Pathophysiology of dyspnea

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ABSTRACT: *Pathophysiology of dyspnea. H.L. Manning, D.A. Mahler.*

Dyspnea may be defined as an uncomfortable sensation of breathing. The sense of respiratory effort, chemoreceptor stimulation, mechanical stimuli arising in lung and chest wall receptors, and neuroventilatory dissociation may all contribute to the sensation of dyspnea. Different mechanisms likely give rise to qualitatively different sensations of dyspnea. In most patients, dyspnea is probably due to a combination of mechanisms. For example, in asthma, a heightened sense of effort, neuroventilatory dissociation, and vagal stimuli arising from bronchoconstriction and airway inflammation may all play a role. Patients with different disorders and different mechanisms of dyspnea use different phrases to describe their breathing discomfort. Hence, the language patients use to describe their dyspnea may provide clues to the etiology of their symptoms.

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Introduction

Dyspnea, defined here as an uncomfortable or unpleasant sensation of breathing, is a common symptom in patients with cardiopulmonary disorders. Few symptoms are more distressing to patients than dyspnea. Unfortunately, in all too many patients, treatment of the underlying condition causing dyspnea is ineffective, or only partially effective. Until further research leads to more effective treatment of such conditions, our best hope for decreasing the breathlessness experienced by these patients is through an improved understanding of the mechanisms that give rise to the sensation of dyspnea.

In this article, we will review the different pathophysiological mechanisms that produce dyspnea and modify its intensity. We will then focus on a number of clinical scenarios in which dyspnea plays a role and demonstrate how one can apply these pathophysiological mechanisms to clinical disorders.

Mechanisms of dyspnea

The sense of respiratory effort

The sense of muscular effort refers to conscious awareness of voluntary activation of skeletal muscles. We are all familiar with the sense of muscular effort: a heavy object requires great effort to move, whereas little effort is needed to move a light object. What feels "heavy" or "light" depends not only on the weight of the object but also on one's strength. Similarly, the sense of respiratory muscle effort is related to the ratio of the pressure generated by the respiratory muscles (P_{breath}) to the maximum pressure generating capacity of the muscles (Pi_{max}), i.e. P_{breath}/Pi_{max} [1]. Thus, the sense of effort increases whenever the inspiratory muscles must generate greater pressure, such as when they face an added elastic, resistive or threshold load, or when the pressure generating capacity of the respiratory muscles is reduced, such as when the muscles are weakened, fatigued or mechanically disadvantaged by an increase in lung volume.

Chemoreceptors

Stimulation of either the peripheral or the central chemoreceptors increases ventilation. These same receptors also contribute to the sensation of breathlessness. Hypoxia stimulates respiration through its effects on the peripheral chemoreceptors, and may cause or contribute to the sensation of breathlessness in patients with lung disease [2–4]. However, many dyspneic patients are not hypoxic, and those that are hypoxic often have only modest improvement in their symptoms after the hypoxia is corrected.

Normal subjects and patients with pulmonary disease also experience breathlessness while breathing CO_2 [5, 6]. Despite that, the clinical relevance of such experimental observations is uncertain because there are many clinical settings, such as interstitial lung disease and pulmonary vascular disease, in which hypercapnia is rare, yet such patients often experience significant breathlessness. Conversely, many patients with COPD and hypercapnia experience little or no dyspnea at rest.

Mechanoreceptors

There are a number of receptors distributed throughout the respiratory system that respond to

mechanical stimuli (some, such as irritant receptors, also respond to chemical stimuli); these receptors are collectively referred to as "mechanoreceptors".

Upper airway receptors. Clinical observations suggest that upper airway and facial receptors modify the sensation of dyspnea. Patients sometimes report a decrease in the intensity of their breathlessness when sitting by a fan or open window. Conversely, some patients report worsening dyspnea when breathing through a mouthpiece during pulmonary function testing. Studies involving dyspnea induced in normal subjects indicate that receptors in the trigeminal nerve distribution influence the intensity of breathlessness [7].

Chest wall receptors. The brain receives projections from a variety of receptors in the joints, tendons, and muscles of the chest that influence ventilation and affect the sensation of breathlessness. Mechanical stimuli, such as vibration, are known to activate these receptors, and may affect the sensation of breathlessness. For example, MANNING *et al.* found that inspiratory vibration of the parasternal intercostal muscles reduced breathlessness induced in normal volunteers [8], and subsequent studies by other investigators have shown that chest wall vibration may reduce dyspnea in patients with COPD [9–10].

Lung receptors. The lung contains several types of receptors that transmit information to the central nervous system. Pulmonary stretch receptors in the airways respond to lung inflation; irritant receptors in the airway epithelium respond to a variety of mechanical and chemical stimuli and mediate bronchoconstriction; and C-fibers (unmyelinated nerve endings) located in the alveolar wall and blood vessels respond to interstitial congestion. Numerous studies suggest that information from these vagal receptors also plays a role in dyspnea [11–13]. The effect of vagally transmitted afferent information from the lungs on dyspnea likely depends upon which receptors are stimulated. Stimulation of vagal irritant receptors appears to intensify the sensation of breathlessness and may impart a sense of chest tightness or constriction [14], whereas stimulation of pulmonary stretch receptors likely decreases the sensation of breathlessness [11].

Integration of Sensory Information. The many sensory inputs related to breathing must reach the cerebral cortex in order to be experienced as dyspnea, and thus the processing of respiratory-related afferent information is an important step in the pathogenesis of dyspnea. Campbell and Howell proposed the concept of length-tension inappropriateness as the cause of breathlessness [15]. According to their theory, dyspnea arose from a disturbance in the relationship between the force or tension generated by the respiratory muscles and the resulting change in muscle length and lung volume. Their theory has since been refined to incorporate the general concept of mismatch between the outgoing motor command to the respiratory muscles and incoming afferent information. In essence, this revised theory of "afferent mismatch" or "neuroventilatory dissociation" suggests that under a given set of conditions, the brain 'expects' a certain pattern of ventilation and associated afferent feedback. Deviations from that pattern cause and/or intensify the sensation of dyspnea.

Dyspnea in common clinical disorders

There is accumulating evidence that in many patients, dyspnea is multifactorial in etiology, and that in most patients, there is no single, all-encompassing explanation for dyspnea. Some features leading to dyspnea are shared by patients with a variety of disorders, whereas others are unique to a particular clinical situation. Moreover, most conditions associated with dyspnea are characterized by more than one mechanism that may produce respiratory discomfort. Unfortunately, our understanding of dyspnea has not generally reached the point where we can conclusively link a specific disease with a specific mechanism (or mechanisms) of dyspnea. However, knowledge of the pathophysiology of a disorder sometimes allows us to formulate rational hypotheses about the underlying mechanisms of dyspnea (table 1). In this section, we review the evidence for potential mechanisms of dyspnea in some of the more common conditions and disorders associated with dyspnea.

Asthma

Asthma is an inflammatory disorder of the airways that is characterized by increased airways resistance and airway closure at abnormally high lung volumes. These pathological and physiological abnormalities give rise to dyspnea in patients with asthma.

Although physicians often gauge the severity of asthma in terms of its effects on expiratory airflow (e.g. FEV_1 and peak expiratory flow rate are standard measures of asthma severity), the most important mechanical abnormalities in asthma that contribute to dyspnea are related to the inspiratory muscles. The inspiratory muscles must generate greater tension to overcome the increase in airflow resistance that accompanies bronchoconstriction. When asthma is accompanied by hyperinflation, the inspiratory muscles become shorter and therefore operate at a less optimal length for developing tension. Hyperinflation may change the radius of curvature of the diaphragm, thereby placing it at a mechanical disadvantage; and hyperinflation represents an additional threshold load for the inspiratory muscles to overcome. As a result of these factors, respiratory motor output increases, and the accompanying increased sense of respiratory muscle effort likely contributes to dyspnea in asthma. Moreover, the inspiratory threshold load, (so-called "auto-PEEP" or "intrinsic PEEP") represents the ultimate example of afferent mismatch

Table 1. – Mechanism(s) of dyspnea in selected disorders. Presence of mechanism(s) is indicated by "x" Although the mechanism(s) listed for each disorder are to some degree speculative, the question mark indicates an even greater degree of uncertainty about the contribution of that mechanism. The sign ± indicates that the mechanism likely plays a minor role in the dyspnea experienced by most patients with the disorder

	Asthma	COPD	LV dysfunction	ILD	Neuromuscular Disease	Pulmonary Embolism
Sense of effort	x[a]	x	x	x	x	
Hypoxia	±	±		±		±
Hypercapnia	±	±				
Irritant receptor	x					
C-fiber			?	?		?
Afferent mismatch	x	x	x	x	x	

[a] the sense of effort probably plays a significant role in moderate and severe asthma and a lesser role in mild asthma.

COPD = chronic obstructive pulmonary disease;
LV dysfunction = left ventricular dysfunction;
ILD = interstitial lung disease.

(neuroventilatory dissociation). During the initial contraction of the inspiratory muscles, there is no volume change; airflow only occurs once the inspiratory muscles have generated sufficient pressure to overcome the elastic recoil (auto-PEEP) of the respiratory system.

Experimental evidence indicates that hyperinflation likely plays an important role in the pathogenesis of dyspnea in asthma. In a group of 21 mild asthmatics given methacholine to induce bronchoconstriction, Lougheed and colleagues found that an increase in end-expiratory lung volume was the single greatest contributor to subjects' breathlessness [16]. Similarly, the best physiologic correlate of relief of breathlessness after the administration of salbutamol was a return of end-expiratory lung volume to baseline.

However, there is also evidence that hyperinflation is not the sole mechanism of dyspnea in asthma. Some patients with chronic asthma have minimal increases in lung volumes, but are quite symptomatic. The work of TAGUCHI *et al.* may shed light on the dyspnea experienced by these patients [13]. TAGUCHI *et al.* used an external resistive load and histamine aerosol to induce dyspnea in a group of normal subjects. Subjects experienced greater breathlessness during histamine-induced bronchoconstriction than when breathing through an external resistance of comparable magnitude, even though end-expiratory lung volume was similar in the two conditions. Inhaled lidocaine ameliorated the sensation of breathlessness associated with bronchoconstriction, but had no effect on the discomfort associated with the external resistive load. Moreover, the inhaled lidocaine provided relief of dyspnea in the absence of any change in end-expiratory lung volume. This study suggests that vagal irritant receptors contribute to dyspnea during bronchoconstriction. In particular, vagal receptors may impart the sensation of chest tightness experienced by many asthmatic patients [14].

COPD

In patients with chronic obstructive pulmonary disease (COPD), the respiratory muscles face many of the same loads outlined above in the discussion of asthma. Furthermore, the increased dead space ventilation requires that for any given workload (and level of CO_2 production), minute ventilation will be greater in patients with COPD than in normal individuals. Just as with asthma, these factors necessitate an increase in respiratory motor output and lead to an increased sense of effort.

Other factors may also contribute to breathlessness in patients with COPD. For example, dynamic airway compression occurs in some patients with COPD and may be a factor in their breathlessness. One mechanism by which dynamic airway compression might cause breathlessness is through simple mechanical distortion of the airways during exhalation. It is interesting that some patients with COPD spontaneously purse their lips during exhalation, and others report improvement in their breathlessness after they are taught to adopt such a breathing strategy. Although pursed lips breathing may influence lung function in several ways, its effects on respiratory sensation may be mediated in part through transmural pressure changes along the intrathoracic airways. O'DONNELL *et al.* demonstrated that when a negative pressure is applied at the mouth in patients with severe COPD, breathlessness increases when the added pressure leads to dynamic compression of the airways [17]. Presumably, receptors in the airways that are sensitive to airway compression or to transmural pressure changes across the airway wall modulate the sensation of breathlessness.

Chemoreceptor stimulation probably plays a modest role in the dyspnea experienced by many patients with COPD. Although patients with COPD may be acutely or chronically hypoxemic, virtually all have persistent dyspnea after their hy-

poxemia is corrected. Many chronically hypercapnic patients are not dyspneic at rest, thereby raising doubts about the contribution of chronic hypercapnia to dyspnea. During acute exacerbations of COPD, patients may develop new or worsening hypercapnia (accompanied by new or worsening respiratory acidosis), which may be a more potent stimulus for breathlessness than chronic, compensated hypercapnia.

Chronic left ventricular dysfunction

Many patients with chronic left ventricular (LV) dysfunction complain of dyspnea even in the absence of overt heart failure. Several mechanisms may contribute to dyspnea in these patients.

Changes in the mechanical properties of the lungs sometimes accompany chronic heart disease, as patients may manifest a decrease in lung compliance and an increase in airway resistance [18]. Most patients with severe chronic LV dysfunction also have an excessive ventilatory response to exercise resulting from increased dead space ventilation [19]. These abnormal demands on the ventilatory muscles occur on a background of reduced respiratory muscle function. Several studies have shown a substantial decrement in inspiratory muscle strength [20, 21]. Furthermore, there is also some evidence to suggest that such patients experience respiratory muscle ischemia during exercise [22]. Together, these factors create a situation in which P_{breath} represents a large fraction of P_{imax}, leading to an increased sense of breathing effort.

Some patients with chronic LV dysfunction have an elevated pulmonary artery wedge pressure at rest, which usually increases further with exercise. Since pulmonary venous hypertension is a potent stimulus to C-fibers, it is tempting to speculate that these receptors contribute to exertional dyspnea in chronic heart failure (CHF) [23]. Most patients with chronic LV dysfunction are not hypercapnic and do not develop significant arterial oxygen desaturation during exercise; thus, it is unlikely that the chemoreceptors play a significant role in the dyspnea experienced by this patient population.

Interstitial lung disease

In patients with interstitial lung disease (ILD), lung compliance is diminished and, because of an increase in dead space, there is an increase in resting ventilation and an exaggerated ventilatory response to exercise. These factors necessitate an increase in respiratory motor output, resulting in an increased sense of effort. However, some patients with ILD are dyspneic at rest, when ventilation and the work of breathing are increased, but not to a level that seems sufficient to account for their dyspnea. Since many interstitial disorders involve a component of alveolitis at some stage in the disease process, one possibility is that vagal receptors stimulated by the inflammatory process also contribute to patients' breathlessness. That possibility is consistent with animal studies demonstrating that the abnormal breathing pattern in experimental pneumonitis (similar to the abnormal breathing pattern in ILD) is vagally mediated [24].

Neuromuscular disease

In patients with disorders such as amyotrophic lateral sclerosis or myasthenia gravis, the mechanical properties of the respiratory system may be normal, but the weakened respiratory muscles (i.e. decreased P_{imax}) require greater neural drive for activation. For example, Spinelli and colleagues found that in patients with myasthenia gravis breathing room air at rest, there was a trend towards greater $P_{0.1}$ (pressure measured 0.1 sec after the airway is occluded) values in the patients with myasthenia than in the control group [25]. The patients with myasthenia also manifested greater fractional electromyograph (EMG) activity (ratio of EMG activity during breathing to EMG activity during maximal volitional effort) of both the diaphragm and intercostal muscles. This heightened neuromotor output is sensed as increased respiratory muscle effort, and is likely the principle mechanism of breathlessness in patients with uncomplicated (i.e. without superimposed respiratory complications such as pneumonia, atelectasis, etc.) neuromuscular disease.

Pulmonary embolism

Although dyspnea is the most common symptom in patients with pulmonary embolism, there has been virtually no systematic study of dyspnea in this disorder. Pulmonary embolism may be associated with a variety of pathophysiological abnormalities, but the dyspnea experienced by patients with pulmonary embolism may be out of proportion to any derangement in respiratory mechanics or gas exchange, particularly in those patients who have not had massive embolism. Anecdotal reports of patients undergoing thrombolysis indicate that dyspnea may be rapidly relieved by clot lysis. Such observations suggest that the receptors causing the sensation of dyspnea lie within the pulmonary vasculature and respond to changes in pressure. The receptor most likely to sense these changes is the pulmonary C-fiber. In animal studies, C-fibers increase their firing in response to elevations in pulmonary artery pressure [26] or pulmonary embolism [27], though irritant and stretch receptors may be stimulated by emboli as well. It seems reasonable to postulate that C-fibers cause, or at least contribute to, the sensation of dyspnea in patients with pulmonary embolism.

Qualitative aspects of dyspnea

In the preceding sections, we have described our current understanding of the different mechanisms contributing to the pathogenesis of dyspnea. Given the existence of several distinct mechanisms of dyspnea, it is logical to ask whether these different mechanisms translate into distinct sensory experiences.

Several recent studies indicate that the answer to that question is "yes": different respiratory stimuli produce different respiratory sensations, and patients with different disorders use different phrases to describe their breathlessness (table 2) [28, 29]. The sense of air hunger appears to arise out of an increased brain stem "drive" to breathe [30]. Patients with conditions in which there is either an increased mechanical load on the respiratory system or neuromuscular weakness or fatigue often report an increased sense of "effort" or increased "work" of breathing [28]. In patients with moderate to severe obstructive lung disease, the respiratory system may be characterized by marked hyperinflation, and tidal volume, especially during exercise, may be limited by the encroachment of end-expiratory lung volume on total lung capacity. Under these conditions, individuals may report a sense of an "inability to get a deep breath" as the dominant feature of their breathing discomfort [31]. Finally, questionnaire studies demonstrate that chest tightness is a prominent feature of the dyspnea of asthma, and may be present even when there is little or no airflow obstruction [14].

Summary

Dyspnea is the product of a complex interaction of signals arising within the brain stem and in a variety of receptors in the upper airway, lungs, and chest wall (figure 1). The cortical processing of these afferent signals determines the intensity and quality of breathlessness. Various studies suggest that that although different disease states share common mechanisms of dyspnea, most pathologic conditions produce breathlessness by more than one mechanism, and each disorder probably has a unique combination of pathophysiological factors that determines the quality and intensity of breathlessness in a particular patient at a given time. Patients with different disorders use different terms and phrases to describe their discomfort; in some cases, the language used by patients to describe their breathlessness may provide clues to the nature of the disorder as well as the underlying mechanism(s) of dyspnea.
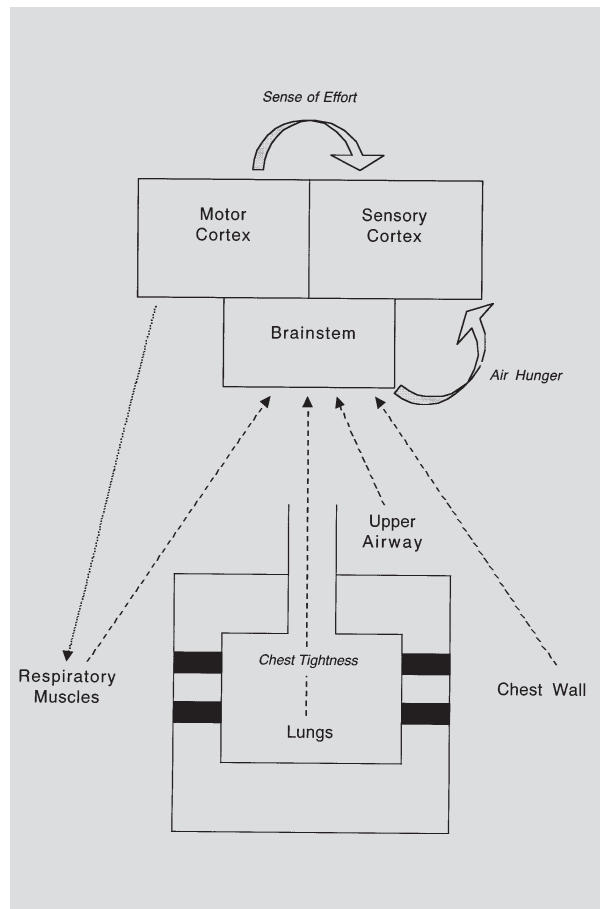

Fig. 1. – Pathways involved in the pathophysiology of dyspnea. For simplicity, receptors in the lungs, chest wall, and upper airways are shown schematically projecting directly to the sensory cortex, but the pathways likely reach the cortex via the brainstem.

Table 2. – Qualitative descriptors of breathlessness (adapted from refs. 28, 32)

Disorder	Description
Asthma – mild	Chest tightness
Asthma – severe	Increased breathing effort
	Inability to get a deep breath
COPD	Increased breathing effort
	Inability to get a deep breath
Interstitial lung disease	Increased effort
	Unsatisfied respiratory effort
Chronic LV dysfunction	Increased breathing effort

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