Lung Function Tests to be Used in Severe Asthma: Spirometry and Bronchodilator Test, Diffusion Capacity for CO, Induced Sputum, Body Plethysmography, Electronic PEF Measurements

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Matjaž Fležar[1,2]

3 University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

2 Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Abstract

Lung function tests are the cornerstone for asthma diagnostic procedure and patient follow-up and is complementary to other phenotyping tools used later for precision diagnosis. Spirometry and bronchodilator tests are used to define degree and reversibility of airway disease, diffusion capacity of the lung for CO is used as exclusion tool for comorbid diseases (particularly COPD), Body plethysmograph is used in small airway asthma to determine the degree of air trapping and hyperinflation, electronic PEF monitoring is used for work-related asthma characterization and targeted sputum examinations (induced sputum protocol) are used in immune phenotyping process. In hands of pulmonologist these tests (not all of them routinely used) are necessary to separate uncontrolled asthma from severe asthma phenotype.

Keywords: lung function tests, severe asthma, work related asthma, asthma phenotyping

Introduction

Asthma from lung function perspective is a disease detected by *smooth muscle hyperresponsiveness* and airway *obstruction,* which is *variable* and *reversible*. All these physiological hallmarks of the disease can be appropriately tested, although the results may vary over the course and intensity of the disease. If chosen in context of a clinical picture of a patient, they can provide most definite diagnostic confirmation of the disease[6].

Clinically used Tests and Physiological Background

Smooth Muscle Hyperresponsiveness

In case of normal spirometry (no obstruction) and pretest probability of asthma between 30 and 70%, a surrogate test to detect airway hyper responsiveness in non-specific or specific bronchial provocation test (methacholine or histamine vs. allergen test) BHR can be used to determine inducible airway constriction, seen in asthma, COPD, some normal persons, in children after childhood bronchiolitis, in smokers and in a course of acute bronchitis. The presence of BHR is linked to respiratory symptoms such as chronic cough, nocturnal cough, wheeze, dyspnea on exertion, periodic dyspnea at rest, inhalational allergy-related lower respiratory symptoms, etc.

In diagnostic procedure of asthma, assessment of BHR is in place if pre-test probability of asthma is at least 30% and not more than 70%. It is also not necessary if the patient present with completely reversible airway obstruction (normalization of flows, volumes and resolution of obstruction – normalization of FEV1/VC ratio) after 400mcg of inhaled short acting bronchodilator drug (e.g., salbutamol). Proper timing of the test

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is necessary because positive test during the acute bronchitis episode and 4-6 weeks after that could produce false positive result and lead physician to false conclusion, that the patient has asthma. Proper timing of the test is also important in elite sportsmen exercising in cold environments (e.g., biathlon runners) and in diagnostic procedure of work-related asthma.

BHR test has a high (over 95%) negative predictive value – to *exclude* asthma. The positive predictive value varies very much in relation to provocation dose of inhaled agent and has over 50% of »false positives« in a range above 2mg cumulative methacholine dose. Therefore, if the test is negative at the time when the patient has symptoms, we can be sure that the patient does *not* have asthma.

BHR is linked to different genetic loci on our chromosomes as is atopy. Current evidence suggests, that BHR has two components: »inducible« – linked to the level of airway inflammation (due to either IgE-mediated and/or neutrophilic-mediated) and »constitutive« – linked to the level of airway remodeling, hypertrophy of bronchial smooth muscles and intrinsic properties of smooth muscle cell. In that concept, it is understandable, that the first part of BHR could be diminished or even abolished by proper anti-inflammatory treatment of airway mucosa and the second being more inaccessible to treatment. In most of asthmatic patients their BHR exists over the entire lifetime, even though the level of BHR may vary significantly and is linked to expression of their symptoms.

Repeated test for BHR is not useful in clinical practice. If the first test is done in a proper time, its positive value can be considered significant. Repeated BHR is also not recommended to assess the success of medical treatment (e.g., inhalation drugs for asthma). However, the test could be repeated in certain circumstances:

1. Periodic asthma (allergen driven seasonal asthma): the test could be positive during pollen season and negative during wintertime; however, this is more an exemption as a rule.
2. Workplace-related asthma: the test could be repeated if new-onset respiratory symptoms appear in a patient working in asthma-risk workplace; 3-5 years after complete removal from workplace, if test was positive (e.g., in retirement).[1,8]

Repeatability of the test in the same person within a week is within two doubling concentrations of the provoking agent. However, inter-laboratory repeatability can reach up to 300% difference. That methodological issue makes the interpretation of repeated test even more difficult.

Bronchial Hyper Responsiveness vs. Bronchial Reversibility

Those terms could not be used interchangeably since they do not necessary represent the same process within the airways. However, many epidemiological studies, looking for population-based bronchial hyper responsiveness have used a significant BD response as a surrogate marker of BHR. Therefore, large population cohort data are hard to interpret. Some patients can have a positive BD test (defined by increase in FEV1 over 12% and 200mL) and negative broncho provocation test, while other with documented BHR could have negative BD response (e.g., COPD patients). As already stated, both BD response as BHR are dynamically changing variables over time, depending both on underlying airway inflammation and structural changes.

Structural Changes in Airways Linked to BHR

Airway Smooth Muscle (ASM)

Human studies in alternations of airway smooth muscle function require bronchial biopsy and are therefore limited. However, epithelial damage of any kind can result in altered smooth muscle function and thickening

of basal membrane. ASM hyperplasia (mediated through growth factors, epithelial inflammatory mediators, and extracellular matrix components) is a key mechanism, most probably irreversible with treatments available nowadays[5].

Epithelial Damage and Inflammation

Epithelial damage (e.g., in viral bronchitis)[10] can be a reason for dysfunction in airway smooth muscle innervation (particularly parasympathetic and NANC-non-cholinergic non-adrenergic) and consequently causing a transient BHR[9,11]. In COPD and smokers' airways that mechanisms are even more prominent. Repair process could lead to collagen deposition, basal membrane thickening and permanent airway narrowing[12].

Techniques to Measure Bronchial Hyper Responsiveness

Direct and Indirect Bronchial Challenge Tests

'Direct' BPTs measure airway smooth muscle function, whereas the 'indirect' tests reflect airway inflammation. Airway caliber is important in determining response to direct stimuli[2]. Therefore, the direct challenges function best to exclude current asthma when they are negative. By contrast, all the indirect challenges (exercise, eucapnic voluntary hyperpnoea, hypertonic saline, adenosine mono phosphate (AMP) and mannitol) critically depend on the presence of airway inflammatory cells[4]. Many of the indirect challenges are dose limited meaning that it is not possible to push the dose beyond a certain limit that is limited by physiology (exercise, eucapnic voluntary hyperpnoea) or solubility (AMP). Comparative studies have demonstrated that the indirect challenges are highly specific but have a relatively low sensitivity compared with methacholine[7]. Due to their high specificity (and low sensitivity), indirect challenge tests function best to confirm the presence of disease and are ideal tools for studying individuals who have or are suspected to have exercise-induced bronchoconstriction[3].

The response to bronchoprovocation agent is dose (or concentration) dependent. Since it is clinically not feasible to test both hyperreactivity and hypersensitivity (due to possibility to induce severe obstruction in former), arbitrary point of decease of FEV1 is chosen as 20% of drop of FEV1 comparing the FEV1 after inhalation of normal saline (0.9% NaCl). Patterns of response are shown on Figure 1.

Airway obstruction is a term that is derived from spirometric flow-volume curve and is defined as a decrease of Index Tiffeneau (FEV1/VC ratio) for 12% below lower limit of normal. Decrease of expiratory flows *per-se* (FEV1 or PEF) is not sufficient for confirmation of obstructive ventilatory defect but can be used (after we define obstruction) as a marker of degree of obstruction (mild, moderate, severe). Since in many cases asthma (as predominantly large/medium airway disease) can affect small airways too, impulse oscillometry and/or body plethysmography measurement are used to define the degree of bronchial system involvement.

Variability of airway obstruction usually (but not always i.e., in non-eosinophilic asthma) parallels the intensity of airway asthmatic inflammation. The variability should be assessed over time; the best tool is to use PEF measurements for at least 2 weeks, three times daily at home environment in the period, when the patient describes asthmatic symptoms. Diary of those measurements (best provided by electronic PEF meter, since compliance of a patient with ordinary PEF meter is less than 30%) is assessed day by day and excess variability is determined by more than 20% fluctuation of PEF.

Reversibility of obstruction is assessed by bronchodilator test. Improvement of airway obstruction after short-acting bronchodilator (in Slovenia standard is 400mcg of salbutamol) for at least 200ml increase on either FVC

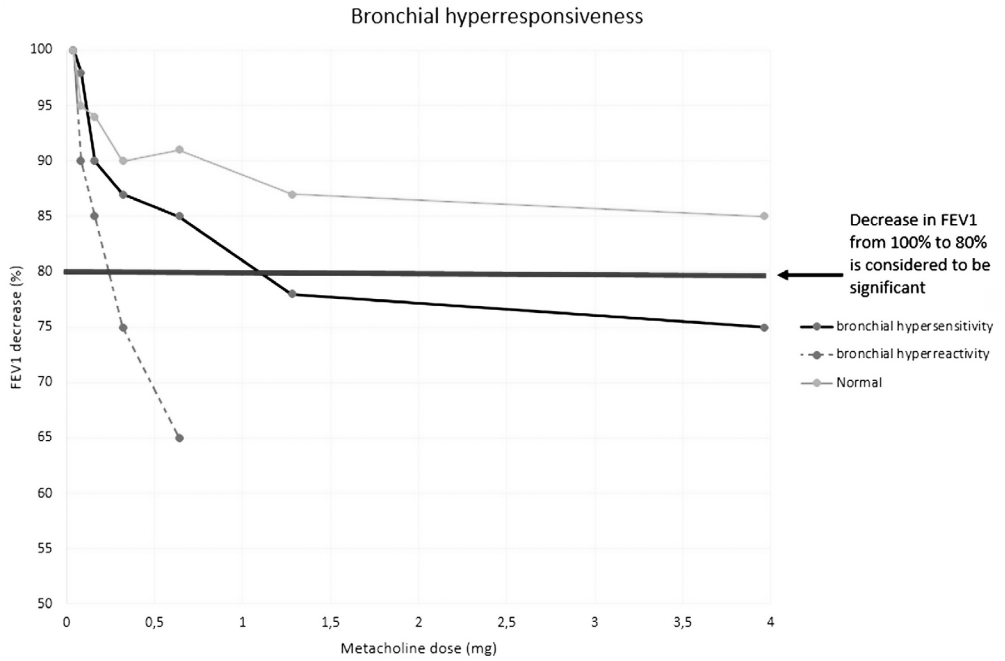

Figure 1. Patterns of response to Broncho provocation agent.

or FEV1 PLUS 12% of pre-bronchodilator value is considered positive. In some cases, both FVC and FEV1 increase simultaneously – in those patients we should think about small airway asthma (increase on FVC can be due to decrease in air trapping after BD and consequently more air available for expiration before airway close during expiration).

Conclusions

Intrinsic airway disease (smooth muscle and epithelial damage due to asthmatic inflammation) can be assessed using lung function measurements. The scope of test differs in respect of timing and activity of disease process (i.e., methacholine testing is used in stable disease, with normal spirometry; BD test is used in acute exacerbation, longitudinal PEF measurements are used in induced-variability environments (e.g., workplace)). Since the disease is very variable over time and place, most test scan be repeated, and dynamic changes are used as a support for diagnosis as for appropriate treatment. Pre BD spirometric measurement should always be used in outpatient follow-up; BD reversibility can detect degree of current airway inflammation. In latter case, exhaled FENO values are valuable in titrating anti-inflammatory treatment.

Workplace asthma can be either true occupational asthma (that developed due to allergens at workplace in a previously non-asthmatic person) or workplace-exacerbated asthma (usually in known asthmatic due to irritants at workplace – »dirty workplace« asthma). Long-term measurements of flows at workplace (electronic PEF) are necessary, best in a period on/off place when the patients are symptomatic[1].

Results of lung function tests should be reproducible. Therefore, standardization of procedure in lung function lab is necessary.

Screening results (done by spirometry on the field, e.g., GP office, etc.) should be confirmed and assessed further at the pulmological level.

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