Pathophysiology of Dyspnea in Chronic Obstructive Pulmonary Disease
A Roundtable

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Effective management of dyspnea in chronic obstructive pulmonary disease (COPD) requires a clearer understanding of its underlying mechanisms. This roundtable reviews what is currently known about the neurophysiology of dyspnea with the aim of applying this knowledge to the clinical setting. Dyspnea is not a single sensation, having multiple qualitative descriptors. Primary sources of dyspnea include: (*1*) inputs from multiple somatic proprioceptive and bronchopulmonary afferents, and (*2*) centrally generated signals related to inspiratory motor command output or effort. Respiratory disruption that causes a mismatch between medullary respiratory motor discharge and peripheral mechanosensor afferent feedback gives rise to a distressing urge to breathe which is independent of muscular effort. Recent brain imaging studies have shown increased limbic system activation in response to various dyspneogenic stimuli and emphasize the affective dimension of this symptom. All of these mechanisms are likely instrumental in exertional dyspnea causation in COPD. Increased central motor drive (and effort) is required to increase ventilation during activity because the inspiratory muscles become acutely overloaded and functionally weakened. Abnormal dynamic ventilatory mechanics and excessive chemostimulation during exercise also result in a widening disparity between escalating central neural drive and restricted thoracic volume displacement. This neuromechanical uncoupling may form the basis for the distressing sensation of unsatisfied inspiration. Interventions that alleviate dyspnea in COPD do so by improving ventilatory mechanics, reducing central neural drive, or both—thereby partially restoring neuromechanical coupling of the respiratory system. Self-management strategies address the affective aspect of dyspnea and are essential to successful treatment.

Keywords: dyspnea; mechanisms; respiratory mechanics; exercise; dynamic lung hyperinflation

Introduction

Denis E. O'Donnell

This roundtable represented a unique opportunity to bring together clinicians and scientists from around the world to discuss dyspnea and the numerous contributing mechanisms along with current research, measurement tools, and treatment options. Clinical trials of new therapeutic agents now commonly include assessments of dyspnea, and physicians are beginning to use tools to measure dyspnea during office visits. Thus, in recent years, there is greater awareness of the important patient-centered outcomes and more interest in learning how to manage the symptoms of chronic obstructive pulmonary disease (COPD). This round table was created with a goal of generating interest in the topic, which may lead to further research and ultimately to the utilization of effective therapeutic options for the management of dyspnea. The article that follows summarizes the main content of the presentations but does not capture all of the discussions that ensued. The presentations cover a diverse range of topics, beginning with an overview of dyspnea as a common clinical problem. Current concepts of the neurophysiologic mechanisms of dyspnea will then be discussed. The pathophysiologic and neurophysiologic underpinnings of exertional dyspnea in COPD will be reviewed to provide a rationale for effective therapeutic interventions. The impact and mechanisms of benefit

of modern treatment options such as bronchodilator therapy, oxygen, and heliox will be considered. Finally, the last section summarizes the impact of education and self-management strategies on symptom alleviation.

Dyspnea: The Clinical Problem

Donald A. Mahler

Dyspnea is common in patients with cardiac or respiratory disease as well as in healthy individuals who are obese and/or deconditioned. Certainly, the problems of obesity and sedentary life style are quite prevalent among elderly people who live in developed countries. Moreover, the aging process causes a gradual deterioration in lung function due to a decrease in lung elasticity, an increase in stiffness of the chest wall, and a decrease in respiratory muscle strength. Thus, there are several reasons why healthy older individuals may experience breathlessness.

In those less than 65 years of age, the prevalence of dyspnea in healthy adults ranges from 10 to 18% (1–6). More than 30% of elderly individuals (i.e., $\geq$ 65 years of age) report breathlessness with activities of daily living, including walking on a level surface or up an incline (7–11). The finding is similar for people from different countries, including France, the United Kingdom, and the United States (9–11). Women appear to experience breathlessness more frequently than men (5, 6, 9, 12, 13).

Various techniques have been used to study the perception of dyspnea. These include breathing through added resistive loads, breathing hypoxic or hypercapnic gas mixtures, and performing an exercise test. Healthy older individuals and patients with obstructive airway disease who have advanced age exhibit a diminished estimation of the intensity of breathlessness when breathing through external resistive loads (14). Cross-sectional studies have also shown a decrease in the ventilatory response to both hypoxia and hypercapnia with advancing age (15, 16). During cardiopulmonary exercise testing, older subjects (mean age 66 years) report higher dyspnea ratings as measured by the slope of dyspnea/power (watts) compared with younger subjects (mean age 19 years) (17). This higher slope in older subjects was evident in both women and in men (17). Moreover, Johnson and colleagues (18) found that healthy older subjects rated breathlessness greater than general fatigue during exertion, whereas healthy young people indicated that fatigue was greater than breathlessness. These overall findings are likely due to the higher level of ventilation observed in older individuals during exercise. However, it is unclear whether the higher ventilation is a direct result of the aging process or more a consequence of sedentary lifestyle, deconditioning, and/or weight gain that typically occur with advancing age. Regardless, the increased ventilatory response observed in older individuals during exertion and the diminished ventilatory capacity (i.e., reduced respiratory muscle strength that occurs with advancing age) contribute to the high prevalence of dyspnea reported by elderly individuals (17).

How common is breathlessness with activity? A telephone survey of patients with COPD living in North America and in Europe documented the frequency of breathlessness with daily activities (19). According to this questionnaire, one-fifth of the patients reported that they were breathless even when just sitting or lying still and 24% when talking. One-third said they were breathless when doing light housework or while getting washed or dressed, and nearly 70% were short of breath when walking up a flight of stairs. It is clear from these data that COPD is associated with a considerable burden of disease, affecting many things that are fundamental to everyday life such as the ability to breathe, talk, sleep, have sex, work, and socialize. Further-more, the severity of dyspnea generally progresses over time in patients with COPD (Figure 1) (20).

The experience of dyspnea encompasses different qualities based on the specific diagnosis. For example, Elliott and colleagues (21) reported that patients with COPD living in the United Kingdom describe "distress" associated with breathlessness. In the United States, Mahler and colleagues (22) found that patients with COPD chose the following three statements from a list of 15 possibilities to describe their experience: "my breathing requires effort" (51%), "I feel out of breath" (49%), and "I cannot get enough air in" (38%). Seventy-five percent of patients studied by O'Donnell and colleagues (23) in Canada selected "increased inspiratory difficulty" and "unsatisfactory inspiratory effort" to describe their perception of breathlessness immediately after cycle ergometry. These descriptors of breathlessness selected by patients with COPD from different countries are quite similar and appear to represent the work and effort of the respiratory muscles associated with breathing.

In the past, several multicenter randomized trials have examined lung function, particularly FEV_1, as the primary outcome measure to assess specific therapy. However, neither inhaled ipratropium bromide nor inhaled corticosteroids have been shown to affect the decline in FEV_1 over time (24, 25). These negative results require the pulmonary community to reconsider the goals of treatment. Accordingly, the severity of dyspnea has become an important outcome measure in clinical trials of patients with COPD. Moreover, the ATS/ERS Task Force has stated that "all patients who are symptomatic merit a trial of drug treatment" (26).

New approaches to the study of dyspnea need to be considered. Whereas many earlier laboratory studies have examined the mechanisms contributing to dyspnea in healthy subjects, it is important to investigate the pathophysiologic mechanisms in patients with respiratory disease. Presently, established instruments or scales are available to measure the intensity of breathlessness (27). However, future efforts should be directed to the development of more responsive instruments for patients to report the severity of dyspnea in clinical trials. Finally, based on our current knowledge, dyspnea should be included as a primary or secondary outcome in multicenter randomized controlled trials investigating the efficacy and effectiveness of various treatments for patients with COPD.
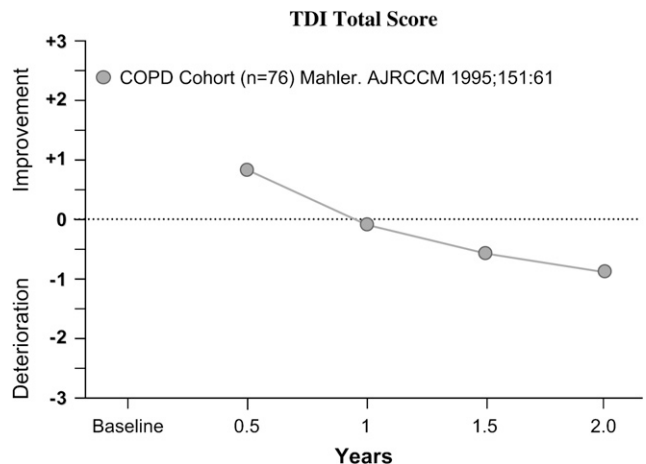

Figure 1. Changes in dyspnea in 76 patients with chronic obstructive pulmonary disease (COPD) who were recruited in an observational study when in a stable clinical state and received standard medical care throughout the two-year period (data from Reference 20).

Chemical and Mechanical Loads: What Have We Learned?

Paul W. Davenport

Dyspnea is not a single sensory modality but rather a combination of modalities: central neural, chemical, and mechanical. Respiratory disruption results in a cognitive awareness of breathing, which is mediated by neural processes. Sufficient disruption leads to distressing emotions, and this dysfunction motivates and elicits behavioral adaptations such as escape behavior. Respiratory sensations of sufficient magnitude can dominate cognitive awareness; hence, there has to be a cognitive neural basis for respiratory somatosensation. It follows that appropriate manipulation of these neural processes will provide insight into the mechanisms mediating dyspnea. The goal of research surrounding dyspnea is to use physiological changes to understand psychological processes and to use psychological changes to understand physiological processes. To investigate dyspnea, the modality mediating the sensation, the threshold, the magnitude of stimulation, the neural mechanisms, and the outcomes/compensations need to be considered.

Animal Studies

To date, many lessons have been learned from external mechanical loading experiments in animal (28–32) and human studies (33–40). Animal studies have been performed mainly in rats (41–45), cats (30, 46–51), and dogs (31, 52–55). Conditioned fear induced by hypercapnia in rats is known to cause changes in the breathing pattern (28, 29). These stimuli elicit neural activation, and the activated neurons can be found using c-Fos expression in several nuclei in the central nervous system (41). Mechanical loads also stimulate these central neural fear centers. Nsegbe and coworkers (28) performed a controlled experiment in which a 1-minute tone (the conditioned stimulus, CS) was paired with a hypercapnic stimulus (8.5% CO_2, the unconditioned stimulus, US). After the CS alone, breath duration was significantly longer in the experimental than in the control group and mean ventilation was significantly lower, thus showing inhibitory conditioning. This conditioning may have resulted from the association between the CS and the inhibitory and aversive effects of CO_2 (28). In another study, the association of an odor and hypoxia elicited a biphasic ventilatory conditioned response, of which the first component is integrated into conditioned arousal (29). These and other studies indicate that chemical and mechanical respiratory stimuli that produce a sensation of dyspnea in humans, can elicit detection, fear, escape behavior and anxiety in animals, thus indicating an animal analog of dyspnea (28, 29, 31).

Human Studies

Human studies have shown similar findings. Hypercapnic conditioning linked to odor resulted in a conditioned ventilatory response with word descriptors related to breathing effort, suffocation, and rapid breath (56, 57). These hypercapnic sensations are modulated by lung volume and breathing effort. Mechanical loads in human studies elicit respiratory perceptions that exhibit a threshold, quantification of magnitude, discrimination of quality, and regulation of breathing pattern (33–36, 39, 40, 58, 59). This perception is modulated by physiological state changes such as respiratory muscle "strength" changes (60), respiratory drive (61, 62), background load on the respiratory muscles (36, 63), hypercapnia (64), and hypoxia (65–67). Intrinsic resistive and elastic loading of the respiratory muscles (68) and hyperinflation (69–72) also elicit respiratory sensations. Functional magnetic resonance imaging (MRI) (69, 73–76) and respiratory-related evoked potentials (RREP) (77) have shown that respiratory chemostimulation, mechanostimulation, and motor drive change brain neural activity (61, 64, 77–80). Brain-evoked activity is also elicited by respiratory muscle stimulation (50, 51, 81, 82), inspiratory occlusion (64, 77, 78), inspiratory loads (79, 80), and mouth stimulation (83, 84). Brain activity is attention dependent (85–89), load threshold dependent (85), and modulated by background load as well.

Respiratory-related Evoked Potentials

Observations from RREP studies have also provided more information regarding human response and the neural gating process. Modality-specific activation of cortical neural processing centers depends on a change in neural activity that gates-in modality-specific information to the brain information processing centers (90–94). This activation leads to cognitive awareness of the modality. The significance of gating-in and gating-out sensory modalities is the need to attend to essential physiological functions. Scalp electroencephalographic measures have been shown to reflect neural markers of increased stimulus redundancy. It has been demonstrated (90, 95, 96) that an auditory mid-latency evoked potential positive peak at about 50 milliseconds (P_{50}) and a negative peak at about l00 milliseconds (N_{100}) after stimulus onset can be used as neural measures of stimulus filtering (i.e., gating). It has been reported (95, 97) that in application of stimulus pairs, with the individual stimuli separated by 500 milliseconds, the second stimulus (S2) normally has a reduced amplitude when compared with the first stimulus (S1). The S2/S1 ratio is normally approximately 0.5, demonstrating the reduction of neural activation of the redundant stimulus; this is defined as gating for these modalities. The N_{100} has reduced S2 amplitude, especially in somatosensory modalities. The N_{100} amplitude and S2/S1 ratio can be modulated by attention and background brain state. Respiratory sensation activates the somatosensory cortex (77, 78, 98) and is closely related to the limb somatosensory system (77).

Respiratory Sensory Gating System Model

The results of the above studies of respiratory mechanosensation, particularly the RREP N_1 response, lead to the respiratory sensory gating system model (Figure 2). This model is based on several assumptions: (*1*) cognitive sensory events reflect neural processes, (*2*) sensory afferents transduce respiratory-related mechanical parameters, (*3*) threshold gating of cognitive awareness, (*4*) perceptual quantification of magnitude, (*5*) respiratory perception modality specificity, (*6*) modulation by initial conditions or state, (*7*) multimodal respiratory afferent activation, (*8*) activation of affective mechanisms, and (*9*) elicited compensatory responses. This model is an oversimplification of the cognitive and neural processes that are hypothesized to mediate cognitive awareness of ventilation. While the model does not provide a full explanation of the mechanisms of respiratory somatosensation, it does predict investigative strategies that will lead to refinement of the model and a new understanding of the neural mechanisms mediating respiratory cognition.

Respiratory mechanosensation is state dependent, where state refers to both the existing background physiological state and the cognitive/behavioral/affective state. Further, it is proposed that respiratory mechanosensory state dependency is a gated neural process. There are two gating stages, a threshold gate and frequency-dependent sensory information processing gate (or filter). Threshold gating is the change in respiratory status to a point of activation of the postulated neural gate allows respiratory information to be transmitted to the somatosensory regions of the cerebral cortex. Sensory information filtering
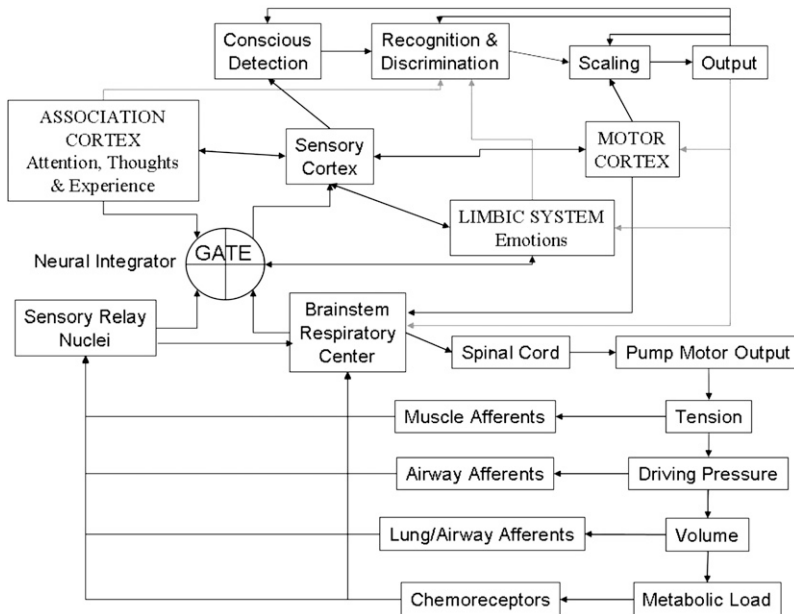
Figure 2. The respiratory sensory gating system model is a helpful way to organize the hypothesized connections, although it does not fully explain the mechanisms.

reflects whether or not attention is directed to primary somatosensory information resulting in further cognitive processing, and possible affective or behavioral responses. This also has a threshold gating element, where activation of primary somatosensory cortex can reach a criterion threshold above which further affective processing is obligatory.

Threshold gating simplified. Threshold gating of respiratory mechanosensation can be demonstrated with a simple experiment. Subjects are unaware of their breathing motion until they are asked to focus their attention on the movement of their thorax. With a change in their attention, they can now feel their chest expand during inspiration and decrease in volume during expiration. As predicted by the model, this experiment tells us the respiratory mechanoreceptors were active during breathing that was undetected, before attending to their breathing. This afferent information did not change when subjects attended to their breathing: subjects only changed the central neural cognitive state by changing attention, that is, attentional modulation of gating. This also means that an unknown central neural mechanism blocked this mechanosensory information from activating neural cognitive centers when subjects did not attend to their breathing. What changed? It is hypothesized that the mechanosensory information that subjects feel with attention to their breathing was gated-out (threshold gate) of their cognitive centers. Neural processes mediating attention (Figure 2) acted on the gate and gated-in respiratory mechanical information. If subjects were then asked to sense if their breathing was comfortable, they made this judgment and moved into the second stage of respiratory perception, affective awareness. They initially gated-in sensory information when they felt their chest move; they then decided if their breathing had a comfortable or uncomfortable qualitative sense. The second stage is the stimulus frequency dependent gating well documented in auditory, visual, and somatosensory modalities.

Cognitive Respiratory Sensation: A Neural Construct

Respiratory motor drive is generated in the brainstem respiratory neural network. This respiratory drive produces the motor breathing pattern, thus resulting in ventilation. Ventilation is monitored by multiple sensory systems, of which we present only four major categories: muscle afferents, lung receptors,

airway receptors, and chemoreceptors. (There are, of course, additional respiratory afferents, but we have limited the number of afferent populations in this model for the sake of simplicity.) These afferent systems provide sensory input to the brainstem respiratory network, yet it is also known that these afferents also project to higher brain centers (49, 50). Respiratory sensations are produced by respiratory changes that preferentially activate one or more of these groups of afferents. However, these sensations do not occur with normal respiratory mechanics, ventilation, and eupneic breathing patterns. This implies that a change of sufficient magnitude (threshold) in these respiratory sensory systems changes central neural information processing (gating), resulting in a cognitive awareness of breathing. Changes in breathing effort also can be perceived. Higher brain centers are activated when ventilatory drive is increased and some neurons show a respiratory rhythm during eupneic breathing (99–101). This suggests that respiratory motor drive is integrated with sensory input by gated comparator mechanisms that are connected into the cognitive centers that mediate the sense of breathing. The background status of ventilation also modulates respiratory sensation. Respiratory sensation and perception is further modulated by attention, experience/learning, and affective state. As noted above, attending to breathing results in cognitive awareness of ventilation.

Experience and learning also are important components of respiratory sensation. Respiratory perception studies for most respiratory modalities begin with a familiarization or training session to train the subject to the sensation elicited by the specific ventilatory perturbation. This means the subject must experience the respiratory change and learn to associate that change with the sensation it produces. The association cortex is the brain region that mediates attention, experience, and learning. Hence, we propose that respiratory sensation is modulated by the association cortex.

Respiratory sensation also is dependent on affective state of the subject. Anxiety and distress elicit profound changes in ventilation and strong respiratory sensations (102). Thus, respiratory sensations are modulated by the affective neural control system. Other sensory modalities can interact to change the sensory threshold. In physical therapy, the distraction of changing

a sensory system modifies the ability of the patient to perform the rehabilitation task (103).

These observations suggest that eliciting a cognitive respiratory sensation depends on the integration of respiratory afferent activity, respiratory motor drive, affective state, attention, experience, and learning. These neural parameters input to a hypothesized gating center that has an output that elicits a cognitive neural response if the combined input exceeds the threshold for gating the respiratory sensation, a gated comparator. Future research is needed to investigate systematically the gating of respiratory sensory cognition, modulation of respiratory sensation by physiological state, the role of affective systems on respiratory sensations, and the role of specific neural systems in regulating respiratory cognition.

Multiple Mechanisms Contributing to Dyspnea

Simon C. Gandevia

Evolution has built in mechanisms at many levels, from the subcellular level to the level of tissues and organs and ultimately to the whole-body level, to optimize acquisition, transport, and delivery of oxygen. A similar, but not identical, set of adaptations allows the removal of carbon dioxide. Presumably this must reflect the critical importance for survival of oxygen usage and carbon dioxide elimination. If dyspnea is taken to mean a perceived difficulty with breathing (a view accepted by most participants at the Roundtable), then it is not surprising that it can be signaled by a range of proprioceptive and visceral ("deep") afferents. Indeed, many different subjective components of dyspnea can be distinguished by patients and normal subjects (104). Furthermore, it would be expected that dyspnea would be associated with the activation of cerebral structures concerned not only with the processing of the afferent input but also with the assessment of the emotional and threat-related consequences of the stimulus that produces it. Indeed, some definitions of dyspnea specifically refer to an unpleasantness in the sensation (in which dyspnea is an "unpleasant" urge to breathe) (105).

When considering the central mechanisms underlying or contributing to the sensation, it remains useful to compare the generation of difficulty in breathing with the difficulty which may occur with the disruption of any voluntary movement and then to add in the effects that are specific to pulmonary ventilation, such as the afferent inputs from chemoreceptors, the upper and lower airway. Hence the list of classes of peripheral receptors that respond to stimuli that are potentially able to generate dyspnea is long: it includes receptors in the upper airway, lower airway, lung parenchyma, and respiratory muscles, as well as peripheral and central chemoreceptors. One lesson that has been learned over several decades from development of ideas about proprioceptive sensations associated with joints in the limbs is that inputs from all classes of mechanoreceptors that can signal any aspect of joint movement and position will be capable of contributing to, and under particular conditions dominating, proprioceptive sensation. Hence, the relevant inputs may arise in specialized mechanoreceptors in the skin, joint, or muscles. Interestingly, at different times, receptors at each of these three locations have been considered quite unimportant for this role; and, with hindsight, their exclusion has been based on somewhat flimsy logic (106). There are also multiple proprioceptive elements (force, position, effort, etc.) that can be separated for a particular circumstance (e.g., lifting a heavy suitcase). Hence, for a sensation as critical as dyspnea, it would be perilous to exclude any particular receptor class with an afferent modulation by respiration from a direct sensory role, and it is essential to recognize that there is more than one type of dyspnea (*see* the contribution to the roundtable by Banzett).

Those proprioceptive mechanisms involved with the detection and grading of loads to limb muscles are also involved in the detection and grading of loads to breathing. There is sufficient evidence from animal and human studies that the relevant afferent classes project to the primary sensorimotor cortex (*see* the contribution to the Roundtable by Davenport). Here, there is the likelihood that it is the relationship between more than one proprioceptive input or "channel" that is critical. For example, if chest wall expansion is less than expected for the delivery of a particular voluntary motor command or "effort," then it can be determined that the respiratory system is loaded, the inspiratory muscles weakened, or that these muscles are operating at a less effective part of their length–tension curve. The degree of such a mismatch will provide an index of the size of the disturbance (107–109). Despite initial studies by Campbell and colleagues (110), there is now overwhelming evidence that signals directly related to hypercapnia generate dyspnea, presumably via the activation of central chemoreceptors. Some of these studies have required complete neuromuscular paralysis to deliver a pure chemoreceptor stimulus decoupled from the usual accompanying hyperventilation (111, 112).

Another basic, nociceptive-like signaling system involves unmyelinated C fibers, which were first studied in detail by Paintal, and by the Coleridges (113, 114). They have receptive fields within the lung (pulmonary C fibers) or bronchi (bronchial C fibers), depending on their accessibility to chemicals injected via the right or left atrium. They are activated by a range of local factors including capsaicin, phenyl diguanide, mechanical distortion, and even cigarette smoke (115). Activation of these fibers in conscious humans generates potent respiratory sensations. It is possible that this occurs not only during pathologic conditions (such as left ventricular failure or pulmonary embolism), but also during the terminal phase of strenuous exercise (116). Other classes of pulmonary afferents probably also contribute to specific sensations relating to cough and chest tightness (117). Recent studies examined the capacity of the pulmonary C fibers to reflexly limit locomotion and voluntary movement. This is the J reflex proposed by Paintal to limit exercise when left ventricular failure was incipient. Unlike the paralysis of locomotor movements and motoneuronal inhibition induced by activation of these afferents in many experimental animals, conscious humans do not develop inhibition of limb motoneurons during activation of these afferents (by intravenous lobeline), but the noxious sensations remain (118). Hence, the potent viscero-somatic component of this reflex response to pulmonary insults has probably been brought under forebrain control in humans, particularly when they are awake, but the sensory and autonomic aspects of the overall response remain intact in humans.

One influential hypothesis about dyspnea was the "length–tension" hypothesis of Campbell (107). It remains conceptually tenable as a way of looking at dyspnea, in which a disparity between achieved and required ventilation is perceived. Alternatives, in the same style, focus on the disparity between achieved and "commanded" ventilation, or on the disparity between commanded ventilation and the size of the inspiratory capacity (*see* the contribution to the Roundtable by O'Donnell). At a central neural level, these types of comparisons are likely to be difficult to distinguish and "part and parcel" of the conscious and unconscious monitoring of respiration, but it is clear that signals from specialized receptors in muscle, joints, and so on, as well as from the lung and upper airways, can all contribute. Signals of central motor command or effort may also bias judgments, particularly

when they are pathologically high, such as when inspiratory muscles are weak. However, recent studies have revealed more than one use for signals of motor command (119), so that their role is not simply to contribute to respiratory "effort" sensation.

Finally, the application of new methods of neuroimaging (positron emission tomography and functional magnetic resonance imaging) (120) and neurostimulation (transcranial stimulation) has provided insight into how the central nervous system is organized when performing respiratory acts and when it receives respiratory stimulation. Apart from the expected somatic inputs to the sensorimotor cortex from thoracic structures (including the diaphragm) and outputs from the primary motor cortical to respiratory muscles, stimuli that generate dyspnea activate many central structures. These were first shown to involve the anterior insula (121), but other areas show activity in different studies including regions of cingulate cortex, the cerebellum (particularly the vermis), and other limbic areas including the amygdala (107, 122–124).

By analogy with the range of areas activated by painful stimuli (125, 126), it is tempting to refer to the areas activated by stimuli generating dyspnea as a dyspnea "neuromatrix." Many of the areas are phylogenetically old and probably reflect the need to evaluate and respond to life-threatening stimuli. However, much remains to be done to understand this system. For example, just as there are differences between the sexes with respect to pain perception (127), such differences are likely to be important in some aspects of the experience of cardiorespiratory sensations (128). Even with the newer methods to assess human brain function, it is not trivial to determine the roles for the various areas which have shown altered activity, as it is difficult to control all the respiratory, emotional, autonomic, and attentional variables.

The Peripheral Mechanisms of Dyspnea

Robert B. Banzett

Dyspnea is not a single sensation—there are at least three distinct sensations of respiratory discomfort including air hunger, work/effort, and tightness. They are described as individual entities because patients and study subjects use different descriptors for each, because they can be evoked separately, and because they have different afferent neural pathways.

In the 1970s and 1980s, all dyspnea was thought to arise from afferent information from the respiratory muscles when they are driven to work harder by chemoreflex or while attempting to overcome a load. This hypothesis suggests that blocking the muscle contraction will block the sensation of dyspnea. Initial studies (110) demonstrated this effect, as the subjects were able to hold their breath longer with less sense of urgency to breathe after total neuromuscular block with tubocurarine. Following criticism of the methodology (129), a repeat study on a single subject (130) confirmed the initial results. In the 1990s, new experiments showed that dyspnea was unchanged by paralysis using both steady-state hypercapnia and breath-hold protocols (111, 112, 131). These experiments refuted the earlier results, and a new schema began to gain acceptance.

Air Hunger

The term "air hunger" was coined in the 1950s (132) to describe the sense of an uncomfortable urge to breathe, as felt at the end of a long breath hold. Subjects and patients volunteer descrip-

tions such as "I'm starved for air," "I'm not getting enough air." The sense of air hunger in both laboratory subjects and patients is also accompanied by more emotional descriptors like "frightening" or "like I was going to die" (111, 133). Experiments with paralyzed subjects have shown that respiratory muscle contraction is not necessary to induce air hunger. Two groups (111, 112) have shown that the air hunger stimulus–response curve for CO_2 is not altered by complete paralysis via neuromuscular block, thus disproving the theory from the 1980s. The most likely afferent stimulus for air hunger is corollary discharge conveying a copy of the medullary respiratory center discharge to the sensory areas of the forebrain (134–136), although a role for direct projection of chemoreceptors to the forebrain (137) has not been disproved.

The intensity of air hunger is set not only by the excitatory stimulus, but also by ongoing inhibition from mechanoreceptors that signal the current level of pulmonary ventilation. Hill and Flack reported a century ago that tidal breathing relieves air hunger at the end of a breath hold even if improvement of blood gasses is prevented (138). We have shown that increased tidal volume (delivered by a ventilator) can relieve air hunger in C1-C2 quadriplegics, suggesting that the pathway must be vagal (139, 140) (Figure 3). We conclude that pulmonary stretch receptor information is capable of relieving air hunger; chest wall afferent information probably has a weaker effect (141). There is some information from animal experiments that suggests this inhibition takes place at a level above the medullary respiratory centers, but below the cortex (142) (Figure 3).

Sense of Effort

The work/effort sensation of dyspnea is often described as "breathing is difficult," "breathing takes a lot of work," or "breathing takes effort" (104, 143). Normal subjects do not perceive work/effort as threatening or frightening as long as the blood gases remain normal (143). Several types of stimuli can evoke the sense of work/effort. When P_{CO_2} is held at normal levels, voluntary hyperpnea (143) and partial paralysis (144) in normal subjects elicit reports of work/effort, but not air hunger. Other stimuli include external loads, elevated end-expiratory volume, and respiratory muscle fatigue. The neural pathways
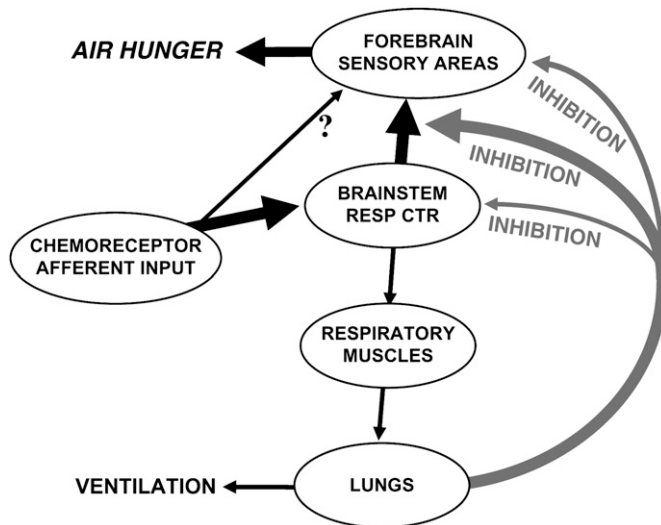

Figure 3. Neural pathways underlying air hunger. Proposed pathways for relief of air hunger by tidal inflation are shown by right hand arrows. Supporting data comes from References 100, 101, and 140.

proposed for these sensations include corollary discharge from motor cortical centers that drive voluntary breathing (108, 145, 146). Muscle mechanoreceptors and metaboreceptors are probably also involved, while corollary discharge from the brainstem is probably not (Figure 4).

Chest Tightness

The sensation of tightness seems to be unique to asthma, evoking descriptors such as the "chest is constricted" and the "chest feels tight." If tightness results from the added work, then it should be abolished when the work of breathing is supported by mechanical ventilation. This theory was refuted by a study demonstrating that work/effort sensation, but not tightness, was reduced when individuals with asthma with bronchoconstriction were mechanically ventilated (117). In another single-patient study, involving a mechanically ventilated C1-C2 quadriplegic, tightness was evoked by bronchoconstriction (R. Brown and R. M. Schwartzstein, personal communication). Further studies are needed to confirm that the pathway for tightness is vagal in origin (Figure 5).

Unsatisfied Inspiration

A challenge before us is to understand how these neural mechanisms operate alone or in combination to produce the dyspnea experienced by patients. For instance, O'Donnell and coworkers have shown that decline in inspiratory capacity is closely related to the magnitude of dyspnea, as patients with obstructive disease become dynamically hyperinflated (23, 147). What neural mechanisms underlie this relationship between a mechanical event and perceived sensation? The mechanisms described for work/effort sensation undoubtedly play a role in sensing the increased work expended against a stiffer respiratory system by disadvantaged inspiratory muscles—indeed, the patients report work and effort. The mechanisms described for air hunger may also play a role as respiratory drive begins to call for more tidal volume than available within the remaining inspiratory capacity. At this stage patients report that they cannot get enough air, that inspiration isn't satisfying—this is similar to subjects' descriptions of air hunger in other circumstances.

It is probable that additional sensations and pathways will be described—for example, the pathways described here do not adequately explain dyspnea associated with pulmonary vascular congestion. Although the concept that dyspnea has at least three distinct sensations is supported by the research to date, more investigation is needed to clarify the neural mechanisms underlying individual dyspnea sensations, to discover additional pathways, and to provide critical tests of the role of each of these individual pathways in the more complex phenomenon of clinical dyspnea.

Exertional Dyspnea in COPD: Mechanics and Neurophysiology

Denis E. O'Donnell

Dyspnea and limitation of physical activity are the main symptoms of COPD and contribute importantly to perceived poor health status in this population. Our understanding of the source and mechanisms of exertional dyspnea continues to grow, and our ability to alleviate this symptom has recently improved. The mechanisms of dyspnea and exercise intolerance in COPD are complex and multifactorial (*see* Reference 147 for review). This review focuses primarily on ventilatory mechanical factors that can potentially be manipulated for the patients' benefit.

Ventilatory Mechanics in COPD

Expiratory flow limitation (EFL) is the pathophysiologic hallmark of COPD and arises because of the dual effects of permanent parenchymal destruction (emphysema) and airway dysfunction, which in turn reflects the effects of small airway inflammation (mucosal edema, airway remodeling/fibrosis, and mucous impaction) (148). Emphysema results in a reduced lung elastic recoil pressure, which leads to a reduced driving pressure for expiratory flow through narrowed and poorly tethered airways in which airflow resistance is significantly increased. EFL is said to be present when the expiratory flows generated during spontaneous tidal breathing represent the maximal possible flow rates that can be generated at that operating lung volume (149) (Figure 6).

In health, the relaxation volume of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of chest wall (148) (Figure 7). In COPD, the increased compliance of the lung, as a result of emphysema, leads to a resetting of the relaxation voume of the respiratory system to a higher level than in health. This has been termed "static" lung hyperinflation (149). In patients with EFL during spontaneous resting breathing, end-expiratory lung volume (EELV) is also "dynamically" determined and is maintained at a level above the statically determined relaxation volume of the respiratory system. In
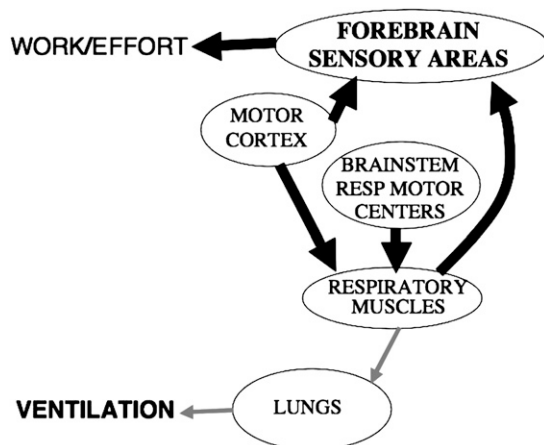

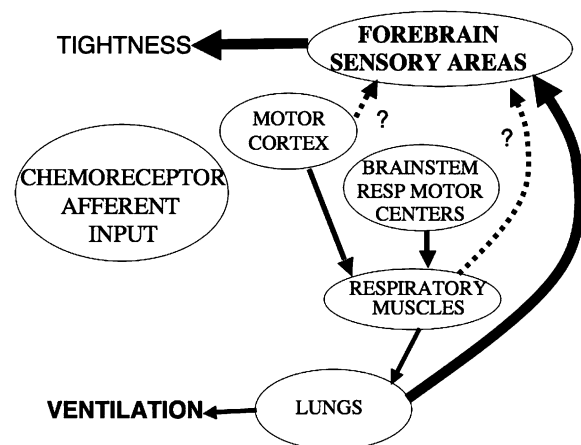*Figure 4.* Neural pathways underlying work/effort sensation.

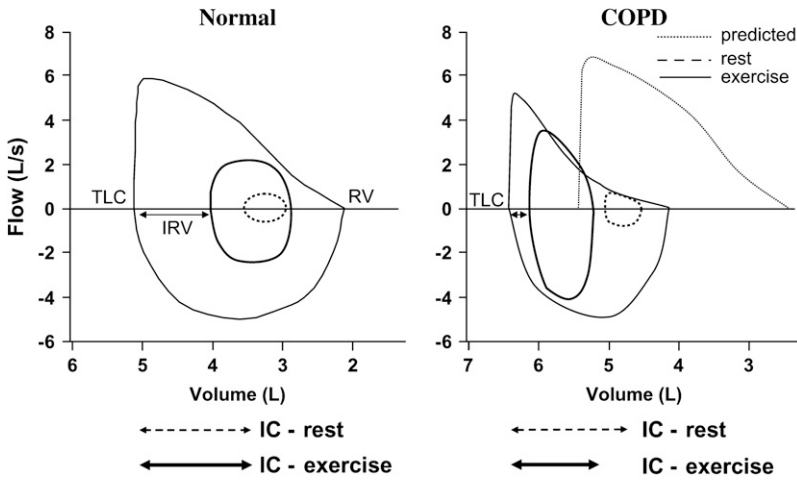*Figure 5.* Neural pathways underlying tightness.

Figure 6. In a healthy subject (*left panel*) and a typical patient with COPD (*right panel*), tidal flow–volume loops at rest and during exercise are shown in relation to their respective maximal flow–volume loops. Peak exercise in COPD is compared with exercise at a comparable metabolic load in the age-matched person. Note expiratory flow limitation (tidal expiratory flow overlapping the maximal curve) at rest and during exercise and an increase in dynamic end-expiratory lung volume (EELV) during exercise in COPD. IC = inspirational capacity; IRV = inspiratory reserve volume; TLC = total lung capacity.

flow-limited patients, the time-constant for lung emptying (i.e., the product of compliance and resistance) is increased in many alveolar units, but the expiratory time available (as dictated by the respiratory control centers) is often insufficient to allow EELV to decline to its normal relaxation volume, thereby resulting in air retention (or trapping) with further lung hyperinflation. EELV in COPD is, therefore, a continuous dynamic variable that varies with the extent of EFL, the prevailing ventilatory demand, and breathing pattern.

The rate and magnitude of dynamic lung hyperinflation (DH) during exercise is generally measured in the laboratory setting by serial inspiratory capacity (IC) measurements (150–152). The IC is the maximal volume of air than can be inhaled after a spontaneous expiration to EELV. Since total lung capacity (TLC) does not change during activity, the change (decrease) in IC reflects the change (increase) in dynamic EELV, or the extent of DH (150–152) (Figure 5). This simple method has been

shown to be reliable (reproducible and responsive) in recent multicenter clinical trials (70, 153). In two studies conducted in approximately 500 patients with moderate-to-severe COPD, the change in EELV during cycle ergometry averaged 0.4 L, with wide variation in the range (70, 153). Eighty-six percent of this population sample showed increases in EELV from rest to peak exercise, confirming the presence of significant DH. Those remaining patients (14%) demonstrated the most severe resting lung hyperinflation and therefore showed little further DH during exercise. The rate of rise of DH was more abrupt in patients with the highest ventilatory demand (reflecting greater ventilation/perfusion abnormalities) and generally reached a maximal value early in exercise.

The negative effects of acute DH during exercise are now well established (*see* Reference 154 for review): (*1*) DH leads to increases in the elastic and threshold loads on the inspiratory muscles, thus increasing the work and oxygen cost of breathing;
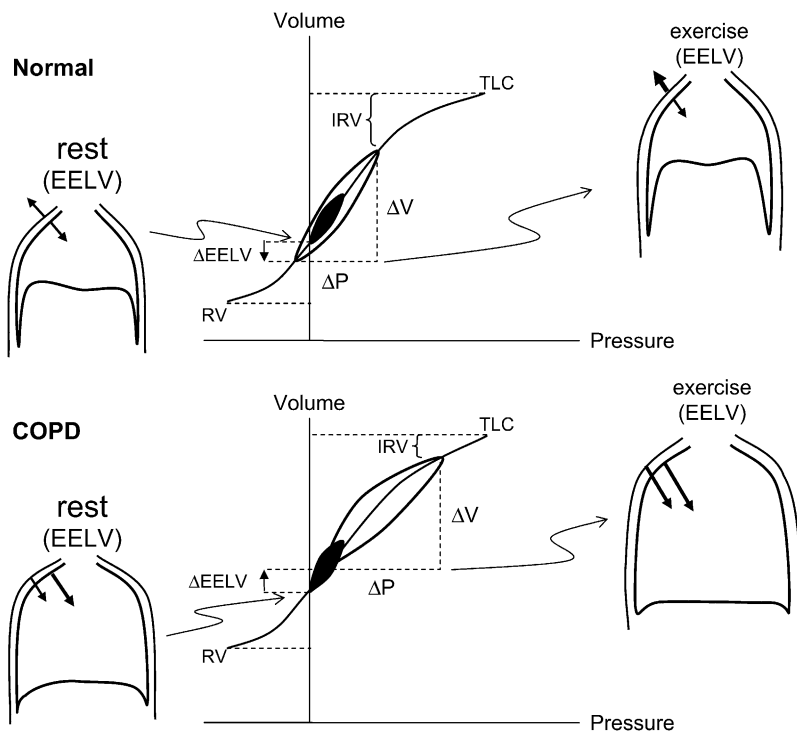

Figure 7. Pressure–volume (P–V) relationships of the total respiratory system in health and in COPD. Tidal pressure–volume curves during rest (*filled area*) and exercise (*open area*) are shown. In COPD, because of resting and dynamic hyperinflation (a further increased end-expiratory lung volume [EELV]), exercise tidal volume (ΔV) encroaches on the upper, alinear extreme of the respiratory system's P–V curve where there is increased elastic loading. In COPD, the ability to further expand tidal volume is reduced (i.e., inspiratory reserve volume [IRV] is diminished). In contrast to health, the combined recoil pressure of the lungs and chest wall in hyperinflated patients with COPD is inwardly directed during both rest and exercise; this results in an inspiratory threshold load on the inspiratory muscles. RV = residual volume; TLC = total lung capacity. Reprinted by permission from Reference 241.

(*2*) DH results in functional inspiratory muscle weakness by maximally shortening the muscle fibers in the diaphragm and other inspiratory muscles; (*3*) DH reduces the ability of tidal volume to expand appropriately during exercise, and this leads to early mechanical limitation of ventilation (Figure 8); (*4*) in some patients, this mechanical constraint on tidal volume expansion in the setting of severe pulmonary V/Q abnormalities (i.e., high fixed physiological dead space) leads to CO_2 retention and arterial oxygen desaturation during exercise; and (*5*) DH adversely affects dynamic cardiac function. All of the above factors are clearly interdependent and contribute in a complex integrated manner to dyspnea and exercise limitation in COPD.

Correlates of Dyspnea

A number of recent studies have shown strong statistical correlations between the reduction in IC during exercise and ratings of exertional dyspnea intensity in COPD (23, 151). This association was tested by evaluating the impact of therapeutic interventions. Improvement in dyspnea after bronchodilators and lung volume reduction surgery correlated well with increased IC, a measure of reduced lung hyperinflation (70, 71, 150, 155). A recent mechanistic study in our laboratory determined that DH early in exercise allowed flow-limited patients to increase ventilation acutely while minimizing respiratory discomfort (156). Thus, as a result of DH early in exercise, the airways are maximally stretched at the higher lung volumes (close to TLC) and EFL is attenuated, allowing patients to maximize expiratory flow rates. Thus, in early exercise, the ratio of inspiratory effort (relative to maximum) to tidal volume displacement remains constant. However, this advantage is quickly negated when tidal volume expands to reach a critically low inspiratory reserve volume (IRV) of approximately 0.5 L below TLC. At this "threshold," tidal volume becomes fixed on the upper, less compliant extreme of the sigmoid-shaped pressure–volume relation of the respiratory system, where there is increased elastic loading of the inspiratory muscles. After reaching this minimal IRV, dyspnea (inspiratory difficulty) rises abruptly to intolerable levels and reflects the widening disparity between inspiratory effort (and central neural drive) and the simultaneous tidal volume response, which becomes essentially fixed (i.e., increased effort:displacement

ratio) (156) (Figure 9). Dyspnea intensity correlates well with the increase in this effort:displacement ratio during exercise in COPD (156). The above studies indicate that, although dyspnea is multifactorial in COPD, mechanical factors contribute importantly and that lung hyperinflation is therefore a promising therapeutic target for the alleviation of this distressing symptom.

Neurophysiology of Dyspnea during Exercise

In COPD, dyspnea intensity during exercise is higher at any given ventilation, work rate, or metabolic load than in health (Figure 10). The precise mechanisms of dyspnea remain obscure, and there are multiple potential sources of respiratory discomfort (147). Possible components include: perception of heightened inspiratory effort; awareness of unrewarded effort; and perceptions arising from dyspneogenic afferent inputs from chemoreceptors and a multitude of mechanosensors in the airway, lung, and chest wall. One approach to the study of dyspnea is to identify the major qualitative dimensions of the symptom in an attempt to uncover different underlying neurophysiologic mechanisms (23) (*see* the contribution to the roundtable by Banzett). Two dominant clusters of qualitative descriptors are commonly selected by patients with COPD to describe their experience of respiratory difficulty at the termination of exercise: (*1*) a sense of heightened effort, work, or heaviness of breathing; and (*2*) the sense of "unsatisfied" inspiration, that is, "I cannot get enough air in" (Figure 11).

Increased Inspiratory Effort

Perceived heightened inspiratory effort is pervasive in health and respiratory disease, but is more intense and occurs at lower levels of exercise in patients with COPD (157). In health, several physiological adaptations minimize respiratory discomfort as ventilation increases to high levels during exercise. These include: reduced intra- and extrathoracic airway resistance, precise control of operating lung volumes, improved pulmonary ventilation/perfusion relations, and alterations of breathing pattern. Collectively, these adjustments optimize dynamic ventilatory mechanics and allow the preservation of harmonious neuromechanical coupling of the respiratory system throughout exercise with avoidance of respiratory discomfort. As ventilation increases during exercise in health, increased efferent inputs from cortical motor centers and the brainstem respiratory center, together with gated afferent inputs from multiple respiratory mechanosensors, are processed and integrated in the sensory cortex/association cortex. In health, if this sensory information is attended to, a conscious determination will generally be made that breathing is comfortable and appropriate for the specific physical task (*see* the contribution to the roundtable by Davenport). At the highest levels of ventilation, the sense of heightened inspiratory effort increases and reflects the increased central (voluntary) motor command output to the ventilatory muscles and may be consciously perceived through corollary discharge (or efferent copy) to the sensory cortex (100, 158) (*see* the contribution to the roundtable by Banzett). Increased respiratory muscular effort in health is always appropriately rewarded by increased mechanical output (and ventilation), even at high exercise intensities. Thus, this perception of increased effort or work of breathing need not be unpleasant and therefore need not elicit an emotive "distress" response (limbic system activation) with corresponding behavioral compensation.

In COPD, all of the physiologic adaptations in health (described above) that optimize neuromechanical coupling and minimize discomfort are seriously disrupted (*see* the section by O'Donnell on pathophysiology of COPD). In COPD, muscular effort is therefore substantially increased at any given ventilation compared with health, reflecting the increased loading and
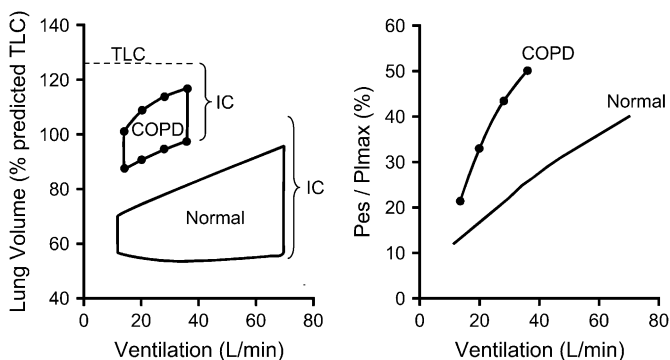

Figure 8. Behavior of operating lung volumes (*left*) and respiratory effort (Pes/PI$_{max}$) (*right*) as ventilation increases during exercise in COPD and in age-matched healthy subjects. In COPD, tidal volume takes up a larger proportion of the reduced inspiratory capacity (IC) at any given ventilation—mechanical constraints on tidal volume expansion are further compounded because of dynamic hyperinflation during exercise. As a result of functionally weakened inspiratory muscles and increased mechanical loading, tidal inspiratory pressures represent a much higher fraction of their maximal force-generating capacity in COPD than in health. Data from Reference 23. TLC = total lung capacity.
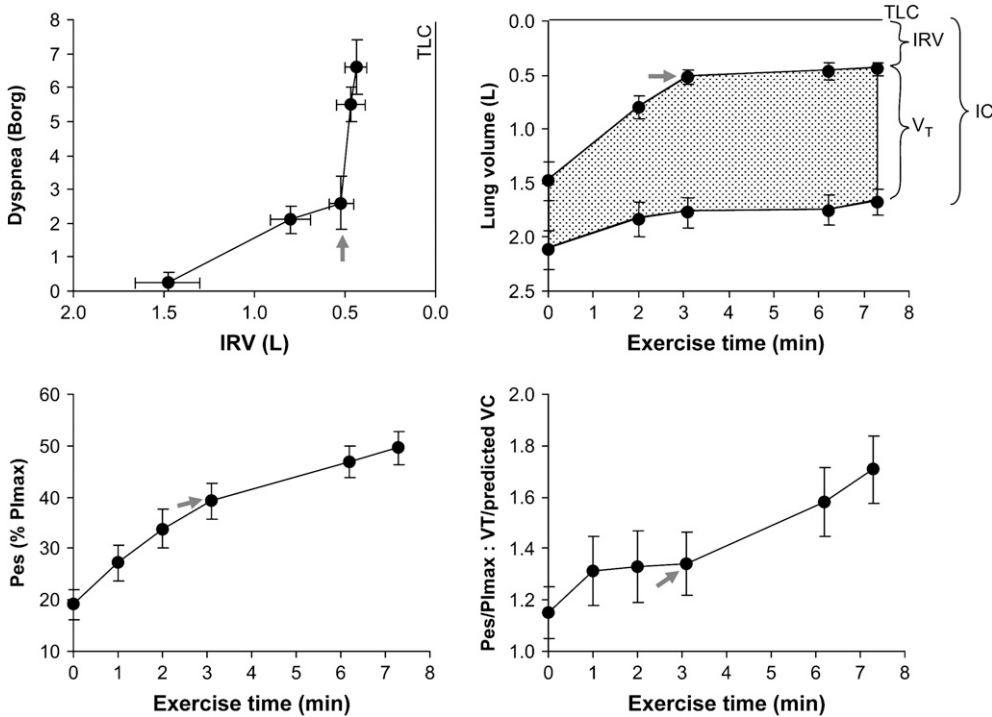
Figure 9. The mechanical "threshold" of dyspnea is indicated by the abrupt rise in dyspnea intensity after a critical minimal inspiratory reserve volume (IRV) is reached, which prevents further expansion of tidal volume (V_T) during constant-load cycle exercise at 75% of the peak incremental work rate in COPD. Beyond this dyspnea/IRV inflection point, dyspnea intensity, respiratory effort (Pes/PI_{max}), and the effort:displacement ratio all continue to rise. *Arrows* indicate the dyspnea/IRV inflection point during exercise. Values are expressed as means $\pm$ SEM. Adapted by permission from Reference 156.

functional weakening of inspiratory muscles. Several studies in COPD have shown that during exercise, there is a close correlation between increased inspiratory effort (measured by tidal esophageal pressure relative to maximum) and the intensity of dyspnea measured by the Borg scale (23, 159). Increased corollary discharge remains a plausible mechanism for perceived increased inspiratory effort, and this idea is consistent with concepts of sensory physiology that have previously been applied to other working skeletal muscle groups. It is conceivable that, in the exercising patient with COPD, increased corollary discharge to the sensory cortex/association cortex (beyond a certain threshold) may be sensed as abnormal and consequently evoke negative threat-related affective responses.

Unsatisfied Inspiration

The distressing sensation of "unsatisfied inspiration" seems to be characteristic of respiratory diseases and is rarely reported in health, even at symptom-limited peak oxygen uptake (VO_2). The "unsatisfied inspiration" descriptor cluster (cannot get enough air in, my breath does not go in all the way, I feel the need for more air) selected by patients with COPD when dyspnea intensity is severe at the end of exercise has obvious semantic overlap with perceived "air hunger" (the uncomfortable urge to breathe) described in health during chemostimulation (with or without mechanostimulation). These discrete respiratory sensations, which are usually accompanied by distress, may very well share common neurosensory mechanisms (i.e., neuromechanical dissociation and limbic system activation). However, this hypothesis needs to be formally tested.

It is reasonable to assume that unsatisfied inspiration is modulated by peripheral sensory inputs that signal that the mechanical/muscular response of the respiratory system is inadequate for the prevailing central neural output. In COPD, restricted volume expansion and disrupted neuromuscular coupling as a result of
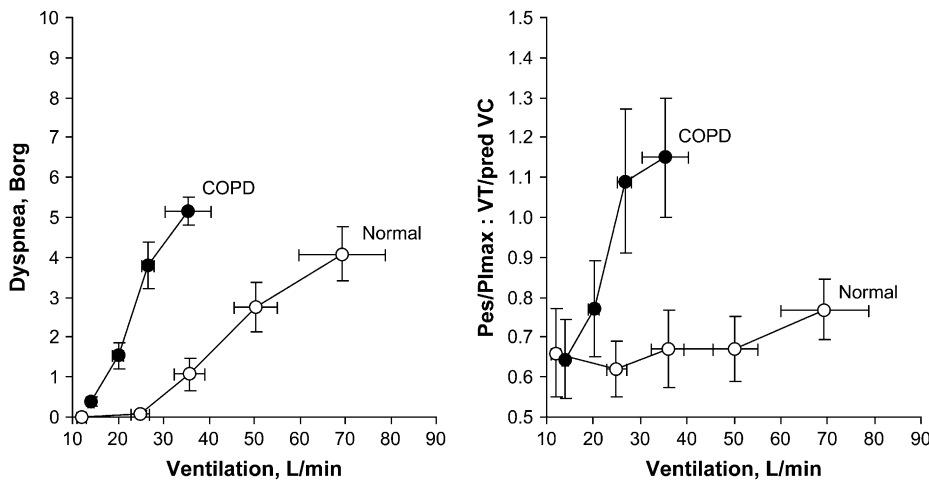

Figure 10. The effort:displacement ratio and dyspnea intensity are shown relative to ventilation during incremental exercise in COPD and in age-matched healthy normal subjects. Tidal swings of respiratory effort (Pes/PI_{max}) relative to the tidal volume response (V_T/predicted VC) and exertional dyspnea intensity are greater throughout exercise in COPD compared with health. Values are shown as means $\pm$ SE. Adapted by permission from Reference 23.
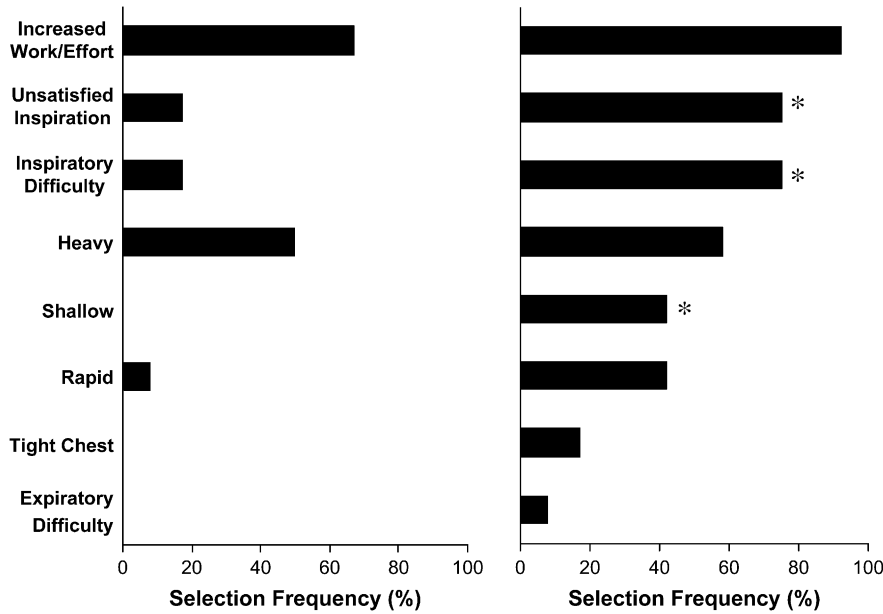
Figure 11. Qualitative descriptors of exertional dyspnea at the end of symptom-limited cycle exercise in COPD (*right*) and in age-matched healthy subjects (*left*). In COPD compared with health, there was a greater (*$P < 0.05$) predominance of awareness of "unsatisfied inspiration," "inspiratory difficulty" and "shallow" breathing. Adapted by permission from Reference 23.
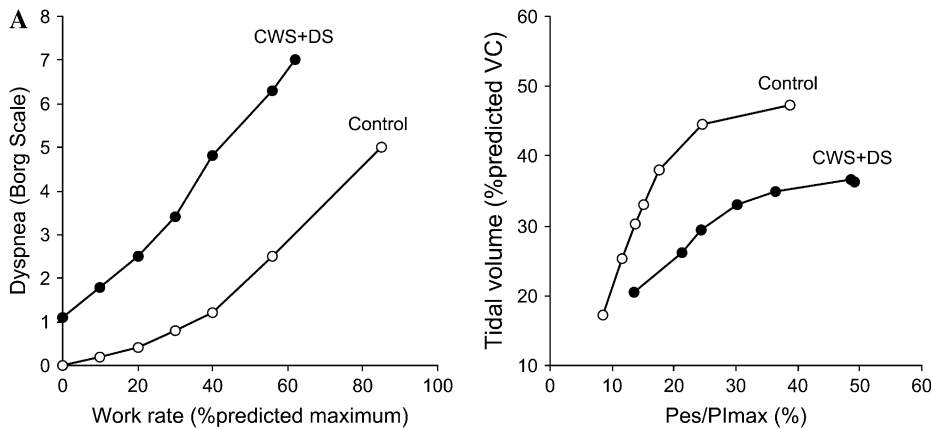

Figure 12. (*A*) Mechanical restriction by chest wall strapping (CWS) in the setting of added chemical loading (DS) induced very severe dyspnea during cycle exercise compared with an unloaded control test in 12 healthy young men. CWS+DS resulted in a blunted tidal volume response to exercise and caused a large increase in the ratio of respiratory effort (i.e., tidal esophageal pressure swings relative to maximum inspiratory pressure [Pes/PI$_{max}$]) to thoracic displacement (i.e., tidal volume expressed as % predicted vital capacity [VC]). (*B*) Qualitative descriptors of exertional dyspnea at the end of symptom-limited cycle exercise in health during an unloaded control test and during mechanical restriction induced by chest wall strapping (CWS) combined with deadspace loading (DS). There was a greater (*$P < 0.05$) predominance of awareness of unsatisfied inspiration, inspiratory difficulty, and shallow breathing with CWS+DS compared with Control. Graphs constructed with data from Reference 163.
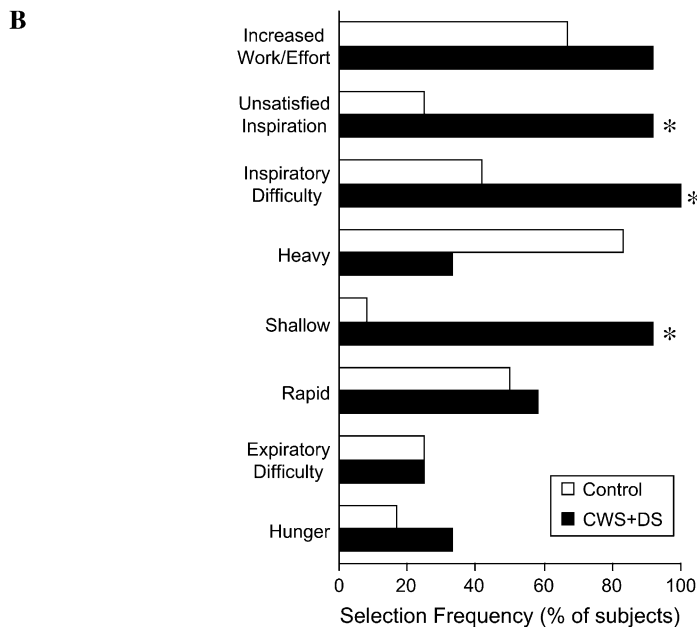
the effects of dynamic hyperinflation are putative mechanisms of unsatisfied inspiration that have recently been considered.

Several studies in resting healthy humans have shown that when chemical drive is increased in the face of voluntary suppression or restriction of the spontaneous breathing response, dyspnea quickly escalates to intolerable levels (138, 160–162). Moreover, resumption of spontaneous breathing (restored tidal volume displacement) was associated with immediate improvement in respiratory comfort, despite persistent (or even increased) chemical loading (138, 160–162). In health, mechanical restriction of tidal volume by chest strapping during exercise-induced severe dyspnea (described predominantly as unsatisfied inspiration) in the setting of added chemical loading (163) (Figure 12). Chest strapping resulted in a blunted tidal volume response to exercise (compared with unloaded control) and caused a large increase in the ratio of respiratory effort (i.e., tidal esophageal pressure swings relative to maximum) to thoracic displacement (i.e., tidal volume expressed as percent of predicted vital capacity) (Figure 12). The relative importance of the various sensory systems that ultimately contribute to an awareness of unsatisfied breathing remain to be determined. However, alteration in afferent inputs from vagal pulmonary receptors and chest wall mechanosensors, which are gated to command obligatory attention in cortical cognitive centers, remain prime candidates for the purpose of sensing abnormal thoracic displacement.

Because of resting and further dynamic hyperinflation during exercise in COPD, the ability to expand tidal volume is constrained as it becomes positioned in the upper noncompliant extreme of the respiratory system's pressure–volume relationship. Tidal volume responses are therefore shallow and become relatively fixed early in exercise despite the escalating drive to breathe. Therefore, effort-displacement ratios rise precipitously when tidal volume expands to reach the minimal IRV, and this index correlates strongly with ratings of dyspnea intensity (Figure 13). Therefore we postulate that in COPD, a mismatch between central neural drive and the mechanical response (*neuromechanical dissociation*), as crudely reflected by the increased effort:displacement ratio, is fundamental to the origin of dyspnea or its dominant qualitative dimension (Figure 14).

At the end of exercise in COPD when dyspnea intensity reaches intolerable levels, the muscle fibers in the inspiratory muscles are maximally shortened (and weakened or possibly fatigued) and thoracic displacement with each breath is greatly constrained in the face of near-maximal contractile muscle effort and chemical drive (i.e., metabolic acidosis and possibly critical

hypoxemia or hypercapnia). In some individuals it is possible that carbon dioxide retention during exercise will directly or indirectly amplify dyspnea (or air hunger) through increased activation of central chemoreceptors. Applying current neurophysiologic constructs for the genesis of dyspnea, the conscious awareness of unsatisfied inspiration may arise from integrated sensory inputs which reach the sensory cortex/association cortex from: (*1*) cortical (motor) and brainstem centers; and (*2*) respiratory mechanosensors in the muscles, lung, and chest wall (*see* Neurophysiology section in this document). The muscle spindles and Golgi tendon organs in the foreshortened, weakened, and possibly fatigued inspiratory muscles are ideally placed to act as the proximate source of this peripheral feedback information of an inadequate volume or ventilatory response (107, 164). However, an important contribution from pulmonary vagal (stretch) mechanosensors in response to volume restriction cannot be ruled out.

The Affective Response

When the sense of heightened effort increases beyond a certain threshold and/or the dissociation between neural drive and the mechanical response reaches a critical level (which likely varies between individuals), it will generate a strong emotional reaction (i.e., fear, distress) in the individual, which in turn will precipitate conditioned behavioral (avoidance) responses. Examples of learned compensatory behavior include: cessation of activity, pursed lip breathing, adoption of leaning forward position, recruitment of accessory muscles, social withdrawal, relaxation techniques, and distraction. These strategies help to attenuate neuromechanical dissociation and to allay anxiety. In some patients these compensations are not possible, and the affective response can quickly escalate to overt panic and overwhelming feelings of lack of control. Extreme fear and foreboding will, in turn, trigger patterned ventilatory and circulatory responses (via sympathetic nervous system activation) that can further amplify respiratory discomfort. It is plausible, based on recent brain imaging studies of healthy individuals during chemical loading, that activation of phylogenetically ancient areas in the brain such as the central limbic structures (including the anterior insula and anterior cingulated gyrus) contribute in a complex manner to the conscious experience of respiratory distress in the dyspneic patient with COPD (123, 165).

Mechanisms of Dyspnea Relief after Bronchodilator Therapy

Denis E. O'Donnell and Katherine A. Webb

All classes of bronchodilators act by relaxing airway smooth muscle tone. Traditionally, improvements in airway function after bronchodilators are assessed by spirometric measurements of maximal expiratory flow rates (166). Postbronchodilator improvements in the FEV_1 signify reduced resistance in the larger airways, as well as in alveolar units, with rapid time constants for lung emptying. Improvements in small airway function are more difficult to measure, but reduced lung volumes as a consequence of enhanced gas emptying in alveolar units with slower mechanical time constants provides indirect evidence of a positive effect. Recent studies have shown that substantial reductions in lung hyperinflation can occur after acute short- and long-acting bronchodilator treatments in the presence of only modest improvements in FEV_1 (70, 153, 167–169). Patients who show expiratory flow limitation during spontaneous resting breathing and those with more severe resting lung hyperinflation have demonstrated the greatest lung volume reduction with
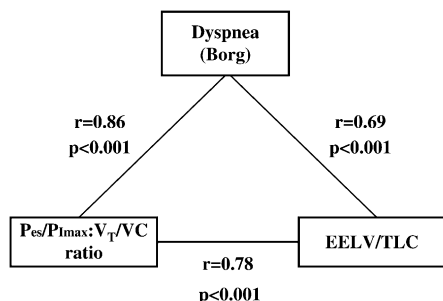
Figure 13. Significant inter-relationships were found between dyspnea intensity, the effort:displacement ratio (i.e., a crude index of neuromechanical dissociation) and the extent of dynamic hyperinflation (i.e., end-expiratory lung volume [EELV]) at a standardized level of exercise in patients with COPD. Pes = esophageal pressure; PI_{max} = maximal inspiratory pressure; TLC = total lung capacity. Reproduced by permission from Reference 147.
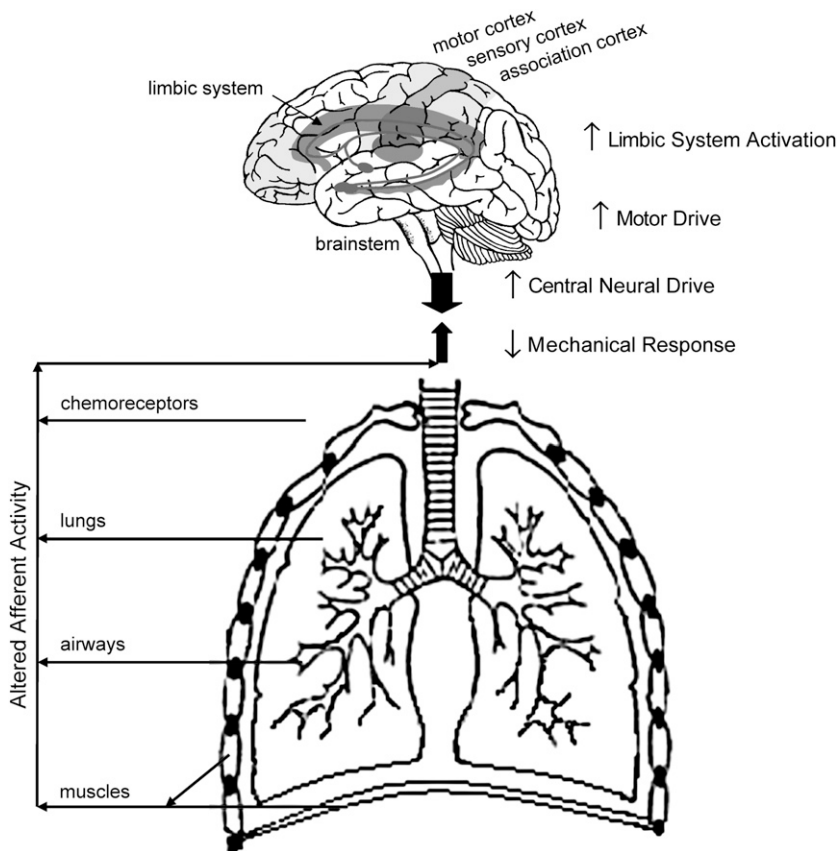
Figure 14. Model of neuromechanical dissociation in COPD. In health during exercise there is a harmonious matching of motor output (via corollary discharge) to the mechanical response of the respiratory system (via afferent peripheral feedback from multiple mechanoreceptors)—*neuromechanical coupling.* In COPD, there is a disparity between respiratory effort and the mechanical response of the system—*neuromechanical dissociation.* This disparity gives rise to sensations of respiratory discomfort such as "unsatisfied inspiratory effort."

bronchodilators (168, 170, 171). Moreover, reductions in lung hyperinflation have been shown to correlate better with improved exertional dyspnea ratings and exercise endurance time than traditional spirometric parameters (167, 172).

Several studies have shown that recruitment of resting IC after pharmacologic lung deflation is associated with increased tidal volume expansion throughout exercise and consequently with increased submaximal and peak ventilation (70, 71, 153, 156, 167) (Figure 15). In many patients, reduction in absolute lung volumes means a delay in the time for end-inspiratory lung volume to reach the minimal dynamic IRV. The mechanical limitation of ventilation is postponed and exercise endurance time is prolonged. This reduced mechanical restriction and increased tidal volume expansion closely correlates with reduced dyspnea intensity ratings after bronchodilator therapy (Figure 16). It is intriguing to speculate that release of volume restriction and concurrent alteration in vagal stretch receptor afferent inputs might directly ameliorate perceptions of "unsatisfied inspiration" (*see* the contribution to the Roundtable by Banzett). Indeed, this specific descriptor was chosen less frequently by patients after active drug compared with placebo in two studies of long-acting bronchodilators (71, 156).

A recent study on the mechanisms of dyspnea relief after tiotropium therapy showed that release of cholinergic tone was associated with improved airway conductance at all lung volumes from TLC to RV (156). After acutely administered tiotropium, static elastic recoil of the lung was unchanged and expiratory timing during spontaneous resting breathing was unaffected. Therefore, lung deflation primarily reflected improvements in the mechanical time constants for lung emptying (i.e., reduced airways resistance). The main impact is therefore on the dynamically determined end-expiratory lung volume through pharmacologic manipulation of expiratory flow limitation. Tiotropium was associated with reduced airways resistance, together with reduced elastic loading of the inspiratory muscles during con-

stant work-rate exercise. This meant that a lower inspiratory effort was required at any given time during exercise. A reduced inspiratory threshold load, reflecting reduced intrinsic PEEP after volume deflation, would be expected to further enhance neuromechanical coupling of the respiratory system. Lung deflation, by increasing sarcomere fiber length, may also favorably affect the force-generating capacity and efficiency of the inspiratory muscles, which again will contribute to reduced effort requirements for a given volume displacement. Tiotropium therapy resulted in a consistent reduction in the effort:displacement ratio throughout exercise (Figure 17), which, in turn, was associated with decrease in dyspnea intensity (156). Thus, avoidance of "high-end" mechanics as a result of bronchodilator-induced reductions in end-expiratory lung volume likely resulted in a more harmonious relationship between central neural drive and the mechanical response, with consequent reduced respiratory discomfort (70, 71, 153, 156, 167, 169). This physiologic benefit is not unique to a particular class of bronchodilator.

The precise neurophysiologic mechanisms of dyspnea relief remain speculative. Reduced motor command output (and central corollary discharge) as a result of bronchodilator-induced inspiratory muscle unloading may be sensed directly as a reduced sense of effort. Improvement in the operating characteristics of the inspiratory muscles secondary to lung deflation would be expected to enhance neuromuscular coupling—the muscle spindles, in particular, may have an important role in sensing this.

It is clear that there are numerous mechanosensors throughout the lungs, airways, and chest wall whose integrated afferent inputs can potentially convey the awareness of improved thoracic motion or volume displacement (after bronchodilator therapy) (*see* neurophysiology section of this roundtable). It is reasonable to speculate that altered peripheral sensory inputs from these sources together with reduced central corollary discharge culminate, in ways that are yet not fully understood, in a decrease in perceived effort and a sense of more satisfied inspiration during
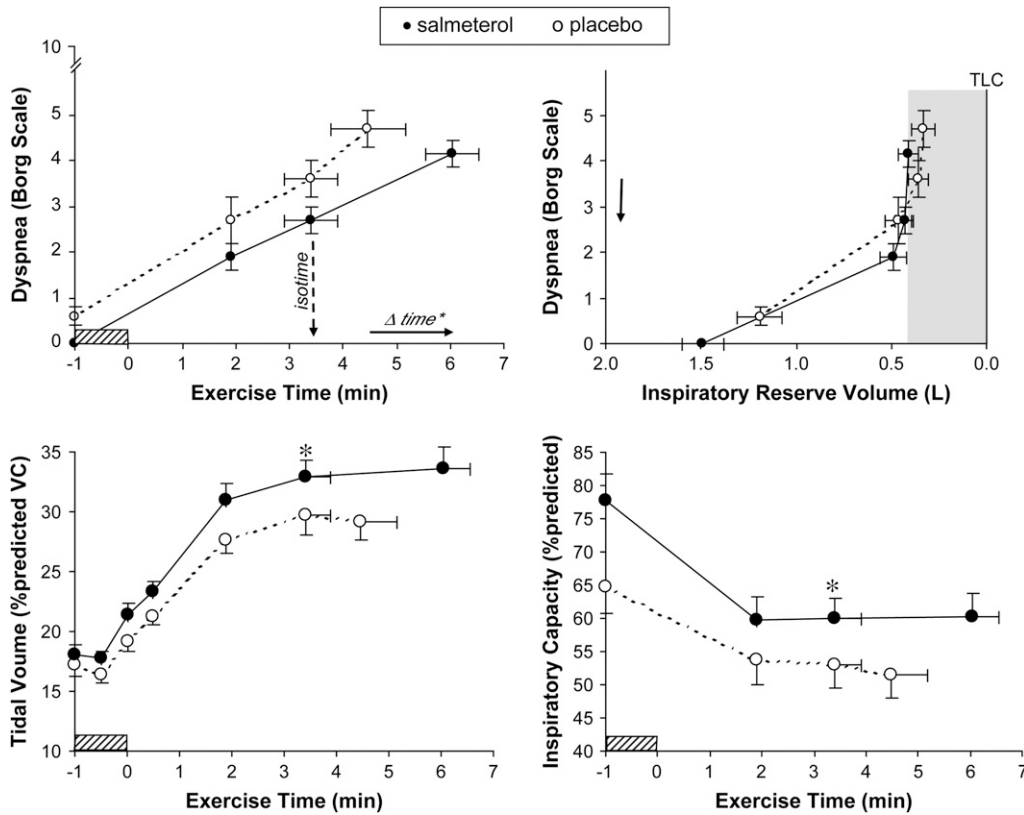
Figure 15. Relationships between dyspnea intensity, tidal volume, and inspiratory capacity are shown during constant-load cycle exercise at 75% of each patient's maximum work rate after salmeterol (*solid circles, solid lines*) and placebo (*open circles, dotted lines*). The relationship between dyspnea intensity and inspiratory reserve volume (IRV) was unchanged after salmeterol, with dyspnea increasing rapidly once a critically reduced IRV (*shaded area*) was reached, which prevented further expansion of tidal volume. At isotime during exercise, measurements of inspiratory capacity and tidal volume increased significantly after salmeterol compared with placebo (*$P < 0.05$). Values are means $\pm$ SEM; points were measured at rest, at standardized times during exercise, and at end-exercise. Adapted by permission from Reference 71.

physical exertion. Emerging evidence supports the idea that the salutary effects of bronchodilators on respiratory sensation in patients with COPD are ultimately linked to reduced volume restriction, reduced contractile muscle effort, and enhanced neuromechanical coupling of the respiratory system.

The Impact of Oxygen and Heliox

Richard Casaburi

Patients with moderate-to-severe COPD are usually substantially limited in their exercise tolerance; for most, exercise intol-

erance is their chief complaint. Exercise limitation in COPD is usually due to ventilatory limitation (173)—as work rate increases, the ventilatory requirement exceeds the ability of the ventilatory apparatus to ventilate the lungs. This occurs both because altered lung mechanics limits ventilatory capacity and
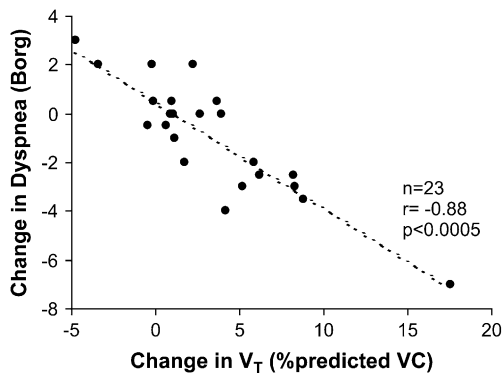

Figure 16. A significant correlation ($r = -0.88$, $P < 0.0005$) was found between differences in dyspnea intensity and tidal volume (VT, standardized as a percent of predicted vital capacity) at a standardized time during cycle exercise after salmeterol compared with placebo in 23 patients with COPD. Reprinted by permission from Reference 71.
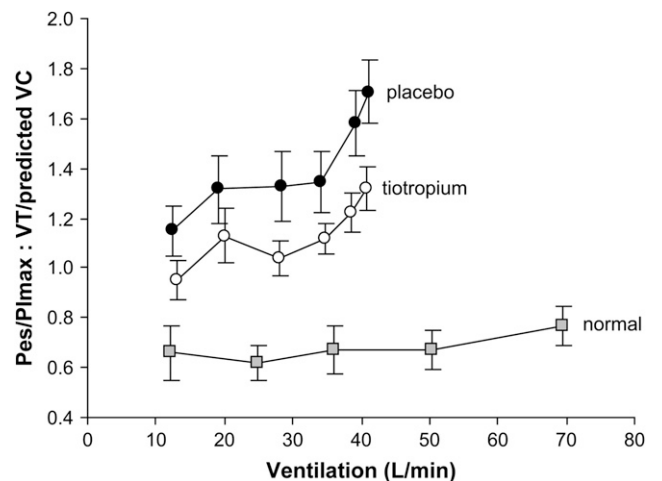

Figure 17. Improvement in the ratio between respiratory effort (Pes/PI_{max}) and tidal volume displacement (VT standardized as a fraction of predicted vital capacity [VC]), an index of neuromechanical dissociation, is shown during exercise after tiotropium and placebo in COPD (n = 11) compared with a previously studied group of age-matched normal subjects (n = 12). The effort:displacement ratio is increased in COPD compared with normal throughout exercise, with an upwards trend after a ventilation of approximately 30 L/min that did not occur in the normal subjects. Compared with placebo, tiotropium reduced this ratio throughout exercise in COPD. Reprinted by permission from Reference 156.

because the ventilatory requirement is high for a given level of exercise. Increased ventilatory requirement is dictated by inefficient pulmonary gas exchange (i.e., high V_D/V_T), as well as by abnormally high stimulation of the respiratory chemoreceptors. Carotid body stimulation is increased in COPD both by hypoxemia and, at heavy exercise levels, by early onset of lactic acidosis, resulting from poor muscle oxygen delivery and muscle dysfunction.

Two inhaled gases have been found capable of increasing exercise tolerance in patients with COPD, though their mechanisms of action are quite different. The mechanisms by which supplemental oxygen and heliox breathing decrease dyspnea on exertion and increase exercise tolerance are discussed in this section.

Effects of Oxygen

Roughly one million patients receive long-term oxygen therapy in the United States; most carry the diagnosis of COPD. We prescribe this treatment principally because of studies reported a quarter of a century ago, which demonstrated that hypoxemic patients with COPD live longer when prescribed supplemental oxygen (174, 175). However, the benefits of oxygen go beyond prolongation of life and also accrue to patients whose hypoxemia is less severe than those currently meeting criteria for long-term oxygen therapy.

Three physiologic effects of supplemental oxygen have the potential to increase exercise tolerance of the hypoxemic patient with COPD: (*1*) hypoxic stimulation of the carotid bodies is reduced, (*2*) the pulmonary circulation vasodilates, and (*3*) arterial oxygen content increases. The latter two mechanisms have the potential to indirectly reduce carotid body stimulation at heavy levels of exercise by increasing oxygen delivery to the exercising muscles and reducing carotid body stimulation by lactic acidemia. The predominant mechanism for oxygen's effect on exercise tolerance has recently been clarified (*see below*).

Ambulatory oxygen therapy has widely been shown to increase exercise performance and to relieve exertional dyspnea in patients with COPD (176–185). Recent studies indicate that reduction in hyperinflation plays an important role in the oxygen-linked relief of dyspnea (176, 183, 184). Interestingly, supplemental oxygen generally increases exercise tolerance in patients with only mild-to-moderate hypoxemia (i.e., levels of hypoxemia not meeting guidelines for long-term oxygen therapy) (179, 181, 183, 185).

We recently demonstrated these principles in a study of 10 patients with severe COPD who did not have clinically significant O_2 desaturation during exercise (185). Each performed five cycle exercise tests at 75% of maximally tolerated work rate. Inspired oxygen fraction ($F_{I_{O_2}}$) was varied (0.21, 0.3, 0.5, 0.75, and 1.0) among tests in randomized order. Pulmonary ventilation (V_E) was measured breath-by-breath and subjects performed inspiratory capacity maneuvers every two minutes. Inspiratory reserve volume was assessed as the difference between inspiratory capacity and tidal volume. At isotime, compared with room air, there were significant reductions in dyspnea score, V_E, and respiratory rate with $F_{I_{O_2}} = 0.3$. Figure 18 shows that respiratory rate fall was paralleled by a substantial increase in inspiratory reserve volume, denoting decreased hyperinflation. The isotime dyspnea rating decrease paralleled that of the respiratory rate decrease (Figure 19). Compared with room air breathing, endurance time increased substantially with $F_{I_{O_2}} = 0.3$ (by $92 \pm 20\%$, mean $\pm$ SE) and increased further with $F_{I_{O_2}} = 0.5$ (by $157 \pm 30\%$). Thus, oxygen supplementation during exercise induced a dose-dependent improvement in endurance and symptom perception in nonhypoxemic patients with COPD, which is apparently related to the decreased hyperinflation and the slower breathing pattern. This effect is maximized at $F_{I_{O_2}}$ of 0.5.
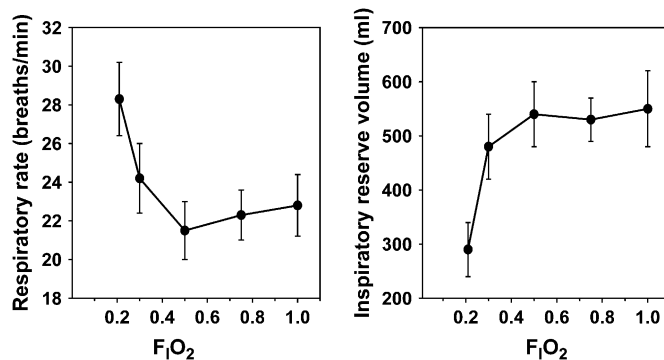
Figure 18. Effect of supplemental oxygen on breathing pattern and hyperinflation in 10 patients with COPD performing constant work rate exercise (isotime values). Adapted by permission from Reference 185.

These subjects also performed four repetitions of the transition between rest and 10 minutes of moderate-intensity constant work rate exercise while breathing air or 40% oxygen in randomized order (186). V_E, gas exchange, and heart rate were recorded breath-by-breath and arterialized venous pH, P_{CO_2}, and lactate were measured serially. During air breathing, the on-transient time constants (τ) for oxygen uptake, carbon dioxide output, heart rate, and V_E kinetic responses were slower in patients with COPD (70 ± 8 s, 98 ± 14 s, 86 ± 8 s, and 81 ± 7 s, respectively) than those seen in healthy subjects. Hyperoxia decreased end-exercise V_E. Hyperoxia did not speed V_{O_2} kinetics, but significantly slowed V_{CO_2} and V_E response dynamics. Only small increases in lactate occurred with exercise, and this increase did not correlate with the τ for V_{O_2}. These results seem inconsistent with a role for increased oxygen delivery in the reduced ventilatory response associated with oxygen breathing.

The mechanisms of hyperoxia-induced decreases in V_E are debated. Short-term studies in health generally show either no change (186–189), or a reduction in V_E during exercise due to a drop in breathing frequency, especially at higher submaximal exercise levels (190–192). In nonhypoxic patients with COPD, the reported range of reduction in exercise V_E varies between
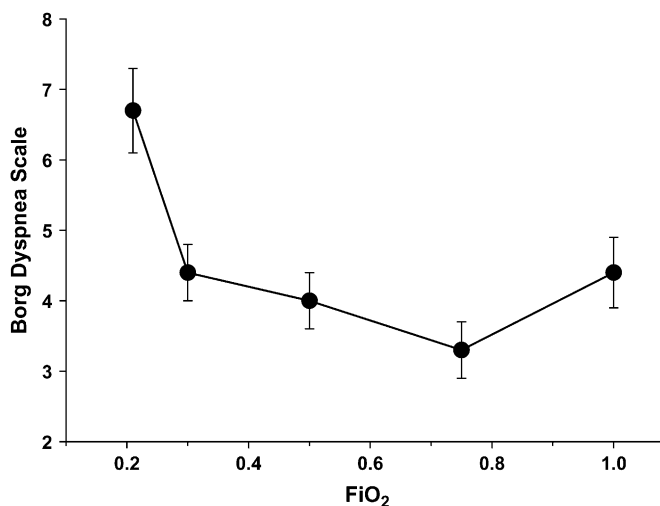
Figure 19. Effect of supplemental oxygen on Borg dyspnea scores in 10 patients with COPD performing constant work rate exercise (isotime values). Adapted by permission from Reference 185.

6 and 15% ($\sim$ 2–6 L/min), again due to a decrease in breathing frequency (190–192). Studies on the effect of hyperoxia on oxygen uptake and ventilatory kinetics and blood lactate levels in normoxic COPD show conflicting results, with the majority showing that V_E–lactate relationships are maintained during hyperoxia (181, 185, 193). Hogan and coworkers (194) recently showed that an oxygen-rich environment in the exercising muscles of healthy individuals attenuated muscle fatigue. A similar effect was suggested during 30% O_2 in mildly hypoxemic patients with COPD (195). Improved oxygenation may alter sensory afferent inputs from muscle mechanoreceptors and metaboreceptors or enhance neuromuscular coupling. Reduced fatigue would result in reduced central motor command output and, possibly, attendant reductions in ventilation (196).

Effects of Heliox

Helium is a low-density gas and will reduce airflow resistance when flow is turbulent (197). Replacing nitrogen with helium in the respired air (i.e., 79% helium, 21% oxygen—heliox) should reduce airflow resistance especially when high ventilatory demand engenders turbulent airflow. Reducing expiratory airflow resistance should, at least in theory, benefit the patient with COPD by allowing expiration to proceed more rapidly and with less effort. Resistive work of breathing will be reduced. Moreover (and perhaps more importantly), dynamic hyperinflation should be reduced by the same mechanism seen when bronchodilators are administered. At a given level of exercise (and ventilatory demand), a fuller exhalation should be possible and end-expiratory lung volume should be lower. During high-intensity exercise, this reduction in operating lung volume should result in less encroachment on lung volumes near the total lung capacity, where flattening of the pressure–volume relationship yields high elastic work of breathing.

Surprisingly, convincing demonstration that heliox improves exercise tolerance in patients with COPD has come only recently. Bradley and colleagues (197) studied the responses of seven patients with COPD to incremental exercise and could not detect differences in exercise tolerance between tests in which subjects inhaled heliox and air. In eight patients with severe COPD (average FEV_1 = 0.56 L) performing incremental exercise tests, Oelberg and colleagues (198) demonstrated that heliox (as compared with air) breathing yielded higher peak V_E (and lower Pa_{CO_2}), but that exercise tolerance was not improved. Johnson and colleagues (199) studied the responses of 33 patients with COPD (average FEV_1 = 34% predicted) who performed incremental treadmill exercise breathing air or a helium–oxygen mixture and found no differences in exercise tolerance. This study can be considered flawed, as a heliox mixture was administered at 10 L/min by nonrebreathing mask; at high levels of ventilation this certainly resulted in low effective helium fractions (likely in the 20–30% range rather than the "desired" 79%).

Constant work rate testing has been found to be a more sensitive measure of the ability of interventions to improve exercise tolerance than incremental exercise testing (200, 201). Palange and colleagues (202) were able to demonstrate in studies of 12 patients with COPD (average FEV_1 = 1.15 L) that breathing heliox, as compared with air, yielded a substantial prolongation of exercise time in a constant work rate test (averaging 9.0 versus 4.2 minutes). Peak minute ventilation was higher. Importantly, though isotime V_E did not differ, isotime inspiratory capacity was lower (signifying less dynamic hyperinflation) and Borg dyspnea rating was lower.

Most recently, Laude and colleagues (203) reported studies of 75 patients with COPD (FEV_1 = 43% predicted) who performed endurance shuttle walk tests (a form of constant work rate test). Endurance time was 36% greater with heliox breathing than with air breathing. These patients also performed a shuttle walk test breathing a mixture of 28% oxygen and 72% helium—a mixture that is both low density and has an elevated oxygen fraction—and found that endurance time was 76% greater than with air breathing. Benefits were greater for those patients with lower FEV_1. Though no physiologic measurements were made to confirm the mechanism of benefit, it seems reasonable to conclude that the combination of prolongation of the time for exhalation (caused by chemoreceptor inhibition from oxygen) and facilitation of faster exhalation (caused by reduction of expiratory airflow resistance by helium) had additive effects on exercise tolerance enhancement (204). Further research will be needed to determine whether 28% oxygen 72% helium is, in fact, the optimal mixture to accomplish the goals of enhanced exercise tolerance and reduced dyspnea in patients with COPD.

The Impact of Education and Symptom Management

Virginia Carrieri-Kohlman

The importance of education and self-management in the study and treatment of dyspnea is recognized only if the provider has an understanding of the true meaning of a symptom for the individual and the factors that are related to the perception of symptoms. A symptom is the individual's consciously appreciated sensation of a physiologic problem. Different than a laboratory sensation, the perception of a symptom involves acknowledgment, interpretation, and assigning meaning to a sensation by the person (205). It is the result of an interaction of multiple physiologic, psychological, social, and environmental factors that affect both the quality and intensity of the perception of the symptom (206).

There are many symptom perception theories. All acknowledge the phases of information input, the person's attention to the information, detection of the sensation as something different, attribution or assigning meaning, the multitude of factors that change the individual's perception of the symptom, and subsequent behavior that results from this process (207) (Figure 20).

Although numerous controlled studies have shown that dyspnea decreases after education and exercise provided to patients in a structured pulmonary rehabilitation program (208), these programs usually last only eight weeks. Many patients are unable to attend structured pulmonary rehabilitation programs because of expense or distance, and yet must manage their dyspnea and related symptoms of cough, sputum, and fatigue on a daily basis. This self-management is defined as the "…therapeutic, behavioral, and environmental adjustments patients and families must undertake with the collaboration and guidance of a health provider to maintain health status and reduce the impact of the disease on daily life" (209). Self-management of symptoms in chronic illness is constant for many years for patients, including patients with COPD and dyspnea. Patients must be the managers of their own symptoms, which includes monitoring the symptoms, choosing strategies to cope, and evaluating whether these strategies relieve the symptoms and the distress they cause.

The illness trajectory for COPD has many phases, beginning with periods of covert symptoms before the dyspnea even affects activities of daily living. Patients may deny symptoms in this stage. It is important to recognize that all of the phases require the patient to use different strategies to manage shortness of breath. Strategies for the relief of dyspnea can be physiologic or cognitive/behavioral in nature. Physiologic strategies are often used
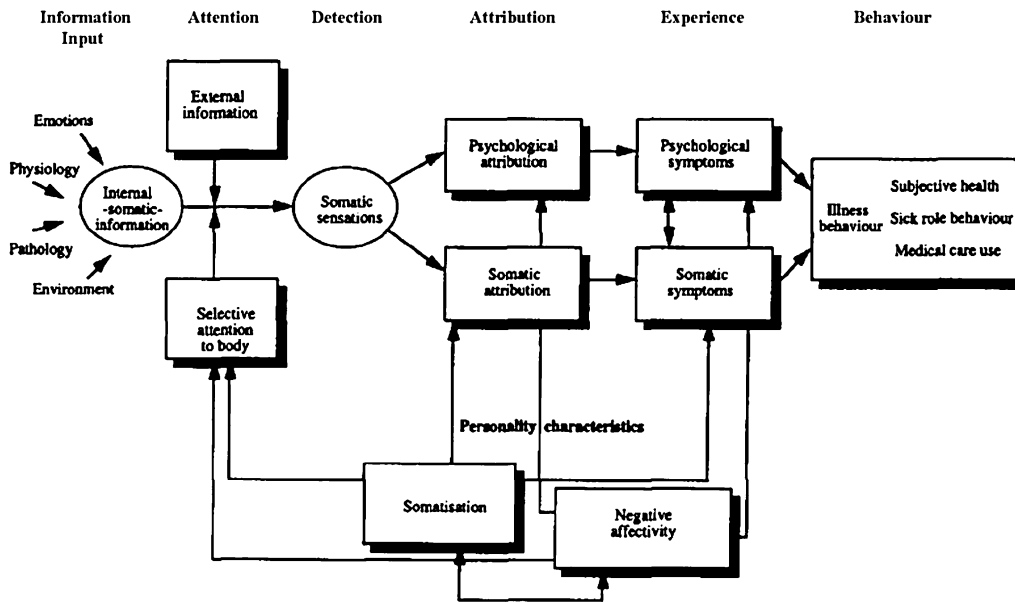
Figure 20. Symptom perception model. Reprinted by permisson from Reference 207.

by patients either unconsciously or after they have been taught the treatment. Several investigators, more recently Bianchi and colleagues (210), have shown that pursed lip breathing decreases dyspnea rated on a modified Borg scale from 2.1 during quiet breathing to 1.8 during pursed lip breathing ($P < 0.04$), and suggested that this may be due to the change in breathing rate, pattern, or lung volume. Other physiologic strategies that have been shown to decrease dyspnea include positive pressure ventilatory support. Bilevel positive airway pressure (BiPAP) 2 hours a day for 5 days in patients with COPD had a significant effect on dyspnea improvement at rest (211). CPAP and pressure support decreased exertional dyspnea and improved exercise performance (212, 213). Patients report fresh air and fans as an important strategy to decrease their dyspnea. Oral mucosal stimulation and warm air have been found to modulate the intensity of dyspnea in the laboratory (214). Vibration with stimulation of chest wall in-phase with respiration so that contracting respiratory muscles are vibrated decreased dyspnea (215). Even something as simple as a position change has been shown to decrease dyspnea (216).

The theoretical principles underlying the use of cognitive/behavioral strategies are that there is an interaction between mind and body and that individuals can be taught new patterns of thinking, feeling, and behaving to cope with symptoms. In addition, feelings of success or failure in carrying out a strategy and a feeling of "being in control" may be as important, or more important, to symptom perception than the actual behaviors. Confidence or a feeling of ability to control dyspnea may decrease the perception of the intensity and distress of the symptom (217). The use of cognitive–behavioral strategies is also guided by the belief that dyspnea, like pain, has an affective component measured by the "unpleasantness" or the "anxiety" and "distress" associated with it. It has been shown that patients can differentiate between these sensory and affective sensations. Dyspnea management strategies can be targeted toward both the affective and sensory components of the symptom (218) (Figure 21). Cognitive–behavioral strategies include but are not limited to relaxation, music, acupuncture, guided imagery, biofeedback, and yoga. The studies reveal mixed results. Three studies with small samples found that relaxation significantly decreased dyspnea during the relaxation session, but this effect was not maintained over time (219–221). In one study, music during walking decreased dyspnea during activities of daily living (ADLs). The mechanism for this improvement is unknown. Pos-

sible mechanisms may include distraction or a decrease in respiratory rate (222). In another study, there was no significant decrease in dyspnea with or without music at the end of a 6-minute walk (223). Acupuncture decreased dyspnea more than a placebo in one study encompassing 13 sessions over 3 weeks (224). In a more recent study, 20 sessions of acupressure for 5 weeks were found to decrease dyspnea with ADL more than a sham procedure (225). In one uncontrolled study of guided imagery in a small group of patients with COPD (n = 30), there was no effect on dyspnea at rest (226). A study comparing 9 months of yoga to a control of physiotherapy demonstrated significant increases in exercise tolerance in the yoga group along with "easier control" of dyspnea attacks (227). One group of investigators found that 18 sessions of ventilatory biofeedback (e.g., of volume and rate of breath given during exercise) significantly decreased dyspnea during exercise more than an exercise-only group or in those patients who only received ventilatory feedback at rest (228).

Education and symptom management can also play a role in relief of dyspnea. Unless accompanied by exercise, education or symptom management programs alone in patients with COPD appears not to improve dyspnea (229–232). In a very early study, talking to a nurse decreased dyspnea more than structured psychotherapy (233). An education program of strategies for ADL and stress management without exercise decreased only one measure of dyspnea at 6 months compared with a control of health teaching in a group of patients with COPD (234).
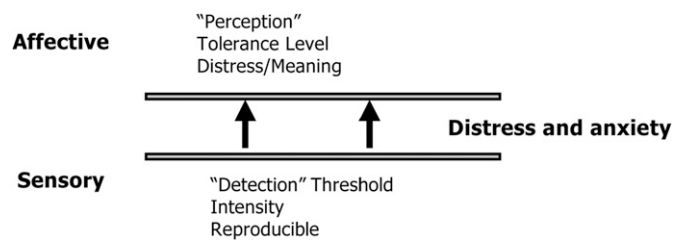

Figure 21. Construct showing the belief that dyspnea, like pain, has affective responses. For further discussion, *see* Reference 218.

Education and limited skills training, although improving health-related quality of life (HRQL) or self-efficacy, did not decrease dyspnea in other studies (235–237). More recently, a self-management program for patients with COPD—providing nurse home visits, exercise at home, action plans, and prescriptions for antibiotics and steroids for exacerbations—significantly decreased hospitalizations and use of health resources, including emergency room visits and unscheduled physician visits. Although there was no change in symptoms, some decrease in symptoms could be assumed with less frequent health care use (238).

Another research group (239, 240) tested a dyspnea self-management program consisting of (1) four individualized sessions of education about dyspnea management strategies over 8 weeks, with reinforcement at 4 and 8 months; (2) an individualized home walking prescription of four walks/week with a pedometer recorded in a "Walk and Shortness of Breath Log"; and (3) biweekly nurse coaching telephone calls. Three groups received varying "doses" of "nurse coached" exercise. One group received only the dyspnea self-management program with no supervised exercise (DM, n = 36). The exposure group (DM-EXP, n = 33) received the dyspnea self management program plus four supervised exercise sessions. The training group (DM-TR, n = 34) received the program plus 24 additional exercise sessions. This self-management program decreased dyspnea with ADL and increased the number of strategies the patients had in their repertoire. More supervised exercise sessions for the DM-TR group increased the exercise performance and decreased the dyspnea during laboratory exercise significantly more than the other two groups (240) (Figure 22).

These studies using cognitive–behavioral strategies to modulate dyspnea have shown early positive findings with small samples; however, there is a need for studies with controlled designs and/or larger samples.

Summary

Denis E. O'Donnell

The effective management of disabling dyspnea in patients with pulmonary disease remains a major challenge for caregivers. However, our understanding of the source and mechanisms of this complex symptom continues to increase and has helped to
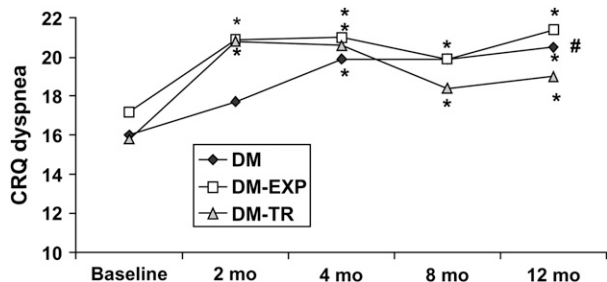

Figure 22. A dyspnea self-management program improved dyspnea as measured by the Chronic Respiratory Disease Questionnaire dyspnea subscale (CRQ dyspnea). The minimal clinically important change = 2.5. DM = dyspnea self-management program; DM-EXP = DM plus 4 supervised exercise sessions; DM-TR = DM plus 24 supervised exercise sessions. Reprinted by permission from Reference 240. *$P < 0.05$; #group by time, P = not significant.

refine future management strategies. Current concepts of the neurophysiology of dyspnea are largely based on psychophysical experiments that measure the sensory response to mechanical and chemical stimuli (or their combination) in healthy humans. Classical neurophysiology in animal models has taught us that multiple sensory systems monitor the ventilatory response to respiratory motor drive. This afferent feedback arises from four primary sources: (1) muscle afferents, (2) pulmonary receptors, (3) airway receptors, and (4) chemoreceptors (Figure 14). Afferent information from these sources projects to both the brainstem respiratory network and to higher brain centers (somatosensory and association cortices). External mechanical loading studies in humans have confirmed that the respiratory stimulus has a threshold for detection, that its magnitude can be quantified, and that it is possible to reliably discriminate different qualities of respiratory sensation. Imposition of mechanical loading also evokes breathing pattern responses, which serve to minimize respiratory discomfort. Brain imaging and respiratory-related evoked potentials have confirmed that mechanostimulation, chemostimulation, and motor drive change brain neuronal activity, which forms the basis for the cognitive awareness of breathing. Respiratory perception is further modulated by attention, experience/learning, and affective state. If respiration is sufficiently disrupted (either by external loading in health or intrinsic cardiopulmonary disease), it will lead to activation of limbic and paralimbic structures that signal the affective response to the perceived threat. This respiratory distress will, in turn, elicit behavioral adaptation.

The relative contribution of somatic proprioceptive and bronchopulmonary afferents on the one hand, and central signals of inspiratory motor command output (or effort) on the other, to the perception of respiratory difficulty cannot currently be quantified with precision. Given the complexity and redundancy of sensory systems, the neural substrate of dyspnea will likely vary with the circumstances under which it is induced. Recent research has focused on the qualitative aspects of dyspnea, with the reasonable assumption that different qualities have different neurophysiological underpinnings. There is evidence that the quality of dyspnea will vary with the nature of the dyspneogenic stimulus or the specific pathophysiological derangement in disease. Among multiple qualitative descriptors, four have been highlighted: (1) perceived sense of increased work or effort, (2) sense of chest tightness, (3) air hunger (an uncomfortable urge to breathe), and (4) unsatisfied inspiration. The air hunger stimulus–response curve is not altered during complete paralysis by neuromuscular blockade and is, therefore, independent of muscular work or effort. The intensity of air hunger is dependent on the level of chemostimulation (added CO_2), but also on ongoing inhibition from pulmonary mechanosensors signaling the concurrent level of pulmonary ventilation. The perceived severity of air hunger is determined by the balance of medullary respiratory motor discharge and the simultaneous mechanosensor feedback.

In patients with advanced COPD, heightened sense of effort (or work) and unsatisfied inspiration are dominant qualitative descriptors selected at the peak of exercise when dyspnea is severe. The descriptor "unsatisfied inspiration" appears to be broadly similar to "air hunger" and may have similar nerophysiological origins, but this needs formal validation. In moderate-to-severe COPD, inspiratory effort (measured by tidal esophageal pressure swings relative to maximum) is inevitably increased during high levels of ventilation when inspiratory muscles become overloaded and functionally weakened. The increased breathing effort reflects the increased motor drive, and it is suggested that cognitive awareness of effort is mediated via increased central corollary discharge to the somatosensory cortex (Figure 14). At higher ventilations during exercise, critical

restrictive ventilatory mechanics occur as a result of resting and further dynamic lung hyperinflation. The distressing perception of unsatisfied inspiration may have its origins in an increasing mismatch between central neural drive (augmented by increased chemo-stimulation) and the relatively limited thoracic volume displacement achieved during tidal breathing (Figure 14). This is not dissimilar to the experimental setting where severe air hunger is induced in healthy subjects if the ventilatory mechanical response is restricted (either voluntarily or by imposition) in the face of increased chemostimulation.

Recent studies that have examined mechanisms of dyspnea relief after a variety of therapeutic interventions have shed light on underlying mechanisms of dyspnea in COPD. All classes of bronchodilators reduce airway smooth muscle tone, improve airway conductance (at all lung volumes), and enhance lung emptying. Bronchodilators accelerate the time constant for lung emptying in heterogeneously distributed alveolar units throughout the lungs, thus reducing the dynamically determined end-expiratory lung volume (EELV) in patients with expiratory flow limitation. A diminished EELV (in absolute terms) means reduced elastic loading and improved functional strength of the inspiratory muscles during exercise. An improvement in the ratio of inspiratory effort to tidal volume displacement as a result of bronchodilator treatment reflects the newly enhanced neuromechanical coupling of respiratory system. Such improvements in dynamic ventilatory mechanics have consistently been associated with reduced dyspnea intensity ratings at any given ventilation during exercise.

Any therapeutic intervention that reduces ventilation during exercise should reduce the rate of dynamic hyperinflation with potential salutary sensory consequences. Supplemental oxygen has been shown to reduce dyspnea intensity in conjunction with the decreased ventilation during exercise, even in patients with COPD who are not severely hypoxemic. Enriched oxygenation during exercise has been consistently associated with a decrease in breathing frequency (and increased expiratory time), which can enhance lung deflation, particularly in patients with severe resting lung hyperinflation. However, the mechanisms of improved dyspnea in patients receiving supplemental oxygen are multifactorial, and reduction in dynamic hyperinflation is not obligatory for dyspnea alleviation. Recent studies have shown that when helium is combined with hyperoxia, additive effects on dyspnea are evident. Inhaled helium reduces airway resistance and likely accelerates the time constant for lung emptying with consequent reduction in the rate of dynamic hyperinflation. The added benefit of reduced neural drive and improved dynamic mechanics on exertional dyspnea intensity is also evident when hyperoxia is combined with bronchodilators in patients with COPD.

The application of new methods of neural imaging and neurostimulation represents an exciting new frontier in dyspnea research and has already provided insights as to how the "neuromatrix" subserving dyspnea perception is organized within the central nervous system. The pattern of limbic system activation during dyspneogenic stimuli is analogous to that observed during painful stimuli and points to the common overriding affective response to a perceived life-threatening situation. Clearly, effective management of chronic dyspnea must incorporate structured cognitive-behavioral and self-management strategies to successfully address this affective dimension of respiratory distress.

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