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Review/Praca poglądowa

Bronchial challenge tests with direct and indirect stimuli – Which are more useful?

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ABSTRACT

There is a large selection of bronchial challenge tests. The most commonly employed tests involve provocation with methacholine, histamine, exercise, a hypertonic saline solution, or mannitol. The first two mentioned tests use pharmacological substances acting directly on bronchial smooth muscles causing constriction and increased blood vessel permeability. The remaining tests are considered as indirect stimuli, which by osmotic mechanisms lead to release of endogenous mediators responsible for quick obturation of the respiratory tract. Studies in recent years concerning direct tests have shown interpretation discrepancies when using approved methods and tools to carry out the tests. Bronchial challenge tests with mannitol, which have greater specificity for asthma, are increasingly being promoted. However, negative results of these tests are frequently encountered in patients with well-controlled asthma which is not the case in tests involving methacholine.

The diagnosis of symptomatic asthma presenting with classic symptoms is not difficult and relies chiefly on a patient's anamnesis, physical examination, and spirometry [1]. Patients with periodic asthma or chronic mild asthma, the most common kind, usually report shortness of breath induced only by exercise, after contact with trigger allergens, or appearing during nighttime. However, these patients are usually symptom-free during a doctor's visit. A common scenario arises where these patients are referred to an allergy/asthma specialist but never present with any wheezes, rhonchi, or obturation in spirometry results. Provoking characteristic symptoms of asthma or changes in spirometry results seems to be a logical approach to speeding up the diagnostic process in patients suspected of

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having asthma or in patients who have been taking asthma medications for years but do not have reliable documentation clearly indicating a diagnosis.

Bronchial hyperreactivity (also known as hyperresponsiveness) is a core characteristic of asthma. The definition of asthma according to GINA included bronchial hyperreactivity beginning from the acceptance of the inflammatory theory of asthma until 2014 [2]. Although bronchial hyperreactivity has been recently removed from the definition of asthma according to GINA, British Thoracic Society (BTS) 2014 criteria state that a bronchial challenge test is needed to provoke obturation in patients suspected of having the condition. There is still a need for a universal test to aid in the diagnosis of asthma [1, 3]. There has been ongoing research for many years into such a test [4, 5].

Bronchial challenge tests serve to measure the bronchial response to various stimuli that lead to impaired airflow in the respiratory tract. These tests are constantly being studied and perfected. Their development is mainly fueled by physicians' need for a quick test capable of confirming or excluding asthma in patients with periodically appearing symptoms of the disease. Development of spirometry studies allow for increasingly precise measurements of ventilation disorders.

The pioneer work of Curry from the 1940s involving histamine and acetylcholine along with its synthetic derivatives showed that inhalatory administration of these substances result in greater bronchial constriction in patients with asthma than in healthy subjects [4, 5]. Bronchial response to the above-mentioned substances was measured using vital capacity (VC) [4, 5]. Forced expiratory volume in 1 s (FEV_1), introduced at the same time by Tiffeneau and Pinelli allowed for the measurement of dynamic ventilatory changes. The FEV_1 measures the effects of stimuli provoking constriction and medications dilating the respiratory tract [6–9]. Further research into these functional tests resulted in newer techniques of measuring dynamic changes in bronchial challenge tests: assessment of airflow (FEV_1, peak expiratory flow (PEF)), airway resistance (Raw) [10], conductance (Gaw) [11], reactance [11, 12], fractional exhaled nitric oxide (FeNO) [13, 14], computer analyzed respiratory sounds [15], and changes in arterial oxygen saturation (SaO_2) [12].

This article will attempt to review current knowledge on bronchial challenge tests used in various clinical centers [16–18].

To date, a number of studies have been published on challenge tests using various stimuli causing impaired airflow in the airways [4, 5, 19–28]. Research on measuring bronchial responsiveness in the 1970s was mainly conducted in centers located in Canada, United States, Holland, England, and France. In Poland, studies involving acetylcholine, and later physostigmine, were conducted by Droszcz et al. in the 1960s [19, 20] while Górski et al. studied tests with polymyxin B in the 1970s [22, 23]. Certain challenge tests require specialized tools to administer the provoking stimuli or measure the effects thereof [29–31].

Challenge tests may be classified according to various characteristics such as the mechanism of action of the provoking agent. According to Pauwels, challenge tests may be divided into specific (usage of a specific 'sensitizing' substance) and nonspecific tests (all other substances) [32]. Another classification involves dividing the tests into direct and indirect challenges. Direct challenge tests use stimuli that directly cause constriction of smooth muscles or dilation of blood vessels such as histamine, acetylcholine, methacholine [4, 5], prostaglandin D2 [33, 34], and leukotrienes C4, D4, E4 [35–37]. Indirect challenge tests use various other stimuli which lead to the release of endogenous histamine and/or other mediators responsible for bronchial constriction such as cold air [38–40], physical exertion [41, 42], hyperventilation [43], hypertonic saline solutions [25, 44, 45], polymyxin B [22, 23], mannitol [46], distilled water [24, 25, 47], propranolol [48, 49], adenosine [50, 51], bradykinin [52, 53], or tachykinin [54].

All the above-mentioned provoking stimuli affect airflow in the respiratory tract in patients both healthy and with disease although patients with asthma usually have a more pronounced response. The most commonly assessed parameter has been FEV_1. A reduction of the FEV_1 of at least 20% (in comparison to the control/initial measurement) after administration of the provoking trigger has been arbitrarily accepted as a positive result.

The control/initial measurement is taken after inhaling the diluting agent used to prepare differing concentrations of the provoking substance. Currently, there is no consensus as to what changes are required in parameters other than FEV_1 in order to obtain a positive result of a challenge test. The most commonly encountered parameter is $PC_{100}Raw$, the concentration of a provoking substance resulting in a 100% increase of airway resistance from the baseline value. The variability of Raw, sGaw (specific airway conductance), and reactance during challenge tests is substantially greater than that of FEV_1 and are assessed less frequently because of this [28].

The majority of research has focused on histamine and methacholine. There is hope in finding a cut-off value for a histamine or methacholine concentration and a cut-off value for the change in FEV_1 which will allow differentiating patients with bronchial hyperreactivity from those without. A complication is the fact that bronchial hyperreactivity, although a core feature of asthma, is not specific for asthma.

Recommendations by the American Thoracic Society (ATS) from 1999 state that the basic substance for a bronchial challenge is methacholine, however, both methods of administering the aerosol (a 2 min continuous inhalation and a dosimetric 5 breath protocol) are accepted as equivalent [28]. Now, 16 years later, it is well known that the $PC_{20}FEV_1$ measured during tests with methacholine being administered by both routes differ among themselves and especially so in patients with low-grade bronchial hyperreactivity [55]. It is also known that how the aerosol is inhaled affect the $PC_{20}FEV_1$ with deep breaths preventing bronchial constriction. The newest recommendations state that the dosimetric 5 breath method of administration should be performed with calm breathing, i.e. at tidal volume [56]. An important factor affecting bronchial response is the size of the inhaled particles. Nebulizers creating an aerosol mainly with particle sizes $<1\,\mu m$ in diameter result in less positive results during challenge tests [55]. This theory is supported by results obtained in a study by Lieutier-Colas et al. investigating provocation with cat