Using the pulmonary function laboratory to assist in disease management: COPD

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BACKGROUND

This is the first of a series of concise manuscripts focused on how best to use the pulmonary function laboratory for diagnosis, assessment of disease severity/risk estimation, and selection of treatment strategies in prevalent respiratory and nonrespiratory diseases. We start with a heterogeneous lung disease in which pulmonary function tests (PFTs) assume a pivotal role in each of these domains: COPD.[1]

OVERVIEW

A 61-year-old man with a smoking history of 21 pack-years was referred to Respirology because of "out-of-proportion" dyspnea (modified Medical Research Council dyspnea scale [mMRC] score = 2-3) relative to preserved FEV_1 and FEV_1/FVC ratio, and a non-significant volume (FVC) response to short-acting bronchodilator. Given the nonobstructive findings on spirometry and lack of improvement after treatment with two different long-acting muscarinic antagonists (LAMAs), the referring physician was uncertain of the diagnosis of COPD. Repeat PFTs showed low $FEF_{25-75\%}$, "scooping" of the expiratory flow-volume curve at low lung volumes, low inspiratory capacity (IC), a mild but consistent increase in residual volume and functional residual capacity (either absolute or relative to TLC), increased specific airway resistance, low DL_{co}, and low alveolar volume/TLC. Cardiopulmonary exercise testing showed excess ventilation and dynamic hyperinflation leading to inspiratory constraints and limiting dyspnea. COPD was confirmed, and treatment was escalated to dual therapy with long-acting β_2 agonist (LABA)/LAMA. A two-month course of dual LABA/LAMA therapy was associated with improvement in dyspnea (mMRC score = 1), allowing the patient to enroll in a structured reconditioning exercise program.

Regrettably, the role of PFTs in COPD management has been progressively devalued in influential guidelines. The 2023 GOLD report, for instance, confirms previous versions by recommending forced spirometry for diagnosis only.[2] Despite suggesting the grading of FEV_1 impairment, little emphasis is given to its use (or to the use of any other functional marker) in treatment choices. Simply sticking to a rigid FEV_1/FVC cutoff for diagnosis can lead to misinterpretation, requiring careful individualization.[3] Findings of decreased available volume for tidal expansion (i.e., low IC) and/or increased "static" lung volumes give unique insights into the genesis and severity of COPD-related dyspnea. There is a large variability in key determinants of breathlessness at a given FEV_1: the severity of lung mechanical impairment (as determined by measurements of lung volumes) and gas exchange inefficiency (as assessed by DL_{co} and carbon monoxide transfer coefficient) is much more informative.[4] As depicted in Chart 1, this knowledge may have important implications for pharmacological and nonpharmacological treatment. Simple tests of functional exercise capacity, such as the six-minute walk test, might prove useful in quantifying patient impairment, in determining the potential need for exertional oxygen supplementation, and in prognostic estimation in multiparametric indexes. As shown herein, incremental cardiopulmonary exercise testing might indicate that "the lungs" do contribute to exertional dyspnea, thereby prompting treatment optimization in equivocal cases.[5]

CLINICAL MESSAGE

It is unlikely that the clinical and surgical management of COPD will ever dispense with functional data. The pulmonologist should combine the information provided by PFTs with clinical data (e.g., dyspnea severity, exacerbation burden), blood workup data (e.g., eosinophil count, IgE and alpha-1 antitrypsin levels), and structural findings (e.g., emphysema burden and distribution, airway disease) to decide on the best clinical or surgical treatment approaches (Chart 1).

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Chart 1. Key pulmonary function test data that are more likely to influence COPD management in individual patients.*

Clinical scenario	Recommendations
Diagnosis	• ↓Post-BD FEV_1/FVC is virtually diagnostic of COPD in the right clinical context • Post-BD FEV_1/FVC ≥ LLN but < 0.7 requires a case-by-case approach to identify other markers of obstruction/airway disease: ↓FEV_1, ↓$FEF_{25-75\%}$ (corrected for FVC or not), ↓FEV_3/FEV_6, "scooping" of the expiratory flow-volume curve, ↑sRaw, ↑RV and/or FRC, ↓DL_{CO} and/or K_{CO}, or V_A/TLC < 0.80. The higher the number of abnormalities, the greater the likelihood of disease. Chest imaging correlation might also be helpful • ↓Post-BD FEV_1/slow VC alone should be used with caution, as it increases the number of false positives for obstruction in the elderly • Spirometry normalization after inhaled BD speaks against COPD but may occur in the initial stages of the disease in a patient with dominant chronic bronchitis • Mild to moderate, proportional decrements in FEV_1 and FVC with ↔ FEV_1/FVC and ↔ TLC (the "nonspecific pattern") may occur in COPD: a volume response to inhaled BD and/or other markers of obstruction might be helpful to confirm COPD in the right clinical context • ↔ DL_{CO} does not exclude COPD: although it speaks against substantial emphysema, it may occur in patients with dominant airway disease/chronic bronchitis • When V_A/TLC < 0.80, K_{CO} might be pseudo-normal despite ↓DL_{CO}. If K_{CO} is reduced despite a low V_A/TLC, extensive emphysema should be suspected • CPET might provide further confirmatory evidence of COPD in equivocal cases: excess ventilation ($\dot{V}_E/\dot{V}CO_2$ nadir ≥ 34 L/L), dynamic hyperinflation, inspiratory constraints, or↑dyspnea-work rate and ↑dyspnea-$\dot{V}_E$ slopes
Disease severity/ risk estimation	• Post-BD FEV_1 yields only a rough estimate of a patient's ventilatory capacity • ↓FVC and/or VC usually indicate more severe disease (↑RV/TLC, frequently ↓IC) • ↓IC and/or IC/TLC are strong predictors of exertional dyspnea. In those with ↔ IC, ↑FRC (and, consequently, ↑TLC) also predicts a greater dyspnea burden • Increased "static" lung volumes at a given FEV_1 provide a better insight into the mechanical abnormalities relevant to dyspnea genesis, the functional reserve required to face the consequences of an exacerbation, and the severity of negative cardiopulmonary interactions, all of which have prognostic implications • Regardless of underlying mechanisms, the severity of DL_{CO} impairment predicts morbidity and mortality • 6MWD independently predicts poorer outcome, being used in multiparametric indexes of disease severity/prognosis • Hypoxemia and, in particular, hypercapnia indicate more extensive disease and poorer prognosis • In patients with dyspnea that is out of proportion (as per the mMRC score) to the severity of FEV_1 impairment, an increased resting and exercise physiological dead space may uncover a key determinant of breathlessness • Excess ventilation and early critical inspiratory constraints during CPET provide important clues regarding disease severity and daily life dyspnea, being associated with poorer survival • Short-term decreases in FEV_1 or FVC of ≥ 20% are considered "significant," although less pronounced decrements might be relevant in patients with greater impairment. Thresholds for year-to-year decrease are not well established and should be considered on a case-by-case basis • Decreases in DL_{CO} of > 4 units or > 15% (whichever is greater) indicate a fast decline, usually associated with progressive emphysema

Continue...▶

Chart 1. Key pulmonary function test data that are more likely to influence COPD management in individual patients.* (Continued...)

Clinical scenario	Recommendations
Clinical management	• A "negative" response to inhaled BD during spirometry should *not* be used as evidence against its use on a long-term basis • A volume response to inhaled BD (i.e., an increase in FVC and/or VC of ≥ 10%, or an increase in IC ≥ 0.2 L) is more relevant to dyspnea improvement than are changes in FEV_1 • A large volume response to inhaled BD (i.e., a large increase in FVC) might be associated with similar improvement in FEV_1: the latter finding should not be unrestrictedly used as evidence of associated asthma • Increased longitudinal variability in FEV_1—particularly when FVC varies little—may suggest associated asthma in the right clinical context, thereby prompting a more liberal use of ICS • Severe lung hyperinflation and/or gas trapping indicate worse abnormalities in the "slow" compartment (small airways): BDs/inhalers with greater distal deposition might be particularly effective • Inspiratory muscle weakness (e.g., MIP < 70% predicted) might prompt inspiratory muscle training in dyspneic, maximally treated patients—particularly if dyspnea is out of proportion (as per the mMRC score) to only mild to moderate gas trapping • BiPAP may be considered for those with pronounced daytime hypercapnia ($Paco_2$ > 50-55 mmHg) and/or recent/frequent hospitalization for acute-on-chronic respiratory failure; conversely, CPAP should be offered to those with comorbid OSA • Resting oxygen supplementation targeting Sao_2 > 90% (88-92% in hypercapnic patients) should be offered to those with Pao_2 ≤ 55 mmHg or Sao_2 < 88% or Pao_2 of 56-59 mmHg and right heart failure or erythrocytosis on room air • Some dyspneic patients do derive symptomatic benefit from exertional oxygen supplementation when Sao_2/Spo_2 < 88% on room air • Patients with FEV_1 of 15-45% predicted, TLC ≥ 100% predicted, severe gas trapping (RV ≥ 175%), and DL_{co} > 20% of predicted are more likely to report benefit after bronchoscopic lung volume reduction • Noninvasive mechanical ventilation during acute exacerbations is indicated in the presence of respiratory acidosis ($Paco_2$ ≥ 45 mmHg, pH ≤ 7.35) • Persistent or worsening hypoxemia (Pao_2 < 40 mmHg) and/or severe/worsening respiratory acidosis ($Paco_2$ ≥ 60 mmHg and increasing, pH ≤ 7.25 and decreasing) despite supplemental oxygen (via Venturi mask or requiring Fio_2 > 0.4) and noninvasive ventilation during exacerbations should prompt admission to intensive care for life-threatening acute respiratory failure
Surgical management	• TLC > 100% predicted, severe gas trapping (RV > 150% predicted), pronounced decrement in VA/TLC, ↔ or near normal DL_{co}, and ↔ arterial blood gases are useful to predict which patients are prone to derive greater symptomatic benefit from giant bullectomy • Post-BD FEV_1 < 45% predicted, RV > 150% predicted, and TLC > 100% predicted help in identifying adequate candidates for lung volume reduction surgery among those with reduced exercise capacity and dominant upper-lobe-predominant emphysema; conversely, the risk of perioperative death increases in those with FEV_1 and/or DL_{co} < 20% predicted • Patients who are not candidates for lung volume reduction and have a homogeneous distribution of emphysema, post-BD FEV_1 and/or DL_{co} < 20% of predicted, and a history of exacerbations associated with moderate to severe hypercapnia ($Paco_2$ > 50 mmHg), pulmonary hypertension, and/or cor pulmonale despite oxygen therapy are potential candidates for lung transplantation

BD: bronchodilator; LLN: lower limit of normal; FEV_3: forced expiratory volume in three seconds; FEV_6: forced expiratory volume in six seconds; sRaw: specific airway resistance; FRC: functional residual capacity; K_{co}: carbon monoxide transfer coefficient; V_A: alveolar volume; CPET: cardiopulmonary exercise testing; $\dot{V}_E$: minute ventilation; $\dot{V}co_2$: carbon dioxide output; IC: inspiratory capacity; 6MWD: six-minute walk distance; ICS: inhaled corticosteroids; mMRC: modified Medical Research Council dyspnea scale; and OSA: obstructive sleep apnea. *Unless otherwise indicated, ↑, ↔, and ↓ values are relative to the statistical limits of normal.

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