The role of the pulmonary function laboratory to assist in disease management: connective tissue diseases

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

BACKGROUND

The respiratory system is variably affected by the systemic consequences of connective tissue diseases (CTDs). These abnormalities contribute to morbidity and mortality, being ascribed to direct autoimmune effects, drug toxicity, and/or opportunist infections. Pulmonary function tests (PFTs) might help recognize respiratory involvement, constituting an important auxiliary tool for CTD management.[1]

OVERVIEW

A 22-year-old woman with systemic lupus erythematosus under treatment with methotrexate and hydroxychloroquine reported worsening dyspnea over 10 months [currently modified Medical Research Council (mMRC) score = 4/4]. Chest CT showed minor atelectatic bands only. A severe and proportional reduction in FEV_1 [32% of the predicted values (pred)] and FVC (28% pred) coexisted with moderately severe decrement in TLC (50% pred), supranormal K_{CO}, and reduced maximal inspiratory pressures. Given the absence of any other cause for extraparenchymal restriction, she was diagnosed with shrinking lung syndrome. Pulse therapy with cyclophosphamide was associated with partial recovery of lung function (FEV_1 and FVC ≈40% pred) and marked clinical improvement (mMRC = 2) four months later (Case #1). A 63-year-old ex-smoker (30 pack-years) woman with undifferentiated systematic rheumatic disease reported nonproductive cough and progressive exertional dyspnea (mMRC = 2) over 6 months, associated with a nonspecific interstitial pneumonia pattern on HRCT. Serial spirometry showed a 10% relative decline in FVC from 2.29 L (67% pred) to 2.06 L (61% pred), fulfilling a functional criterion for progressive pulmonary fibrosis.[2] Oral azathioprine was related to improvement in both FEV_1 and FVC (≈78% pred) and dyspnea (mMRC = 1).

Although respiratory involvement is thought to occur at later stages of CTDs, they may be the initial presentation ("lung dominant"). Conversely, some patients may remain asymptomatic for a long time despite impaired PFTs or abnormalities in chest imaging. Interstitial lung disease (ILD) and pulmonary hypertension are the most common respiratory complications. A spectrum of other manifestations, however, may occur including airway disease (bronchiectasis, bronchiolitis), other pulmonary vascular disease (pulmonary embolism, chronic thromboembolic pulmonary hypertension), pleurisy, and respiratory muscle weakness.[3]

A restrictive ventilatory defect is the typical presentation of ILD (Case #2) but may also occur in the presence of respiratory muscle weakness (Case #1) and pleural space disease. The two last complications are typically associated with a supranormal K_{CO} ("extraparenchymal" restriction), provided there is no anemia or another cause for an out-of-proportion decrease in DL_{CO} relative to lung volume.[4,5] Conversely, an isolated reduction in hemoglobin-corrected DL_{CO}, in turn, may signal incipient ILD or some sort of pulmonary vascular involvement.[5] Each CTD has predominant patterns of respiratory involvement with routine pulmonary function assessment recommended accordingly. The conjunction of PFT findings suggests the type of respiratory complication (Chart 1). In most diseases, serial measurements of FVC and (if possible) DL_{CO} at least yearly are used in order to evaluate progression in CTD-ILD.[1-3]

CLINICAL MESSAGE

Respiratory symptoms are a frequent feature of CTDs. Proper diagnosis of the underlying causes might be challenging, notably in patients with multiple comorbidities (e.g., COPD, asthma, heart failure) and obesity. The pulmonologist should be familiar with the pattern of abnormalities expected in the most frequent diseases (Chart 1), interpreting testing results and considering concurrent clinical, laboratory, and imaging findings.

AUTHOR CONTRIBUTIONS

All authors equally contributed to this manuscript.

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.

	Respiratory involvement	PFTs recommendation	Most frequent PFTs findings
Scleroderma spectrum	• Some degree of pulmonary involvement is present in more than 80% of patients • Main manifestations are ILD and pulmonary vascular disease, leading to PAH • Other pulmonary complications include thromboembolic disease, pleural disease, aspiration pneumonitis, airway disease, and lung cancer • More than one of these processes may be presentin each patient	• All patients should have complete PFTs (spirometry, plethysmography, and DLco) performed at the initial presentation • ↓DLco (< 65% pred) without significant lung volume reduction or a decrease in DLco ≥20%/year suggests PH, particularly in a patient with long-standing limited cutaneous sclerosis • A ratio of FVC/DLco (in % pred) > 1.6 also suggests PH	• The combination of ↓ TLC and JHb-corrected DLco suggests ILD • An absolute decline in FVC > 5% pred and/or DLco > 10% pred within 1 year of follow-up suggests CTD-ILD progression • ↓ Hb-corrected DLco with normal lung volumes can be seen in pulmonary vascular disease or early ILD • ↓ TLC with preserved DLco (usually accompanied by high Kco) suggests respiratory muscle weakness, pleural disease and/or abnormalities of thoracic cage mobility • Flow-volume loops can help identify upper airway obstruction when blunted peak inspiratory flow is present • The combination of airflow limitation (↓FEV1/FVC), normal or ↓ DLco, and HRCT with expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules may establish a "clinical" diagnosis of bronchiolitis obliterans • Both obstructive and restrictive patterns have been noted in follicular bronchiolitis, although restriction is more common • A ↑ DLco suggests pulmonary hemorrhage • Sitting and supine FVC decline (>10%), ↓ maximum voluntary ventilation, and ↓ maximal inspiratory and expiratory pressures are helpful to confirm and monitor respiratory muscle weakness • A six-minute walk test is useful for detecting exercise-induced oxygen desaturation
Rheumatoid arthritis	• ILD and pleural disease are the most common abnormalities • The leading cause of upper airway obstruction is cricoarytenoid arthritis; less common causes include rheumatoid nodules on the vocal cord or vasculitis in recurrent laryngeal or vagus nerves • Lower airway involvement includes bronchiolitis obliterans, follicular bronchiolitis, and bronchiectasis • ↑risk of pulmonary embolism • Abnormalities of thoracic cage mobilitylikely due to pleurisy, myopathy, and thoracic rigidity	• The role of surveillance for lung disease in patients with rheumatoid arthritis is unclear Respiratory symptoms or abnormalities in respiratory examination should trigger the evaluation with a chest radiograph • Additional studies are utilized (PFTs, HRCT) based on the findings of the clinical evaluation, chest radiograph and the degree of clinical suspicion for associated pleuropulmonary disease	
SLE	• Most patients show involvement of the lung, pulmonary vasculature, pleura, and/or diaphragm at some point during thecourse of the disease • Respiratory manifestations include pleuritis (with or without effusion), pneumonitis, ILD, PH, shrinking lung syndrome, and alveolar hemorrhage • The risk of thromboembolic involvement is increased in those with antiphospholipid antibodies or with lupus anticoagulant	• Full PFTs are obtained to assess the pattern and severity of respiratory impairment. • Distinguishing between diffuse alveolar hemorrhage and acute lupus pneumonitis is difficult. DLco could help differentiate these entities (↑ DLco is suggestive of alveolar hemorrhage), but the patients are usually too ill to undergo the testing in practice	
Sjogren's syndrome	• Approximately 10-20% show airwaysand/or pulmonary interstitial involvement indicated by symptoms, abnormal PFTs, and/or chest radiograph • Involvement of exocrine glands may affect the upper respiratory tract • Bronchiolitis is the main small airway lesion, including follicular, chronic, and obliterative forms • A valve effect phenomenon may ensueand result in lung cysts or bullae. Theymaycoexist with bronchiectasis, micronodules, ground-glass opacity, and/or air-trapping	• Baseline complete PFTs and chest radiograph may be considered to evaluate for the presence of underlying pulmonary manifestations • In patients with chronic respiratory symptoms, crackles on chest examination, or an abnormal chest radiograph, full PFTs and HRCT are useful to evaluate/grade pulmonary involvement • In a patient with respiratory symptoms, the interval for repeat HRCT and PFTs must be determined individually according to the nature and severity of functional impairment	
Idiopathic Inflammatory myositis	• ILD is a major cause of morbidity and mortality, affecting 30-40% of patients • Respiratory muscle weakness maybe sub clinical, more frequently seen inpatients with severe skeletal muscle weakness. Hypercapnic respiratory failure has been reported, rarely as the presenting manifestation • Spontaneous pneumomediastinum, pulmonary hypertension (Group 3 from ILD), and venous thromboembolism are other complications	• PFTs help distinguish the cause of dyspnea (e.g., ILD versus respiratory muscle weakness) and assess the severity of respiratory impairment • Hypercapnia due to respiratory muscle weakness should be considered in the presence of complaints of daytime sleepiness, reduced maximal respiratory pressures (<30% pred), and FVC < 55% pred	

Chart 1. Most relevant respiratory involvement and overall recommendations for pulmonary function testing (PFT) in different connective tissue diseases. Key PFT findings consistent with each respiratory complication are described in the third column. ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; % pred: percentage of predicted values; PH: pulmonary hypertension; SLE: systemic lupus erythematosus; Hb: hemoglobin; and Kco: carbon monoxide transfer coefficient of the lung.

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