PATHOPHYSIOLOGY OF DYSPNEA

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Patients with cardiopulmonary disease often have respiratory distress, which physicians refer to as dyspnea. Dyspnea is responsible for substantial disability and for millions of patient visits each year. Although dyspnea has been defined in several ways, 14 we define it as “an uncomfortable sensation of breathing.” This review will focus on the mechanisms of dyspnea, because a greater understanding of those mechanisms may lead to better therapy for this often troubling symptom.

Problems in the Study of Dyspnea

Dyspnea differs from other sensations in that the neural pathways underlying it are not well understood. For example, free nerve endings transmit pain signals to the central nervous system, but there are no specialized dyspnea receptors. Similarly, although the auditory, visual, olfactory, and somatosensory portions of the cerebral cortex have all been mapped, the region of the cerebral cortex that processes information related to dyspnea remains unidentified. There is no area of the cortex that when stimulated causes dyspnea or any other respiratory sensation, nor is there a cortical lesion that abolishes the sensation of dyspnea or the perception of other respiratory-related stimuli.

The study of dyspnea is further complicated by difficulty in defining the precise physical stimulus that causes it. When a person inadvertently touches a hot stove, pain arises from a quantifiable thermal stimulus. However, when a patient with chronic obstructive pulmonary disease (COPD) becomes dyspneic walking up a flight of stairs, is his or her respiratory discomfort due to the metabolic work of the task, increased airway resistance, weakened or mechanically disadvantaged ventilatory muscles, or changes in arterial blood gases? Often there is no single easily identifiable stimulus comparable to temperature to explain respiratory sensations.

Much of our understanding of the pathophysiology of dyspnea is derived from studies of respiratory sensations induced in young, healthy subjects. The studies that have been conducted in patients have focused largely on those with COPD and have used chemical stimuli (hypercapnia or hypoxia), added respiratory loads, breath holding, or exercise as the stimulus for dyspnea. The studies have used the techniques of psychophysics 5 6 and scales such as the Borg scale (a category scale that denotes the intensity of sensation with numbers and descriptive terms) 7 and visual analogue scales 8 to describe the relation between external stimuli (such as resistive loads) or internal measures (such as pleural pressure) and the intensity of respiratory discomfort. The relevance of many of these experimental models of dyspnea to spontaneously occurring dyspnea in patients is uncertain. For example, breathing through a narrow orifice may reasonably approximate the increased work of breathing experienced by patients with obstructive lung disease, but the pressure changes along the airway in normal subjects breathing through an external resistance are quite different from those in patients with narrowed bronchi or diminished elastic recoil of the lungs. Thus, caution must be exercised in extrapolating from normal subjects or patients with COPD to patients with other disorders associated with dyspnea.

Mechanisms of Dyspnea

Dyspnea includes several qualitatively distinct sensations that probably arise from different pathophysiologic mechanisms. When normal subjects were made breathless by performing eight respiratory tasks, they selected different groups of phrases to characterize their dyspnea with each task. 9 In two studies of patients with dyspnea caused by cardiopulmonary disorders, the various patient groups selected unique combinations of qualifying phrases to characterize their breathing discomfort (Table 1). 10 11

Dyspnea is frequently associated with conditions in which respiratory drive is increased or the respiratory system is subject to a mechanical load. These conditions are characterized by a sensation of air hunger or increased effort or work of breathing. 10 11 Some disorders are associated with the stimulation of irritant receptors in the lungs; patients with these disorders may describe their discomfort by phrases such as “breath stops,” “chest tightness,” and “constriction.” In addition to these qualitative factors, the intensity of dyspnea may be modified by the relative match between the respiratory motor command or signal originating in the central nervous system and afferent feedback arising from various receptors in the respiratory system. Figure 1 summarizes the signals that contribute to the sensation of dyspnea, which will be discussed below.

Sense of Respiratory Effort

The sense of muscular effort is the conscious awareness of the voluntary activation of skeletal muscles. Although in theory the sense of effort could arise from either the central nervous system or the muscles, the bulk

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of evidence suggests that it arises from simultaneous activation of the sensory cortex at the time the muscles are signaled to contract.\textsuperscript{12} We have all experienced the sense of muscular effort: a very heavy object requires great effort to move, whereas little effort is expended to move a light object. However, under some circumstances, such as muscle weakness or fatigue, even a small task may involve substantial effort.

The sense of effort is related to the ratio of the pressure generated by the respiratory muscles to the maximum pressure-generating capacity of the muscles.\textsuperscript{13} The sense of respiratory effort increases whenever the central motor command to the respiratory muscles must be increased — that is, when the muscle load is increased, or when the muscles are weakened by fatigue, paralysis, or an increase in lung volume. There is a striking overlap between the settings in which the motor command to the respiratory muscles is increased and those in which normal subjects or patients become breathless. For example, in normal subjects breathing at both normal and increased lung volumes, effort and breathlessness closely parallel one another over a range of added loads.\textsuperscript{14}

There are, however, other clinical and experimental observations that the sense of effort fails to explain. For a given level and pattern of ventilation, both patients and normal subjects are more breathless when they are hypercapnic than when they are eucapnic,\textsuperscript{15} even though respiratory effort should not differ between the two conditions, since respiratory motor output, and presumably motor command, are similar. If ventilation is suppressed below the level dictated by chemical drive, effort and breathlessness closely parallel one another over a range of added loads.\textsuperscript{14}

Table 1. Respiratory Sensations Associated with Various Conditions.*

<table>
<thead>
<tr>
<th>Sensation</th>
<th>COPD</th>
<th>CONGESTIVE HEART FAILURE</th>
<th>INTERSTITIAL LUNG DISEASE</th>
<th>NEUROMUSCULAR AND CHEST-WALL DISEASE</th>
<th>PREGNANCY</th>
<th>PULMONARY VASCULAR DISEASE</th>
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</thead>
<tbody>
<tr>
<td>Rapid breathing</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Incomplete exhalation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shallow breathing</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased work or effort</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of suffocation</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air hunger</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest tightness</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy breathing</td>
<td>X</td>
<td></td>
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</table>

*Adapted from Simon et al.\textsuperscript{10} and Elliott et al.\textsuperscript{11}

The sense of respiratory effort is believed to arise from a signal transmitted from the motor cortex to the sensory cortex coincidently with the outgoing motor command to the ventilatory muscles. The arrow from the brain stem to the sensory cortex indicates that the motor output of the brain stem may also contribute to the sense of effort. The sense of air hunger is believed to arise, in part, from increased respiratory activity within the brain stem, and the sensation of chest tightness probably results from stimulation of vagal-irritant receptors. Although afferent information from airway, lung, and chest-wall receptors most likely passes through the brain stem before reaching the sensory cortex, the dashed lines indicate uncertainty about whether some afferents bypass the brain stem and project directly to the sensory cortex.
a marked increase in breathlessness occurs, even though indexes of respiratory effort (such as ventilation) decrease.\textsuperscript{16,17} When the relation between effort and breathlessness was studied in normal subjects maintaining a constant level of ventilation, the two sensations were, dissociated; as end-tidal carbon dioxide increased, breathlessness also increased, but the sense of effort decreased.\textsuperscript{18}

Thus, although the weight of evidence suggests that effort and breathlessness are not the same, the sense of effort may be the predominant factor contributing to breathlessness when the respiratory muscles are fatigued or weakened or when the load on them is increased. There are other settings, however, in which the sense of effort seems to play a less important part.

**Chemoreceptors**

Hypercapnia

Hypercapnia has long been known to cause dyspnea. Early studies suggested that stimulation of chemoreceptors itself was not a direct cause of dyspnea; rather, dyspnea was thought to arise only as a consequence of the evoked changes in respiratory-muscle activity. This interpretation was supported by studies in a normal subject who was paralyzed\textsuperscript{20} and in a patient with quadriplegia\textsuperscript{20} in whom large increases in end-tidal carbon dioxide produced no respiratory discomfort. Thus, in the absence of respiratory-muscle activity, hypercapnia appeared not to cause dyspnea.

More recent work, however, has established that hypercapnia causes dyspnea independently of any associated reflex increase in respiratory-muscle activity. Ventilator-dependent patients with quadriplegia who lack inspiratory-muscle function had air hunger when end-tidal carbon dioxide was raised by 7 to 11 mm Hg.\textsuperscript{21} In a similar study in four normal subjects who were receiving mechanical ventilation after the induction of paralysis by a neuromuscular-blocking drug, all had severe air hunger when end-tidal carbon dioxide was raised by 5 to 10 mm Hg. The subjects likened the sensation to that experienced while hypercapnic before they were paralyzed.\textsuperscript{22} Thus, in these studies, hypercapnia caused breathlessness in the absence of respiratory-muscle activity.

Although both normal subjects and patients with pulmonary disease become breathless when carbon dioxide is added to their inspired gas, it is not clear how hypercapnia relates to dyspnea in patients. Patients with COPD, neuromuscular disease, and other disorders associated with chronic hypercapnia and metabolic compensation may have little dyspnea at rest. It seems likely that the effects of carbon dioxide on dyspnea are mediated through changes in pH at the level of the central chemoreceptors, and on that basis one might expect acute and chronic (compensated) hypercapnia to differ markedly in the respiratory sensations they elicit. There are also many clinical settings (e.g., asthma) in which dyspnea develops under eucapnic or hypocapnic conditions.

**Hypoxia**

Among the lay public and many health care providers, there is a widely held belief that breathlessness arises primarily from lack of oxygen. Although the beneficial effects of oxygen therapy on longevity in patients with chronic hypoxia due to COPD are well established,\textsuperscript{23} few studies have formally examined the effects of hypoxia on breathlessness. Normal subjects are more breathless during exercise when breathing a hypoxic gas mixture, and less breathless when breathing 100 percent oxygen, than they are when breathing air.\textsuperscript{24} In patients with COPD, the administration of oxygen improves breathlessness.\textsuperscript{25} Despite these observations, hypoxia may play a limited part in the breathlessness experienced by patients with cardiopulmonary disease. Some patients with hypoxia do not have dyspnea; many patients with dyspnea are not hypoxic, and those who are often have only a slight improvement in their symptoms after the hypoxia is corrected.

**Mechanoreceptors**

Upper-Airway Receptors

Clinical observations suggest that upper-airway and facial receptors modify the sensation of dyspnea. Patients sometimes notice a decrease in the intensity of their dyspnea when sitting by a fan or open window. Conversely, the dyspnea of some patients worsens when they breathe through a mouthpiece during pulmonary-function tests. Studies of induced dyspnea in normal subjects indicate that receptors in the trigeminal-nerve distribution influence the intensity of dyspnea.\textsuperscript{25,26} The same mechanism may also be operative in patients with COPD in whom exercise tolerance increases and dyspnea decreases when they breathe cold air.\textsuperscript{27} It is unclear whether the receptors responsible for the effect of airflow on dyspnea sense the mechanical effect of airflow or the temperature changes that accompany it.

**Lung Receptors**

The lung contains a variety of receptors that transmit information to the central nervous system. Pulmonary stretch receptors in the airways respond to lung inflation and participate in the termination of inspiration; 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.\textsuperscript{28} Information from these receptors may also play a part in dyspnea.

Dynamic airway compression occurs in many patients with COPD and may contribute to their dyspnea. One mechanism by which dynamic airway compression might cause dyspnea is through the simple mechanical distortion of the airways during exhalation. Breathing with pursed lips, a breathing strategy adopted spontaneously by some patients with COPD and learned by others (e.g., during a pulmonary-rehabilitation program), may derive its effect by altering the changes in transmural pressure along the airway. When a negative pressure is applied at the mouth in patients
with severe COPD in such a way that dynamic airway compression increases, the sensation of breathlessness increases. Presumably, receptors sensitive to the deformation of the airway or to changes in transmural pressure across the airway wall transmit the information that mediates the sensation of dyspnea.

Afferent information from the lungs reaches the central nervous system by way of the vagus nerve. Although vagal input alters the pattern of breathing in humans, relatively little is known about the contribution of vagal afferents to the sensation of dyspnea. Anesthesia of the vagus nerve increases breath-holding time in normal subjects, and in uncontrolled studies it decreased breathlessness in some patients with cardiopulmonary disease.

Studies comparing the sensations associated with bronchoconstriction and those associated with breathing through an external resistance help shed light on the role of vagal afferents. Induced bronchoconstriction causes greater dyspnea than breathing through an external resistance of comparable magnitude; inhaled lidocaine ameliorates the sensation associated with bronchoconstriction but has no effect on the discomfort associated with the external resistive load. When qualitative aspects of sensation were examined in patients with asthma, the patients described a sensation of chest tightness or constriction in only 3 percent of the trials involving an external resistive load, as compared with 92 percent of the trials involving induced bronchoconstriction. These studies suggest that information from vagal irritant receptors increases the intensity of dyspnea and alters its quality as well. In contrast, when information from pulmonary stretch receptors is reduced, dyspnea at a given chemical drive to breathe increases.

Thus, the effect on dyspnea of vagally transmitted afferent information from the lungs probably depends on which receptors are stimulated. Stimulation of vagal irritant receptors appears to intensify the sensation of dyspnea and may impart a sense of chest tightness or constriction, whereas stimulation of pulmonary stretch receptors probably decreases the sensation of dyspnea.

Chest-Wall Receptors

The brain receives projections from a variety of receptors in the joints, tendons, and muscles of the chest wall that might influence the sensation of dyspnea. In normal subjects, hypercapnic tolerance increases when they are allowed to take larger breaths. In normal subjects in whom dyspnea was induced by a combination of hypercapnia and inspiratory resistive loading, application of a physiotherapeutic vibrator over the parasternal intercostal muscles reduced dyspnea, whereas vibration over the deltoid muscles had no effect. Similar findings have since been reported in patients with chronic lung disease. However, vibration of the parasternal region during expiration increased dyspnea. These studies suggest that afferent information from the chest wall modifies the intensity of dyspnea and that the temporal relation of the information to neuromotor output is an important determinant of the effect on dyspnea.

Afferent Mismatch

The concept of length–tension inappropriateness as the cause of dyspnea was proposed in 1963. According to this theory, dyspnea arises from a disturbance in the relation between the force or tension generated by the respiratory muscles and the resulting change in muscle length and lung volume. This theory has since been refined to incorporate the general concept of a mismatch between outgoing motor signals to the respiratory muscles and incoming afferent information. Although the hypothesis has not been tested directly, a number of clinical observations are consistent with this theory. In both patients and normal subjects, temporary suppression of ventilation during speaking or eating causes a mismatch between the respiratory motor command and afferent feedback from receptors in the lungs, airways, and chest wall and may cause dyspnea. An analogous phenomenon may occur in patients receiving mechanical ventilation in whom the ventilator settings (e.g., inspiratory flow rate and tidal volume) selected by the physician or respiratory therapist may not match those desired by a patient with heightened respiratory drive; under those conditions, the patient may experience dyspnea.

Experimental data are also consistent with the concept of afferent mismatch. When normal subjects breathe carbon dioxide, their ventilation increases and most experience dyspnea. However, if minute ventilation is reduced but end-tidal carbon dioxide is maintained at a constant level, the subjects report a marked increase in the intensity of breathlessness, even though the chemical drive to breathe has not changed. Other aspects of afferent information more subtle than the global level of ventilation may also modify dyspnea. For example, when normal subjects are forced to breathe at an inspiratory flow rate lower than that which they have chosen as most comfortable, they experience a sense of air hunger. These studies and the aforementioned clinical observations suggest that under a given set of conditions, the brain “expects” a certain pattern of ventilation and associated afferent feedback and that deviations from this pattern cause or intensify the sensation of dyspnea.

Dyspnea in Some Common Disorders

Although none of the factors outlined above appear to explain the pathogenesis of dyspnea in all patients, each may contribute to the sensation under some circumstances. Unfortunately, our understanding of dyspnea has not reached the point where we can conclusively link a specific disease with a specific mechanism of dyspnea. Furthermore, in most diseases associated with dyspnea the discomfort is probably caused by more than one of these mechanisms. Nonetheless, knowledge of the pathophysiology of a disorder sometimes allows us to formulate rational hypotheses about the underlying mechanisms of dyspnea (Table 2).

In asthmatics, a number of factors increase the burden
Asthma
Increased sense of effort
Stimulation of irritant receptors in airways

COPD
Increased sense of effort
Increased sense of effort
Hypoxia
Hypercapnia
Dynamic airway compression

Mechanical ventilation
Factors associated with the underlying condition

Pulmonary embolism
Stimulation of pressure receptors in pulmonary vasculature or right atrium (?)

Dyspnea is matched to the patient’s requirements for flow and tidal volume, afferent mismatch may intensify the sensation of dyspnea.

Finally, pulmonary embolism is an example of a disorder in which none of the mechanisms of dyspnea discussed thus far clearly apply. Although the dyspnea associated with pulmonary embolism has not been studied systematically, it often appears out of proportion to any derangement in respiratory mechanics or gas exchange. Anecdotal reports of patients undergoing thrombolysis indicate that dyspnea may be rapidly relieved by clot lysis (Markis J: personal communication). One possibility is that pressure receptors in the pulmonary vasculature or right atrium or C fibers in pulmonary vessels mediate the sensation of dyspnea.

**Approach to Patients with Dyspnea**

A detailed discussion of the evaluation and treatment of dyspnea is beyond the scope of this article; interested readers are referred to any of several textbooks. Instead, we focus briefly on a few selected aspects of treatment that are most closely linked to an understanding of the pathophysiology of dyspnea.

The initial goal of the treatment of dyspnea is to correct the underlying disorder causing the symptoms. Unfortunately, in all too many patients, treatment of the underlying disorder is ineffective or only partly effective, and dyspnea persists. For example, in many patients with COPD, therapy with bronchodilators and corticosteroids results in only minor improvement, and airflow obstruction and dyspnea persist. In these patients, a number of strategies may reduce dyspnea. Since, for any given muscular task, greater effort is required if the muscle is weak than if it is strong, one potential approach is to strengthen the respiratory muscles. In patients with COPD, theophylline improves dyspnea independently of its role as a bronchodilator, possibly by decreasing neural drive and the sense of effort through its effects on respiratory-muscle performance.

One can also attempt to alleviate dyspnea by minimizing the role of chemoreceptor stimulation. Administration of oxygen reduces dyspnea in patients with hypoxia who have COPD or interstitial lung disease. Supplemental oxygen may also benefit patients with COPD and only mild hypoxia for whom oxygen would not be prescribed to reduce mortality. Patients can minimize the discomfort arising from dynamic airway collapse by learning the technique of pursed-lips breathing. Finally, the ability of many drugs, including opioids, benzodiazepines, and phenothiazines, to relieve dyspnea has been studied, but only opioids were effective in controlled studies.

**Conclusions**

Dyspnea has been described as a “synthetic sensation, like thirst or hunger” that is the result of a comp-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>Increased sense of effort</td>
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<tr>
<td></td>
<td>Stimulation of irritant receptors in airways</td>
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<tr>
<td>Neuromuscular disease</td>
<td>Increased sense of effort</td>
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<td></td>
<td>Increased sense of effort</td>
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<td>Stimulation of pressure receptors in pulmonary vasculature or right atrium (?)</td>
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</table>
plex interaction of signals arising from within the central nervous system, both from the automatic centers in the brain stem and from the motor cortex, and from a variety of receptors in the upper airways, lungs, and chest wall (Fig. 1). Most conditions that cause breathlessness probably do so by more than one mechanism, and different conditions share common mechanisms. However, each condition probably has a unique combination of physiologic factors that determines the quality and intensity of dyspnea in a particular patient at a given time. Our capacity to alleviate the symptom of dyspnea depends in large part on our ability to define these mechanisms in our patients.

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REFERENCES


