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

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BACKGROUND

Interstitial lung disease (ILD) encompasses a large and heterogeneous group of diffuse parenchymal disorders which are typically associated with low lung compliance and impaired gas exchange. A comprehensive evaluation of pulmonary function (spirometry, "static" lung volumes, DLco, oxygenation) is recommended in the initial assessment and follow-up in all patients with suspected or confirmed ILD.[1]

OVERVIEW

A 78-year-old never smoking woman reported a 12-year history of dry cough which had been unsuccessfully treated as secondary to gastroesophageal reflux disease. She also complained of progressive dyspnea (mMRC = 2) over the past few months. Physical examination revealed fine, Velcro-like crackles over the lower lung fields. Spirometry showed normal FEV_1 and FVC with an FEV_1/FVC ratio above normal (113% of the predicted value);

Assessing dysfunction at rest

- Spirometry may suggest a restrictive ventilatory defect: ↓ FVC plus ↔ or ↑ FEV_1/FVC
- ↑ mid-expiratory flows may unravel incipient/mild restriction
- ↓ TLC confirms restriction; however, ↓ FRC and ↓ RV may coexist with still-preserved TLC
- (F)VC might be preserved despite extensive fibrosis if TLC and RV decrease in tandem
- Although all "static" lung volumes are typically reduced, RV may be relatively preserved, resulting in a high RV/TLC ("complex restriction")
- DLco might be reduced even when lung volumes are still within normal limits
  - o A severely reduced DLco (< 40%) and a low IC are strong predictors of disabling dyspnea

Assessing dysfunction on exercise

- The 6MWT is helpful in quantifying functional impairment and the severity of exertional hypoxemia
- Longitudinal interpretation of changes in the 6MWT distance should carefully consider known confounders, e.g., O_2 flows, walking aids, variations in body weight, locus of symptom limitation
- Continuous monitoring of SpO_2 might provide a better metrics of the overall burden of exertional hypoxemia than end-exercise SpO_2
- CPET might be helpful in exposing excessive ventilation for the metabolic demand and mechanical constraints in patients with "out-of-proportion" dyspnea
- Cycling-based CPET, however, usually underestimates the severity of exertional hypoxemia compared with walking (treadmill)

Uncovering evidence of, or risk factors for, disease progression

- Absolute decline in FVC ≥ 5% pred within 1 yr (e.g., from 50% to 45% pred)
- Absolute decline in Hb-corrected DLco ≥ 10% pred within 1 yr
- Any form of pulmonary fibrosis with one of the following in the past 2 years should be considered for lung transplant referral: relative decline in FVC ≥ 10% (e.g., from 60% to 54% pred); relative decline in DLco ≥ 15%; relative decline in FVC ≥ 5% in combination with worsening of respiratory symptoms or radiographic progression
- Other criteria for referral to lung transplant include: FVC < 80% pred, DLco < 40% pred, or increasing supplemental O_2 requirements at rest/exercise

Identifying prognostic factors at rest and exercise

- Evaluation of changes over time (6-12 months) usually provide more accurate prognostic information than baseline values alone
- FVC and DLco consistently remain in different multidimensional indexes to predict mortality in IPF, e.g., the GAP index (**G**ender, **A**ge, and **P**hysiology variables)
- Absolute decline in FVC > 10% pred, though smaller declines (5-10% pred) have also been associated with worse prognosis in IPF
- Low walking distance (< 207-350 m) and desaturation during the 6MWT
- Low peak $\dot{V}O_2$ (< 61% pred or ≤ 13.8 mL/kg/min) and high $\dot{V}E/\dot{V}co_2$ nadir (> 34 L/L) during CPET

Caveats and Pitfalls

- The bulk of the evidence derives from studies with patients with IPF
- The value of PFTs in the differential diagnosis of ILDs is limited, though IPF is typically associated with more severe hypoxemia than other prevalent ILDs, such as sarcoidosis and most connective tissue disease-lLDs
- Obstruction, alone or combined with restriction, might be seen in some ILDs, e.g., lymphangioleiomyomatosis. chronic eosinophilic pneumonia, hypersensitivity pneumonitis, sarcoidosis, and connective tissue disease-lLDs
- ↓ DLco (corrected for hemoglobin) in the presence of normal or near normal lung volumes should raise the suspicion of pulmonary vascular disease or combined pulmonary fibrosis and emphysema in subjects with a smoking history

Figure 1. Key physiological abnormalities in patients with interstitial lung diseases (ILDs) that underpin clinical complaints and represent risk factors for poor clinical outcomes. Some caveats and limitations of pulmonary function tests (PFTs) in this context are described in the bottom. FRC: functional residual capacity; IC: inspiratory capacity; 6MWT: six-minute walk test; CPET: cardiopulmonary exercise testing; pred: predicted; yr: year; Hb: hemoglobin; $\dot{V}O_2$: oxygen consumption; $\dot{V}E$: ventilation; and $\dot{V}co_2$: carbon dioxide production.

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conversely, TLC, RV, and DLco were all reduced (67%, 57%, and 43% predicted, respectively). Chest HRCT indicated "probable" usual interstitial pneumonia. In this context, idiopathic pulmonary fibrosis was diagnosed after careful exclusion of other conditions associated with usual interstitial pneumonia.

Pulmonary function tests (PFTs) might provide ancillary information for ILD diagnosis, being instrumental to grade severity, gauge progression, and help in treatment choices (Figure 1). The typical spirometric findings of reduced FVC with a normal or increased FEV_1/FVC ratio might not be present in the initial stages of the disease. As this pattern is not always related to restriction, confirmation with measurements of lung volumes is usually required (i.e., TLC < lower limit of normal).[2] A common mistake is the assumption that a preserved FVC rules out restriction: a sizeable fraction of patients with early/mild ILD—as in the present case—shows low TLC but preserved (F)VC, provided RV decreases in tandem with TLC.[3] Not infrequently in mild disease, FVC is still preserved, but the mid-expiratory flows are supranormal, indicating increased lung elastic recoil. Despite spirometric values within normal range and normal-to-mildly reduced TLC, patients with mild fibrosis usually present with impaired gas transfer at rest (low DLco), leading to an excessive ventilation to the metabolic demand during cardiopulmonary exercise testing.[4] Lower baseline FVC and DLco, and oxygen desaturation during the six-minute walk test are known predictors of poor survival.[1] Recent data indicate that a severely reduced DLco (< 40% predicted) signals multiple interconnected mechanisms (hypoxemia, low O_2 delivery, hemodynamic abnormalities, greater mechanical constraints) that jointly conspire to decrease exercise tolerance in these patients.[5] Repeated measurements of FVC and DLco should be used in conjunction with the burden of respiratory symptoms and chest imaging to establish whether there is, or not, disease progression (Figure 1).

CLINICAL MESSAGE

"Full" PFTs (i.e., not only spirometry) associated with the six-minute walk test and, in selected cases, cardiopulmonary exercise testing, are important to ILD management across the spectrum of disease severity. Longitudinal assessment with the patient serving as the control of him/herself is paramount, paying particular attention to (F)VC in association with DLco and exertional hypoxemia.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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