Introduction

It is essential for humans to maintain oxygen homeostasis in the body. Ventilation is modulated in response to $\text{PO}_2$, $\text{PCO}_2$ and pH to maintain homeostasis of oxygen and carbon dioxide levels in the body, and control the breathing pattern (respiratory frequency, tidal volume, minute ventilation, and inspiration-expiration pattern) to minimize respiratory efforts. The brainstem respiratory neuronal network receives redundant stimulatory input on exposure to hypoxia and hypercapnia. One comes from the sensory discharge of carotid arterial chemoreceptors which sense changes in arterial blood gases and the other comes from the sensory feeling of dyspnea perceived by the forebrain, which augments respiratory neural output from the lower brainstem and ventilation.

Dyspnea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. Dyspnea is not a uniform sensation and has many different qualities [2]. Different types of dyspnea exist across patients with a variety of diseases [3]. In patients with chronic obstructive pulmonary disease (COPD) and pulmonary congestive heart failure, their dyspnea worsens particularly during exercise. Also, patients with pulmonary fibrosis, bronchial asthma, and terminal lung cancer suffer unbearable distress in breathing itself even at rest when these diseases are severe. The changes in the arterial blood gases are involved with the intensity of dyspnea [4]. However, the mechanism of dyspnea cannot be explained only by changes of blood gas or ventilation. Dyspnea reduces daily activity, impairs the physical condition, and further increases dyspnea, which also reduces the quality of life, forming a vicious cycle. In clinical practice, reduction of dyspnea of patients with pulmonary diseases is crucial. Therefore, one of the goals in pulmonary rehabilitation...
rehabilitation is reduction of dyspnea to break the vicious cycle. However, the mechanism of dyspnea perception has not been fully elucidated as it is complex, involving the peripheral and central nervous system, cerebral function, and even mental condition. Consequently, sufficiently effective methods to relieve dyspnea have not been fully established.

It has been postulated that afferent information from sensory receptors may directly cause dyspnea, and that motor output may be consciously perceived as a "sense of effort" via motor command collateral discharge (i.e., ascending copy of motor command from the respiratory center) to the sensory cortex and that a mismatch between the respiratory motor command and accomplished motor output detected by respiratory mechanoreceptors (i.e., integrated mechanical respiratory sensation) causes dyspnea[5]. Here we review the existing theories which explain the mechanisms of dyspnea perception from the viewpoint of the peripheral and central nervous system. We also propose our integrated model to explain the mechanism of dyspnea perception and discuss the pathogenesis of dyspnea in patients with various diseases. In our integrated model, dyspnea results from disassociation or mismatch between intended respiratory neural output from the respiratory neural network and the actually accomplished ventilatory output. Perceived dyspnea enhances the central command from the hypothalamus to the lower brainstem, which augments respiratory neural output from the lower brainstem [5,6]. Therefore, although dyspnea is uncomfortable sensation and should be relieved, it plays a role to alert the subject to the inadequate status of breathing. This review would contribute to better understanding of dyspnea perception mechanisms and more efficient practice of pulmonary rehabilitation in patients with various pulmonary diseases.

2 Receptors involved in perception of dyspnea

Various kinds of receptors exist in the body and continuously monitor the various aspects of respiratory status such as chemical composition of the arterial blood and mechanical movement of the thorax and lungs. They are also involved in perception of dyspnea[7] (Table 1). Dyspnea consists of multiple types of unpleasant or uncomfortable respiratory sensations[5,8-10]. Actually, in many patients, dyspnea begins with physical impairment that is accompanied by stimulation of pulmonary and extrapulmonary receptors and the transmission of their afferent information to the cerebral cortex, where the information is processed and perceived as uncomfortable and unpleasant[5,11-13].

2.1 Chemoreceptors

The levels of pH, P<sub>CO₂</sub> and P<sub>O₂</sub> in the arterial blood are regulated by the magnitude of changes in lung ventilation. In contrast, the changes in pH, P<sub>CO₂</sub> and P<sub>O₂</sub> influence the activity of the respiratory center. Hypercapnia activates the central chemoreceptors in the medulla, which induce excitement of the respiratory neuronal network and increase respiratory output [14-17] (Figure 1). Peripheral chemoreceptors, such as the carotid body, are also excited by hypercapnia. However, they are relatively less activated as compared to hypoxia[18] (Figure 2). Further investigation is necessary to determine whether or not they are involved in perception of dyspnea.

Table 1: Afferent sources for respiratory sensation

<table>
<thead>
<tr>
<th>Factor</th>
<th>site</th>
<th>excite or inhibit</th>
<th>neural respiratory output</th>
<th>ventilation volume</th>
<th>intensity of dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO&lt;sub&gt;₂&lt;/sub&gt;</td>
<td>central/peripheral receptor</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>hypoxia</td>
<td>peripheral receptor</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>respiratory nervous cell in the brainstem</td>
<td>inhibit</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>cerebral</td>
<td>inhibit</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>respiratory muscle</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>lung expansion</td>
<td>lung stretch receptor</td>
<td>excite</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>stimulation to lung / airway</td>
<td>irritant receptor</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>heart failure</td>
<td>atrial baroreceptor</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>J-receptor</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>cool air to the face</td>
<td>cold receptor</td>
<td>excite</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>chest wall expansion</td>
<td>muscle spindle</td>
<td>excite</td>
<td>→</td>
<td>← (IPV) / ↑ (OPV)</td>
<td>↓</td>
</tr>
<tr>
<td>anxiety</td>
<td>cerebral</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>exercise</td>
<td>central/peripheral receptor</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>hypothalamus</td>
<td>excite</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>respiratory muscle</td>
<td>-</td>
<td>→</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

not afferent information from central and peripheral receptors, which are excited by hypercapnia and hypoxia, directly induces sensation of dyspnea.

2.1.1 Hypercapnia
A change in PCO₂ is sensed by central chemoreceptors in the ventrolateral medulla[14-17] (Figure 1). "Air hunger", which is the perception of not getting a sufficient amount of (or needing more) air, is evoked from increased PCO₂[19]. The mechanism by which hypercapnia induces dyspnea remains to be elucidated. Chonan et al. reported that the intensity of dyspnea increases as a result of an elevation of PCO₂ in normal subjects, suggesting that CO₂ directly plays a role in shaping the sensation of dyspnea[4]. However, not all patients with chronic respiratory failure with hypercapnia are dyspneic. Chronically persistent hypercapnia rarely causes dyspnea, although acute onset hypercapnia is often accompanied by dyspnea. Hypercapnia induces dyspnea independent of respiratory afferent input[20]. Although recent investigations have suggested that hypercapnia can induce breathlessness[21], the mechanisms of hypercapnia-induced dyspnea cannot be simply explained.

2.1.2 Hypoxia
Hypoxia is sensed by the peripheral chemoreceptors such as the carotid body. However, animals of which peripheral chemoreceptors are ablated increase ventilation in response to hypoxia indicating the existence of hypoxic chemoreceptors in the brain. Fukushi et al. reported that brainstem astrocytes play a role in sensing of hypoxia[22]. Hypoxia is one of the important factors which induces the sensation of dyspnea, and it follows that alleviation of hypoxia relieves dyspnea. However, the mechanism of how hypoxia induces dyspnea has not been fully elucidated. When breathing oxygen, patients with COPD can reduce breathlessness and improve exercise tolerance[23]. It has been reported that supplemental oxygen have profound ameliorating effects on dyspnea and exercise endurance in patients with COPD[24]. Acute hypoxic loading in normal subjects during exercise increases the intensity of breathlessness without any specific effect on ventilation[25]. During high-altitude hypoxia the increased intensity of exercise-induced breathlessness is not related to the level of hypoxia per se, but rather it is related to the level of reflexly increased ventilation [26]. In patients with dyspnea with COPD, however, it is unclear whether or not exercise-induced breathlessness is altered with supplemental oxygen[27]. Considering the presence of patients with COPD with severe hypoxemia who do not perceive dyspnea and of patients without hypoxemia who perceive severe dyspnea, the role of hypoxia in the perception of dyspnea is not simple.

2.2 Vagal receptors
There are vagal receptors that respond to mechanical and chemical stimuli in the respiratory tract and lung. Among them, irritant receptors, C-fibers, and slowly adapting stretch receptors are involved in respiratory sensation. Irritant receptors located around the epithelial cells of the bronchial walls are rapidly adapting receptors. They are activated by mechanical and chemical stimulation and send information to the sensory cortex via the vagal nerve. It is thought that irritant receptors are involved in increasing respiratory output and dyspnea perception [28]. C-fibers, which represent the majority of vagal afferents innervating the airways and lung, can be activated by inhaled irritants such as capsaicin and certain endogenous substances. Vagal afferent C-fibers project to the nucleus tractus solitaries (NTS) in the medulla[29]. Prostaglandin E2 inhalation increases the magnitude of the dyspneic sensation without changes in airway resistance or lung volume, suggesting that
afferent vagal activity from C-fibers is involved in sensation of dyspnea [30]. Bronchopulmonary C-fibers generally do not respond to an elevated inspiratory CO₂ concentration (when alveolar CO₂ concentration <10 %) under normal physiological conditions. However, a high concentration of CO₂ stimulates vagal broncho-pulmonary C-fiber afferents during inflammation [31], and it is possible that stimulation of these receptors with CO₂ provides a signal for dyspnea. Juxta-capillary receptors (J-receptors) are non-myelinated C-fibers located within alveolar septa. Slowly adapting stretch receptors are stimulated as the lungs expand; they are activated by sensing lung volume changes and then send afferent signals to the NTS, which terminates inspiration (Hering-Breuer inspiratory reflex). It is thought that slowly adapting stretch receptors also send afferent information to the insular cortex and limbic system via the thalamus and play a role in reduction of dyspnea [5,32-35]. Slowly adapting stretch receptor activation alone provides potent relief of dyspnea [32], independent of vagal influences on inspiratory drive [36]. The relief of distress after the onset of rebreathing is more rapid and more substantial in normal subjects and recipients of heart transplants than it is in patients with bilateral lung transplants, suggesting that afferent information from the slowly adapting stretch receptors has an inhibitory effect on the sensation of respiratory distress [37]. Inhaled furosemide greatly alleviates the sensation of dyspnea [33], elicits slowly adapting receptor activation and suppresses irritant receptors [38,39], which may inhibit bronchoconstriction, relax airway smooth muscle and reduce dyspnea. Nonomura et al. reported that Piezo2 expressed in vagal sensory neurons is a stretch sensor channel which detects lung inflation [40].

Interruption of vagal nerve transmission may relieve or increase dyspnea. For example, Hamilton et al. reported that airway anesthesia increases breathlessness [41]. Vagotomy worsens respiratory distress induced by airway occlusion, suggesting that pulmonary vagal afferents are involved in the reduction of respiratory distress induced by airway occlusion in anesthetized cats [42]. On the other hand, vagal interruption markedly alters the dyspnea caused by unilateral pulmonary venous obstruction [43]. Inhaled lidocaine decreases the sensation of dyspnea induced by histamine inhalation during bronchoconstriction, suggesting that afferent vagal activity plays a role in the genesis of dyspnea during bronchoconstriction [28].

### 2.3 Chest wall receptors

Muscle spindles and tendon organs in the muscle of the chest wall sense muscle tension and contraction; their afferent activity is involved in sensation of dyspnea [1,44]. The role of these chest wall mechanoreceptors in dyspnea sensation has been examined in studies by transection or blockade of the spinal cord. Spinal anesthesia at the Th1 level did not reveal any effects on the sensation of CO₂ rebreathing, breath holding, or load-detection ability [45]. In high level (C1-C2) quadriplegic patients, the ability to detect lung volume change was comparable to that of normal subjects [46], suggesting that pulmonary afferent information is perceived via the vagus nerves. Similarly, in a patient with spinal cord transection at C3, the ability to detect added resistive loads was present [47]. These results indicate that spinal cord blockade or transection does not prevent the ability to detect lung volume change or alter the sensations induced by an increase in PCO₂, breath holding, or added respiratory loads. In-phase chest wall vibration (i.e., vibration of inspiratory muscle during inspiration and expiratory muscle during expiration) reduces dyspnea, while out-of-phase vibration (i.e., vibration of inspiratory muscle during expiration and expiratory muscle during inspiration) increases dyspnea [48,49]. These results indicate that chest wall mechanoreceptors innervated via spinal neurons have an important modifying effect on dyspnea, although respiratory muscle activity does not seem to be essential to the perception of dyspnea. In addition, it must be noted that respiratory muscle stretch gymnastics as pulmonary rehabilitation may contribute reduction of dyspnea [50].

### 2.4 Upper airway receptors

Of the receptors that can sense pressure, airflow, and mechanical and chemical stimuli in the upper airway, those responding to inspiratory airflow operate as thermoreceptors responsive to decreases in luminal temperature of the upper airways; these are called “cold receptors” [51]. It is possible that the changes in activities of these receptors responding to changes in ventilation are involved in the perception of dyspnea. Stimulation of cold receptors in the upper airway with nasal inhalation of l-menthol reduces the sensation of respiratory discomfort, and a flow of cold air against the face also reduces the sensation of breathlessness [52,53]. Increased information from cold receptors in the upper airway, which are projected to the sensory cortex, decreases the sensation of respiratory discomfort. Hamilton et al. reported that anesthesia of receptors in the larger airway increases breathlessness at a similar level of ventilation, suggesting that afferent information from the receptors in the upper airway mediates relief of dyspnea [41]. However, the mechanism through which the receptors in the upper airway modify dyspnea has not been fully understood.

### 3 Brain regions for dyspnea perception

Afferent information from most of the respiration-related sensory receptors is transmitted to the medulla, relayed upward, and finally projected to the cerebrum, including the somatosensory cortex and limbic system via the thalamus. Neural signals from the peripheral sensors are relayed through the NTS to the thalamus and then to the gyrus cingula, insula, and other higher centers [54-58]. The thalamus is activated by vagus nerve afferents [34]. A direct connection between the NTS and the limbic system has also been suggested [59]. Neuroimaging studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed that the limbic and paralimbic system, including the amygdala, insula, hippocampus and anterior cingulate are activated during inspiratory loading, expiratory loading and hypcapnia [60-65]. The limbic and paralimbic regions and cerebellum are activated during air hunger perception [62] (Figure 3). Neural activation occurs in the right anterior insula, cerebellar vermis, and medial pons during respiratory discomfort.
Dyspnea consists of multiple types of unpleasant or uncomfortable respiratory sensations,[5,8-10] which indicates that various mechanisms are involved in dyspnea perception. We review widely-accepted existing major theories that explain the central mechanisms of dyspnea perception. We also propose our integrated model.

4 Central mechanisms of dyspnea sensation

Dyspnea consists of multiple types of unpleasant or uncomfortable respiratory sensations,[5,8-10] which indicates that various mechanisms are involved in dyspnea perception. We review widely-accepted existing major theories that explain the central mechanisms of dyspnea perception. We also propose our integrated model.

4.1 Motor command theory

It has been suggested that motor command from the respiratory center to the respiratory muscle is closely related to the magnitude of dyspnea and it plays a key role in inducing dyspnea[44,68]. According to this theory, motor output can be consciously perceived as "a sense of effort" via collateral discharge (i.e., copy of efferent motor command from the respiratory center) to the sensory cortex. Killian et al. reported that the perceived magnitude of respiratory effort, breathlessness and tension all increase as the tension develops and that the perceived magnitude of tension increases as tension increases but it is unaffected by the operating length, suggesting that breathlessness and effort are psychophysically identical. Given this motor command theory, hypoxia and hypercapnia increase respiratory output, which induces a sense of respiratory effort, that is, dyspnea[68]. Although the motor command theory is plausible, this theory does not provide a full explanation to the mechanism of dyspnea. Moreover, Chonan et al. reported that dyspnea associated with hypercapnia is increased when ventilation is voluntarily reduced to a level below that of free breathing in normal subjects. Dyspnea increases when ventilation is decreased[4]. Schwartzstein et al. also showed that the dissociation between ventilation and afferent information from chemoreceptors that senses the carbon dioxide level induces breathlessness[69]. To elucidate the mechanism of dyspnea, it is necessary to consider not only the sense of respiratory effort but also the afferent information from sensory receptors.

The problem with the "sense of respiratory effort" concept is that the specific receptors and pathways of ascending corollary discharge from the respiratory center to the cerebrum have not yet been identified. Eldridge and Chen reported that some mesencephalic neurons show a respiratory-associated rhythmic firing pattern correlated with the level of respiratory drive from the medulla and that these neurons are involved in the mechanism that conveys information about respiration to the cortex[36]. It has also been thought that respiratory-associated neural activities of the midbrain and thalamus are part of corollary discharge[70,71] (Figure 4). Central pathways causing dyspnea from sensory information remain to be further elucidated.

Figure 3: Activated regions during air hunger

Adopted from Evans et al. [62] with permission. Imaging was performed using a functional magnetic resonance imaging scanner, showing significant regional signal increases associated with air hunger perception in healthy right-handed subjects. The limbic and paralimbic regions and cerebellum were activated during air hunger perception. Signal intensity is represented by an arbitrary gray scale (light gray indicates threshold T=5.1, P<0.05 corrected for multiple comparisons, darker shades indicate increasing T score). Relevant local maxima are labeled as follows: AC, anterior cingulate; In, insula; IPS, intraparietal sulcus; SMA, supplementary motor area; V, cerebellar vermis.

Figure 4: Firing rate of thalamic neurons and integrated phrenic activity in progressive hypercapnia

Adopted from Chen et al. [71] with permission. Activities of thalamic neurons and phrenic nerve were recorded, while short-term progressive hypercapnia stimulation was intended and the ventilator was temporarily turned off. Histogram of thalamic neuron’s firing rate (SPIKES per 0.1 s) and integrated phrenic activity (INT.PHR.) plotted for 11 consecutive breaths, showing that there is a threshold of respiratory drive level required to elicit respiratory-associated rhythmic activity. The ventilator was turned off 30 s before breath No. 1.
4.2 Mismatch theory
The length-tension inappropriateness theory that dyspnea arises from disturbance in the relation between the lung volume and the force or tension generated by respiratory muscles was proposed by the group of Campbell[72,73]. However, this theory lacks proof of the mechanism. The length-tension inappropriateness theory has been refined to the leading theory that dyspnea results from disassociation or mismatch between respiratory motor output from the respiratory center and incoming afferent information of sensed respiratory movement[8,69]. This mismatch theory considers both the mechanism of afferent information from sensory receptors and the motor command theory. The mismatch theory includes not only information from respiratory muscles and lung volume, but also information emanating from receptors throughout the respiratory system. The quantitative and phase mismatch between respiratory motor output from the respiratory center and incoming afferent information from respiration-related mechanoreceptors may cause dyspnea[20,44,74,75]. This theory is consistent with numerous clinical observations. For example, patients with mechanical ventilation often perceive dyspnea even if blood gas values are adequate when the patients’ respiratory frequency (i.e., timing) and tidal volume do not match ventilator settings.

4.3 Our integrated model
By integrating the above theories, we propose the following model of the mechanism of dyspnea perception. In our integrated model, dyspnea results from disassociation or mismatch between intended respiratory neural output from the respiratory neural network and the actually accomplished ventilatory motor output.

Ventilation in humans is modulated in response to PO₂, PCO₂, pH, body temperature, arousal level, and mental condition to maintain homeostasis of oxygen and carbon dioxide levels in the body, and control the breathing pattern (respiratory frequency, tidal volume, minute ventilation, and inspiration-expiration pattern) to minimize respiratory efforts. The respiratory neural network in the lower brainstem generates motor output, which regulates the patency of the upper airway and drives respiratory pump muscles, such as the diaphragm and intercostal muscles. Additionally, copies of neural respiratory output information from the brainstem respiratory center are projected to the limbic system and cerebral cortex via the midbrain and thalamus, as a kind of sensation that reflects the degree of the respiratory effort (motor command corollary discharge)[1]. The actual ventilatory motor output accomplished through the motor command from the lower brainstem and respiratory muscle activities is monitored by mechanoreceptors in the lungs, chest wall, airways, and muscle spindles of the respiratory muscles, and the information is transmitted to the lower brainstem and integrated. This integrated mechanical respiratory sensation is projected to the higher brain centers, such as the thalamus, limbic system, and cerebral cortex. Then, the integrated mechanical respiratory sensation and motor command corollary discharge are compared in the higher brain center, and the quantitative and phase mismatch or disassociation between them is perceived as dyspnea. Therefore, when the augmented motor command is associated with sufficiently increased ventilation, e.g., during light exercise, dissociation does not occur. In such a circumstance, dyspnea is not perceived, and the subject rather feels comfortable with a sense of comfortably increased ventilation. Information on blood gas conditions, which is transmitted from peripheral and central chemoreceptors and also monitored and integrated at the lower and higher brain centers (integrated chemical respiratory sensation), modifies respiratory sensation.

Mental condition also affects the threshold and sensibility of perception of dyspnea. The limbic and paralimbic systems (especially the amygdala), which are involved in the formation of emotion, affect respiration[76-80]. Strong emotional changes may induce neural activity synchronized with respiration in these brain regions. Onimaru and Homma reported the functional coupling of the rhythmic activity in the piriform-amygdala complex with the medullary inspiratory activity in limbic-brainstem-spinal cord preparation of newborn rats[81]. The neurons in the limbic system are activated during CO₂-stimulated breathing at a level sufficient to induce dyspnea[60]. Neural activation occurs in the right posterior cingulate cortex during respiratory discomfort related to loaded breathing[56]. Several studies have indicated that dyspnea in patients with COPD is worsened by the presence of anxiety and depression, independent of pulmonary function[82-85]. It has also been shown that patients with COPD with panic attacks or panic disorders rated their intensity of dyspnea higher than those without panic[86]. However, Ng et al. reported that the degree of dyspnea sensation did not differ between depressed and non-depressed COPD patients[87]. The relationship between psychological factors and the level of dyspnea sensation remains to be elucidated.

Perceived dyspnea enhances the central command that descends as the respiratory drive command from the hypothalamus to the lower brainstem, and it augments respiratory neural output from the lower brainstem. Such a respiratory feedback modulation system controls the ventilation to an appropriate level[5,6]. (Figure 5).

5 Dyspnea in patients with various diseases
Based on our integrated model that dyspnea results from disassociation or mismatch between motor command corollary discharge and integrated mechanical respiratory sensation, we are able to explain the perception mechanisms of dyspnea in patients with various diseases. In patients with COPD, elevated respiratory resistance due to airway obstruction increases the mechanical work of breathing. Then, afferent impulses from muscle spindles in respiratory muscles increase and integrated mechanical respiratory sensation is enhanced. Furthermore, the increase in afferent impulses from the peripheral chemoreceptors, due to the reduction of arterial blood PO₂, enhances integrated chemical respiratory sensation. However, undernutrition, muscle atrophy and insufficient supply of oxygen to respiratory muscles induce respiratory muscle weakness, which impedes the realization of the respiratory motor output corresponding to the increase of the motor command. Airway obstruction also makes it difficult to accomplish brain-intended
ventilatory volume and timing. Increases in the mismatch between motor command corollary discharge and integrated mechanical respiratory sensation cause dyspnea.

In patients with interstitial pneumonia or pulmonary fibrosis, the lungs are stiff and it is difficult to accomplish the lung expansion, ventilatory output and ventilatory pattern corresponding to motor command, which increases the mismatch between motor command corollary discharge and integrated mechanical respiratory sensation. Augmented effort to expand the stiffened lung increases the tension of the intercostal and afferent impulse from the muscle spindle during inspiration, which increases the mismatch between the motor command corollary discharge and integrated mechanical respiratory sensation and results in dyspnea. Further, insufficient lung expansion decreases the impulses from the slowly adapting stretch receptors, which augments dyspnea. Reduction of arterial blood P\textsubscript{O\textsubscript{2}} enhances integrated chemical respiratory sensation and motor command, which also increases motor command, induces hyperventilation and increases dyspnea.

In patients with acute pulmonary embolism, increases in pulmonary arterial pressure and edema of the interstitial tissue activate J-receptors around the pulmonary capillary, and increase the afferent signal to the higher center, which increases motor command and increases respiratory frequency and ventilation. Impairment of pulmonary gas exchange reduces arterial blood P\textsubscript{O\textsubscript{2}}, which increases afferent impulse from the peripheral chemoreceptors, enhances integrated chemical respiratory sensation and then further increases motor command. An increase in the motor command corollary discharge that is greater than the increase in ventilation results in dyspnea.

In patients with terminal lung cancer, cancerous lesions stimulate irritant receptors and J-receptors and impair gas
exchange which lowers arterial blood \( P_{O_2} \) and elevates arterial blood \( P_{CO_2} \), leading to increases in afferent projection from the peripheral chemoreceptors, enhancing integrated chemical respiratory sensation and further increases motor command. However, cancerous lesions and pleural effusion cause restrictive ventilatory impairment, lung expansion impairment and inhibition of the slowly adapting stretch receptors, which prevent sufficient ventilation and gas exchange and increase the mismatch between motor command corollary discharge and integrated mechanical respiratory sensation. Furthermore, pain, anxiety, and depression in cancer patients merge to emotionally lower the threshold of dyspnea perception, which also increases dyspnea.

6 Conclusion
Although the mechanism of dyspnea perception is complex as it involves the peripheral and central nervous system, cerebral function and even mental condition, we propose that dyspnea results from disassociation or mismatch between the intended respiratory neural output from the respiratory neural network and actually accomplished ventilatory volume and pattern. It should be elucidated where and how in the brain the motor command corollary discharge and integrated mechanical respiratory sensation are compared. Those who are engaged in pulmonary rehabilitation should make efforts to better understand the pathophysiology of dyspnea based on respiratory neurophysiological knowledge so that they can provide more effective pulmonary rehabilitation by improving management of patients’ dyspnea.

7 Conflicts of Interest
The authors declare no competing financial interests.

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