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Dyspnea and its interaction with pain

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Definition of dyspnea

A wide range of respiratory sensations such as shown in Table 1 can be sensed by humans. Among these respiratory sensations, the last three sensations, i.e., chest tightness, work/effort sensation, and respiratory discomfort (air hunger), are the main sensations that constitute the sensation of "dyspnea." Although dyspnea is often defined as an uncomfortable sensation of breathing, this definition is too simple to understand the precise mechanisms of dyspnea. According to the definition proposed by the American Thoracic Society [1], dyspnea is a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations which vary in intensity. This broad definition may contribute to the better understanding of mechanisms of dyspnea and improvement of therapeutic approaches to dyspnea. Although it is the primary symptom of many diseases of the respiratory systems, dyspnea can also arise in other forms of diseases such as those affecting cardiovascular or neuromuscular systems. Dyspnea is commonly observed in several clinical settings such as cancer, chronic obstructive pulmonary disease, and cardiac failure, and it is not rare for anesthesiologists to take care of these patients in the operating room, intensive care unit, or palliative care unit.

Sensory infrastructure of the respiratory system

Assuming that dyspnea is generated through the sensory infrastructure of the respiratory system (Fig. 1), stimulation of sensory receptors in the respiratory system is the natural starting point of the generation and modulation of dyspnea. Several sensory receptors in the respiratory system such as shown in Table 2 are considered to be responsible for generation and modulation of dyspneic sensation. These receptors play significant role in the control of breathing. The control of breathing consists of three controls, namely, chemical control, neural control, and behavioral control, and the stimulation of sensory receptors in the respiratory system contributes to all three controls. In other words, control of the breathing system is associated with the generation and modulation of dyspnea through activation of sensory receptors in the respiratory system.

Measurements of dyspnea

Dyspnea may be evaluated by assessing the functional impairment caused by dyspnea associated with daily

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Table 1 Different types of respiratory sensation

Respiratory sensations
Respiratory motion
Lung position
Irritation
Urge to cough
Pain
Chest tightness
Work/effort sensation
Respiratory discomfort (air hunger)

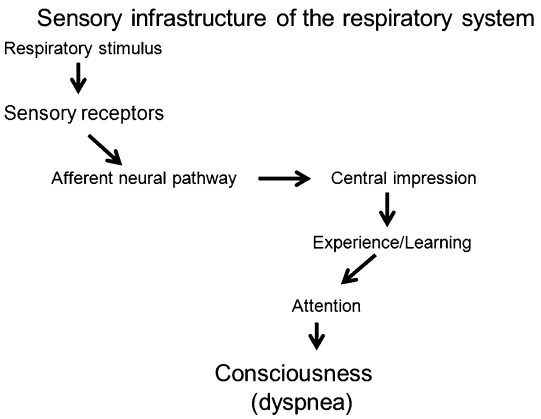

Fig. 1 Sensory infrastructure of the respiratory system

Table 2 Receptors responsible for generation and modulation of dyspnea

1. Vagal receptors (irritant, pulmonary stretch, C-fiber)
2. Chemoreceptors (peripheral, central)
3. Muscle and tendon receptors
4. Upper airway receptors
5. Central corollary discharge receptors

activities of life, because the dyspneic patient is frequently unable to perform the daily activities of life as a result of discomfort associated with breathing. A simple scale that can be used to measure functional dyspnea was originally developed by Fletcher [2], who first published a five-point scale. Similar categorical scales such as the Medical Research Council (MRC) scale [3] and the oxygen cost diagram (CD) [4] have been used clinically for many years, but these scales have the notable drawback of lacking clear limits between grades. Nevertheless, evaluation of dyspnea using this type of scale is useful. For example, Boushy et al. [5] found that grades of preoperative dyspnea correlated with postoperative survival. Similarly, Mittman [6] reported that an increased risk of death after thoracic surgery from 8% in patients without dyspnea to 56% in patients who were dyspneic.

The visual analogue scale (VAS) and the modified Borg scale [7] are the most commonly used scales in clinical dyspnea research. Patients or subjects rate their dyspnea intensity on a scale from 0 to 10 where 0 represents 'no discomfort at all' and 10 represents 'the worst discomfort imaginable.' The VAS consists of a 100-mm horizontal or vertical line anchored at one end by a label such as 'no discomfort' and the other end by a level such as 'intolerable discomfort.' The Borg scale is a 10-point category-ratio scale with verbal expressions of severity anchored to specific numbers. The reliability and validity of the VAS and the Borg scale as a measure of dyspnea have been reported [8]. However, the use of single-dimensional tools such as VAS may incur the strong risk of oversimplifying assessment of the dyspnea problem. Considering that dyspnea, similar to pain, is a multidimensional subjective experience, the use of multidimensional tools for assessment of dyspnea seems to be more appropriate than the use of unidimensional tools. However, the multidimensional nature of dyspnea is seldom recognized in measurement methods, and existing measurement instruments have not been adequate to address this problem. Recently, Banzett et al. [9] introduced the first multidimensional dyspnea profile (MDP), an instrument under development in their laboratory, for evaluation of experimentally induced dyspnea. Their results demonstrated that the MDP was sufficiently sensitive and specific to show clear differences in sensory qualities with different stimuli, suggesting that the clinical use of MDP for measuring the multiple dimensions of dyspnea may be promising.

Motor command–afferent mismatch

According to the recent theory of dyspnea, dyspnea is the result of a mismatch or a dissociation between motor command and incoming afferent information from sensory receptors. Campbell and Howell [10] proposed the concept of length–tension inappropriateness of the respiratory muscles as the cause of dyspnea. The term length refers to the change in lung volume whereas tension refers to the respiratory muscle tension required to produce that change. The importance of respiratory muscle contraction in genesis of dyspnea was supported by the breath-holding experiments of Campbell et al. [11] who reported that totally paralyzed normal subjects had no sensation comparable to breath-holding even when the apnea lasted for 4 min. However, several studies [12, 13] have shown that the contractile activity of respiratory muscles is not essential to generation of dyspnea. For example, Banzett et al. [13] examined changes in air hunger sensation following the addition of CO_2 to inhalation during total neuromuscular blockade in the presence of adequate

ventilation, concluding that respiratory muscle contraction is not important in the genesis of air hunger evoked by hypercapnia. The original hypothesis of Campbell and Howell was expanded by Schwartzstein et al. [14], who incorporated the concept that dyspnea is the result of a dissociation between the ventilatory drive and the degree of ventilation produced. In other words, by using the afferent feedback from peripheral sensory receptors, the brain can assess the effectiveness of the motor commands issued to the ventilatory muscles. This dissociation between neural activity and consequent mechanical or ventilatory outputs has also been termed neuromechanical dissociation [15]. Experimental and clinical data are consistent with the concept of neuromechanical dissociation [15–17]. Thus, when the matching between motor command and incoming afferent information from sensory receptors is appropriate, no dyspnea occurs or the intensity of dyspnea should be minimum (Fig. 2). In contrast, when the matching between motor command and incoming afferent information is inappropriate, the resultant neuromechanical dissociation can cause dyspnea or intensify the sensation of dyspnea.

Similarity of pain and dyspnea

Although dyspnea and pain are distinctly different sensations, dyspnea shares many clinical, physiological, and psychological features with pain [1]. Considering the analogies between pain and dyspnea, it is quite conceivable that there may be some neurophysiological link between pain and dyspnea. There is much evidence to show that dyspnea activates several distinct areas in the brain cortex such as the anterior right insula, the cerebellar vermis, the amyglada, the anterior cingulated cortex, and the posterior cingulated cortex [18–21]. These brain areas are similarly activated by pain and other unpleasant sensations. For example, a variety of painful stimulations produce strong insular activation [22–24], and a similar area can be activated during nausea [25] and during thirst [26]. The thalamus appear to be the pivotal part of the pathway relaying pain and dyspnea, and thalamocortical projections to the specific cortical regions seem to be common to both pain and dyspnea. However, this does not necessarily mean that dyspnea and pain activate identical neural structures or that they share identical neural pathways.

Interaction between pain and dyspnea

Pain and dyspnea are frequently coexistent in many clinical situations, and there is some evidence to suggest a causal association between pain and dyspnea. Because dyspnea shares many clinical, physiological, and psychological features with pain, it is quite conceivable that the two symptoms can interact with one another. However, the interaction between dyspnea and pain has not been fully explored, and information about the interaction between the two symptoms is apparently insufficient. In a previous study [27], it has been shown that pain produced a small but consistent increase in dyspneic sensation whereas dyspnea caused either no effect on pain or even a slight attenuation in pain. The explanation for the finding that pain augments the dyspneic sensation is that pain stimulus increases ventilatory drive and thereby may cause an increase in the sense

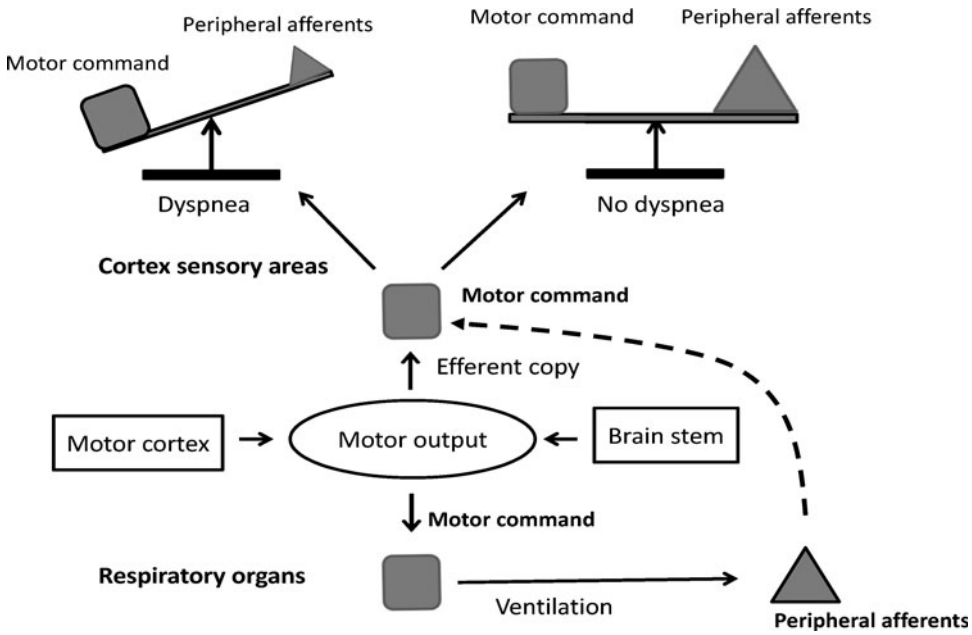

Fig. 2 The concept of motor command–afferent mismatch

of dyspnea. This explanation coincides with the concept of the motor command theory that dyspnea is closely related to the intensity of inspiratory effort yielded by the central motor output. A recent neurophysiological study by Morélot-Panzini and co-workers [28] showed that experimentally induced dyspnea can inhibit the spinal nociceptive flexion reflex. It is likely that that dyspnea, similar to pain, might induce counterirritation, causing a C-fiber stimulation, and thereby might trigger endogenous analgesic mechanisms at the subcortical level through the activation of diffuse noxious inhibitory descending controls (DNICs) [29].

Sex difference in interaction between pain and dyspnea

It has been reported that the DNIC is less sensitive in females than in males [30]. Sex difference in pain sensitivity has been a major topic of pain research and, compared with males, females report less tolerance of nociceptive stimuli [31]. In contrast, although women with COPD appear to experience dyspnea more frequently than men after adjusting for smoking burden and lung function [32], there is no clear evidence to show that sex difference exists in dyspnea. Considering the sex difference in pain sensitivity, it is possible that there may be a sex difference in the interaction between dyspnea and pain. In our recent study, we demonstrated that a sex difference exists in the responses of thermal pain threshold to dyspnea in healthy young subjects [33]. Thus, dyspnea causes an increase in thermal pain threshold in male subjects whereas thermal pain threshold does not change appreciably in female subjects, indicating that there is a difference in pain response between male and female. This sex difference in the inhibitory influence of dyspnea on pain sensation may in part be explained by the difference in the sensitivity of DNICs between males and females [30]. Detailed analysis of the relationship between maximal negative airway pressure and changes in thermal pain threshold revealed that an increase in negative airway pressure causes a progressive increase in thermal pain threshold only in males. Because negative airway pressure probably reflects the increased activity of respiratory muscles as a consequence of heightened ventilatory demand, response to the heightened activity of respiratory muscles may be a crucial factor that causes the sex difference in thermal pain threshold.

Effects of different types of dyspnea on pain perception

Although dyspnea consists of qualitatively distinct sensations, whether different types of dyspnea differently interact with pain has not been fully examined. The sensation of work/effort increases when muscle load is increased. Thus, work/effort stimulus may activate C-fibers in the respiratory system, which in turn activates DNICs. Chest tightness may stimulate C-fiber as well as vagal irritant receptors through bronchoconstriction. In contrast, air hunger may not stimulate C-fibers in the respiratory system. Therefore, it is possible that air hunger would have little or no effect in producing analgesia, compared with the effects of work/effort and chest tightness. We examined whether different forms of dyspnea exert a different effect on pain. Our results experiment showed that both air hunger and work/effort cause a similar degree of pain inhibition (Fig. 3). The inhibition of pain during air hunger may not be explained exclusively by the mechanisms of DNICs because air hunger stimulus may not activate C-fibers in the respiratory system, and without C-fiber stimulation DNICs may not be activated. Rather, it is likely that additional networks located in the limbic/paralimbic system and subcortical structures contribute to pain inhibition during air hunger. In fact, there is much evidence that several brain areas such as the anterior cingulate cortex, insular cortex, and amygdala, which are activated by air hunger, have descending projections to the midbrain and brainstem, specifically to the periaqueductal gray

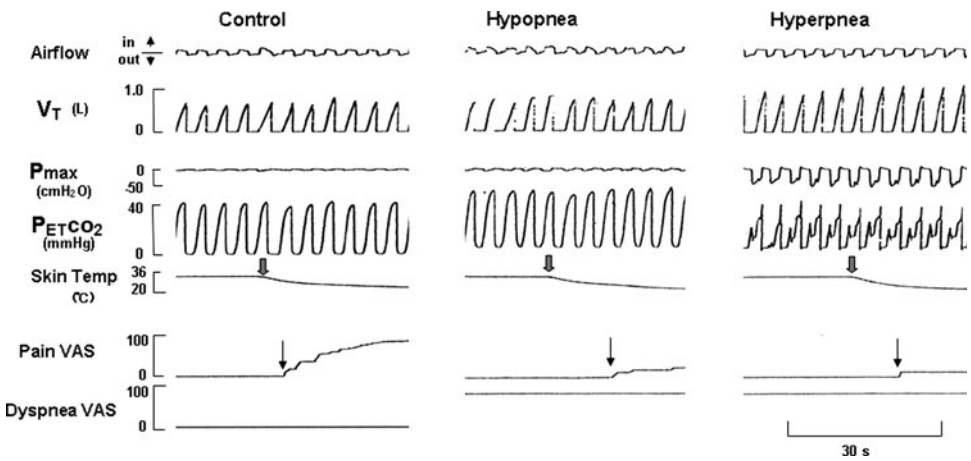

Fig. 3 Effects of air hunger and work/effort on pain threshold. Pain was induced by a cold pressure test, and pain threshold time was measured. Hypopnea and hyperpnea caused air hunger and work/effort sensation, respectively. Note that both air hunger and work/effort caused prolongation of pain threshold time and a slower rise in pain visual analogue score (*VAS*) than that of the control response, indicating an inhibition of pain

matter (PAG) and the rostral ventromedial medulla (RVM) [34, 35]. It is quite likely that activation of corticolimbic areas by air hunger is capable of producing descending inhibition of spinal nociceptive activity through connection to the PAG and RVM, causing an analgesic effect.

In conclusion, dyspnea seems to activate not only DNICs but also corticolimbic inhibitory controls, thus causing analgesia.

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