The pulmonary function laboratory in the investigation of dyspnea of unknown origin

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

BACKGROUND

Chronic dyspnea (i.e., dyspnea for at least 3 months) negatively impacts the health-related quality of life of ~10% of the general population. In a sizable fraction of these individuals, the underlying cause remains unclear after detailed clinical assessment, basic pulmonary function tests, and chest imaging, characterizing dyspnea of unknown origin (DUO). The "lung doctor" is frequently called to assess these patients for diagnostic clarification, an endeavor fraught with complexities in most circumstances.

OVERVIEW

A 67-year-old, nonsmoking, sedentary woman (BMI = 34.6 kg/m^2) reported progressive exertional dyspnea after SARS-CoV-2 infection two years before (a modified Medical Research Council dyspnea score of 3-4). Her medical history was positive for systemic arterial hypertension, depression, and fibromyalgia. Extensive investigation at rest was inconclusive (Figure 1). Incremental cardiopulmonary exercise testing revealed a tachypneic breathing pattern with a consistent reduction in dynamic inspiratory capacity despite the lack of resting hyperinflation; moreover, she reported disproportionate dyspnea relative to the achieved work rate (a Borg scale score of 5/10 at 45 W, > the 95th percentile).[1] These findings raised the suspicion of inspiratory muscle weakness/fatigue[2]: although MIP and MEP were reduced, they were still within the limits of normal. Of note, however, 12-s maximal voluntary ventilation (MVV; 38 L/min) was reduced both in % of predicted (47%) and relative to the MVV estimated from FEV_1 (73 L/min). Electroneuromyography of the extremities of the upper and lower limbs was consistent with myopathy

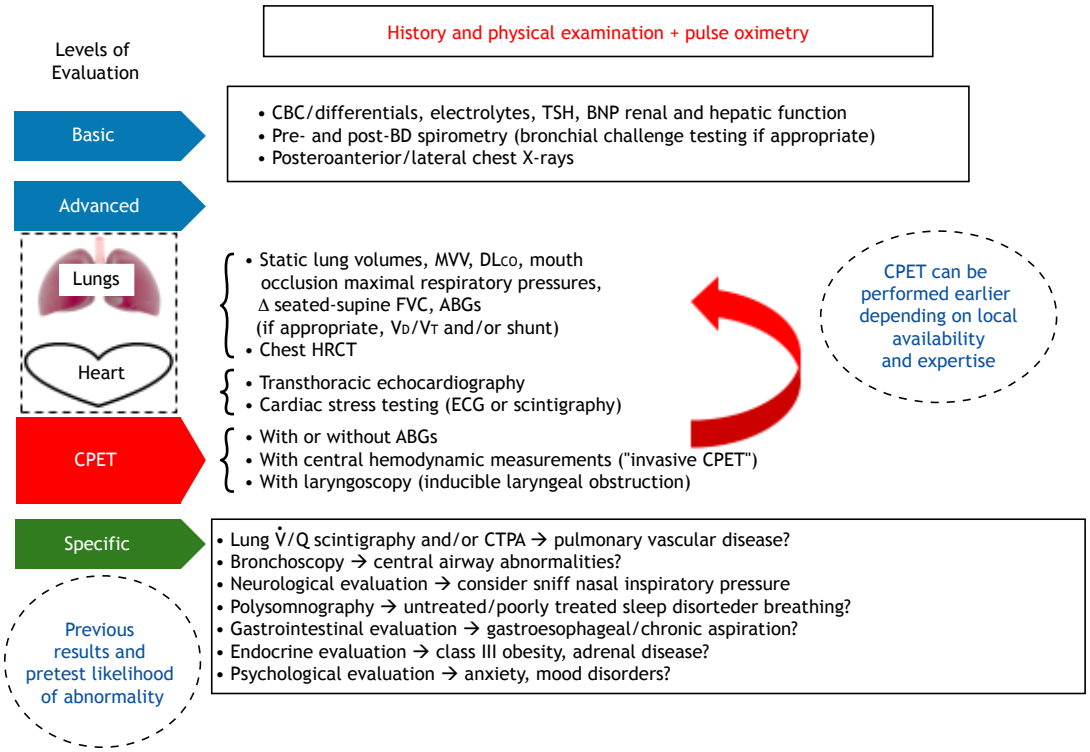

Figure 1. Suggested workup of patients with chronic dyspnea of unknown origin. The levels are based on the complexity of the tests and the epidemiology of the disease(s) that can be uncovered. Note that the sequence can be modified on the basis of clinical impression and depending on local resources and expertise. Modified with permission from Berton et al.[7] CBC: complete blood cell count; BNP: brain natriuretic peptide; BD: bronchodilator; MVV: maximal voluntary ventilation; ABGs: arterial blood gas analysis; V_D/V_T: dead space to tidal volume ratio; ECG: electrocardiography; CPET: cardiopulmonary exercise testing; V̇/Q: ventilation/perfusion; and CTPA: CT pulmonary angiography.

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.

with myotonic discharges. At this writing, the patient is under investigation for myotonic dystrophy versus channelopathies, potentially triggered by SARS-CoV-2 and associated with an inflammatory response.

DUO is a heterogeneous syndrome that is frequently multifactorial. Only a minority of patients with DUO (including our patient) report dyspnea in the absence of any active disease known to elicit the symptom (dyspnea without an apparent cause). More commonly, however, there is dyspnea with multiple potential causes in patients who present with cardiopulmonary or systemic diseases and who are deemed to be "optimally treated" (residual exertional dyspnea).[3] There is no uniformly accepted algorithm for the investigation of DUO (Figure 1). The value of more sophisticated pulmonary function tests—particularly those assessing the small airways[4]—remains elusive. Cardiopulmonary exercise testing is frequently useful to rule out major cardiopulmonary disease, showing the negative consequences of obesity, simple deconditioning, and, occasionally, hyperventilation/dysfunctional breathing.[5] Dynamic inspiratory capacity measurements are paramount,[6] and arterial blood gas analysis (or arterialized capillary blood gas analysis) is often required. In the present case, increased metabolic demands secondary to obesity led to normal peak oxygen uptake despite reduced peak work rate.[5] An apparently normal MIP might be misleading because 1) overactivation of the accessory inspiratory muscles during the static maneuver might not be dynamically sustained (MVV, exercise); and 2) thresholds for an abnormal test result can vary up to 50% depending on the set of reference values.[5]

CLINICAL MESSAGE

The principles of Bayesian inference considering disease prevalence locally and the pretest likelihood of abnormality should be applied to judge the best investigative steps in individual patients with DUO. By following a logical stepwise sequence (Figure 1), the pulmonologist can minimize costs and enhance the diagnostic yield while avoiding futile and potentially iatrogenic procedures.

REFERENCES

1. Neder JA, Berton DC, Nery LE, Tan WC, Bourbeau J, O'Donnell DE; et al. A frame of reference for assessing the intensity of exertional dyspnoea during incremental cycle ergometry. Eur Respir J. 2020;56(4):2000191. https://doi.org/10.1183/13993003.00191-2020
2. Berton DC, Gass R, Feldmann B, Plachi F, Hutten D, Mendes NBS, et al. Responses to progressive exercise in subjects with chronic dyspnea and inspiratory muscle weakness. Clin Respir J. 2021;15(1):26-35. https://doi.org/10.1111/crj.13265
3. Neder JA. Residual Exertional Dyspnea in Cardiopulmonary Disease. Ann Am Thorac Soc. 2020;17(12):1516-1525. https://doi.org/10.1513/AnnalsATS.202004-398FR
4. Neder JA, Berton DC, O'Donnell DE. Small airway disease: when the "silent zone" speaks up. J Bras Pneumol. 2023;48(6):e20220414. https://doi.org/10.36416/1806-3756/e20220414
5. Neder JA, Berton DC, O'Donnell DE. The Lung Function Laboratory to Assist Clinical Decision-making in Pulmonology: Evolving Challenges to an Old Issue. Chest. 2020;158(4):1629-1643. https://doi.org/10.1016/j.chest.2020.04.064
6. O'Donnell DE, Milne KM, Vincent SG, Neder JA. Unraveling the Causes of Unexplained Dyspnea: The Value of Exercise Testing. Clin Chest Med. 2019;40(2):471-499. https://doi.org/10.1016/j.ccm.2019.02.014
7. Berton DC, Mendes NBS, Olivo-Neto P, Benedetto IG, Gazzana MB. Pulmonology approach in the investigation of chronic unexplained dyspnea. J Bras Pneumol. 2021;47(1):e20200406. https://doi.org/10.36416/1806-3756/e20200406