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Physiologic changes and clinical correlates of advanced dyspnea

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Abstract

Purpose of review—To discuss the pathophysiology of dyspnea as it relates to patients suffering with chronic respiratory illness or end-stage disease.

Recent Findings—There are several publications highlighting important new concepts in this field. A new multidimensional model of dyspnea, similar to that developed for pain, sheds new insight into the pathophysiology, while research in pulmonary rehabilitation, exercise testing and distractive auditory stimulation has contributed to our understanding. Finally, there are new data on the emotional response of laboratory-induced dyspnea.

Summary—Dyspnea is a complex symptom widely prevalent in advanced disease that involves multiple etiologies and pathophysiologies. The sensation of dyspnea is subjective and often evokes discomfort, fear and anxiety. We recommend that this symptom be evaluated whenever vital signs are taken.

Keywords

Dyspnea/physiopathology; Dyspnea/etiology; Palliative care; Emotions

Introduction

Dyspnea is defined by the American Thoracic Society as the “subjective experience of breathing discomfort (1).” While previous definitions have sometimes merged this true *symptom* with physical *signs* (e.g. “exhibits labored breathing”), the American Thoracic Society considers dyspnea as a symptom. Thus dyspnea can only be described by the person who experiences it. Most awake patients can give a meaningful rating of the severity of their dyspnea, as with the familiar ratings of pain. We believe that dyspnea assessment ought to be as routine as pain assessment, i.e., dyspnea should be the “6th vital sign”, as previously suggested (2). Physical signs are notoriously unreliable in assessing a patient’s dyspnea or pain (3,4), and should only be used when patients are unable to report what they feel.

Breathing is one of the most important primal biological drives, like thirst, hunger, and pain (5). It has greater immediacy than most primal drives – a few minutes without air means death. As a consequence, the sense of not getting enough air rouses strong unpleasant emotional responses that can have the adaptive value of evoking corrective behavior. When corrective behavior is impossible, as in the case of an impaired respiratory system, it is not surprising that strong aversive emotional consequences follow. This underscores the need for adequate palliative care.

Dyspnea is widely prevalent in patients with advanced disease and is about as common a symptom as pain (6). Among those suffering with dyspnea, many will adjust their activities of daily living to avoid the discomfort. Dyspnea is a complex symptom with multiple causes and presents a significant challenge for the provider. While preferred therapeutic approaches are directed at correcting the underlying pathophysiology, this is often not practical or possible, and non-specific palliative approaches are required.

Mechanisms of Dyspnea

Dyspnea has multiple, often coexisting etiologies giving rise to qualitatively distinct sensations that vary in intensity. These sensations are reported by patients with a variety of descriptors. This review will discuss the pathophysiology of dyspnea as it relates to patients suffering with chronic respiratory illness or end-stage disease. We are aware of three separable sensations that contribute to dyspnea: air hunger, work/effort, and tightness. This may not be a complete list as the neural mechanisms of dyspnea are still being defined.

The most unpleasant sensation (7) is the sense that one is not getting enough air, termed by investigators as 'air hunger' or 'unsatisfied inspiration' (8-10). Patients may state that they are "starved for air" or "suffocating". Air hunger can be viewed as the mismatch between one's automatic drive to breathe and the achieved ventilation. Various afferents, such as arterial chemoreceptors, react to changes in arterial partial pressures of oxygen, carbon dioxide and pH. Afferent signals are sent to the medullary region of the brainstem to set the demand for alveolar ventilation ('respiratory drive') to match metabolic need. This drive is relayed via efferent nerves to the respiratory pump muscles while, simultaneously, a copy of this message ('corollary discharge') is sent to perceptual areas in the cerebral cortex causing increases in air hunger (11,12). Mechanoreceptive afferents, including slowly adapting pulmonary stretch receptors, provide breath-by-breath feedback reporting whether this ventilation is achieved, and reduce air hunger as ventilation increases (13). In summary, increasing respiratory drive, decreasing ventilation or both will give rise to air hunger.

Another common component of dyspnea is the sense that breathing requires too much work or effort. This sensation may be caused by excessive impedance to breathing (high resistance or stiff lungs/chest wall), or it may be caused by respiratory muscle weakness (neural or muscular impairment). In the laboratory it can be simulated with external resistance or partial neuromuscular block (10,14). It is likely that this sensation arises both from the afferents originating in the working respiratory muscles and from the awareness of outgoing motor command from the motor cortex, as well as perhaps from the medulla (corollary discharge) (15). Although the sense of excessive respiratory work was formerly thought to be the primary or only source of the sensation of dyspnea, that concept was disproved by studies showing that severe air hunger could be induced in the absence of respiratory work (16,17). Nonetheless, the sense of respiratory work does contribute to patient discomfort. In addition, some of the interventions used to reduce work of breathing result in increased minute ventilation, one of the key factors in reducing air hunger.

The sensation of chest tightness in asthmatics appears to come directly from peripheral receptors and is relatively specific for bronchospasm. Interestingly, the complaint of tightness was reproducible in asthma subjects following methacholine challenge; however, when subjects were made to breathe against external resistive loads much larger than the internal load resulting from bronchospasm, they did not report this complaint (18). Tightness was also not relieved by fully supporting work of breathing in patients on mechanical ventilation (19). It is therefore difficult to attribute chest tightness to a sense of work.

Affective and emotional dimensions

Dyspnea and emotion may interact in both directions. Laboratory air hunger is able to evoke anxiety, fear, and frustration even in healthy subjects who fully understand that they are in no danger (7). In turn, emotions may act on dyspnea either by increasing respiratory drive or by altering the cognitive interpretation of dyspnea. Some emotional disorders may actually evoke dyspnea in otherwise healthy people (e.g., dyspnea is the leading symptom of panic disorder); in less extreme cases it is likely to exacerbate dyspnea from organic causes. In patients dyspnea is often accompanied by depression and anxiety. Anxiety, depression, fatigue and psychological inability to cope with disease were shown to be predictors of dyspnea in patients with advanced lung cancer (20). In severe COPD patients, pulmonary rehabilitation not only improved dyspnea and health-related quality of life, but also resulted in improvement in self-reported depression and anxiety levels (21). A study looked at distractive auditory stimuli during a 6 minute walk test in patients with mild to severe COPD and reported a significant improvement in exercise-induced dyspnea (22). One hypothesis that can be generated from these data is that improvements in emotional state, or alternatively measures of distraction, may cause less dyspnea and at the same time, result in objective improvement in exercise capacity. The effect of emotions on dyspnea is far from clear, however; the little direct information available suggests that anxiolytic and antidepressant drugs improve mood in dyspneic subjects, but may not improve dyspnea (23-26). This source of apparent inconsistency may be due to failure to measure the appropriate dimensions of dyspnea (27)

Clinical correlates

Common pulmonary disease states such as COPD and idiopathic pulmonary fibrosis (IPF) have different but overlapping pathophysiologies. On the other hand, it is common for patients with advanced systemic disease to have concomitant pulmonary and cardiovascular disease; this is especially true in patients treated in the palliative care setting. The resulting dyspnea varies in both quality and intensity, and also in subjective response. One method of approaching the dyspneic patient is to first consider whether the underlying physiology, such as expiratory flow limitation, decreased lung or chest wall compliance, or respiratory muscle weakness, can be improved by treatment.

Expiratory Flow Limitation

A leading pathophysiology of dyspnea is expiratory flow limitation due to inflammation and remodeling of the small airways. This is a prototypical feature of both asthma and COPD. Expiratory flow cannot be increased regardless of expiratory effort. Another important feature is that the maximal expiratory flow is less at lower lung volumes. As a result, patients with expiratory flow limitation usually breathe at a hyperinflated resting volume and take longer to empty their lungs due to various degrees of air trapping. During episodes of respiratory distress or exercise, hyperinflation increases further, and so called “dynamic hyperinflation” develops (28). This leads to increased work and oxygen requirements, inspiratory muscle weakness due to a poor position on the length-tension curve (exacerbated by compromising the shape of the diaphragm), and a reduction in the ability to generate desired tidal volumes during exercise. If a patient has a defect in gas-exchange, as in severe emphysema, dynamic hyperinflation may contribute to both hypercapnia and hypoxemia. It is not surprising that these patients have significantly lower exercise thresholds for dyspnea related to dynamic hyperinflation (15).

Poor Respiratory System compliance

Restrictive lung disease is a term to describe any disease process resulting in decreased functional lung volumes but in the absence of evidence of increased resistance or flow limitation. The term applies to diseases causing reduced chest wall or lung compliance (i.e.,

'stiff' lungs or chest wall), and also to diseases causing respiratory muscle weakness. Conditions with low lung compliance, however, should be approached differently than neuromuscular disease. In general, the underlying mechanisms of dyspnea in conditions of poor respiratory system compliance are less well defined than for expiratory flow limitation.

One of the hallmark diseases of poor lung compliance is interstitial lung disease (ILD) of which idiopathic pulmonary fibrosis is the most common. In ILD, there is greater recoil pressure of the lung causing reduced lung compliance and decreased lung volumes. This is usually manifested by reduced vital capacity and functional residual capacity. There is also a heterogeneous defect in gas exchange, often exacerbated by ventilation-perfusion mismatching and increased right-to-left shunting, resulting in hypoxemia (29). Although previous studies have not convincingly shown the relationship between hypoxemia and dyspnea in ILD patients, the administration of oxygen was found to increase exercise duration in one study (30).

Thoracic restriction using a non-expandable corset has been used as a laboratory model of restrictive disease. This limits tidal volume and produces rapid shallow breathing along with sensations of both air hunger and work/effort (8,31,32). In summary, the inability to generate adequate tidal volumes in response to increased neural motor output is likely the basis for the dyspnea and rapid, shallow breathing observed in ILD.

Although pulmonary edema reduces lung compliance while increasing respiratory work and worsening blood gasses, there is probably an additional source of dyspnea in play. The role of juxta-pulmonary receptors (J-receptors) has gained interest as a prominent mechanism causing dyspnea in pulmonary edema (33). J-receptors are vagal afferents and were shown in animals to be activated by increases in pulmonary venous pressure, as would occur during left heart failure. There is some evidence that these receptors give rise to breathing discomfort even in the absence of other sequelae of pulmonary edema (34).

Respiratory muscle weakness

Respiratory muscle weakness is not an uncommon finding in palliative care. It can be found in various forms of neuromuscular disease such as myasthenia gravis, multiple sclerosis, or amyotrophic lateral sclerosis, with metabolic derangements such as hypokalemia or hypophosphatemia, in cases of malnutrition or cachexia, and in critical illness neuropathy. Unfortunately, patients with these conditions are often diagnosed at advanced stages when muscle weakness is severe.

Weakness of the respiratory muscles leads to hypoventilation and significant morbidity. When inspiratory muscles, such as the diaphragm, external intercostals, and the sternocleidomastoids are unable to generate adequate tidal volumes, breathing frequency increases to compensate for the decrease in alveolar ventilation. As muscle weakness progresses and tidal volumes decrease, the ability to compensate diminishes. This fall in alveolar ventilation will eventually cause dyspnea, hypercapnia, and clinical hypoxemia.

Respiratory muscle weakness is also a cause of ineffective cough. The cough reflex, which requires both inspiratory and expiratory muscle capacity, is the primary defense against aspiration. Inadequate clearing of oral secretions increases a patient's risk of pneumonia.

Malignancy

Dyspnea in malignancy originates from a complex interplay of the mechanisms described above with the addition of disease-specific sequelae. A former heavy smoker with advanced lung cancer, for example, would have expiratory flow limitation from a combination of COPD in addition to the primary lung mass or its metastases. In addition to this, one should consider the possibility of reduced gas exchange from radiation pneumonitis, pulmonary vascular

disease as a complication of pulmonary embolism or chemotherapy, and chest muscle weakness as a result of treatment-related myopathy or paraneoplastic syndrome. Often these patients suffer from coexisting ischemic heart disease and deconditioning which further exacerbate symptoms.

Travers et al (35) studied cancer patients who experienced moderate to severe dyspnea at rest and with exercise and compared them with age, sex and stage-matched cancer patients without baseline dyspnea (control group). Patients with lung cancer, COPD, ischemic heart disease, and cardiac arrhythmias were excluded. The study found that at peak exercise, dyspnea intensity was greater, peak oxygen uptake was reduced, and breathing pattern was more rapid and shallow in the study patients compared with controls. They postulated that dynamic respiratory muscle weakness and the consequent reduced inspiratory capacity may have caused the observed difference in dyspnea intensity between these two groups of cancer patients. While this may have been true in this cohort, it remains exceedingly difficult to identify the etiologies of dyspnea in cancer patients with comorbid disease.

When perception of dyspnea is altered

The limbic system plays a predominant role in the perception of both dyspnea and pain. Functional magnetic resonance imaging studies have identified the right anterior insular cortex (and to a lesser extent the amygdala) to be the most activated structures in normal subjects experiencing laboratory-induced dyspnea (36-38). Additional work has linked the insular cortex to the perception of pain (39).

As difficult as it is to distinguish the etiology or the type of dyspnea in COPD or cancer patients with multiple cardiopulmonary issues, it is often a greater challenge to approach the patient who complains of severe dyspnea despite there being no identifiable cause. This is likely more common among elderly, depressed patients whose perceptions of dyspnea are often altered. Conversely, respiratory failure may be difficult to diagnose in patients who have higher thresholds for dyspnea who do not complain until breathing has been severely compromised

Conclusion

Dyspnea is a complex symptom widely prevalent in the palliative care setting, and is about as common a symptom as pain. While healthy individuals rarely perceive dyspnea during exercise, patients with advanced disease often experience dyspnea during mild exertion and even at rest. Since the sensation of not getting enough air is associated with fear and anxiety, there is invariably a strong emotional component to dyspnea, especially as one's adaptive breathing response becomes inadequate to match the respiratory drive. Various mechanisms interact with each other sending afferents to the brainstem and cortex, efferents back to the respiratory muscles, and various messages to the association cortex and limbic centers of the brain. We recommend that dyspnea be assessed in conjunction with vital signs in the palliative care setting, where relief of dyspnea, like pain relief, may result in improved quality of life.

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