(Mis)Interpreting changes in pulmonary function tests over time

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

BACKGROUND

Pulmonary function tests (PFTs) are frequently repeated to judge whether potential changes, either spontaneously or after treatment, exceed test variability or surpass the effects of aging.[1] Although cutoffs for "significant" changes over time are available (Table 1), assessing their clinical relevance is substantially more complex. The reader should also consider the intervening effects of disease complications, comorbidities, thoracic surgery, and changes in body weight.

OVERVIEW

A 76-year-old man with mild interstitial pulmonary fibrosis ("patient A") but worsening dyspnea underwent PFTs 4 months after the last assessment. FVC and TLC decreased by ≈12%, raising concerns for disease progression. Alveolar volume (V_A), however, decreased in tandem with TLC (V_A/TLC remained ≈0.9). As DL_{CO} varied minimally (−3%), carbon monoxide transfer coefficient (K_{CO})—DL_{CO}/V_A—increased from 89% predicted to 148% predicted, indicating extraparenchymal restriction. Severe inspiratory muscle weakness was confirmed, and further investigations revealed motor neuron disease.[2]

A 10-year-old boy with cystic fibrosis ("patient B") showed recurrent, "significant" drops in FVC and, consequently, FEV_1 (up to 24%), indicating worsening gas trapping. After stabilization, both parameters markedly decreased again, leading the reader to suggest another exacerbation. Unbeknownst to him, however, the patient had developed bilateral transudative pleural effusions caused by hypoproteinemia and leading to decreased TLC.

A 55-year-old woman with severe asthma ("patient C") showed reduced FVC and FEV_1 over a one-year follow-up period. The results prompted changes in treatment, with deleterious consequences for dyspnea. Plethysmography revealed minor decreases in functional residual capacity (FRC) and RV, as well as a large reduction in TLC; of note, the BMI had increased from 38.7 kg/m^2 to 47.9 kg/m^2. Cardiopulmonary exercise testing revealed abnormalities consistent with morbid obesity.[3]

Assessing changes in PFTs is often more clinically valuable than making a single comparison with predicted values. The sources of confusion, however, are multiple.[4] For instance, it may arise when several parameters are followed, as some of them might indicate worsening just by chance (false positives). FEV_1 is arguably the most

Table 1. Suggested cutoffs for a "significant" decrease (i.e., changes above the measurement variability, changes associated with disease progression/worsening, or a combination of the two) in selected lung function parameters in adults.

Clinical scenario	FVC	FEV_1	DL_{CO}
"Normal" lung function			
Short-term	≥ 12% from baseline and 200 mL	≥ 12% from baseline and 200 mL	> 4 mL/min/mmHg
Year-to-year	≥ 15% from baseline	≥ 10-15% from baseline > 30-40 mL/year	> 10% from baseline
COPD			
Short-term	≥ 20% from baseline	≥ 20% from baseline	> 4 mL/min/mmHg or > 15% from baseline, whichever is greater
Year-to-year	Unknown	Unknown	Unknown
Asthma	≥ 12% from baseline and 200 mL	≥ 12% from baseline and 200 mL	Unknown
IPF and other progressive fibrosing ILDs	≥ 10% from baseline or a relative decline of ≥ 5 < 10% plus worsening respiratory symptoms, increasing fibrosis on chest imaging, or a combination of the two	Unknown	> 15% from baseline
Pulmonary hypertension	Unknown	Unknown	> 4 mL/min/mmHg or > 15% from baseline, whichever is greater

IPF: idiopathic pulmonary fibrosis; and ILD: interstitial lung disease.

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.

reliable parameter because it decreases in obstructive and restrictive diseases. However, it may decrease in a patient with obstructive disease because of the effects of incident restriction ("patient B"), and vice-versa. Moreover, wide fluctuations in FEV_1 over time are characteristic of asthma. Clinically relevant reductions in lung volumes and gas exchange efficiency[5] might be missed by FEV_1 alone. Establishing whether the rate of decline in FEV_1 in COPD is accelerated or not is even more challenging because of highly variable rates. Among lung volumes, FRC is the least variable over time (± 10%), but it is exquisitely sensitive to increases in BMI ("patient C").

CLINICAL MESSAGE

Discriminating between statistical significance and clinical significance is key to a cogent interpretation of longitudinal PFTs. If a change in a reproducible parameter (such as FEV_1 or FVC) is above the threshold of natural variability (Table 1), its practical relevance should be judged in light of clinical information. "Nonsignificant" decreases may sum up across sequential tests, leading to relevant decrements that are better appreciated when discrete values are plotted against time. In most circumstances, it is more likely that an actual change has occurred when it is demonstrated in more than two sequential measurements.

REFERENCES

1. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-968. https://doi.org/10.1183/09031936.05.00035205
2. Neder JA, Berton DC, O'Donnell DE. Pitfalls in the interpretation of pulmonary function tests in neuromuscular disease. J Bras Pneumol. 2020;46(4):e20200352. https://doi.org/10.36416/1806-3756/e20200352
3. Neder JA, Berton DC, O'Donnell DE. Obesity: how pulmonary function tests may let us down. J Bras Pneumol. 2020;46(3):e20200116. https://doi.org/10.36416/1806-3756/e20200116
4. Kohansal R, Soriano JB, Agusti A. Investigating the natural history of lung function: facts, pitfalls, and opportunities. Chest. 2009;135(5):1330-1341. https://doi.org/10.1378/chest.08-1750
5. Neder JA, Berton DC, O'Donnell DE. Integrating measurements of pulmonary gas exchange to answer clinically relevant questions. J Bras Pneumol. 2020;46(1):e20200019. https://doi.org/10.1590/1806-3713/e20200019