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Review/Praca poglądowa

Bronchial allergen challenge – An old, but still useful tool in research and diagnostics

Prowokacja oskrzelowa z alergenem – stare, ale nadal przydatne narzędzie badawcze i diagnostyczne

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ARTICLE INFO

Article history:
Received: 05.12.2016
Accepted: 06.02.2017
Available online: 16.02.2017

Keywords:
- Allergen
- Bronchial allergen challenge
- Bronchial provocation test

Słowa kluczowe:
- alergen
- oskrzelowa prowokacja alergenem
- test prowokacji oskrzeli

ABSTRACT

A bronchial allergen challenge may serve both as a diagnostic as well as investigative procedure. Its usage in the diagnosis of asthma is infrequent due to its time-consuming nature as well as (in our opinion) an unfounded fear for a patient's safety. It is quite useful in the diagnostics of workplace related illnesses. Due to its ability to produce a controlled, long-lasting allergic-inflammatory reaction in the bronchi, this procedure is commonly used in research settings as well as in the assessment of new substances which may potentially have a place in the treatment of asthma, for ex. through the blocking of late asthmatic reactions. Changes stimulated by a bronchial allergen challenge may be evaluated by many methods using different materials, i.e. samples obtained from direct biopsies, bronchoalveolar lavages, exhaled breath condensates, or measured fractional exhaled nitric oxide. This procedure is a seemingly ideal research and diagnostic tool, however, a common protocol for its execution has not yet been accepted. Recent legal regulations have resulted in difficulties obtaining various allergens for challenge tests. Hopefully this is a temporary and minor setback for this very useful and constantly developing procedure.

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http://dx.doi.org/10.1016/j.alergo.2017.02.004

A bronchial allergen challenge (BAC) is a procedure that involves the sequential inhalation of increasing doses of an allergen that is suspected of causing symptoms in allergic patients [1]. This procedure is performed for various reasons, but always during a symptom-free period in patients that have or are suspected of having an allergy to a given allergen.

It was first used as a diagnostic tool to assess whether a given (suspected) allergen was the causative factor of symptoms in a patient. In 1981, Spector and Chai had already proposed that the main indication for a BAC could be the examination of a given allergen's role as the culprit in asthma in certain patients. We currently know that a correlation between clinical symptoms and [positive] skin test results is usually sufficient evidence for this. However, a [concise] medical history and results of the above-mentioned tests are sometimes divergent, and it is in such situations, without a doubt, that the BAC finds its niche [2]. Often enough a BAC may also serve to provide definitive evidence in situations where a patient simply cannot be convinced that the source of their asthma is a beloved pet. The BAC is still considered a valuable diagnostic tool in workplace-related illnesses, especially in baker's or car sprayer's asthma [3].

It's currently known that the BAC is a safe procedure provided that it is carried out by trained personnel in a center equipped with first aid capabilities in case of an anaphylactic reaction [4, 5]. Contraindications to the procedure include: 1) unstable asthma requiring constant use of medications which may affect the test, 2) asthma which required a hospitalization within the last year, 3) infections of the respiratory tract within the last 4 weeks, 5) $FEV_1 < 70\%$ of the predicted value, 6) time immediately after an influenza vaccination (<1 week), 7) regular usage of beta-blockers, 8) other general contraindications to spirometry (i.e. Recent myocardial infarction, stroke, abdominal or thoracic surgery, aneurysms, seizures, untreated arterial hypertension, pregnancy, breastfeeding, etc.) [6].

The first description of an allergen challenge with fresh grass pollen as a diagnostic tool in patients with hay fever appeared in a textbook by Blackley in 1873 [7]. During the 1940s, inhalation of an aerosolized allergen was introduced and spirometry was used to measure the bronchial response [8]. The 1950s saw Herxheimer and colleagues, taking advantage of the advances in spirometry, present for the first time a biphasic allergic response of the respiratory system after the inhalation of an allergen. They called the first part of this response the 'early asthmatic reaction' (EAR), and the second part the 'late asthmatic response' (LAR) [9].

By measuring the forced expiratory volume in one second (FEV_1), they found that the EAR appears after about 15 min and is characterized by a decrease [in the FEV_1] of at least 20% in comparison to the initial value. Usually the EAR resolves within 60 min, however, the LAR (a second 15–20% decrease of the FEV_1) appears around 3 to 8 h later and may last even more than a day.

We would like to present results of our own study involving a BAC in a group of patients ($n = 32$) allergic to house dust mites. A biphasic asthmatic response (EAR+ LAR+) was observed in 13 (40.6%) of the studied patients, an isolated early reaction (EAR+ LAR−) in 9 (28.1%), an isolated late reaction in 2 (6.25%), and a negative reaction (EAR− LAR−) in 8 (25%). A positive result was noted in 75% of the patients of which 62.5% had a LAR+ [10]. Our results do not differ fundamentally from those of other authors [11].

A quite large retrospective study assessing the effects of various allergens on the intensity of the LAR was recently published. House dust mites seemed to exacerbate this reaction more severely than pollen, and animal allergens were positioned in-between the two [12].

From our own experience, we can add that not all pollens uniformly stimulate a bronchial response in patients with seasonal allergic rhinitis. In fact, patients allergic to grass pollen exhibited positive reactions substantially more often than patients allergic to birch tree pollen (90% vs 50%) when challenged with their respective allergens [13].

The 1970s saw challenge tests flourish, both non-specific (histamine, methacholine) and specific (with a selected allergen) [14–16]. Different challenge protocols were, and still are, used in various research centers using assorted tools for dosing allergen extracts [16, 17].

A study published in 2015 showed that the different BAC protocols similarly decrease spirometric indices and increase the eosinophil count in the sputum [18].

Aqueous solutions of allergens are most commonly used [19], dry powders less so [10, 20, 21], and then recombinant allergens, with the latter being used solely for nasal challenges, for the time being [22].

Allergens may be administered by (jet) nebulizers, such as the Wright (no longer in production) or DeVilbiss 646, dry powder nebulizers, [allergen] challenge chambers [23], simulated workplace environments, or even by exposure to live animals such as cats [24].

In addition to the article that showed that differing methods of allergen administration give similar results in select parameters, a multitude of other works appeared questioning whether varying bronchial challenge protocols can be considered equivalent. Some of these publications showed that the result of a challenge may be affected by the depth of inspiration before or during inhalation of the administered provoking substance with deep breathing preventing bronchoconstriction which may consequently produce false negative results in patients with clearly hyperreactive bronchi [25, 26]. Similarly, a dosimetric method of administering the provoking substance is less sensitive and does not detect bronchial hyperreactivity in patients which have had positive results when challenged using a method requiring 2 min of calm breathing (at tidal volume). Authors have proposed alternative thresholds of the $PC_{20}FEV_1$ for methacholine used to identify bronchial hyperreactivity based on if it was administered with a 5-breath protocol or 2 min [tidal volume] inhalation [27]. The most recent publications show that only nebulizers approved by ATS guidelines (from 1999) should be used when assessing the degree of bronchial hyperreactivity with methacholine. Newer nebulizers require further studies [28].

The previously mentioned [allergen] provocation chamber is an ideal tool for research studies, however, its diagnostic usefulness in individual patients is limited [29].