Exertional dyspnea in chronic obstructive pulmonary disease: mechanisms and treatment approaches
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Purpose of review
The purpose of this review is to identify new advances in our understanding of dyspnea in patients with chronic obstructive pulmonary disease (COPD). Specifically, we highlight new scientific discoveries concerning the language of dyspnea, its underlying mechanisms and its clinical management.

Recent findings
Recent studies have confirmed that dyspnea is multidimensional and that sensory intensity and quality dimensions of the symptom are readily distinguishable by the individual. When respiratory discomfort is sufficiently unpleasant in COPD, an emotive response is evoked which encompasses feelings of fear and anxiety. Such descriptors appear to be unique to the disease state and are rarely reported in health. Recent brain imaging studies have proposed a central role of the limbic and paralimbic systems in the genesis of perceived dyspnea or its affective component. There is new indirect evidence that the elaboration of endogenous opioids may modulate dyspnea intensity during exercise in COPD. New physiological studies in COPD have provided novel insights into mechanisms of dyspnea both in early disease and in the setting of coexistent obesity.

Summary
The effective management of dyspnea in COPD remains a significant challenge for caregivers but recent treatment innovations such as helium–oxygen, inhaled furosemide and breathing feedback techniques have yielded early positive results.

Keywords
bronchodilators, chronic obstructive pulmonary disease, dyspnea, exercise, heliox, inhaled furosemide

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exercise tolerance is distinctly different in health and disease [7].

Qualitative descriptors of dyspnea in chronic obstructive pulmonary disease
The pathophysiology of COPD and its sensory consequences are best considered in the context of the aging respiratory system, as most patients with the disease are elderly [8,9]. Williams et al. [10] recently addressed the important question of whether the language used to describe dyspnea could also be used to accurately categorize older individuals into those who have a diagnosis of COPD versus those who do not. They found that only patients with COPD volunteered words with affective connotations such as ‘frightening’ and ‘worried’ to describe their breathing difficulty. They also found that 85% of individuals could be correctly categorized within their original group (COPD or non-COPD) using these descriptors of perceived respiratory difficulty. This work bolstered the argument that self-reported descriptions of dyspnea that encompass its emotive dimension (e.g. fear or anxiety) are more likely to have pathophysiological origins. This paper also highlights the importance of using greater precision in the language of dyspnea both for the purpose of clinical assessment and in the research setting.

The affective dimension of perceived dyspnea
A recent study by Banzett et al. [11**] tested the validity of the multidimensional model of dyspnea. These investigators tested the hypothesis that different types of laboratory-induced dyspnea are capable of evoking different affective responses. In this study of 12 healthy individuals, the sense of air hunger (induced by constraining ventilation in the setting of hypercapnia) provoked a consistently greater affective response (i.e. more unpleasantness) than the sense of increased respiratory work/effort (induced by maximal eucapnic voluntary hyperpnea against inspiratory resistance) even though the intensity of these sensations were graded to be of similar magnitude by the participants.

Brain imaging
Von Leupoldt et al. [12**] recently demonstrated that the perception of laboratory-induced dyspnea and pain are processed in common areas of the brain, including the anterior/mid insula, anterior cingulated cortex, amygdala and medial thalamus. These phylogenetically ancient areas of the brain are involved in the processing of emotions such as fear and anxiety (i.e. affective responses). They are known to become activated when threatening sensations such as dyspnea and pain are perceived, and likely represent a motivational drive originating in central limbic structures that initiates fight-or-flight behaviors to avoid the potential risk of suffocation or severe tissue damage. Recent advances in our understanding of dyspnea that have emerged from studies of brain imaging have been comprehensively reviewed by Davenport and Vovk [13].

Together, the studies of Williams, Banzett and Von Leupoldt highlight the importance of the much neglected affective component of dyspnea. There is now increasing support for the hypothesis that activation of central limbic structures contributes importantly to the conscious experience of perceived respiratory difficulty during physiological stress in humans. The corollary is that similar neural mechanisms are at play in the COPD patient during exercise when the perceived respiratory discomfort is sufficient to evoke an emotive response.

The role of endogenous opioids
It has long been proposed that the elaboration of endogenous opioids during physiological stress may modulate dyspnea or its affective dimension in COPD [14]. A recent randomized, double-blind, placebo-controlled, crossover study in 17 patients with moderate-to-severe COPD showed that the administration of naloxone, an opioid antagonist, consistently increased (vs. placebo) dyspnea intensity ratings during high-intensity constant-work-rate treadmill exercise [15]. There were no significant differences in physiological responses to exercise between treatments. Therefore, the increased dyspnea during naloxone was not related to any concomitant increase in central respiratory drive (or ventilation) due to reversal of endogenous opiate effects on ventilatory control. The differential impact of naloxone on the intensity, unpleasantness and affective domains of dyspnea in COPD remains to be determined. Collectively, these recent studies are sure to reignite interest in the study of the affective component of dyspnea in COPD. Further systematic study of interventions that ameliorate dyspnea by selectively targeting the central nervous system (e.g. behavioral modification, opioids, anxiolytics, etc.) are urgently needed.

Exertional dyspnea in chronic obstructive pulmonary disease
The study of the origins of exertional dyspnea in COPD has been hampered by the inability to precisely quantify central neural respiratory motor drive and/or sensory information from peripheral afferents in the lungs, airways, respiratory muscles and chemoreceptors. Moreover, the remarkable redundancy inherent in all somatosensory systems confounds interpretation of the results of traditional psychophysical experiments that utilize chemical and mechanical loading of the respiratory system to mimic the effects of disease. Current constructs of exertional dyspnea in COPD that emphasize the central role of increased contractile respiratory muscle effort and neuromechanical uncoupling of the respiratory system have been reviewed elsewhere and are summarized in Fig. 1 [9,16].
Figure 1 Proposed neurophysiological model of perceived respiratory discomfort (dyspnea) during exercise.

Briefly, the somatosensory cortex calibrates and interprets the appropriateness of the mechanical/muscular response of the respiratory system to the prevailing level of central respiratory motor drive. When the mechanical/muscular response of the respiratory system is constrained, by disease, below the level dictated or preprogrammed by central respiratory motor drive then the intensity of ‘unsatisfied inspiration’ increases in direct proportion to the widening disparity between drive and mechanics (i.e., neuromechanical uncoupling). Increased activation of central limbic structures as a result of neuromechanical uncoupling is also a likely component of ‘respiratory distress’. \( V'O_2 \) and \( V'CO_2 \), metabolic rate of oxygen consumption and carbon dioxide production; Type III and IV mechanosensitive and metabosensitive afferents in the peripheral locomotor (and respiratory) muscles and their vasculature; PSRs, pulmonary stretch receptors; C-fibers, bronchopulmonary C-fibers; J-receptors, juxtapulmonary capillary receptors; GTOs, Golgi tendon organs; \( pCO_2 \), partial pressure of carbon dioxide; \([H^+]\), hydrogen ion concentration; \([La^-]\), lactate ion concentration; \( PaO_2 \), arterial partial pressure of oxygen; \( SaO_2 \), arterial blood oxygen saturation. Adapted with permission from [16].
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Exertional dyspnea in mild chronic obstructive pulmonary disease

Previous studies in more advanced COPD have shown that dyspnea is consistently associated with increased central respiratory drive and increased ventilatory stimulation. This in turn reflects increased chemostimulation secondary to the effects of disruption in ventilation/perfusion relationships and pulmonary gas exchange. Mechanical constraints on tidal volume expansion as a result of dynamic pulmonary hyperinflation also undoubtedly contribute. Oir et al. [17**] were the first to study mechanisms of activity-related dyspnea in symptomatic patients with mild COPD (FEV$_1$ post bronchodilator at least 80% predicted and FEV$_1$/FVC <0.7). These authors found that exercise capacity was significantly reduced and exertional dyspnea intensity was higher at a given work rate in the mild symptomatic COPD compared with age-matched healthy individuals. Despite the largely preserved FEV$_1$, the mild COPD group had higher ventilatory requirements for a given metabolic load throughout exercise, likely as a result of nonuniformity in ventilation/perfusion relations. Indeed the existence of such disruptions in pulmonary gas exchange in early COPD has recently been confirmed by Rodriguez-Roisin et al. [18**]. In addition, these patients with mild airway obstruction (by FEV$_1$ criteria) had evidence of extensive small airway dysfunction. During exercise they showed significant dynamic pulmonary hyperinflation (with average increase in end-expiratory lung volume of 0.54 l) and a relatively rapid and shallow breathing pattern. Such dynamic hyperinflation is associated with increased elastic and inspiratory threshold loading of the inspiratory muscles and disrupts the normally harmonious relationship between increasing contractile respiratory muscle effort and simultaneous thoracic volume displacement during exercise, that is, neuromechanical coupling.

To test the hypothesis that lung hyperinflation contributes to dyspnea even in mild COPD, the current authors examined the effect of acute administration of an inhaled anticholinergic bronchodilator [19*]. Bronchodilator therapy (compared with placebo) was associated with consistent reduction of pulmonary resistance, dynamic hyperinflation and work of breathing during exercise. These mechanical improvements were linked to significant reduction in dyspnea intensity ratings at standardized ventilation during exercise.

These studies have uncovered significant abnormalities in airway function in symptomatic patients with relative minor spirometric abnormalities and provide a solid physiological rationale for bronchodilator treatment in selected individuals. However, a limitation of these studies was that they were conducted in symptomatic patients; further studies are required to determine if these results can be extrapolated to patients with mild COPD who do not report troublesome dyspnea during daily activity.

Dynamic lung hyperinflation during daily activities in chronic obstructive pulmonary disease

Several studies have confirmed the importance of lung hyperinflation as a limiting factor for exercise performance and as a contributor to dyspnea in patients with COPD; however, there are no data about its impact on daily activities. In a study by Garcia-Rio et al. [20*], 110 moderate-to-severe COPD patients performed a 6-min walk test, an incremental and a constant work-rate cycle exercise test and daily physical activity assessment measured by accelerometer. By multivariate linear regression, the extent of dynamic hyperinflation during the incremental exercise test (change in end-expiratory lung volume) and the 6-min walking distance were the best independent predictors of daily activity.

Impact of obesity on exertional dyspnea in chronic obstructive pulmonary disease

The prevalence of obesity and COPD is increasing dramatically throughout the Western World. Although both conditions have been studied in isolation, little is known about their interaction with respect to effects on dynamic respiratory mechanics and dyspnea. Ora et al. [21*] recently studied 18 obese COPD and 18 normal-weight COPD patients, well matched for age and FEV$_1$ (~50% predicted), at rest and during incremental cycle exercise. Contrary to current assumptions regarding the deleterious effects of combining these two disorders, the investigators found that obese patients with COPD did not experience greater dyspnea or exercise limitation than normal-weight patients with comparable FEV$_1$. They argued that the negative consequences of obesity (i.e. increased metabolic load, increased ventilatory requirements and increased oxygen cost of breathing) were partly counterbalanced by the advantages (with respect to respiratory muscle performance) of breathing at a lower absolute lung volume. A similar conclusion was reached in a previous study, which examined the effects of obesity on exercise performance and respiratory sensation in individuals without airway obstruction [17**].

Therapeutic approaches

The effective management of dyspnea in COPD remains a significant challenge for caregivers but recent treatment innovations such as helium–oxygen, inhaled furosemide and breathing feedback techniques have yielded early positive results.

A new application for an old drug

Several published studies have found that single-dose inhalation of furosemide, a powerful loop diuretic, appears
to modulate the activity of sensory afferents in the lungs and airways of laboratory animals. Inhaled furosemide was also shown to decrease the intensity of dyspnea provoked experimentally in healthy humans at rest [22]. Ong et al. [23] were the first to provide evidence that such treatment may have a possible clinical application in COPD. Jensen et al. [24] conducted a randomized, double-blind, placebo-controlled, crossover study to explore possible mechanisms of action of this drug in 20 patients with moderate-to-severe COPD. Nebulized furosemide treatment was associated with modest but consistent improvements in exercise endurance time and dyspnea; however, the magnitude of effect varied across patients. In that study, inhaled furosemide was associated with improvements in airway function with concomitant increases in dynamic inspiratory capacity, tidal volume and mean tidal expiratory flow rates. The mechanisms of improved airway function remain conjectural (e.g., reduced airway mucosal edema or modulation of vagal reflexes). Nevertheless, these preliminary studies on the effects of furosemide in both health and COPD collectively confirm that this drug has potential dyspnea-relieving properties (at least in selected individuals) that deserve further exploration.

Adjuncts to pulmonary rehabilitation in chronic obstructive pulmonary disease

Pulmonary rehabilitation is one of the most powerful interventions [25] at our disposal to improve activity-related dyspnea and quality of life in COPD. The mechanisms of improvement are complex but include both psychological (improved self-efficacy) and physiological (reduced ventilatory requirements) factors. A major challenge has been the provision of an adequate training stimulus to achieve consistent physiological improvements in patients with severe ventilatory limitation and incapacitating dyspnea. This problem has prompted the development of a number of experimental strategies aimed at unloading the respiratory muscles and improving dynamic mechanics during exercise training (e.g., oxygen, heliox, bronchodilators, noninvasive mechanical ventilation) [26–31]. Eves et al. [32] recently demonstrated that breathing a mixture of helium–hyperoxia (60%–40%helium–hyperoxia) was superior to breathing room air in increasing the intensity and duration of the exercise-training stimulus in normoxic COPD patients during a 6-week rehabilitation program. This result supports the hypothesis that the higher training intensity achieved during multimodality exercise training the greater the clinical benefit. It remains to be determined whether adjunctive helium–oxygen combinations are superior to more traditional approaches, which combine maximal bronchodilation with oxygen supplementation during exercise training.

Biofeedback techniques

Ventilation feedback training is another interesting technique that has been employed to improve the impact of pulmonary rehabilitation in COPD. The rationale here is to modify the respiratory pattern during exercise and specifically to reduce the respiratory rate (by increasing expiratory time) so as to facilitate lung deflation and reduce dynamic hyperinflation. In the study of Collins et al. [33], 64 moderate-to-severe COPD patients were divided into three groups and randomized to three interventions: ventilation feedback plus exercise, ventilation feedback alone and exercise alone. After 6 weeks of training, they found that ventilation feedback alone or in combination with exercise training modified breathing pattern (slower inspiratory and expiratory times with decrease in ventilation). Only ventilation feedback plus exercise training successfully reduced dynamic hyperinflation and dyspnea intensity ratings, compared with the other two interventions. However, the incorporation of breathing pattern biofeedback into the exercise-training regimen was not shown to have superior effects on cycle exercise endurance compared with unassisted training. Regardless, this study was the first to show that biofeedback methods can be successfully employed to improve dynamic respiratory mechanics and perceived respiratory discomfort during activity in COPD.

Conclusion

For patients with COPD, the effective amelioration of dyspnea remains an elusive goal. However, our understanding of the nature and source of this troublesome symptom continues to grow. Recent studies have elucidated the multidimensional nature of dyspnea and have shown that individuals can reliably discriminate between the intensity, quality and affective domains of this symptom. The affective dimension may be the dominant contributor to respiratory distress in mechanically compromised patients with COPD and may have its neurological origin in over-activation of the limbic and paralimbic systems of the brain. The ability to evaluate the impact of therapeutic interventions on dyspnea, in terms of its quality and affective response, opens up exciting new opportunities to advance this field of study. The stage is now set to more systematically test new therapeutic approaches that target the central nervous system and that modify the emotive response to perceived respiratory discomfort. Preliminary studies on the effect of innovative interventions such as helium–oxygen inhaled furosemide and computerized ventilation biofeedback techniques all show promise and deserve further scrutiny.

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($1001–5000), and has received industry-sponsoring grants from Boehringer Ingelheim, GSK, and Merck Frost Canada ($10001 or more) and from Novartis and Pfizer ($50,001–100,000).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


This is the first large study to demonstrate that the measurement of endurance time operating lung volumes, ventilation, and ratings of dyspnea intensity is highly reproducible in COPD during high intensity, constant work rate cycle exercise.


This paper highlights the importance of using greater precision in the language of dyspnea both for the purpose of clinical assessment and in the research setting.


It is the first study to show that laboratory-induced air hunger was associated with an affective response whereas mechanical loading sufficient to induce increased work or effort was not.


This study demonstrated that the perception of laboratory-induced dyspnea and pain (and their affective responses) are centrally processed in areas of the brain that constitute the limbic and paralimbic systems.


This study demonstrated that naloxone increases dyspnea perception during exercise in patients with COPD. This effect was independent of any change in the physiological response and likely reflects central inhibition of the activity of endogenous opioids.


Symptomatic patients with GOLD stage I COPD can have significant pathophysiological abnormalities that lead to clinically important dyspnea and exercise intolerance.


This important study provides a comprehensive assessment of the abnormalities in pulmonary gas exchange that exist across the COPD severity range. It highlights the existence of significant gas exchange abnormalities even in patients with milder COPD.


This study demonstrated that release of cholinergic tone of airway smooth muscle in mild symptomatic COPD is associated with consistent and potentially important improvements in dynamic respiratory mechanics.


This is the first study to show a correlation between the extent of dynamic hyperinflation during cycle exercise and impairment of daily activities, in patients with COPD.


This study demonstrates that the combination of obesity and COPD does not result in an increase dyspnea perception. The negative mechanical effects of obesity are partly counterbalanced by the beneficial effects of breathing at relatively lower lung volumes.


This study confirmed that inhaled furosedomide has potential dyspnea-relieving properties in COPD patients and that its effect is due in part to a bronchodilator effect.


This study demonstrated that breathing a mixture of helium–hyperoxia increases the intensity and duration of the exercise training in patients with COPD during pulmonary rehabilitation.


This study showed that ventilatory feedback during exercise training was effective in decreasing dynamic lung hyperinflation and exertional dyspnea intensity.