Dyspnoea: underlying mechanisms and treatment

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Humans can sense a wide range of respiratory sensations such as respiratory motion, lung position, irritation, urge to cough, pain, chest tightness, sense of effort, and respiratory discomfort. Among these respiratory sensations, specific aspects such as chest tightness, sense of effort, and respiratory discomfort mainly contribute to the sensation of ‘dyspnoea’. Thus, dyspnoea appears not to be a single respiratory sensation. Although dyspnoea often arises as the primary symptom in many diseases of the respiratory systems, it is also the cardinal symptom of cardiovascular diseases or neuromuscular dysfunction. Dyspnoea is frequently the symptom that motivates a patient with pulmonary disease to seek medical assistance. Because dyspnoea is a common symptom in patients with cancer, pulmonary diseases, heart failure, and neuromuscular diseases, anaesthetists frequently encounter patients with dyspnoea in various clinical situations. This review aims to provide anaesthetists with an outline of pathophysiology and treatment of dyspnoea to assist in their care of patients with dyspnoea.

Mechanisms of dyspnoea

Since dyspnoea consists of qualitatively distinct sensations, there must be a neuroanatomic basis for it. In this context, it is necessary to look for the sensory receptors, sensory pathways, and thalamic or cortical centres that are responsible for the perception of dyspnoea.

Dyspnoea is the result of a complex interaction of physiological, psychosocial, social, and environmental factors. Although several sensory receptors located throughout the respiratory system are considered to be responsible for generation of dyspnoea, there is no afferent receptor solely responsible for the sensation of dyspnoea. Afferent information from the sensory receptors is processed at the cortex along with the respiratory motor command from the cortex and brainstem, and a mismatch between the motor command and the incoming afferent information may result in dyspnoea. Dyspnoea is not a single sensation and there are at least three distinct sensations including air hunger, work/effort, and chest tightness. Like pain, dyspnoea has at least two distinct separate dimensions, that is, a sensory and an affective dimension. Recent neuroimaging studies suggest that neural structures subserving pain and dyspnoea might be shared, and therefore the neurophysiological and psychophysical approaches used to understand pain can be applied to dyspnoea research. Although effective treatment of dyspnoea remains an elusive goal at the moment, a better understanding of the pathophysiology and neurophysiology of dyspnoea may provide a rationale for effective therapy of dyspnoea. In this context, treatment strategies in dyspnoea should be similar to those used in pain.

Keywords: dyspnoea; mechanisms; neurophysiology; pathophysiology; therapy

Sensory receptors

Chemoreceptors

Changes in arterial blood pH, PCO₂, and PO₂ can be sensed by the central and peripheral chemoreceptors and the stimulation of these causes an increase in respiratory motor activity.1 2 The dyspnoea produced by hypercapnia and hypoxia results largely from chemically induced respiratory motor activity.3 The breathing discomfort associated with acute hypercapnia is not a reflection of respiratory muscle activity but rather a reflection of respiratory motor output, which is characterized by phrases such as ‘air hunger’, ‘urge to breathe’, and ‘need to breathe’. In this regard, it has been reported that the sensation of severe air hunger arises from increased PCO₂ in patients with quadriplegia and normal subjects with respiratory muscle paralysis who are mechanically ventilated.4 5 Patients with congenital central hypoventilation syndrome who lack a ventilatory response to CO₂ do not feel breathless during CO₂ rebreathing or during prolonged breath hold.6 Although the sensation of dyspnoea associated with hypoxia has been less well studied, it has been reported that when ventilation and PCO₂ are held near normal, PO₂ has to decrease to below 6.7 kPa to induce a sharp increase in air hunger sensation.7 There is evidence from animal studies that carotid chemoreceptor signals project directly to the cortex,8 although this does not prove that they are perceived.
Metaboreceptors

Metaboreceptors located in skeletal muscle are believed to respond to local changes in the tissue environment with respect to the by-products of metabolism. Metaboreceptors may be a source of afferent neurological signals that lead to a perception of dyspnoea during exercise as hard exercise produces a sensation of dyspnoea with an increase in ventilation in healthy subjects while the subjects are neither hypoxaemic nor hypercapnic, and as metabolic acidosis occurs relatively late in high intensity exercise. However, the role of metaboreceptors during exercise, and the origin of exercise-induced dyspnoea, is still undetermined.

Vagal receptors

There is some evidence that a source of cool air directed onto the face may reduce breathlessness in adults, suggesting that stimulation of cold receptors located in the upper airway may be responsible for the relief of breathlessness. Some of these cold receptors are innervated by the vagus nerve and monitor the changes of flow in the upper airway by detecting changes in temperature. In addition to the cold receptors, there are at least four or five different types of airway receptors innervated by the vagus that may mediate dyspnoea and other sensations, although the role of vagal afferents is uncertain and is likely to be complex. The major receptors in the lung parenchyma are slowly adapting stretch receptors (SARs), rapidly adapting stretch receptors (RARs), and C-fibre receptors.

Slowly adapting stretch receptors

RARs are found in the smooth muscle of the larger airways and correspond to the myelinated afferent nerve fibres in the vagus. Inhalation of CO₂, volatile anaesthetics, and furosemide is known to affect the activity of SARs. Inhalation of CO₂ inhibits their activity by a direct action on the receptor with action on 4-aminopyridine-sensitive K⁺ channels, whereas volatile anaesthetics may inhibit or stimulate the receptors, depending on their concentration and the type of SARs. It has been postulated that inhaled furosemide acts indirectly on sensory receptors in the airway epithelium and its vicinity, and an animal study has shown that SARs are sensitized by inhalation of furosemide. Inhaled furosemide has been shown to improve experimentally induced dyspnoea. As it is generally accepted that stimulation of SARs probably decreases the sensation of dyspnoea, it is possible that the alleviation of dyspnoea with inhaled furosemide may be associated with increased SAR activity.

Rapidly adapting stretch receptors

Although the structure of RARs has not been fully delineated, RARs are known to have non-myelinated terminals connected to thin myelinated vagal afferents (Aδ). These receptors adapt rapidly to maintained inflation or deflation of the lungs. The respiratory modulation of RARs is irregular in both its timing with the breathing cycle and its pattern of discharge. RARs are activated by a large number of mechanical and chemical irritant stimuli (ammonia, ether vapour, cigarette smoke, etc.), by inflammatory and immunological mediators, and by airway and lung pathological changes. Therefore, RARs are also known as pulmonary irritant receptors. Pneumothorax is a powerful stimulus to dyspnoea in humans. An animal study showed that pneumothorax preferentially stimulated RARs, suggesting that RARs may contribute to the generation of dyspnoea. However, there has been no clear-cut evidence to show that direct stimulation of RARs causes dyspnoea in humans. In this connection, it has been shown that cough induced by citric acid inhalation, which probably activates RARs, does not generate a sensation of dyspnoea but can aggravate it. An animal study showed that inhaled furosemide not only sensitizes SARs but also it desensitizes RARs. Thus, the relief of dyspnoea with inhaled furosemide might be partly associated with the decreased activity of RARs.

C-fibre receptors

Two groups of C-fibre receptors have been distinguished on the basis of their circulatory accessibility through either the pulmonary or the bronchial circulation. These receptors are also known as juxta-pulmonary capillary receptors, or J receptors for short, since these receptors seemed to be localized close to the alveolar capillaries and to respond to increased interstitial fluid outside the capillaries. Pulmonary C-fibre receptors are those arising from the endings located in the lung parenchyma, and are directly accessible to a challenging drug injected into the pulmonary artery, whereas bronchial C-fibre receptors located further downstream innervating the airway mucosa, are accessible to the challenging drug injected into the left atrium or directly into the bronchial artery. Pulmonary C-fibre endings are relatively insensitive to autacoids such as bradykinin, histamine, serotonin, and prostaglandins, whereas bronchial C-fibre endings are sensitive to a wide range of intrinsic chemicals including histamine, bradykinin, and prostaglandins, either injected into the bronchial artery or administered as aerosol. In contrast, the two groups of C-fibre receptors respond similarly to inhalation of volatile anaesthetics.

Pulmonary congestion is a powerful stimulant of pulmonary C-fibre sensors, but not a strong cause of dyspnoea in humans, except with the added stimulus of exercise. Small i.v. dose of capsaicin, a known C-fibre stimulant, causes a raw sensation in the chest of humans but no dyspnoea sensation. I.V. lobeline, a pulmonary C-fibre stimulant, causes short-latency noxious sensations in the larynx and chest. These sensations are different from the dyspnoea sensation in normal control subjects and were not perceived in patients with bilateral lung transplant. These findings suggest that a dyspnoeaic sensation is not induced by direct stimulation of pulmonary C-fibre afferents.

Chest wall receptors

Afferent signals from mechanoreceptors in the joints, tendons, and muscles of the chest project to the brain and may contribute to generation and modification of dyspnoea.
There is convincing evidence for a short-latency projection from intercostal muscle afferents (Groups I, II, or both) to the human cerebral cortex.32

Vibration of the chest wall activates muscle spindles and when they are activated out of phase with the respiratory cycle in normal humans, a sensation of dyspnoea can be induced, suggesting that the muscle spindles play an important role in production of dyspnoea and that the central mechanism that receives the intercostal afferents may have a certain gate operating in relation to the sensation of dyspnoea.33–35 There is also substantial evidence that phrenic nerve afferents may modulate diaphragmatic activity.36,37 In addition, animal studies have shown that the electrical stimulation of phrenic nerve afferents evokes potentials in the sensorimotor cortex.38,39 In humans, similar respiratory-related cortical potentials can be evoked by inspiratory occlusion.40 It has been also shown in animal experiments that diaphragmatic fatigue is associated with alterations in the transmission of phrenic sensory activity to the cortex and also marked changes in spontaneous cortical activity.39 Although little is known about the role of phrenic afferents in humans, they can be expected to play a role in respiratory proprioception and to participate in generation and modulation of dyspnoea.

Neural pathways of dyspnoea

Little is known about ascending pathways responsible for dyspnoea. Since dyspnoea involves several distinct types of sensation, it would be expected that the afferent mechanisms responsible for dyspnoea are probably more complicated than for pain. The afferent activity from respiratory muscles and vagal receptors is relayed in the brainstem and projected to the thalamic area. Neurophysiological studies in animals have shown rostral projections from the brainstem respiratory motor neurones to the midbrain and thalamus.41,42

Recent neuroimaging studies have shown that dyspnoea activates several distinct areas in the brain cortex including the anterior right insula, the cerebellar vermis, the amygdala, the anterior cingulated cortex, and posterior cingulated cortex.43–48 These areas are similarly activated by pain and other unpleasant sensations (Fig. 1). For example, a variety of painful stimulations produce strong insular activation49–51 and a similar area can be activated during nausea52 and thirst.53 Although the thalamus appears to be the pivotal part of the pathway relaying pain and dyspnoea and thalamic-cortical projections to the specific cortical regions seem to be common to both pain and dyspnoea, it is possible that dyspnoea and pain do not necessarily activate identical neural structures or share identical neural pathways.

Motor command and central corollary discharge

The sensation of dyspnoea may simply represent a conscious awareness of the outgoing respiratory motor command. While the brainstem or the motor cortex sends efferent commands to the ventilatory muscles, a neurological copy of these commands is simultaneously sent to the sensory cortex (Fig. 2). This exchange between the motor and sensory cortex is called a corollary discharge and is thought to be the mechanism by which conscious awareness of the effort of breathing occurs.54 The rostral projections from brainstem respiratory motor neurones to the midbrain and thalamus51,42 could represent the pathway of the central corollary discharge to the sensory cortex.

Although increased work of breathing is not the sole cause of dyspnoea, increased effort is a common cause of breathing discomfort, as muscle weakness and increased mechanical load cause a heightened sense of respiratory effort. The concept of a ‘corollary discharge’ is the most widely accepted hypothesis used to explain the origin of the sense of effort.3 However, evidence for corollary discharge is functional rather than structural as specific receptors and pathways have not been identified.

Motor command–afferent mismatch

A recent theory of dyspnoea postulates that a mismatch or dissociation between motor command and incoming afferent information from sensory receptors causes dyspnoea. Campbell and Howell54 suggested that an imbalance in the relationship between tension and displacement in respiratory muscle may be the neurophysiological mechanisms causing dyspnoea and proposed the concept of length–tension inappropriateness of the respiratory muscles as the trigger of dyspnoea. They suggested that under normal conditions, there is an appropriate relationship between the respiratory muscle tension and the volume or flow that results. The concept of length–tension inappropriateness of the respiratory muscles in genesis of dyspnoea was supported by breathing experiments.55 The results of these experiments also suggested that direct projections from chemoreceptors and medullary corollary discharge would not be perceptible. However, the view that the contractile activity of respiratory muscles is essential to generation of dyspnoea has been refuted by several studies5,56 in subjects paralysed by high spinal injury or complete neuromuscular block. These studies clearly demonstrated that respiratory muscle contraction is not important in the genesis of air hunger evoked by hypercapnia (Table 1). The original concept proposed by Campbell and Howell54 was expanded and refined by the incorporation of the general concept that dyspnoea is the result of dissociation or mismatch between central ventilatory drive and the magnitude of ventilation produced.57 In other words, dyspnoea is the result of dissociation between ongoing motor signals to the respiratory muscles and incoming afferent information. The potential sources of the afferent information include not only the respiratory muscles but also several different receptors throughout the respiratory system. This dissociation between central respiratory motor activity and afferent feedback has also been termed neuromechanical dissociation.58 The concept of neuromechanical dissociation is difficult to prove since we cannot easily quantify the central respiratory activity.
and afferent feedback signals from peripheral receptors in humans. Nevertheless, experimental and clinical data support the theory of neuromechanical dissociation.58–60 Thus, when there is an appropriate matching between motor command and incoming afferent information from sensory receptors, there should be no sensation of dyspnoea (Fig. 2). In contrast, when the matching is inappropriate, the resultant neuromechanical uncoupling can contribute to the genesis of dyspnoea.

Central neural processing of dyspnoea

Although it has been hypothesized that dyspnoea might not be a single sensation but may include at least two distinct dimensions (sensory and affective),61–65 it is still unclear whether a functional differentiation also exists in the cortical processing of dyspnoea. When normal subjects experienced severe air hunger, there was strong activation of the anterior insular cortex.46 A recent study46 suggested that the right posterior cingulate cortex may be related to the affective dimension of dyspnoea induced by loaded breathing. However, more recently, a study67 suggested that the unpleasantness of subjectively perceived dyspnoea may be processed in the right human anterior insula and amygdala.

All of these studies show that activation of the anterior insular cortex was a common finding, suggesting that the unpleasant sensations produced by different respiratory challenges are processed in the same areas.

It is not completely understood how the insula gives rise to the perception of dyspnoea. However, it has been suggested that corollary discharges from increased medullary brainstem motor command to the respiratory muscles may activate the insula, presumably even without peripheral afferent feedback from respiratory mechanoreceptors.47 Also, although it is not clear whether pain and dyspnoea are processed by the same cortical structures or simply by neighbouring cortical structures, it is evident that the insular cortex plays an important role in the perception of both sensations.67–70 In this connection, it has been suggested that common brain areas might process the unpleasantness of both sensations, in particular, areas of the affect-related limbic system such as the insular cortex and anterior cingulated cortex.67 However, these areas are not specifically devoted to the processing of perceived unpleasantness.71–73 There is growing evidence to suggest that the anterior insula cortex acts as a centre of interoception and plays a fundamental role in conscious awareness of
subjective feelings rather than simply a role in processing of perceived unpleasantness. A study of patients with right-hemispheric insular lesions suggests that lesions of the right insular cortex are associated with reduced sensitivity for the perception of dyspnoea and pain, in particular for their perceived unpleasantness. A recent study showed that the perceived affective unpleasantness of both dyspnoea and pain is reduced in patients with mild-to-moderate asthma, compared with healthy controls, suggesting that the periaqueductal grey may play an important role in a down-regulation of insular cortex responses to dyspnoea and pain in asthmatic patients who have repeated dyspnoea experiences over the course of the disease. Although these studies address important topics, they should be interpreted with caution as there are concerns that limit a simple extrapolation of these results to clinical situations.

**Quality of dyspnoea**

Recent evidence shows that dyspnoea is a multidimensional sensation and there are at least three distinct sensations, such as a sensation of air hunger, a sensation of work/effort, and a sensation of chest tightness. Several studies provide additional direct information on the relationship between quality of dyspnoea and the underlying mechanism producing discomfort. The sensation of air hunger has been shown to be associated with an increase in respiratory drive, particularly in the presence of hypoxia or hypercapnia. Therefore, it is likely that the sensation of air hunger is associated with stimulation of chemoreceptors. The sensation of work/effort increases when the muscle load is increased due to derangements of ventilatory mechanics or when the muscles are weakened by fatigue, paralysis, or an increase in lung volume. Since the central respiratory motor command has to be increased in the face of worsening mechanical load on the respiratory system to maintain adequate ventilation, the sensation of work/effort is associated with the amplitude of respiratory central command. It is quite likely that a sensation of chest tightness is associated with bronchoconstriction since asthmatic patients frequently describe their symptoms as a sense of chest tightness or constriction. The results of induced bronchoconstriction in

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**Table 1** Quality of dyspnoea and the underlying mechanisms

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Receptors</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Hypercapnia</td>
<td>Central chemoreceptors</td>
<td>Air hunger</td>
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<tr>
<td>Hypoxia</td>
<td>Peripheral chemoreceptors</td>
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<tr>
<td>Respiratory motor command</td>
<td>Central corollary discharge</td>
<td>Work/effort</td>
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<td>Muscle contraction</td>
<td>Chest wall receptors</td>
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<tr>
<td>Muscle fatigue</td>
<td>Muscle spindles</td>
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<td>Mechanical loads</td>
<td>Joint receptors</td>
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<td>Mechanical loads</td>
<td>Tendon receptors</td>
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<tr>
<td>Bronchoconstriction</td>
<td>RARs, C-fibre receptors</td>
<td>Chest tightness</td>
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<tr>
<td>Lung inflation</td>
<td>SARs</td>
<td>Dyspnoea relief</td>
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**Fig 2** Motor command–afferent mismatch. Dyspnoea is the result of a dissociation between amplitudes of the central efferent discharge (motor output) and afferent sensory inputs (feedback) from peripheral mechanoreceptors.
asthmatic patients showed that the sensation of tightness does not arise from the work of breathing, suggesting that it does not depend on respiratory muscle afferents but on stimulation of airway receptors such as RARs and C-fibre receptors that respond to bronchoconstriction. It is likely that simultaneous stimulation of different types of receptors interacts and causes qualitatively and quantitatively different effects on the sensation of dyspnoea.

Like pain, dyspnoea is influenced not only by sensory input but also by non-sensory factors such as emotion and attention. It is a commonplace clinical observation that some patients with high negative emotionality report symptoms of breathlessness out of proportion to the impairment of their pulmonary disease. Emotions play an important role in perception of dyspnoea not only in adult patients but also in paediatric patients. Several recent studies examined the influence of emotion and attention on the distinct dimensions of perceived dyspnoea. For example, it has been reported that rating for the degree of unpleasantness of dyspnoea increases from positive to negative emotional state, but the intensity of dyspnoea is unaffected by emotional stimulation. It has also been reported that attention distraction reduces the affective but not the sensory dimension of perceived dyspnoea in healthy subjects and in patients with chronic pulmonary disease (COPD). The differentiation between the affective and sensory dimension of dyspnoea may be important to the enhancement of the accuracy of the diagnostic process and may contribute to the development of new psychotherapeutic interventions aiming to improve the dyspnoea.

**Interaction between pain and dyspnoea**

Dyspnoea is as common as pain in many diseases and some evidence for the causal association between pain and dyspnoea has been reported. The similarities between dyspnoea and pain suggest that there may be common pathways and networks for the two sensations, and that they may interact. Despite the prevalence of simultaneous dyspnoea and pain, their interaction has not been fully explored and data are limited. It has been shown that perception of dyspnoea was slightly increased by ischaemic tourniquet pain, whereas dyspnoea caused either no effect

![Fig 3 Schematic of DNIC. PAG, periaqueductal grey; RM, rostral medulla; PN, projection neurone; PAF, primary afferent fibre. A thick broken line indicates the neural pathway for counterirritation.](https://academic.oup.com/bja/article-abstract/106/4/463/232320)
on pain or even a slight attenuation in pain.94 The finding that pain aggravates dyspnoea can be explained by the motor command theory that an increase in ventilatory drive is closely linked to the increased sense of dyspnoea. A recent neurophysiological study95 demonstrated that dyspnoea induced by inspiratory threshold loading can inhibit the spinal nociceptive flexion reflex, which provides evidence that analgesia can be induced by dyspnoea. A possible explanation for this is that dyspnoea, like pain, might stimulate C-fibres in respiratory muscles or the lungs, and thereby activate diffuse noxious inhibitory descending controls (DNIC)96 known to project onto spinal dorsal horn interneurones while triggering endogenous analgesic mechanisms at the subcortical level (Fig. 3).

Considerable attention has been paid to gender difference in pain sensitivity in recent years, and several studies have demonstrated that women may be more sensitive to nociceptive stimuli than men,97–99 and have a lower pain threshold and tolerance.99 A difference in DINC has also been described, with females reporting more intense pain than males.100 In contrast, there is no clear evidence of gender difference in dyspnoea, although women with COPD experience greater dyspnoea than men.101 102 and dyspnoea was worse in men than in women in lung cancer patients.103 With regard to the interaction between dyspnoea and pain, a recent study showed that dyspnoea increased the thermal pain threshold in young male subjects, but had no appreciable effect in young female subjects, suggesting a sex difference in pain response.104

### Treatment of dyspnoea based on the neurophysiological mechanisms

A detailed discussion of treatment of dyspnoea is beyond the scope of this article. Thus, only some selected aspects of treatment of dyspnoea that are closely linked to the neurophysiological mechanisms of dyspnoea are discussed.

The initial goal of the treatment of dyspnoea is to correct the underlying disorder causing the symptoms. However, there are many cases in which treatment of the underlying disorder is ineffective, and troublesome symptoms persist. Effective therapy of dyspnoea remains an elusive goal at the moment. As noted previously, dyspnoea includes at least three distinct sensations such as air hunger, work/effort, and chest tightness. This distinction is helpful in selecting the dyspnoea treatment as it is associated with the pathophysiological mechanism of dyspnoea (Table 2).

### Decrease in ventilatory drive

Several studies have shown that opioids improve both dyspnoea and exercise performance in patients with COPD.105–107 In cancer patients, a significant improvement in dyspnoea after a single bolus dose of morphine has been reported in placebo-controlled crossover studies.108 109 Opioids have also been shown to produce a significant improvement in aerobic exercise capacity in patients with heart failure.110 Endogenous opioids modulate the increase in ventilatory output and dyspnoea during severe acute bronchoconstriction in asthmatic patients.111 Thus, opioids are the mainstay of the drug management of dyspnoea in many different clinical situations. The mechanisms of action of opioids are not fully elucidated. However, opioids are respiratory depressants that reduce the central processing of neural signals within the central nervous system. Thus, the mechanisms of action of opioids in the relief of dyspnoea are associated with a decrease in central respiratory motor command. Alkalizing agents such as sodium bicarbonate112 and tris-hydroxymethyl aminomethane (THAM)113 have been shown to improve experimentally induced dyspnoea in healthy subjects and the reduction in ventilatory drive may be the main mechanism responsible for the relief of dyspnoea.

### Changes in perceptual sensitivity

Opioids and anxiolytics can alter perceptual sensitivity, and this change in perception can blunt the patient’s response to dyspnoea stimuli. Although the effectiveness of opioids in improving dyspnoea is fairly consistent, there are conflicting results from trials of the effectiveness of various anxiolytics in reducing dyspnoea.114–116 For example, one study116 showed that diazepam had no effect on breathlessness and noticeably reduced exercise tolerance whereas promethazine reduced breathlessness and improved exercise tolerance without altering lung function. However, another

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**Table 2 Different quality of dyspnoea and its treatment**

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<thead>
<tr>
<th>Quality of dyspnoea</th>
<th>Treatments</th>
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<tbody>
<tr>
<td>Air hunger</td>
<td>Decrease in ventilatory drive</td>
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<td>Work/effort</td>
<td>Changes in perceptual sensitivity to sensation</td>
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<td>Alterations in vagal afferent information</td>
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<tr>
<td>Chest tightness</td>
<td>Decrease in ventilatory drive</td>
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<td>Alterations in afferent information from chest wall and respiratory muscles</td>
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<td>Changes in perceptual sensitivity to sensation</td>
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**Specific pharmacological and non-pharmacological approaches**

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<th>Opioids, THAM, bicarbonate, oxygen</th>
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<td>Opioids, anxiolytics</td>
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<td>Airway anaesthesia, vagal block, inhaled furosemide</td>
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<td>Opioid, anxiolytics</td>
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study\textsuperscript{115} showed that promethazine had no significant effect on breathlessness nor on the relationship between breathlessness and ventilation whereas chlorpromazine caused a marked reduction in breathlessness without affecting ventilation and without causing detectable sedation. Despite these conflicting observations, it is reasonable to use anxiolytics in those with morbid anxiety or those having the panic and fear associated with acute episodes of severe dyspnoea.

Alterations in vagal afferent information

Several studies\textsuperscript{117–120} have shown that vagal blockade or airway anaesthesia has an inconsistent effect on dyspnoea induced by breathholding, exercise, and i.v. adenosine in normal subjects. These findings suggest that vagal afferents are responsible for both attenuation and aggravation of dyspnoea sensation. The effects of vagal blockade or airway anaesthesia in patients with pulmonary disease are variable. Although vagal nerve block was reported to be very effective in a patient with unilateral pulmonary venous obstruction,\textsuperscript{119} it was also reported that the perception of dyspnoea in patients with interstitial pulmonary disease was not diminished by airway anaesthesia.\textsuperscript{118}

Assuming that inhaled furosemide alleviates dyspnoea mainly through vagal mechanisms, it may be a potential treatment for dyspnoea. Inhaled furosemide produced an improvement of severe dyspnoea in patients with advanced cancer\textsuperscript{121 122} and in patients with COPD during exercise.\textsuperscript{123 124} However, other reports have shown no beneficial effect in patients with cancer\textsuperscript{125} and in patients with a previous exposure to sulphur mustard.\textsuperscript{126} It is possible that the effectiveness of inhaled furosemide may depend on the underlying lung pathology, and may not act on vagal receptors when the tracheobronchial mucosa and nerve endings are severely damaged.

Alterations in afferent information from chest wall and respiratory muscles

It has been shown that in-phase chest wall vibration in patients with COPD relieves the sensation of dyspnoea at rest.\textsuperscript{127} However, chest wall vibration had little impact on dyspnoea during exercise in patients with COPD.\textsuperscript{128} Furthermore, a recent study\textsuperscript{129} showed that vibration does not relieve the sensation of air hunger, suggesting that the effect of vibration is specific to the form of dyspnoea. The utility of retrosternal block with 35–50 ml of lidocaine 1% has been described as a novel treatment of dyspnoea of various aetiologies.\textsuperscript{130} Three mechanisms were proposed as possible mechanisms of action for retrosternal block: (i) changes in afferent information from chest wall and respiratory muscles, (ii) a direct inhibitory effect on the autonomic parasympathetic cholinergic nerve supply of the airways and lungs, and (iii) a direct effect of the local anaesthetic on the central nervous system. There is a reduction of respiratory muscle function in patients with COPD, and it has been shown that inspiratory muscle training increases respiratory muscle strength and the resultant improved respiratory muscle function is associated with reduced dyspnoea ratings in patients with COPD.\textsuperscript{131}

Other pharmacological and non-pharmacological treatments

Other pharmacological treatments for dyspnoea include oxygen, nitrous oxide, bronchodilators, corticosteroids, and antibiotics. Administration of oxygen in hypoxic patients can cause a reduction in hypoxic ventilatory drive by decreasing peripheral chemoreceptor activity and thereby produces a relief of dyspnoea.\textsuperscript{81 132} It has been reported that a low concentration of nitrous oxide relieves experimentally induced dyspnoea without changing respiratory load compensation.\textsuperscript{133} Bronchodilators can reduce the resistive load in asthma or in patients with COPD who have reversible bronchoconstriction.\textsuperscript{134} Corticosteroids will relieve dyspnoea by decreasing airway inflammation and oedema.\textsuperscript{135} Non-pharmacological approaches such as lung volume reduction surgery, exercise training, and ventilatory support and also non-interventional methods such as education and relaxation for the control of dyspnoea are occasionally used.\textsuperscript{136} However, it is not clear if these consistently benefit patients with different types of disease.

In conclusion, although the mechanisms of dyspnoea have not been fully clarified, there is growing evidence that dyspnoea is the result of a complex interaction of physiological, psychosocial, social, and environmental factors. As pain shares many clinical, physiological, and psychological features with dyspnoea, our knowledge of how pain is perceived can be applied to the study of dyspnoea. Recent neuroimaging studies showed that like pain, dyspnoea causes neuronal activation in the limbic system, particularly the anterior insular which is associated with affective unpleasantness. A better understanding of the mechanisms, assessment, and treatment of dyspnoea may lead to better therapy for this distressing symptom.

Acknowledgement

Parts of the contents in this review were presented at a symposium sponsored by the Japanese Society of Anesthesiologists and published as the symposium proceedings [J Anesth 2010; December 14 (Epub ahead of print)].

Conflict of interest

None declared.

Funding

This work was supported in part by a grant from the Ministry of Health, Labour and Welfare of Japan (19-4).

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