Breathlessness in patients with chronic airflow limitation. Mechanisms and management

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Breathlessness in Patients with Chronic Airflow Limitation*

Mechanisms and Management

Denis E. O'Donnell, MD, F.C.C.P.

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Breathlessness is a common and often incapacitating symptom in patients with advanced chronic airflow limitation (CAL) and may seriously curtail their ability to exercise. In its later stages, the disease is essentially irreversible and management strategies must necessarily be directed toward symptom alleviation. Currently, the effective management of breathlessness has remained an elusive goal, but our understanding of the source and mechanisms of this distressing symptom continues to grow. This review represents a pragmatic consideration of the pathophysiologic basis of breathlessness in CAL in an attempt to identify specific sources of this unpleasant sensation that might be amenable to treatment.

**Breathlessness: Physiologic Correlates**

Although breathlessness generally intensifies as pulmonary function declines, there is wide overlap in the relationship between breathlessness and commonly measured resting physiologic parameters such as dynamic expiratory flow rates, static lung volumes, and arterial blood gases. The study of sensory-mechanical interrelationships in CAL is preferably undertaken in the setting of induced breathlessness during chemical loading, external mechanical loading, broncho-provocation, or exercise. Since breathlessness in CAL is primarily activity related, mecha-

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Key words: breathlessness; chronic airflow limitation; COPD; dynamic compression; dynamic hyperinflation; exercise

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given $\dot{V}_E$/MBC. The source of this variability is multifactorial and likely includes variability in the extent of intrinsic mechanical loading of the ventilatory muscles, their contractile strength, and functional characteristics. Variation in the extent of dynamic airway compression is also a potential contributing factor. Other little studied factors that may contribute to intersubject variability in exertional breathlessness in CAL include variation in cardiorespiratory receptor activation in the presence of raised pulmonary artery pressure or concomitant left ventricular dysfunction. In addition, variability in behavioral responses to ventilatory stress is undoubtedly important.

**Intrinsic Mechanical Loading and Breathlessness in CAL**

The most important mechanical abnormality in patients with CAL is expiratory flow limitation. One possible consequence of expiratory flow limitation is dynamic airway compression (DC) that occurs if transpulmonary pressures exceed the critical pressure at which flow is maximal (Pcr). It has been postulated that DC and distortion of the airways mouthwards from the flow-limiting segment contribute to breathlessness in CAL. The second consequence of expiratory flow limitation is dynamic lung hyperinflation (DH). In the setting of increased ventilatory demand when expiratory flow is reduced and expiratory time is insufficiently long, inspiration begins before lung volume has declined to the level normally dictated by the balance of static recoil of the lung and chest wall and end-expiratory lung volume (EELV) increases. The potential sensory consequences of DC and DH are considered below.

**Dynamic Airway Compression and Breathlessness in CAL**

To examine the effects of DC on respiratory sensation, we applied a flow-proportioned negative pressure (expiratory assist) at the mouth during expiration using a specially modified rolling-seal spirometer during tidal breathing in nine demonstrably flow-limited patients with severe CAL (FEV$_1$ = 27 ± 9 percent predicted, mean ± SD). Accordingly, we induced DC by transmural airway pressure manipulation without altering pressure-flow relationships or airway mechanics upstream from the flow-limiting segment. Expiratory assist (EA) resulted in unpleasant respiratory sensation, which in many subjects was anecdotally akin in quality to their previous experience of breathlessness. By contrast, EA in normal subjects, in whom DC was not induced, resulted in a pleasant sensation of unimpeded expiration. The mechanism by which airway distortion and compression results in unpleasant respiratory sensation was not precisely elucidated in that study but may result from the stimulation of sentient airway mechanoreceptors that are distributed in abundance throughout the upper airways. Alternatively, DC could contribute to breathlessness indirectly via stimulatory influences on ventilation in these severely mechanically compromised patients: a mean EA of $-9.7$ cm H$_2$O/L/s resulted in a mean increase of 12 percent in $\dot{V}_E$. Although DC represents a potential source of breathlessness in CAL, it would appear that significant DC is seldom encountered at rest or during moderate activity in such patients. We have argued that in demonstrably flow-limited patients during spontaneous breathing at rest, expiratory transthoracic pressures attain, but do not exceed, the critical flow-limiting pressure (Pcr), thus obviating DC and its deleterious sensory consequences. Similarly, during constant-load submaximal exercise in patients with severe CAL, the results of two studies suggested that transpulmonary pressures appear to be modulated to closely match Pcr. Furthermore, the application of positive expiratory pressure (+4 cm H$_2$O) at the mouth, an intervention that would be expected to attenuate DC if it existed, did not have any consistent salutary effect on respiratory sensation in exercising patients with CAL.

The close matching of transthoracic pressures and Pcr during expiration is possibly an adaptive response that operates at a conscious level in response to sensory information from mechanoreceptors in central airways. This strategy would not only minimize DC, but would also avoid the unpleasant sensation that likely occurs when there is dissociation between expiratory effort (reflected by the change in intrathoracic pressures) and anticipated mechanical consequence (change in expiratory flow). However, this adaptation may fail at higher exercise levels prior to breakpoint where transthoracic pressures have been shown in some instances to greatly exceed Pcr. Under these conditions, unpleasant sensation induced by DC may indeed contribute to the global sensory experience of exertional breathlessness.

In a recent study, we examined qualitative aspects of breathlessness at the breakpoint of incremental exercise in CAL (n=23). It is noteworthy that 65 percent of this sample reported inspiratory difficulty alone, 25 percent reported both inspiratory and expiratory difficulty, and only 10 percent reported predominant expiratory difficulty. Thus, perceived expiratory difficulty, which would be expected to arise when transthoracic pressures exceed Pcr, is much less frequently reported than inspiratory difficulty at exercise termination in patients with CAL, supporting the contention that DC per se is not a...
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predominant source of breathlessness in the majority of such patients.

Breathlessness and Dynamic Lung Hyperinflation in CAL

In contrast to normal subjects, EELV in patients with CAL often increases above resting values early in exercise (Fig 1). Acute increases in EELV of 0.31±0.55 L and 0.30±0.32 L (mean±SD) have been reported with considerable variation noted in the range. In flow-limited patients, EELV is dynamically determined and largely dictated by breathing pattern responses. To the extent that avoidance of DC and the attendant unpleasant sensation is desirable (see above), termination of expiration (or onset of inspiration) before expiratory flow is complete and the resultant DH may be effected at a conscious level in response to sensory input from airway mechanoreceptors. Regardless of the mechanism, it is evident that while DH serves to optimize expiratory flows in the setting of increased ventilatory demand, it does so only at the expense of serious negative mechanical and sensory consequences.

The effects of acute DH on ventilatory muscle function have only recently been fully appreciated. Dynamic lung hyperinflation results in elastic loading of the respiratory muscles: tidal volume (VT) oscillates at a stiffer portion of the pressure-volume relationship of the respiratory system. Dynamic lung hyperinflation also results in inspiratory threshold loading: with each breath, the inspiratory muscles must generate enough pressure to overcome the inward elastic recoil of the respiratory system at end expiration before any inspiratory flow begins; DH further compromises the ability of already disadvantaged respiratory muscles (particularly the diaphragm) to generate pressure, and functional inspiratory muscle weakness is further aggravated by increased velocity of shortening (VT/Ti) as ventilation increases.

In contrast to normal subjects, patients with CAL lose the ability to reduce EELV below passive FRC with exercise. Therefore, expiratory muscles cannot share to the same extent in the work of breathing being undertaken by the inspiratory muscles.

Recently we systematically studied the role of DH in exertional breathlessness of CAL using a multiple regression model with Borg ratings as the dependent variable: ΔBorg=0.16+0.03(ΔEELVdyn, percent TLC)+0.15(ΔF)+0.05(ΔVT, percent VC), r=0.78, p<0.001 (where Δ=change from rest, EELVdyn=(percent TLC)=dynamic end-expiratory lung vol-

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**Figure 1** Left (A), Lung volumes during exercise, standardized for ventilation, in CAL (n=23) and age-matched normal subjects (n=10). Patients with CAL have significantly (p<0.001) greater lung hyperinflation and diminished inspiratory reserve volume (IRV) at any given ventilation. Values are mean±SEM. Right (B), Relationship between actual and predicted changes in Borg breathlessness ratings during exercise in patients with CAL (r=0.78, p<0.001). EILV=end-inspiratory volume; VT=tidal volume; TLC=total lung capacity (From O'Donnell DE, Webb KA. Am Rev Respir Dis 1993; 148:1351-57, by permission.)
Neuroventilatory Dissociation

A detailed discussion of the neurophysiologic basis of breathlessness is beyond the scope of this review (excellent comprehensive reviews are available). The relative importance of peripheral respiratory mechanoreceptor activation, medullary activation, or central motor command output in the genesis of the global sensory experience of breathlessness is not precisely known and remains speculative. Current theories of the origin of breathlessness emphasize the central importance of motor output or neural activation of the ventilatory muscles. Certainly, there is considerable experimental evidence that breathlessness, under a variety of conditions, increases as a function of motor output as reflected by the pressures generated by the ventilatory muscles expressed as a fraction of their maximal pressure generation. The previously outlined correlation between breathlessness ratings and \( \frac{V_e}{MBC} \) supports this notion since this ratio also crudely reflects motor output relative to its maximum. It has been proposed that motor output can be consciously perceived as “sense of effort” via collateral discharge or efferent copy from respiratory-related neurons in the medulla to the sensory cortex. “Sense of effort” is a discrete respiratory sensation that is distinguishable from peripheral muscular sensations relating to muscle tension development or displacement.

Effort is generally expressed in physiologic terms as a function of the ratio of esophageal pressure (Pes) to the maximal pressure-generating capacity (P_{max}). This ratio correlates strongly with breathlessness. In exercising patients with CAL, resistive loading and particularly acute increases in elastic/threshold loading result in greater tidal excursions of inspiratory pressure required to maintain ventilation in pace with metabolic demand. Moreover, maximal power output is reduced by acute DH. Thus, the inspiratory muscles are forced to operate at a high fraction of their maximal force-generating capacity and perceived inspiratory effort is greatly increased. While heightened inspiratory muscle contractile effort undoubtedly contributes to breathlessness in CAL, awareness of disproportionate or unsatisfied inspiratory effort, i.e., “cannot get enough air in,” is almost uniformly reported by breathless patients (personal communication). This latter qualitatively discrete sensation may have its physiologic origins in neuroventilatory dissociation (NVD) of the respiratory pump.

The concept of NVD implies that, in addition to motor output, sensory feedback from peripheral respiratory mechanoreceptors contributes importantly to respiratory sensation. Thus, during resting spon-

**Neuroventilatory Dissociation**

![Diagram](image_url)
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The effective management of breathlessness in CAL awaits a clearer understanding of the neural pathways that subserve respiratory sensation and the mechanisms whereby sensory inputs are processed and modulated at the level of the spinal cord and brain. Current approaches to management are based primarily on our understanding of the pathophysiologic mechanisms of breathlessness. Since breathlessness in CAL is encountered under conditions of increased ventilation, increased impedance to inspiratory muscle action, or functional inspiratory muscle weakness, it follows that any measure that will reduce ventilatory demand or that will unload or strengthen the inspiratory muscles should theoretically ameliorate dyspnea. The neurophysiologic corollary of this is that any intervention that will reduce the amplitude of motor output or enhance neuroventilatory coupling will relieve breathlessness. In addition, the associated anxiety may itself be amenable to treatment.

The study of therapeutic aspects of breathlessness has been greatly facilitated by the recent development of validated instruments that permit us to critically evaluate the impact of an intervention on symptom intensity. Traditionally, therapeutic approaches to breathlessness have focused on measures designed to improve ventilatory capacity or reduce ventilatory demand, i.e., increase ventilatory reserve. In patients with advanced disease and relatively fixed pathophysiologic derangements, in general, only modest improvements in ventilatory reserve can be achieved.

Improving Ventilatory Capacity

Bronchodilator Therapy: As a first step, every effort should be made to reduce the resistive and elastic load on the inspiratory muscles by optimizing bronchodilation. In some instances, adjunct anti-inflammatory medication may confer additional benefits. Relief of breathlessness can be achieved with various bronchodilators in the presence of only small improvements in FEV1, i.e., <15 percent. In this setting, improvement may be more closely linked to reduced gas trapping with concomitant enhancement of inspiratory muscle function. In this regard, there is preliminary evidence that reduced exertional breathlessness following anticholinergic medication in CAL is a function of reduced lung hyperinflation and consequent reduction of motor output. Similarly, reduced breathlessness and improved exercise tolerance after oral theophyllines has been shown to be associated with reduction of thoracic gas volumes.

Inspiratory Muscle Training: Recently, considerable efforts have been expended toward improving the performance properties of the respiratory muscles in order to achieve relief of breathlessness by enhancing ventilatory capacity. Specific inspiratory muscle training (IMT) has been shown to increase the strength and endurance of inspiratory muscles and improve symptoms in individual patients with CAL with demonstrable muscle weakness. However, a recent meta-analysis of available controlled studies of IMT failed to show significant subjective or objective improvement in most patients.
sults may be explained by the fact that, in CAL, respiratory muscles undergo adaptive structural and biochemical changes in response to intrinsic mechanical loading that results in relative preservation of muscle function, at least under resting conditions.41

**Reducing Ventilatory Demand**

*Exercise Training:* Manipulation of the components of the mass balance equation for ventilation, i.e., $\dot{V_e} = 0.86 \times \dot{V}CO_2/PaCO_2 [1 - VD/VT]$ so as to reduce ventilatory demand for practical purposes is largely confined to reducing CO$_2$ production (\(\dot{V}CO_2\)). Thus, exercise training at high intensities in motivated younger patients with moderate CAL has been shown to enhance aerobic capacity.42 In these patients, post-training reductions in lactate levels and $\dot{V}CO_2$ resulted in reduced ventilation at a given external power output.42 However, reduction of $\dot{V}e$ by altering the anaerobic threshold is less consistently achieved in patients with CAL with more advanced disease, where modest improvements in ventilatory reserve are more likely to be attributable to enhanced mechanical efficiency following training. Controlled studies that have examined the impact of supervised multimodality exercise training on breathlessness have shown consistent benefit even in patients with severe disease.43-45 Although much of this improvement may be explained by behavioral factors, i.e., desensitization to breathlessness, physiologic improvements may also contribute. In a recent study, we examined possible contributing factors to relieve breathlessness after exercise training in 23 patients with severe CAL. Reduced $\dot{V}e$/workrate slopes emerged as the only independently significant (albeit weak) predictor of change in Borg ratings ($r = 0.47$, $p < 0.025$).45 In a second study, we found that significant posttraining reductions in $\dot{V}e$/MBC occurred in the absence of significant changes in base excess measurements, suggesting that factors other than improved aerobic metabolism are important.46 We attributed the reduced ventilatory demand to enhanced mechanical efficiency.46

*Oxygen Therapy:* Supplemental oxygen (O$_2$) has been shown to relieve exertional breathlessness and to improve exercise tolerance in most patients with CAL when compared with compressed air.47-50 The mechanisms of relief are still debated, but in hypoxemic patients they are likely related, in part, to reduced ventilatory demand secondary to blunted peripheral chemoreceptor sensitivity. However, central effects of O$_2$ on perceived discomfort at a given level of ventilation cannot be ruled out.50 Symptomatic relief may be linked to enhanced O$_2$ delivery (or utilization) to exercising limb and ventilatory muscles which results in delayed lactate accumulation, reduced $\dot{V}CO_2$, and reduced $\dot{V}e$ at a given work rate.50 In association with reduced $\dot{V}e$, we have found in a recent controlled study that O$_2$ therapy improves ventilatory mechanics during exercise: significant reductions in acute DH occurred in patients receiving 60 percent O$_2$ when compared with compressed air.50 Reduced DH correlated significantly ($p < 0.05$) with reduced Borg ratings after accounting for the change in $\dot{V}e$.50 Thus, O$_2$ relieves breathlessness not only by reducing motor output but also by improving neuroventilatory coupling. It is noteworthy that the beneficial effects of supplemental O$_2$ on breathlessness and exercise tolerance are observed in patients with CAL who do not meet current American Thoracic Society criteria for long-term O$_2$ therapy.49,50

*Opiates and Anxiolytics:* Opiates effectively relieve breathlessness in many patients with CAL.51,52 Postulated mechanisms include reduced motor command output or altered central perception of inspiratory difficulty at a given ventilation.51 However, serious adverse effects, particularly respiratory depression, preclude their routine use except in the palliative treatment of the terminally breathless patient.

Benzodiazepines have the potential to relieve breathlessness by their anxiolytic action and/or by reducing respiratory motor output. However, several controlled studies of various benzodiazepines have failed to demonstrate any consistent improvement over placebo.53,54 Moreover, the active drugs tended to be poorly tolerated.53 Limitations of these studies include small sample sizes and uncertainty as to whether the patients with CAL studied suffered from morbid anxiety in addition to breathing difficulty. However, given the prevalence of severe anxiety in breathless patients with CAL, it is reasonable to recommend a trial of anxiolytic therapy on an individual basis with careful monitoring of the symptomatic response.

**Mechanical Unloading of Inspiratory Muscles**

Currently, in the experimental setting, the efficacy of new methods of inspiratory muscle unloading is being evaluated in the management of breathlessness in CAL. In this respect, low-level continuous positive airway pressure (CPAP) administered acutely has been shown to ameliorate breathlessness and significantly improve exercise capacity in some patients with severe disease.14,15,55 Continuous positive airway pressure works by counterbalancing the effects of DH on the inspiratory muscles.55 Since the salutary effects of CPAP are achieved at a low level,55 i.e., 4 to 5 cm H$_2$O, its principal mechanical effect is thought to be that of negating the inspiratory threshold load with some reduction of the elastic work of breathing. Therefore, CPAP enhances neuroventilatory coupling and restores a more har-
A. BORG SCALE

Very severe 7
Severe 6
Somewhat severe 5
Moderate 4
Slight 3
Slight 2
Very slight 1
Nothing at all 0

CPAP
C1
C2

TIME (minutes)

FIGURE 3 Left (A), Intensity of breathlessness (Borg scale) against time during CPAP-assisted exercise and bracketing unassisted control periods (C1, C2) in a 71-year-old man (FEV1=90 percent predicted, RV=290 percent predicted) (From O'Donnell DE, Sanii R, Younes M. Am Rev Respir Dis 1988; 138:1510-14, by permission). Right, (B), Low-level CPAP improves the relationship between tidal Pes/Plmax and instantaneous changes in volume during exercise in CAL; autoPEEP=auto or intrinsic positive end-expiratory pressure.

In summary, while the most obvious mechanical defect in CAL is increased expiratory resistance, the major mechanical consequence is inspiratory muscle loading. Qualitatively, breathlessness in CAL primarily encompasses the perception of inspiratory difficulty and is commonly expressed in terms of heightened inspiratory effort or awareness of unrewarded inspiratory effort. Intensity of breathlessness correlates closely with physiologic indices such as VE/MBC or Pes/Plmax, which ultimately reflect motor output (expressed relative to maximum). In the clinical setting, breathlessness in CAL is encountered under conditions of increased ventilation, impeded inspiratory muscle action, or functional weakness. During exercise, acute DH represents an important source of breathlessness in CAL and variation in its extent contributes to intersubject variability in symptom intensity for a given ventilation. Without a precise monious balance between perceived inspiratory effort (Pes/Plmax) and the anticipated mechanical consequence (change in respired volume) (Fig 3). It should be emphasized that CPAP levels should be carefully titrated to the individual patient's subjective response; levels in excess of the inspiratory threshold load will result in further hyperinflation and attendant potentially deleterious mechanical, hemodynamic, and sensory consequences. Theoretically, CPAP could be used as an adjunct to exercise training.56 By prolonging exercise duration, CPAP may permit some very breathless patients to reach the hitherto unattainable threshold at which physiologic training effects are achieved. The potential utility of CPAP in the rehabilitative setting warrants further investigation.

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