allergy* 1987; 42:456–63.
- 12 Cockcroft DW, Murdock KY, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. *Am Rev Respir Dis* 1987; 135:264–7.
- 13 Warner JO. Significance of late reactions after bronchial challenge with house dust mite. *Arch Dis Child* 1976; 51:905–11.
- 14 Arvidsson MB, Löwhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. *Allergy* 2004; 59:74–80.
- 15 Arvidsson MB, Löwhagen O, Rak S. Early and late phase asthmatic response in lower airways of cat-allergic asthmatic patients – a comparison between experimental and environmental allergen challenge. *Allergy* 2007; 62:488–94.
- 16 Rosenberg GL, Rosenthal RR, Norman PS. Inhalation challenge with ragweed pollen in ragweed-sensitive asthmatics. *J Allergy Clin Immunol* 1983; 71:302–10.
- 17 Pulimood TB, Corden JM, Bryden C, Sharples L, Nasser SM. Epidemic asthma and the role of the fungal mold *Alternaria alternate*. *J Allergy Clin Immunol* 2007; 120:610–7.
- 18 Sastre J. Molecular diagnosis in allergy. *Clin Exp Allergy* 2010; 40:1442–60.
- 19 Quiralte J, Llanes E, Barral P *et al.* Ole e 2 and Ole e 10: new clinical aspects and genetic restrictions in olive pollen allergy. *Allergy* 2005; 60:360–5.
- 20 Alvarez-Cuesta E, Bousquet J, Canonica GW *et al.* Standards for practical allergen-specific immunotherapy. *Allergy* 2006; 61 (Suppl. 82):1–20.
- 21 van Kampen V, Rabstein S, Sander I *et al.* Prediction of challenge test results by flour-specific IgE and skin prick test in symptomatic bakers. *Allergy* 2008; 63:897–902.
- 22 Takhar P, Corrigan CJ, Smurthwaite L *et al.* Class switch recombination to IgE in the bronchial mucosa of atopic and non-atopic patients with asthma. *J Allergy Clin Immunol* 2007; 119:213–8.
- 23 Haselden BM, Kay AB, Larché M. Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. *J Exp Med* 1999; 189:1885–94.