The role of the pulmonary function laboratory to assist in disease management: Asthma

José Alberto Neder[1], Danilo Cortozi Berton[2], Denis E O'Donnell[1]

BACKGROUND

Asthma is a heterogeneous, chronic airway inflammatory disease in which pulmonary function tests (PFTs) might provide valuable information for diagnosis, assessment of clinical control, and estimation of future risk.

OVERVIEW

A 57-year-old never-smoking woman reported a 10-year history of recurrent dyspnea and occasional wheezing that worsened after COVID-19 two years earlier. Dyspnea progression was associated with weight gain (BMI = 33 kg/m^2) in a background of type 2 diabetes and hypertension. She did report asthma in childhood, and her symptoms were typically precipitated by changes in the weather. Spirometry revealed mild and similar decreases in FEV_1 and FVC, with normal FEV_1/FVC ratio. Inhaled bronchodilator (BD) was associated with proportional increases in FEV_1 (↑ 0.37 L and 22%) and FVC (↑ 0.39 L and 18%), with normalization of spirometry. DL_{CO} was preserved. On the basis of her clinical history and functional data, she was diagnosed with asthma, with marked clinical improvement after a few weeks of treatment with medium-dose inhaled corticosteroids.

Reduced FVC and/or FEV_1 with normal FEV_1/FVC is a nonspecific finding that might signal restriction and/or obstruction. A commensurate improvement in FEV_1 and FVC with the use of an inhaled BD indicates lung volume recruitment, revealing underlying airway disease. If these changes are large enough to normalize the results of spirometry, asthma is the most likely diagnosis. It should be noted, however, that "fixed" airflow obstruction with variable degrees of hyperinflation and gas trapping can be seen in patients with remodeled airways and severe asthma. Variable airflow obstruction over time is commonly seen in patients with asthma, usually improving either spontaneously or secondary to treatment. In equivocal cases, airway hyperresponsiveness can be revealed by bronchial challenge testing.[1] Once treatment is initiated, between-visit variability in FEV_1 and BD responsiveness might provide ancillary information to gauge disease stability. Although it is not mandatory that maintenance or as-needed medications are withheld before testing, repeating PFTs under similar therapeutic conditions allows more meaningful interpretation. Low post-BD FEV_1 (particularly < 60% predicted)[2,3] and higher BD responsiveness[3] are independent predictors of increased risk of exacerbation, even in patients with relatively modest symptom burden (Chart 1). Indirect airway hyperresponsiveness testing with the use of hypertonic saline to determine the dose of inhaled corticosteroids has been reported to decrease the number of asthma exacerbations in children when compared with treatment based only on symptoms.[4]

CLINICAL MESSAGE

PFTs are central to the diagnosis and follow-up of patients with asthma. For instance, undiagnosed obstruction in asthma patients is more common among those who have never undergone spirometry or who have never been referred to a pulmonologist.[5] However, PFT results should not be used in isolation. The best management approach involves a longitudinal assessment of clinical endpoints (symptom control and exacerbation frequency) and laboratory data (eosinophil count, total IgE, and specific IgE) under the modulating influence of key comorbidities (obesity, rhinosinusitis, nasal polyposis, and gastroesophageal reflux disease). There is renewed interest in using lung function parameters to improve asthma phenotyping, which may shed novel light into more complex biological mechanisms (endotypes) relevant to disease pathophysiology and, ultimately, treatment choices.[6]

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualization, writing, reviewing, and editing.

CONFLICTS OF INTEREST

None declared.

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology, Kingston Health Science Center & Queen's University, Kingston (ON) Canada.
2. Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

Chart 1. Key information provided by pulmonary function testing and relevant to asthma management in individual patients.

Clinical scenario	Recommendations
Diagnosis	• In the right clinical context (e.g., recurrent wheezing, breathlessness, chest tightness, and/or cough brought on by characteristic triggers and relieved by BD therapy), variable airflow obstruction documented by BD testing or other tests is indicative of asthma.
	1) FEV_1/FVC below the lower limit of normal indicates obstruction, although elderly patients with asthma can present with FEV_1/FVC that is above the lower limit of normal but of < 0.7. Care should be taken to avoid overdiagnosis of obstruction in those with supranormal FVC caused by dysanapsis, i.e., a mismatch of airway tree caliber to lung size, particularly in children and adolescents.
	2) Excessive variability in lung function can be revealed by at least one of the following: 2.1) A "significant" response to inhaled BD from a baseline of obstruction: an increase in FEV_1 ≥ 10% predicted. Expressing FEV_1 changes relative to predicted rather than relative to baseline is recommended because ≥ 12% from baseline is easier to be reached the lower the FEV_1, the opposite being true for ≥ 200 mL.
	2.2) A "significant" response to inhaled BD from a baseline of apparent normality might be seen in patients with increased bronchomotor tone: the clinical significance of this finding requires careful clinical correlation.
	2.3) Excessive variability in twice-daily PEF measurements over 2 weeks (> 10% in adults and > 13% in children). Daily diurnal PEF variability is calculated as the highest value minus the lowest value divided by the mean of the highest and lowest values averaged over the period using the same flow meter.
	2.4) Improvement in lung function after 4 weeks of ICS-containing treatment: an increase in FEV_1 > 12% and > 200 mL (or a > 20% increase in PEF)
	2.5) Excessive variation in lung function between visits: variation in FEV_1 > 12% and > 200 mL in adults; variation in FEV_1 > 12% or variation in PEF > 15% in children
	2.6) The limitations of the % change from baseline approach (item 2.1) also apply to the effects of ICS and the between-test variability; thus, care should be taken to interpret changes in patients with markedly low or high baseline values.
	2.7) A positive exercise challenge: Decreases in FEV_1 of 10-25%, 26-50%, and > 50% indicate mild, moderate, and severe exercise-induced bronchoconstriction, respectively.
	2.8) A positive bronchial challenge test: A decrease in FEV_1 ≥ 20% with standard doses of methacholine (direct stimulation of airway smooth muscle receptors) or ≥ 15% with standardized indirect airway challenges (eucapnic voluntary hyperventilation, hypertonic saline, or dry powder mannitol) releasing endogenous mediators to cause airway smooth muscle contraction. Direct inhalation challenges are considered more sensitive but less specific; thus, indirect challenges can be used in order to confirm asthma after a positive methacholine test.
	2.9) A positive methacholine challenge test is not diagnostic of asthma without a suggestive clinical history, and, despite a high negative predictive value, it does not always rule out asthma in patients who have no symptoms at the time of testing. The severity of airway hyperresponsiveness can be used with clinical data to estimate the post-test likelihood of asthma.
	• A large volume response to inhaled BD (FVC) in a patient with COPD might be associated with a similar improvement in FEV_1: the latter finding should not be strictly interpreted as asthma. This common mistake has contributed to an increase in the prevalence of asthma-COPD overlap.
	• Increased longitudinal variability in FEV_1 in a patient with COPD, particularly when FVC varies only modestly, can be suggestive of asthma in the right clinical context, prompting a more liberal use of ICS.
	• Although not specific for asthma, subtle abnormalities such as low maximal mid- and end-expiratory flows, exaggerated flow-volume loop expiratory concavity, and increased specific airway resistance might help in diagnosing mild obstruction in suspected patients.
	• Analysis of the flow-volume loop morphology might occasionally suggest upper/central airflow obstruction, which can mimic asthma. Care should be taken to ensure that these abnormal patterns are reproducible and not related to poor technique.
	• Impulse oscillometry may be helpful in diagnosing asthma via bronchodilation or bronchoprovocation in patients with preserved spirometry. Thresholds to define airway hyperresponsiveness during bronchial challenges are also available.
	• Although a low DL_{CO} is rarely seen in asthma patients (unless there is another cause for impaired gas exchange), a normal DL_{CO} is not necessarily suggestive of asthma in the presence of obstruction, because it may occur in a patient with COPD in whom chronic bronchitis predominates over emphysema.
	• Obesity frequently creates challenges to asthma diagnosis, leading to a false-positive diagnosis (e.g., central airway compression and increased small airway collapse on forced expiration) or a false-negative diagnosis (FVC underestimation leading to "preserved" FEV_1/FVC ratio). Clinical history and laboratory data might provide important ancillary information for diagnostic clarification.

Continue...▶

Chart 1. Key information provided by pulmonary function testing and relevant to asthma management in individual patients. (Continued...)

Clinical scenario	Recommendations
Response to treatment	• Spirometry is usually recommended 3-6 months after treatment initiation, in order to record the patient's personal best lung function, and periodically thereafter (at least once every 1 or 2 years or more frequently in at-risk patients and in patients with severe asthma).
	• If the patient has persistent symptoms (e.g., dyspnea, exercise intolerance, excessive use of relievers) or airflow obstruction, more frequent testing may be warranted (e.g., at intervals of 3-6-months). Test results can be used in order to determine whether symptoms reflect poor asthma control or an alternative diagnosis/complication.
	• If symptoms are well controlled and prior spirometry is normal, follow-up spirometry can be obtained less frequently (every 1-3 years).
	• A volume response (e.g., Δinspiratory capacity > 200 mL and ΔFVC or vital capacity > 15%) might be more relevant to symptom improvement than a flow response (i.e., a significant increase in FEV_1 but not in FVC).
Disease severity/risk estimation	• Individuals with FEV_1 between 60-80% predicted have 2.5-fold-increased risk for future acute episodes, and those with FEV_1 < 60% predicted have > 4-fold-increased risk for future acute episodes when compared with those with FEV_1 > 80% predicted.
	• A 20% greater exacerbation risk is observed for every 10% increase in BD responsiveness.
	• Although the diagnosis of asthma is based on spirometry, a higher dyspnea burden can be explained by greater air trapping (increased RV) and/or lower inspiratory capacity at a given FEV_1.
	• Decreases ≥ 20% in PEF from predicted or from the patient's personal best signal an exacerbation of asthma: the exacerbation is considered "moderate" if the PEF is between 51-70% and "severe" if the PEF is of ≤ 50% of predicted.
	• PEF readings might prove useful in detecting unsuspected severe airflow obstruction in those who are "poor perceivers" of asthma symptoms.
	• Marked hypoxemia (a PaO_2 of < 60 mmHg and an SpO_2 of < 90%) is rare during uncomplicated asthma attacks, suggesting life-threatening exacerbation and possible complications (e.g., pneumonia, atelectasis caused by mucus plugging, and spontaneous pneumothorax).
	• The respiratory drive is usually increased in patients with acute asthma, resulting in hyperventilation and low $PaCO_2$. Therefore, a normal $PaCO_2$ during an asthma exacerbation might signal a severe episode. Hypercapnia and respiratory failure can develop rapidly with any further airway obstruction or with respiratory muscle fatigue. Progressive hypercapnia during an exacerbation of asthma is generally an indication for mechanical ventilation.

BD: bronchodilator; and ICS: inhaled corticosteroid(s).

REFERENCES

1. Lougheed DM, Webb KA, O'Donnell DE. Breathlessness during induced lung hyperinflation in asthma: the role of the inspiratory threshold load. Am J Respir Crit Care Med. 1995;152(3):911-20. https://doi.org/10.1164/ajrccm.152.3.7663804
2. Osborne ML, Pedula KL, O'Hollaren M, Ettinger KM, Stibolt T, Buist AS, et al. Assessing future need for acute care in adult asthmatics: the Profile of Asthma Risk Study: a prospective health maintenance organization-based study. Chest. 2007;132(4):1151-1161. https://doi.org/10.1378/chest.05-3084
3. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations [published correction appears in Am J Respir Crit Care Med. 2018 Apr 1;197(7):971]. Am J Respir Crit Care Med. 2017;195(3):302-313. https://doi.org/10.1164/rccm.201602-0419OC
4. Ciółkowski J, Hydzik P, Rachel M, Mazurek-Durlak Z, Skalska-Izdebska R, Mazurek H. Childhood asthma treatment based on indirect hyperresponsiveness test: Randomized controlled trial [published online ahead of print, 2023 Jun 21]. Pediatr Pulmonol. 2023;10.1002/ppul.26556. https://doi.org/10.1002/ppul.26556
5. Cherian M, Magner KMA, Whitmore GA, Vandemheen KL, FitzGerald JM, Bergeron C, et al. Patient and physician factors associated with symptomatic undiagnosed asthma or COPD. Eur Respir J. 2023;61(2):2201721. https://doi.org/10.1183/13993003.01721-2022
6. Reyna ME, Bedard MA, Subbarao P. Lung Function as a Biomarker of Health: An Old Concept Rediscovered. Am J Respir Crit Care Med. 2023;208(2):117-119. https://doi.org/10.1164/rccm.202305-0911ED