

Chapter 5

Current Clinical Diagnostic Tests for Asthma

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Abstract Asthma involves variable airflow obstruction in both large and small airways. The physiological consequences of obstruction include increased airway resistance and decreased expiratory flow rates, which lead to air trapping and dynamic hyperinflation. This chapter reviews current methods for pulmonary function testing to detect these physiological changes for both diagnosis and monitoring.

Keywords Spirometry • Peak expiratory flow rate • Airway hyperresponsiveness • Bronchodilator reversibility • Bronchoprovocation • Methacholine

5.1 Introduction

Asthma is characterized by airway hyperresponsiveness leading to variable airflow obstruction which may occur as a result of both intrinsic (genetic) and extrinsic (environmental) factors. The variable and reversible nature of the obstruction distinguishes asthma from other obstructive lung diseases. Asthma involves both large and small airways, and the physiological consequences of obstruction include increased airway resistance and decreased expiratory flow rates, which lead to air trapping and dynamic hyperinflation. Pulmonary function testing can detect these physiological changes for both diagnosis and monitoring. This is important, as studies have shown that physicians are often inaccurate in diagnosing asthma and predicting reversibility of obstruction based on history and physical examination alone (Russell et al. 1986; Scott et al. 2012).

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5.2 Spirometry

Spirometry is recommended in all adults and children at least 5 years of age in which asthma is a consideration (NAEPP 2007). Spirometry involves the patient inhaling to total lung capacity (TLC) and then blowing out as much as possible to residual volume (RV). The resulting forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) are measured. In order to get accurate results, long-acting bronchodilators should be stopped for 12 h and short-acting beta-agonists should be stopped for 6 h prior to performance of spirometry.

Asthma is characterized by an obstructive ventilatory defect, with a reduction in FEV1 out of proportion to FVC, and a low FEV1/FVC ratio. Visually, this is detected as an expiratory scooping on the flow volume loop. Classically, obstruction is defined as an FEV1/FVC ratio less than 70 %. However, recent data suggest that using the lower limit of normal (LLN) is more accurate. LLN is determined by the fifth percentile predicted based on the patient's age, race, gender, height, and other factors. LLN is often greater than 70 % in the younger population, while it is less than 70 % in the older population. While evidence to favor use of either the fixed ratio or LLN for asthma is lacking, it does appear that use of a fixed ratio of 70 % increases the likelihood of underdiagnosing obstruction in the younger patient population, which contains most asthmatic patients (Hansen et al. 2007).

In addition, asthma is characterized by a low forced expiratory flow of 25–75 % (FEF25–75 %), defined as the slope of the spirometry curve between the 25th and 75th percentile. A decreased FEF25–75 % is indicative of small airway obstruction. While an FEF25–75 % less than 60 % of predicted is considered abnormal, values are more variable than FEV1, and the utility of an isolated decrease in FEF25–75 % in the setting of otherwise normal spirometry is otherwise unclear. Nevertheless, evidence suggests that a reduced FEF25–75 % correlates with bronchial hyperresponsiveness on bronchoprovocation testing (Alberts et al. 1994; Drewek et al. 2009).

Spirometry is often repeated after administering a bronchodilator to confirm reversible/variable airflow obstruction. Reversibility is characterized by an increase in either the FEV1 or FVC by more than 12 % and 200 ml. Reversibility supports the diagnosis of asthma, although some patients with chronic obstructive pulmonary disease (COPD) have reversible airflow obstruction. Additionally, in rare cases of severe asthma, reversibility may be minimal until the patient's inflammation is controlled with corticosteroids (NAEPP 2007).

Two important points need to be made. Normal spirometry does not rule out a diagnosis, as spirometry may be normal between asthma flares, especially in those with milder disease. Second, with more severe asthma, one can develop a pseudorestrictive pattern. In this condition, worsening air trapping leads to an increase in the RV and a decline in the FVC with a consequent increase in the FEV1/FVC ratio. Using the ratio of inspiratory capacity (IC) to expiratory reserve volume (ERV) can help distinguish pseudorestriction from true parenchymal

restriction. IC is the maximum volume that can be inspired from resting expiratory levels (tidal volume plus inspiratory reserve volume). The ERV is the maximum volume that can be expired from the end tidal expiration (from functional residual capacity, FRC). IC:ERV is normally 2–3 to 1. With asthma, the increased RV results in a decrease in the ERV, leading to a ratio that may be greater than 6:1. In parenchymal restriction, however, the ratio is often less than 2:1. In addition, pseudorestriction should improve or reverse with bronchodilators.

5.3 Lung Volumes

Asthma is characterized by elevated RV, FRC, and TLC. The most commonly used methods of measuring lung volumes include body plethysmography, nitrogen wash-out, and inert gas dilution. All three methods measure FRC and, when added to inspiratory capacity determined from spirometry, give TLC. Body plethysmography calculates lung volume based on Boyle's principle: at a constant temperature, the volume of a gas is inversely proportional to the pressure. The patient sits in an enclosed box and then starts to pant against a closed mouthpiece. Changes in the pressure within the box are proportional to the volume of compressible gas within the lung. Because the shutter on the mouthpiece is closed at FRC, this is the volume measured. Both inert gas dilution and nitrogen washout depend on the principle that if an initial volume of gas with a known concentration of either nitrogen or inert gas is inhaled, the concentration in the exhaled gas can allow calculation of lung volume. Starting the process when the patient is at FRC allows calculation of this volume. The downside of these techniques is that only communicating gas is measured. Noncommunicating air spaces, such as distal to areas with high resistances, will not be included. Thus, in obstructive lung disease, gas dilution techniques underestimate TLC, and body plethysmography is preferred (Ferris 1978).

5.4 Diffusion

Diffusion capacity for carbon monoxide (DLCO) is measured by having the patient inhaling air with a certain concentration of carbon monoxide (CO) from RV to TLC. After a 10 s breath hold, the patient exhales, and the amount of CO remaining can be used to determine how much CO was transferred to the blood during that period. DLCO is normal or even elevated in asthma. This is likely due to the increased negative pressures needed for breathing in the setting of obstruction, leading to an increase in pulmonary blood volume. Furthermore, this pulmonary volume will be diverted more toward the upper lung zones, which have more reserve to accommodate the increased blood flow, and are better ventilated (Keens et al. 1979; Collard et al. 1994).

5.5 Peak Expiratory Flow Rate Measurement

The measurement of the peak expiratory flow rate (PEFR) is a simple method to evaluate air flow obstruction. PEFR can be measured in the physician's office or at home. Strict attention should be paid to proper technique, as improper technique can lead to nonvalid results. Patients should stand upright, to take in as deep a breath as possible, and then place the peak flow meter in the mouth, making sure that the tongue does not obstruct the device. The patient should close his/her mouth tightly against the device and then blow out as hard and fast as possible. The patient should then hold the breath normally for a little while and then repeat the process two more times. The highest of the three values should be used. Patients are encouraged to measure PEFR early in the morning as well as in the evening. PEFR is normally lower in the morning and higher in the evening, a difference which is exaggerated in asthma. A diurnal variation greater than 20 % is diagnostic of asthma, and higher variability correlates with poorer asthma control. Nevertheless, PEFR should not be used to diagnose asthma. There is a wide variability in PEFR reference values, and the values will vary with the brand of equipment used. In addition, less severe obstruction tends to be underestimated, while more severe obstruction tends to be overestimated. Nevertheless, if an asthmatic patient establishes a personal best when he/she is clinically well, monitoring PEFR in reference to this baseline can be useful. If the peak flow rates are 80–100 % of the personal best, the patient is in the green zone, and this correlates with good asthma control. Values of 50–80 % represent the yellow zone, and medical care should be sought, and asthma control likely needs to be improved. Values less than 50 % of the patient's personal best represent the red zone and require immediate physician attention. Of note, PEFR monitoring has not been shown to be superior to monitoring of clinical symptoms.^{10–12} Nevertheless, guidelines suggest considering PEFR monitoring for patients with moderate to severe asthma, those with a history of severe exacerbations, those who poorly perceive air-flow obstruction, and those who prefer this method of monitoring (NAEPP 2007).

5.6 Bronchoprovocative Testing

Demonstration of airway hyperresponsiveness by bronchoprovocative testing is useful in evaluating patients who have asthma symptoms but normal spirometry. A significant proportion of these patients will not have asthma, and given the high negative predictive value, a negative bronchoprovocative test essentially rules out asthma (McGrath and Fahy 2011). On the other hand, a positive test is consistent with asthma. Patients with other conditions, including allergic rhinitis, cystic fibrosis, and COPD, may have positive tests as well. In these cases, the clinical history should be used in conjunction with the results of the bronchoprovocative test.

As the test involves induction of bronchospasms, patients may deteriorate clinically during the test. Patients with lower reserve, specifically those with an FEV1

less than 50 % of predicted volume or those with less than 1 l of reserve, should not undergo testing. An FEV1 between 60 and 70 % is a relative contraindication. Other relative contraindications include acute coronary syndrome or stroke within the past 3 months; severe, uncontrolled hypertension; and significant hypoxemia. Generally, it is necessary to withhold albuterol for at least 8 h prior to the test, ipratropium for at least 24 h, and long-acting beta-agonists for at least 24 h. Caffeine-containing products, including coffee, tea, cola, and chocolate, may affect the test and should not be consumed on the day of the study (Henderson et al. 1993).

There are two types of provocative tests: direct and indirect. Direct testing involves administering medications (usually either methacholine or histamine) that act on smooth muscle receptors to constrict the airway. Histamine is not FDA approved; thus, methacholine is most commonly used in the United States. Methacholine is administered via nebulization and 2 min tidal breathing or with a five breath dosimeter, in doubling concentrations until the FEV1 drops more than 20 % or the highest concentration is reached. The level of methacholine required is noted as PC20. A level less than 16 is characterized as mild airway hyperreactivity, less than 4 as moderate hyperreactivity, and less than 1 as severe hyperreactivity. Values greater than 16 indicate no significant hyperreactivity. The exact cutoff for diagnosis of asthma depends on pretest probability, although in the setting of moderate pretest probability, a level less than 8 is predictive of asthma.

Indirect stimuli result in the release of inflammatory mediators which mediate subsequent bronchoconstriction. These include cold air, exercise, eucapnic hyperventilation, hypertonic saline, mannitol, and adenosine (Argyros et al. 1996). While direct testing allows for better characterization of dose response, indirect testing is often more clinically meaningful. Specifically, for exercise-induced bronchospasms, eucapnic hyperventilation, in which the patient voluntarily hyperventilates a mixture of 5 % CO₂ and 95 % room air for 6–8 min, is the most sensitive bronchoprovocative test (Holley et al. 2012).

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