Dyspnea is a distressing symptom that is defined as "the subjective experience of breathing discomfort".(1) The onset of dyspnea can be acute (during the transition from rest to physical activity) or chronic (persisting for more than one month).(1) Chronic dyspnea is one of the most common symptoms of many chronic diseases and conditions, such as cardiorespiratory diseases, cancer, and obesity, reducing exercise tolerance, physical activity levels, and health-related quality of life.(2) Epidemiological studies have estimated that 56-98% of patients with chronic respiratory diseases and 50-70% of patients with cancer complain of dyspnea, which can be the cause of up to 50% of admissions to ERs, with a peak incidence in patients between 55 and 69 years of age.(3)

Pathogenesis-directed therapy of underlying mechanisms is the cornerstone of the management of chronic dyspnea; however, dyspnea can persist despite optimal treatment of the underlying pathophysiology.(4) Identification of chronic dyspnea requires careful medical history taking, as well as physical examination and testing, typically including electrocardiography, chest X-ray, pulse oximetry, spirometry, and blood workup.(5) Nevertheless, even after the aforementioned clinical assessments, the origin of chronic dyspnea can remain unexplained in a large proportion of patients.(6) Therefore, it has been proposed that physiological stress-induced cardiopulmonary exercise testing (CPET) can help identify etiologies of dyspnea that are often missed in standard clinical examinations.(7)

In a review article published in the current issue of the JBP, Berton et al.(8) highlight the clinical utility of CPET in the evaluation of dyspnea. On the basis of clusters of findings in the literature, the authors describe a comprehensive approach to the predominant pathophysiological responses (Figure 1) that can lead to intolerable dyspnea during exercise, namely: a) oxygen delivery/utilization mismatch; b) mechanical ventilatory impairment; c) impaired gas exchange/ altered ventilatory control; d) increased metabolic demands due to obesity; and e) dysfunctional breathing/hyperventilation disorders. In addition, the authors contrast those pathophysiological patterns with normal responses to CPET found in the literature, thus providing greater mechanistic insight into the genesis of dyspnea.

The review article by Berton et al.(8) makes a significant contribution to this field of study. The authors have provided pragmatic identification and interpretation of CPET responses that, if integrated into standard clinical examination and testing, can help health care professionals and clinicians identify potential sources of dyspnea. In 2020, Neder et al.(7) took another important step toward the identification of sources of dyspnea by establishing a frame of reference (established in healthy men and women between 20 and 85 years of age) for assessing the intensity of exertional dyspnea based on percentiles derived from the Borg scale score (0-10) at standardized work rates and minute ventilation during CPET.

Traditionally, CPET measures cardiovascular, respiratory, and metabolic responses. Berton et al.(8) highlighted the need for CPET to include additional assessments, such as pulmonary arterial pressure measurement and laryngoscopic assessment of vocal fold motion, to identify potential origins of dyspnea when central hemodynamic abnormalities or laryngeal obstruction are suspected. In this context, research increasingly acknowledges the utility of assessing inspiratory neural drive by diaphragmatic electromyography (EMGdi) with an esophageal catheter during CPET.(9) In fact, in a wide range of cardiorespiratory diseases, dyspnea is likely to be related to the load/capacity imbalance of the respiratory muscles.(10) The EMGdi recordings during exercise are closely related to dyspnea across levels of disease severity as well as in healthy individuals.(11,12) In addition, technological advances in the assessment of EMGdi have overcome the technical barriers of the past, such as the patient burden associated with esophageal catheter placement.(9) With regard to the complexity of analyses of EMG data, further advances have enabled a semi-automated method, leading to a more time-efficient analysis of EMGdi signals.(13) Therefore, the evaluation of inspiratory neural drive through its surrogate measure of EMGdi activity during CPET may offer an additional mechanistic insight into the origins of dyspnea across different pathologies.

Dyspnea is a multidimensional symptom resulting from multiple mechanisms (Figure 1). In patients with chronic lung diseases, recent evidence has shown that apart from ventilatory constraints, gas exchange abnormalities, and central hemodynamic impairment, insufficient adjustments in the perfusion of extradiaphragmatic respiratory muscles during exercise, assessed by near-infrared spectroscopy with indocyanine green (NIRS-ICG) for the determination of blood flow index (BFI), are associated with a greater perception of dyspnea.(14,15) One potential mechanism is that local reduction of respiratory muscle oxygenation during exercise increases respiratory muscle metabolic acidosis and sensory afferent traffic innervating respiratory muscles.
II–IV fibers) to the somatosensory cortex, thereby increasing the sensory intensity of unsatisfactory inspiration.\(^{(15)}\) With the major advantage of avoiding arterial catheterization, NIRS-ICG for the determination of BFI provides a reliable, minimally invasive tool that can be integrated into the standardized CPET for collecting complementary information concerning respiratory muscle (and locomotor muscle) perfusion in order to detect or confirm the absence of this potential origin of dyspnea in various clinical populations.\(^{(16)}\)
Identifying the etiologies of chronic unexplained dyspnea is undoubtedly a challenging process. The use of CPET and the translation of the advances described above to clinical settings is a logical step forward in facilitating the determination of the causes of chronic unexplained dyspnea, and the approach can be tailored to the unique physiology of each patient. More importantly, detailing the major physiological mechanisms may facilitate the choice of the appropriate therapeutic interventions.

AUTHOR CONTRIBUTIONS

ZL: conception. ZL, DL, and RG: drafting, revision, and approval of the final version of the manuscript.

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