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Dyspnoea: underlying mechanisms and treatment

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Editor's key points

- Dyspnoea is a distressing symptom in respiratory disease.
- The mechanisms involved are complex and not fully understood.
- There are similarities between pain and dyspnoea perception and neural pathways.
- Better understanding of the mechanisms should improve treatment.

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

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.

Sensory receptors

Chemoreceptors

Changes in arterial blood pH, P_{CO_2}, and P_{O_2} 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 P_{CO_2} 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 CO_2 do not feel breathless during CO_2 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 P_{CO_2} are held near normal, P_{O_2} 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.[9] 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,[10] 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.[11 12] 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.[13] The major receptors in the lung parenchyma are slowly adapting stretch receptors (SARs), rapidly adapting stretch receptors (RARs), and C-fibre receptors.[11 14]

Slowly adapting stretch receptors SARs are found in the smooth muscle of the larger airways and correspond to the myelinated afferent nerve fibres in the vagus. Inhalation of CO_2, volatile anaesthetics, and furosemide is known to affect the activity of SARs.[15 16] Inhalation of CO_2 inhibits their activity by a direct action on the receptor with action on 4-aminopyridine-sensitive K^+ channels,[17] whereas volatile anaesthetics may inhibit or stimulate the receptors, depending on their concentration and the type of SARs.[18] It has been postulated that inhaled furosemide acts indirectly on sensory receptors in the airway epithelium and its vicinity,[19] and an animal study has shown that SARs are sensitized by inhalation of furosemide.[16] Inhaled furosemide has been shown to improve experimentally induced dyspnoea.[20 21] As it is generally accepted that stimulation of SARs probably decreases the sensation of dyspnoea,[22] 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).[14 15] 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,[23] 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.[24] An animal study showed that inhaled furosemide not only sensitizes SARs but also it desensitizes RARs.[16] 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.[25 26] 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.[25 27 28] In contrast, the two groups of C-fibre receptors respond similarly to inhalation of volatile anaesthetics.[26]

Pulmonary congestion is a powerful stimulant of pulmonary C-fibre sensors,[29] 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 dyspnoeic sensation.[30] I.V. lobeline, a pulmonary C-fibre stimulant, causes short-latency noxious sensations in the larynx and chest. These sensations are different from the dyspnoeic sensation in normal control subjects and were not perceived in patients with bilateral lung transplant.[31] These findings suggest that a dyspnoeic 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 amyglada, 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 activation[49-51] and a similar area can be activated during nausea[52] and thirst.[53] Although the thalamus appears to be the pivotal part of the pathway relaying pain and dyspnoea and thalamocortical 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.[2] The rostral projections from brainstem respiratory motor neurones to the midbrain and thalamus[41 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 Howell[54] 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 breath-holding 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 studies[4 5 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 Howell[54] 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

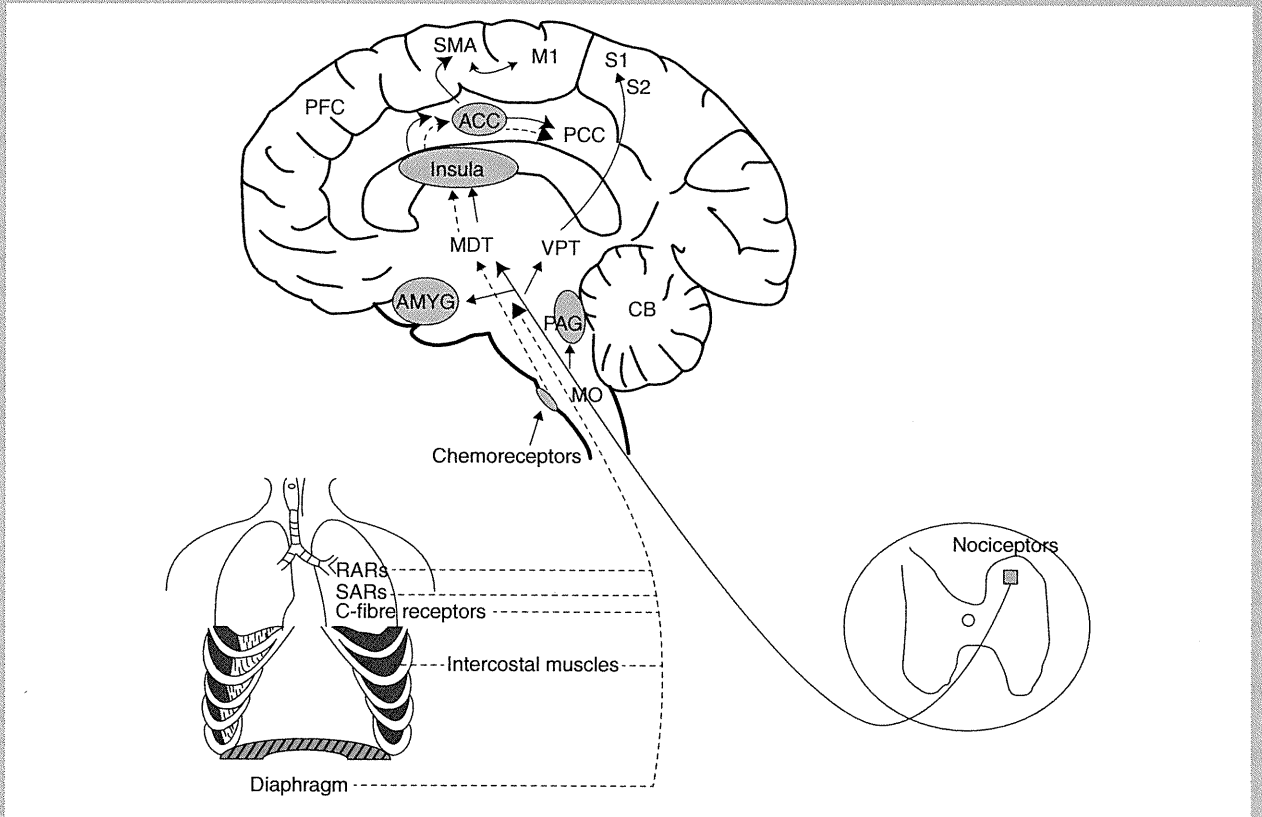

Fig 1 Schematic illustration of ascending pathways, subcortical structures, and cerebral cortical structures involved in processing of dyspnoea and pain. ACC, anterior cingulate cortex; AMYG, amygdala; CB, cerebellum; MDT, medial dorsal thalamus; MO, medulla oblongata; M1, primary motor cortex; PAG, periaqueductal grey; PCC, posterior cingulate cortex; PFC, prefrontal cortex; SMA, supplementary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPT, ventroposterior thalamus.

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.[66] A recent study[46] suggested that the right posterior cingulate cortex may be related to the affective dimension of dyspnoea induced by loaded breathing. However, more recently, a study[67] suggested that the unpleasantness of subjectively perceived dyspnoea may be processed in the right human anterior insula and amygdale. 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.[47] 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

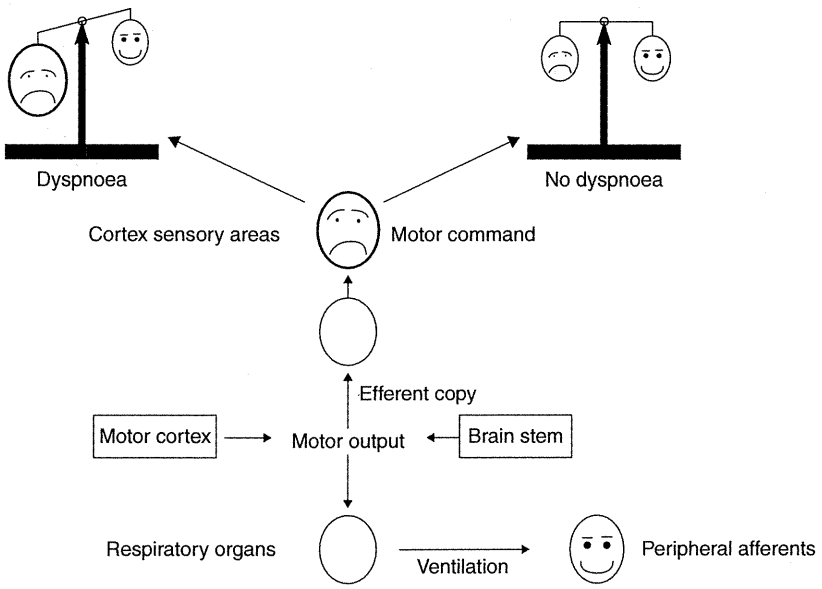

Fig 2 Motor command–afferent mismatch. Dyspnoea is the result of a dissociation between amplitudes of the central efferent discharge (motor output) and afferent sensory inputs (feedback) from peripheral mechanoreceptors.

Table 1 Quality of dyspnoea and the underlying mechanisms

Stimulation	Receptors	Quality
Hypercapnia	Central chemoreceptors	Air hunger
Hypoxia	Peripheral chemoreceptors	
Respiratory motor command	Central corollary discharge	Work/effort
Muscle contraction	Chest wall receptors	
Muscle fatigue	Muscle spindles	
Mechanical loads	Joint receptors	
	Tendon receptors	
	Metaboreceptors	
Bronchoconstriction	RARs, C-fibre receptors	Chest tightness
Lung inflation	SARs	Dyspnoea relief

subjective feelings rather than simply a role in processing of perceived unpleasantness.[74]

A study of patients with right-hemispheric insular lesions[69] 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[70] 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.[75]

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.[3 76–80] 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.[5 6] 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[81 82] or when the muscles are weakened by fatigue,[83] paralysis, or an increase in lung volume.[84] 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.[85] The results of induced bronchoconstriction in

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.[80] It is likely that simultaneous stimulation of different types of receptors interacts and causes qualitatively and quantitatively different effects on the sensation of dyspnoea.[86]

Like pain, dyspnoea is influenced not only by sensory input but also by non-sensory factors such as emotion and attention.[3 87–89] 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.[90] Several recent studies examined the influence of emotion and attention on the distinct dimensions of perceived dyspnoea.[64 91 92] 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.[64] It has also been reported that attention distraction reduces the affective but not the sensory dimension of perceived dyspnoea in healthy subjects[91] and in patients with chronic pulmonary disease (COPD).[92] 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.[93] 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

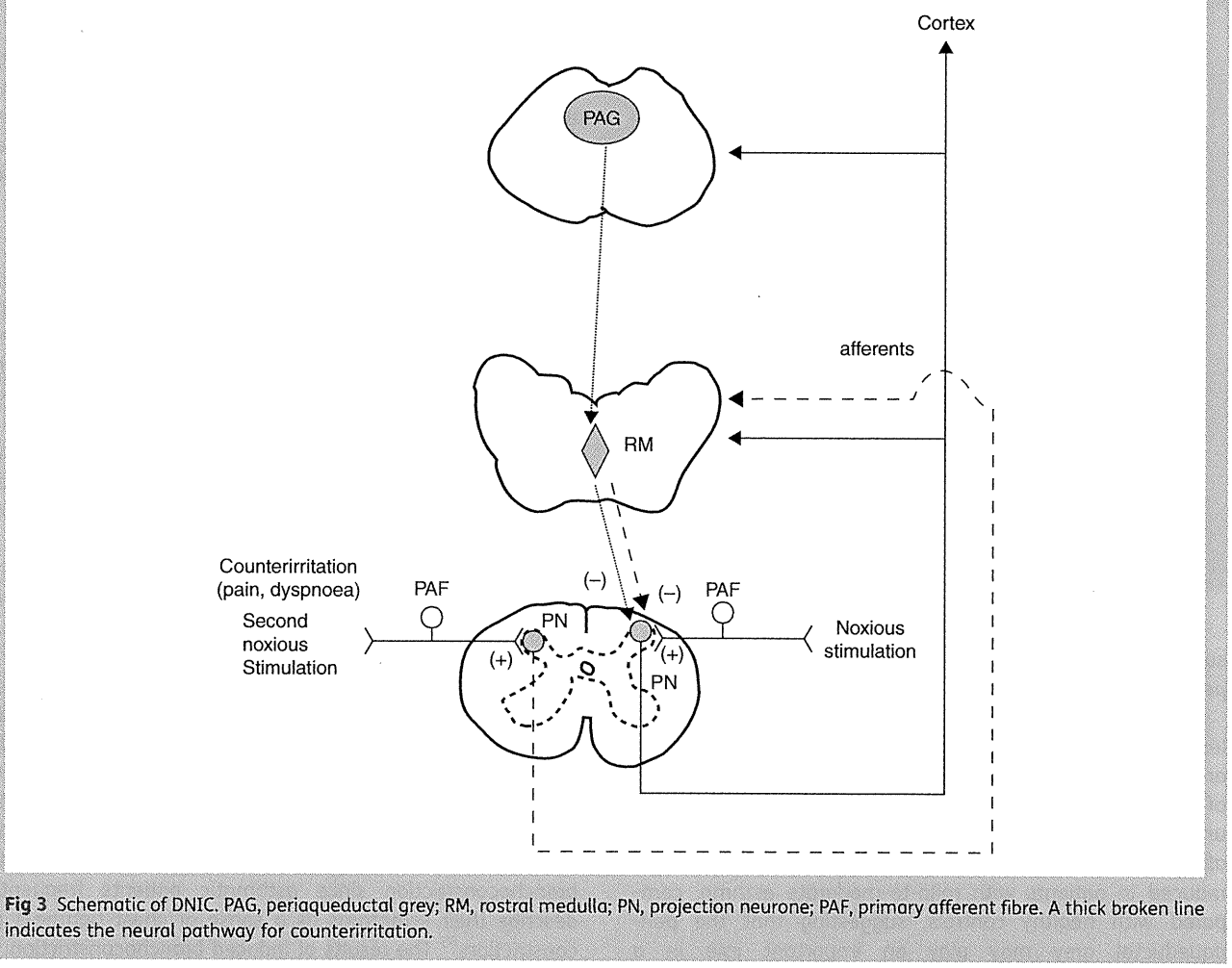

Fig 3 Schematic of DNIC. PAG, periaqueductal grey; RM, rostral medulla; PN, projection neurone; PAF, primary afferent fibre. A thick broken line indicates the neural pathway for counterirritation.

Table 2 Different quality of dyspnoea and its treatment

Quality of dyspnoea	Treatments	Specific pharmacological and non-pharmacological approaches
Air hunger	Decrease in ventilatory drive	Opioids, THAM, bicarbonate, oxygen
	Changes in perceptual sensitivity to sensation	Opioids, anxiolytics
	Alterations in vagal afferent information	Airway anaesthesia, vagal block, inhaled furosemide
Work/effort	Decrease in ventilatory drive	Opioids, THAM, bicarbonate, oxygen
	Alterations in afferent information from chest wall and respiratory muscles	Vibration
	Changes in perceptual sensitivity to sensation	Opioids, anxiolytics
Chest tightness	Alterations in vagal afferent information	Airway anaesthesia, vagal block, inhaled furosemide
	Changes in perceptual sensitivity to sensation	Opioid, anxiolytics

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 study[95] 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 bicarbonate[112] 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 study[114] 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

study[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[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 dyspnoeic 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,[119] it was also reported that the perception of dyspnoea in patients with interstitial pulmonary disease was not diminished by airway anaesthesia.[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[121 122] and in patients with COPD during exercise.[123 124] However, other reports have shown no beneficial effect in patients with cancer[125] and in patients with a previous exposure to sulphur mustard.[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.[127] However, chest wall vibration had little impact on dyspnoea during exercise in patients with COPD.[128] Furthermore, a recent study[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.[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.[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.[81 132] It has been reported that a low concentration of nitrous oxide relieves experimentally induced dyspnoea without changing respiratory load compensation.[133] Bronchodilators can reduce the resistive load in asthma or in patients with COPD who have reversible bronchoconstriction.[134] Corticosteroids will relieve dyspnoea by decreasing airway inflammation and oedema.[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.[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.

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Effects of different forms of dyspnoea on pain perception induced by cold-pressor test

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ABSTRACT

Although dyspnoea has been shown to attenuate pain, whether different forms of dyspnoea exert a similar inhibitory effect on pain has never been tested. We examined the effects of two different forms of dyspnoea, i.e., "air hunger" sensation (AIR HUNGER) and "work/effort" sensation (WORK/EFFORT), on pain induced by a cold-pressor test. Dyspnoea was induced by two different dyspnoea stimuli (i.e., AIR HUNGER and WORK/EFFORT stimuli) and the magnitudes of both sensations were evaluated by using a visual analogue scale (VAS). At equi-dyspneic VAS levels of two different forms of dyspnoea, pain was induced and the unpleasantness of pain was assessed by pain VAS, pain threshold time (PTT) and pain endurance time (PET). Both AIR HUNGER and WORK/EFFORT caused an increase in PTT and an increase in PET or a decrease in maximal pain VAS. Our findings suggest that AIR HUNGER and WORK/EFFORT exert a similar analgesic effect although the WORK/EFFORT-induced analgesia was slightly more effective.

1. Introduction

It has been shown that dyspnoea occasionally evokes analgesia (Nishino et al., 1999, 2008; Morélot-Panzini et al., 2007). The sensation of "air hunger" (AIR HUNGER) and the sensation of "work/effort" (WORK/EFFORT) are two qualitatively different sensations of dyspnoea (Lansing et al., 2000). Whether or not different types of dyspnoea differently interact with pain has not been fully explored. The study of Morélot-Panzini et al. (2007) not only clearly showed that the acute dyspnoea induced by an addition of inspiratory threshold loading, i.e., respiratory WORK/EFFORT, causes inhibition of the spinal nociceptive flexion reflex (RIII reflex) but also speculated that the inhibition of pain reflex might occur through a subcortical mechanism of diffuse noxious inhibitory controls (DNIC) (Le Bars et al., 1979a,b). The DNIC system involves a spinal–medullary–spinal feedback loop in which stimulation of Aδ- or C-fibers plays an important role (Bouhassira et al., 1987). Less is known of how another form of dyspnoea, i.e., AIR HUNGER, might affect pain sensation.

In generation of AIR HUNGER, an increase in activity of chemoreceptors together with a decreased activity of pulmonary stretch receptors plays a major role (Lansing et al., 2000) whereas the role of C-fiber stimulation from chest wall muscles and lungs may be negligible. Assuming that the DNIC might be the main mechanism of dyspnoea-evoked analgesia, AIR HUNGER stimulus would have little or no effect of producing analgesia, compared with the effect of excessive respiratory work or effort (Banzett et al., 2007; Morélot-Panzini et al., 2007). It is well known that human pain sensitivity varies widely between subjects, and several studies (Chen et al., 1989; Birklein et al., 2008; Nishino et al., 2010) showed that there are different groups of normal healthy subjects whose responses to cold pain stimulation can be easily dichotomized (i.e., pain-sensitive and pain-tolerant subjects). Although the differences in pain sensitivity may modulate the dyspnoea-induced analgesia, no information is available as to how the individual differences in pain sensitivity can affect the dyspnoea-induced analgesia. The aim of the present study was to compare the effects of two different forms of dyspnoea on pain perception induced by cold pressure test in pain-sensitive and pain-tolerant subjects.

2. Materials and methods

2.1. Subjects

The study protocol was approved by the Institutional Ethical Committee of Chiba University (Chiba, Japan), which conforms to the standard set by the Declaration of Helsinki (2008) of the World Medical Association. Studies were carried out in 45 young healthy male subjects whose ages ranged from 22 to 30 yr. None had clinical evidence of respiratory, cardiovascular, neurological or neuromuscular disorders. Each subject gave informed consent to the methodology of the study. None was a smoker or was aware of

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the hypothesis tested in the studies. Mean heights and weights of the subjects were 172.4. ± 6.2 cm and 67.6 ± 9.7 kg (mean ± SD).

2.2. Instruments

The subjects were tested in the sitting posture in an air-conditioned, temperature (24–25 °C) controlled room. They breathed through an experimental apparatus containing a face mask, a pneumotachograph, and a one-way valve system. The experimental apparatus had a resistance of 2.5 cm H_2O/l/s and the total apparatus dead space was 140 ml. Ventilatory airflow was measured with the pneumotachograph (HI201, Nihon Kohden, Tokyo, Japan), and tidal volume (V_T) was obtained by electrical integration of the inspired flow signal. Mask pressure (P_{mask}) was measured with a pressure transducer (Transpac IV; Abbott Critical Care Systems, Chicago, IL). End-tidal carbon dioxide tension (P_{ETCO_2}) and end-tidal oxygen partial pressure (P_{ETO_2}) was measured with an infrared CO_2 analyzer and a polarographic O_2 analyzer, respectively (NEC-Sanei-1H21A, Tokyo, Japan) through a port in the face mask.

Skin temperature was measured using a temperature sensor (Mon-a-therm Skin Probe, Tyco Healthcare Group LP, Tokyo, Japan) taped securely on the back of the subject's left foot.

The degrees of pain and dyspnoea were continuously rated by using visual analogue scales (VAS) which consisted of a horizontal 10 cm line with equally spaced markers. The subject could control the position of the knob of the linear potentiometer along this line.

2.3. Induction of dyspnoea and pain

While the subject was breathing through the respiratory circuit in which an extra dead space of 300 ml was incorporated, dyspnoea was induced by two different dyspnoea stimuli, i.e., (1) relative hypopnea against the increased respiratory dead space and (2) hyperpnea against inspiratory-flow-resistive loading. The unpleasant sensation felt during relative hypopnea was designated AIR HUNGER and the subject was asked to rate the magnitude of this sensation by using a 10-cm visual analogue scales (air hunger VAS). The numerical value of zero indicated "no discomfort at all", 100 indicated a sensation that was "intolerable discomfort". During the experiments the subject was asked to breathe at fixed rate of 15/min set by a metronome while the subject's tidal breath was displayed as a line on the oscilloscope.

The AIR HUNGER stimulus was started by maintaining or gradually decreasing the tidal volume until the target air hunger VAS reached the approximate value of 70. Once the target value of air hunger VAS was attained, the subject was asked to keep this level of tidal volume as a new tidal volume target while the new target line for tidal volume was drawn on the screen of oscilloscope.

During hyperpnea stimulus, flow resistive loading was imposed by placing plastic tube resistors (3.5 mm in diameter and 10 cm in length with a resistance of 60 cm H_2O/l/s at a flow rate of 0.5 l/s) in inspiratory limb of the one-way valve system. Each subject was asked to sense the effort or work he was expending with his breathing muscles to inflate his chest. The sensation felt during hyperpnea was designated WORK/EFFORT and the subject was asked how hard it is to breathe and to rate the intensity of this sensation by using a 10-cm visual analogue scale (work/effort VAS). The numerical value of zero indicated "felt none", 100 indicated a sensation that was "maximum imaginable". In order to differentiate clearly this sensation of WORK/EFFORT from the above-mentioned AIR HUNGER sensation, the concepts of AIR HUNGER and WORK/EFFORT were explained according to the standard script employed in previous studies (Moosavi et al., 2000; Lansing et al., 2000). We also commented that in contrast to AIR HUNGER, the sensation you were feeling during hyperpnea against the flow-resistive loading might not be necessarily uncomfortable. The subject was asked to gradually increase his tidal volume against resistive loading until the target work/effort VAS reached the approximate value of 70, and when the target value of work/effort VAS was obtained, the subject was asked to maintain this level of tidal volume as a new target tidal volume. After the initiation of dyspnoea stimuli, it took usually 3–5 min for breathing patterns and VAS values to stabilize.

Pain was induced by a cold-pressor test. The left foot of each subject was immersed up to the malleolus of ankle in the iced water container (Foot Bub Jet MCR-3600, ALINCO Co., Tokyo, Japan). Local skin adaptation was prevented by stirring and bubbling the ice water (0–1 °C). The subject was asked to keep his foot in the ice water as long as possible, or to the cut-off limit of 2 min was reached. During the immersion of the left foot in the iced cold water, the subject was asked to concentrate his attention on pain sensation and to rate continuously the unpleasantness of pain by using a 10-cm visual analogue scale (pain VAS). The numerical value of zero indicated "no discomfort at all", 100 indicated a sensation that was "intolerable discomfort". The continuous pain VAS ratings were conducted by manipulating the linear potentiometer.

Immediately after the completion of cold water test run, all the subjects put their feet into the warm water box (38 °C).

2.4. Experimental protocol

The subjects were given a short training period to accustom them to the use of the VAS both for pain and dyspnoea. During this training period, the subjects were screened for cold pain tolerance by immersing their hands into the iced water. If the subjects retracted their hands immediately or claimed excruciating pain, they were pain-sensitive candidates (n = 25), and if they reported only light to moderate pain during a 1-min of the immersion of their hands in the ice-water, they were pain-tolerant candidates (n = 20).

After the screening test, the subjects started to breathe through the respiratory circuit with or without the extra dead space. The distal limb of experimental apparatus was connected to a T-Piece system supplied with 100% oxygen (2–3 l/min).

When a stable test condition was obtained, in each subject the cold pressor test was performed under three test conditions, i.e., control, AIR HUNGER, and WORK/EFFORT, in a randomized order with an interval of 10–15 min. During the control condition, the subject was asked to breathe through the respiratory circuit without the extra dead space at the fixed rate of 15/min but no target tidal volume was given. During the AIR HUNGER and WORK/EFFORT runs, the subject was asked to maintain the target tidal volume at the fixed respiratory rate of 15/min while breathing through the respiratory circuit with the extra dead space.

2.5. Data analysis

Pain threshold time (PTT) was defined as the time from immersion of the foot in the ice water to the onset of pain sensation. Pain endurance time (PET) was the duration from the ice water immersion of subject's foot until the withdrawal of the foot. The subjects who withdrew their feet before the cut-off time was designated "pain-sensitive". PET was measured in pain-sensitive subjects. When the subject reaches the cut-off time of 2 min, the subject was designated "pain-tolerant" and the maximal value of pain VAS before the cut-off time was obtained.

A sample size calculation was based on the results of our previous study (Nishino et al., 2010) in which the mean values of PTT were 12.2 ± 5.8 s (mean ± SD) in pain-tolerant group. A minimum difference in PTT means of 6 s was considered necessary. Thus for a two-side, 0.05 level of significance test with at least 80% power, the

sample size of at least 19 would be necessary to detect a statistically significant result in each of two groups.

Values of respiratory variables during the control condition, AIR HUNGER, and WORK/EFFORT were obtained from 1-min recording before the start of the cold pressor test. Minute ventilation (V_I) is defined as the product of V_T and respiratory frequency. The peak negative mask pressure, defined as the peak inspiratory airway pressure (P_{max}), was also obtained. The data were expressed as median[interquartile range], and statistical analysis was performed by non-parametric tests (Friedman's repeated measures of ANOVA followed by Student–Newman–Keuls test and Mann–Whitney rank sum test). The association between two variables representing pain threshold and tolerance was quantified by using the Pearson product moment-correlation test. All analyses were performed with the statistical package SigmaStat (SigmaStat 3.0, SPSS Inc., Chicago, IL) and Primer of Biostatistics (McGraw Hill Medical, Ver. 6.0, Blacklick, OH). $P < 0.05$ was considered significant.

3. Results

As expected from our previous investigation (Nishino et al., 2010), a clear-cut dichotomy of pain responses to cold-pressor test was observed. Of 45 subjects, two subjects (pain-sensitive candidates) could not tolerate the hypopnea-induced dyspnoea and one subject (pain-tolerant candidates) could not tolerate the hyperpnea-induced dyspnoea, and they dropped out of the experimental protocol. All the other subjects completed the experimental protocol and thus the experimental data were obtained from 23 pain-sensitive subjects and 19 pain-tolerant subjects.

3.1. Breathing information

In all subjects the values of P_{ETO_2} were always above 150 mm Hg and no evidence of hypoxemia was observed during the experiments. Information as to changes in ventilatory variables is listed in Table 1. Although the values of V_T, V_I, and P_{max} were much higher whereas the values of P_{ETCO_2} were much lower during WORK/EFFORT than those during AIR HUNGER, the values of dyspnoea VAS during WORK/EFFORT are almost the same to those during AIR HUNGER. This indicates that two different forms of dyspnoea matched in terms of magnitude of sensation. The changes in ventilatory variables are essentially similar both in pain-sensitive subjects and pain-tolerant subjects.

3.2. Representative tracing

Fig. 1 shows a typical example of experimental records obtained in a pain-sensitive subject under three different breathing conditions (a: control; b: AIR HUNGER; c: WORK/EFFORT). Compared with the control, both AIR HUNGER and WORK/EFFORT delayed the start and rise of pain VAS in response to cold stimulation, indicating the inhibitory effect of these different forms of dyspnoea on pain perception. Similar pain responses during AIR HUNGER and WORK/EFFORT were observed in pain-tolerant subjects who tolerated the cold-pressor test for the whole 2 min (Fig. 2).

3.3. Pain threshold and pain tolerance

Specific information regarding pain threshold and tolerance in the two groups during pain-induced tests is listed in Table 2. In response to immersion of the subjects' feet into the ice-water container during the control condition, all subjects started to feel pain within 20 s. In the pain-tolerant subjects, the values of PTT during both AIR HUNGER and WORK/EFFORT were significantly longer than those during the control, and the maximal pain VAS values during AIR HUNGER and WORK/EFFORT were significantly lower than those during the control. Similarly, the values of PTT and PET were significantly longer during both AIR HUNGER and WORK/EFFORT than those during the control in the pain-sensitive subjects. However, in the pain-sensitive subjects the PTT and PET values during WORK/EFFORT were significantly longer than those during AIR HUNGER ($P < 0.05$), suggesting that the dyspnoea-induced analgesia may be slightly more effective during WORK/EFFORT in this group of subjects..

3.4. Relationship of changes in pain variables during hypopnea vs. during hyperpnea

The ΔPTT (increase in PTT = PTT during dyspnoea minus PTT during control) during AIR HUNGER were significantly correlated with ΔPTT during WORK/EFFORT in the pain-sensitive subjects (Fig. 3a) whereas there was no significant correlation between ΔPTT during AIR HUNGER and ΔPTT during WORK/EFFORT in the pain-tolerant subjects (Fig. 3b). In addition, comparison of slopes of these two regression lines showed that there is a significant difference ($P < 0.05$) between the slopes of two regression lines. It is also appreciated that the values of ΔPTT during AIR HUNGER are distributed in a wider range, compared with the values of ΔPTT during WORK/EFFORT.

Fig. 4 shows the relationship between the ΔPET values (increases in PET = PET during dyspnoea minus PET during control) during AIR HUNGER and the ΔPET values during WORK/EFFORT in the pain-sensitive subjects (Fig. 4a), and the relationship between Δpain VAS values (decreases in maximal pain VAS) during AIR HUNGER and the Δpain VAS values during WORK/EFFORT in the pain-tolerant subjects (Fig. 4b). There were significant relationships ($P < 0.01$) between ΔPET during AIR HUNGER vs. ΔPET during WORK/EFFORT, and Δpain VAS during AIR HUNGER vs. and Δpain VAS during WORK/EFFORT.

4. Discussion

4.1. Major findings

Our study demonstrated that both AIR HUNGER and WORK/EFFORT similarly exert an inhibitory influence on cold-pressor-induced pain. This finding is compatible with the observation of our previous study (Nishino et al., 2008) in which we showed that dyspnoea produced by the combination of hypercapnia and elastic respiratory loading causes an increase in thermal pain threshold in male subjects. Few studies have investigated the effect of different forms of dyspnoea on pain, and the study of Morélot-Panzini et al. (2007) is the only study comparable with the present study. However, our present study used a different pain stimulus, different dyspnoea stimuli, and a very different outcome measure from Morélot-Panzini et al. (2007), and thus, a simple comparison between the two studies may not entirely valid.

Our finding that WORK/EFFORT attenuated the cold-pressor-induced pain is in agreement with the finding of Morélot-Panzini et al. (2007) who showed that dyspnoea induced by inspiratory threshold loading inhibits the RIII reflex.

Morélot-Panzini et al. (2007) speculated that WORK/EFFORT types of dyspnoea, like pain, might induce counterirritation while causing a stimulation of C-fibers in respiratory muscles and/or lungs, and thereby might trigger endogenous analgesic mechanisms at the subcortical level through the activation of DNIC (Le Bars et al., 1979a,b) to project onto spinal dorsal horn interneurons. The stimulation of C-fibers triggers DNIC and the DNIC system involves a spino-bulbo-spinal feedback loop in which the subnucleus reticularis dorsalis (SRD) in the caudal medulla plays a key

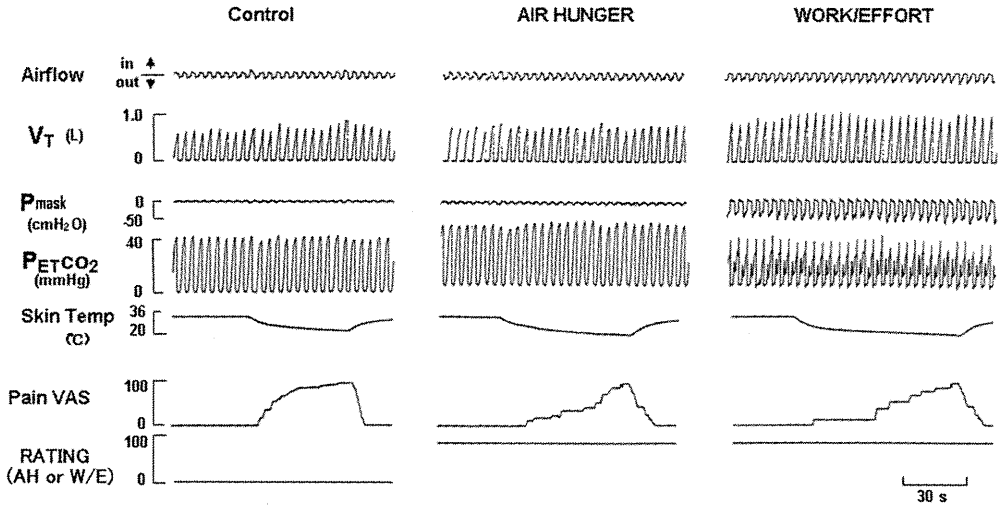

Fig. 1. Experimental record illustrating the effect of dyspnoea on pain perception in a pain-sensitive subject. V_T = tidal volume; P_{mask} = mask pressure; P_{ETCO_2} = end-tidal CO_2 partial pressure; AH = AIR HUNGER; W/E = WORK/EFFORT. Note that VAS ratings of AIR HUNGER and WORK/EFFORT during the cold-pressor test might not precisely reflect the actual measured values since the subject was asked to concentrate his attention exclusively on pain perception.

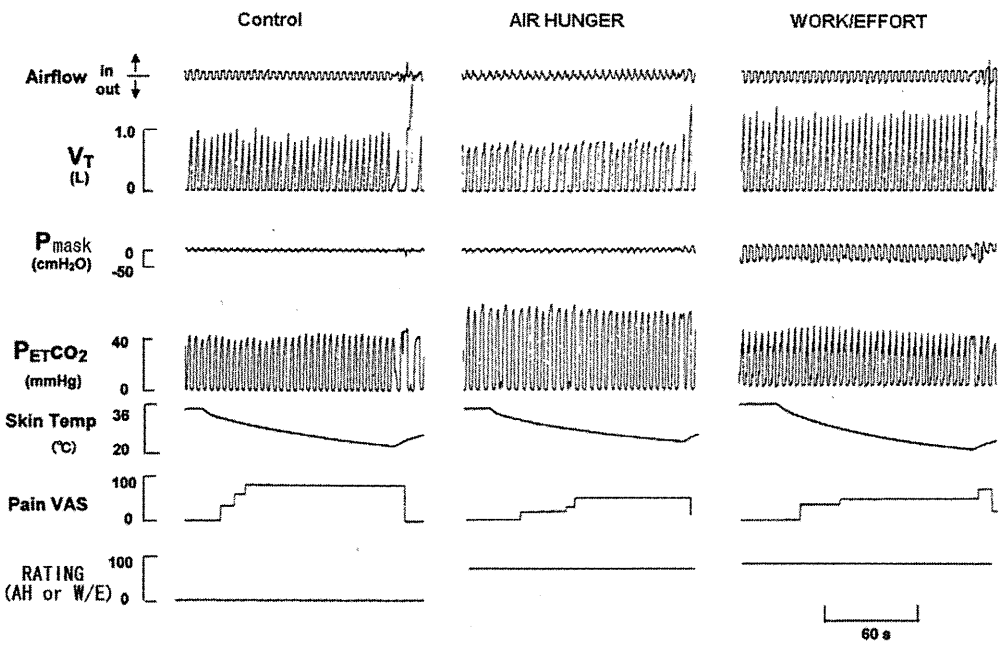

Fig. 2. Experimental record illustrating the effect of dyspnoea on pain perception in a pain-tolerant subject. See legend of Fig. 1 for definition of abbreviations.

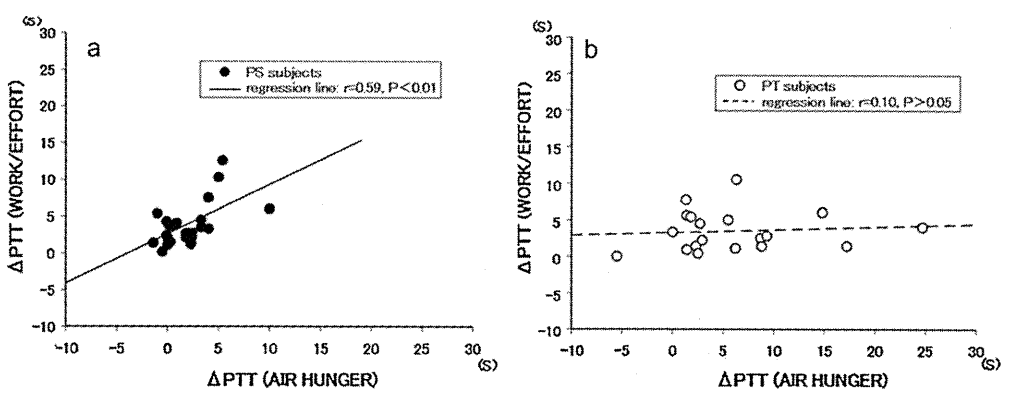

Fig. 3. Relationships of ΔPTT during AIR HUNGER and ΔPTT during WORK/EFFORT. (a) pain-sensitive subjects; (b) pain-tolerant subjects.

Table 1
changes in respiratory variables during cold-pressor tests.

	Control	AIR HUNGER	WORK/EFFORT
Total subjects ($n=42$)			
(Breathing variables)			
V_T (l)	0.64[0.60–0.69]	0.68[0.62–0.76]	1.07[0.99–1.26]*,#
RF (bpm)	15.0[14.8–15.2]	15.0[14.7–15.1]	14.8[14.7–15.0]
V_I (l/min)	9.6[9.0–10.6]	10.0[9.4–11.4]	16.1[14.6–18.3]*,#
P_{ETCO_2} (mm Hg)	41.0[39.1–42.0]	52.4[49.2–55.9]*	43.9[42.2–45.6]*,#
P_{max} (cm H_2O)	Not measured	3.0[2.0–3.5]	33.1[27.4–43.1]#
VAS rating	0	69.2[63.8–72.0]*	65.2[62.0–70.5]*
Pain-tolerant subjects ($n=19$)			
(Breathing variables)			
V_T (l)	0.67[0.60–0.72]	0.71[0.67–0.79]	1.12[0.99–1.30]*,#
RF (bpm)	15.0[14.8–15.2]	15.0[14.7–15.2]	14.8[14.6–15.1]
V_I (l/min)	10.0[9.1–10.9]	10.7[9.8–11.9]	16.6[14.6–19.2]*,#
P_{ETCO_2} (mm Hg)	40.7[38.8–42.0]	51.6[48.8–53.4]*	44.1[40.6–45.9]*,#
P_{max} (cm H_2O)	not measured	3.0[2.2–3.9]	36.6[29.2–45.2]#
VAS rating	0	69.6[66.5–73.0]*	64.8[62.3–69.5]*
Pain-sensitive subjects ($n=23$)			
(Breathing variables)			
V_T (l)	0.63[0.59–0.68]	0.64[0.59–0.71]	1.05[0.98–1.20]*,#
RF (bpm)	15.0[14.8–15.2]	14.9[14.6–15.1]	14.8[14.7–15.0]
V_I (l/min)	9.5[8.8–10.2]	9.5[8.7–10.7]	15.4[14.3–17.7]*,#
P_{ETCO_2} (mm Hg)	41.4[39.7–42.5]	55.1[50.6–56.2]*	43.7[42.6–45.6]*,#
P_{max} (cm H_2O)	not measured	2.9[1.9–3.4]	32.0[26.8–41.6]#
VAS rating	0	68.2[61.4–71.3]*	66.6[61.6–71.5]*

* $P<0.01$, compared with the values during control.
# $P<0.01$, compared with the values during AIR HUNGER.

Table 2
Changes in pain variables during cold-pressor tests.

	Control	AIR HUNGER	WORK/EFFORT
Pain-tolerant subjects ($n=19$)			
PTT (s)	8.8[6.4–12.2]	13.6[10.2–20.9]*	12.5[8.6–14.7]*
PET (s)	120	120	120
Pain VAS	77.3[66.0–83.6]	68.6[54.7–75.7]*	65.7[44.3–74.8]*
Pain sensitive subjects ($n=23$)			
PTT (s)	4.0[3.0–4.9]	6.0[3.4–7.7]*	7.0[5.9–9.4]*,#
PET (s)	28.0[20.3–45.4]	36.0[22.1–72.6]*	48.9[30.7–63.5]*,#
Pain VAS	100	100	100

* $P<0.01$, compared with the values during control.
# $P<0.05$, compared with the values during AIR HUNGER.

role in transmission and modulation of pain (Villanueva and Le Bars, 1995). Unlike the dyspneic stimuli that cause WORK/EFFORT, dyspneic stimuli that cause AIR HUNGER do not appear to involve C-fiber activation since AIR HUNGER can be generated even without the chest wall movement and/or respiratory muscle movement (Banzett et al., 1989, 1990). Our finding that AIR HUNGER causes dyspnoea-induced analgesia suggests that the activation of Aδ- and/or C-fibers may not be essential to inhibition of pain perception during dyspnoea and that DNIC may not be the sole mechanism of dyspnoea-evoked analgesia. Indeed, the preliminary observation made by Morélot-Panzini et al. (2007) showed that the AIR HUNGER type of dyspnoea did not cause inhibition of the RIII reflex, indicating that AIR HUNGER type of dyspnoea might not evoke analgesia at a spinal level.

Putting all these pieces of information together, it is likely that AIR HUNGER reduces pain at the perceptual level, while WORK/EFFORT reduces pain at the subcortical spinal level.

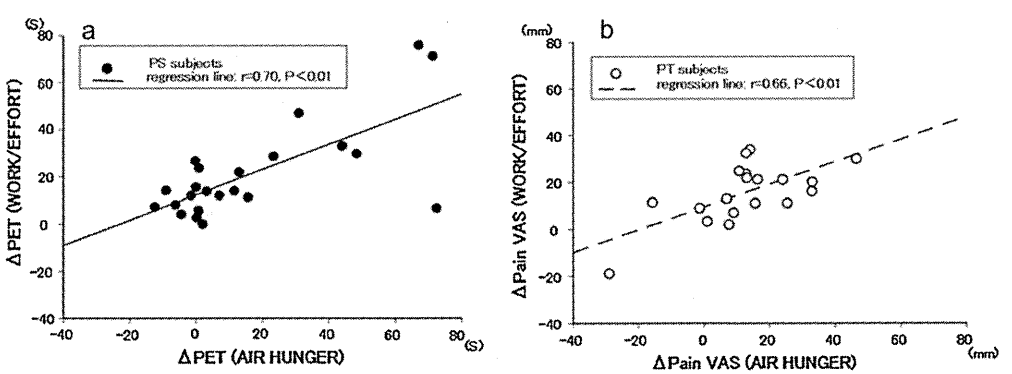

Fig. 4. Relationships of ΔPET during AIR HUNGER vs. ΔPET during WORK/EFFORT and Δpain VAS during AIR HUNGER vs. Δpain VAS during WORK/EFFORT. (a) pain-sensitive subjects; (b) pain-tolerant subjects.

4.2. Possible mechanisms of pain inhibition by work/effort and air hunger

In our experiments, AIR HUNGER was induced mainly by hypercapnia whereas WORK/EFFORT was induced mainly by hyperpnea against inspiratory-flow-resistive loading. The methodology used in our study fits with a recent theory of dyspnoea which postulates that dyspnoea, whether it is AIR HUNGER or WORK/EFFORT, is the result of the dissociation between central ventilatory drive and afferent sensory inputs from the peripheral mechanoreceptors (O'Donnell et al., 2009).

It has been shown that hypercapnia can produce significant changes in heat pain thresholds in humans (Grönroos and Pertovaara, 1994), probably due to a mechanism involving release of endogenous opioids (Gamble and Milne, 1990). However, it is not clear whether the release of endogenous opioids is due to the direct effect of hypercapnia or due to the indirect effect of AIR HUNGER. The results of human studies also suggest the elaboration of endogenous opioids in the presence of severe respiratory stress with flow-resistive loading (Akiyama et al., 1993; Santiago et al., 1981). Thus, it may be possible that endogenous opioids can be released during AIR HUNGER as well as WORK/EFFORT and that the released endogenous opioids can contribute to production of analgesia though an activation of central opioidergic system, although the exact location of its action is unknown.

Obviously, pain inhibition during dyspnoea, particularly AIR HUNGER type of dyspnoea, cannot be explained exclusively by the mechanisms of DNIC in which the important role of serotonergic mechanisms is implicated (Chitour et al., 1982; Sandrini et al., 1993).

Our results showed that WORK/EFFORT produces a slightly stronger analgesic effect than AIR HUNGER in the pain-sensitive subjects whereas no such observation was obtained in the pain-tolerance subjects. Thus, it is conceivable that the DNIC system may play more vital role in dyspnoea-induced analgesia in the pain-sensitive subjects than in the pain-tolerant subjects.

A detailed analysis of our data revealed that the effects of WORK/EFFORT on cold-pressor-induced pain were not completely identical to those of AIR HUNGER. For example, the ΔPTT values during AIR HUNGER are distributed in a wider range than the ΔPTT values during WORK/EFFORT. In addition, AIR HUNGER caused shortening rather than prolongation of PTT and PET in some subjects. Furthermore, the relationship between the ΔPTT during AIR HUNGER vs. the ΔPTT during WORK/EFFORT was less robust in the pain-tolerant subjects than the pain-sensitive subjects. This lack of correlation between the ΔPTT during AIR HUNGER vs. the ΔPTT during WORK/EFFORT in the pain-tolerant subjects may indicate that the analgesic effects of AIR HUNGER and WORK/EFFORT do not always parallel and supports the notion that the two different forms of dyspnoea exert the analgesic effect through different neural pathways.

4.3. Limitation of the study

In this study we intended to produce two different sensations with two different dyspnoea stimuli. All the subjects stated that they understood the definitions of AIR HUNGER and WORK/EFFORT in the training period. However, we did not debrief the subjects on the sensations they felt during the application of different dyspnoea stimuli after each experimental session. Therefore, we cannot exclude completely the possibility that some subjects could not distinguish a clear qualitative difference in the sensations of AIR HUNGER and WORK/EFFORT.

The cold-pressor test to induce pain employed in this study is a close analogue for many types of naturally occurring pain (Chen et al., 1989) and has the advantage of being widely used and safe. However, this test has a methodological disadvantage of ceiling effect. In fact, in our study a considerable number of subjects are pain-tolerant and the true tolerance time was unknown for these subjects. Since this ceiling effect reduces the effectiveness of data analysis, we had to use the values of maximal pain VAS instead of PET to examine the effects of dyspnoea on pain tolerance in the pain-tolerant subjects. However, the finding that in the pain-tolerant subjects the relationships between the values of ΔPET during AIR HUNGER and WORK/EFFORT is similar to the relationship between the values of Δpain VAS during AIR HUNGER and WORK/EFFORT suggest that the maximal pain VAS may be a useful measure of pain tolerance. Our study was performed only in young healthy men while women were excluded to avoid the interference by sex difference in the effect of dyspnoea on pain (Nishino et al., 2008). Thus, it is clear that a simple extrapolation of our results to other sex or other age ranges, or the clinical situations may not be valid.

In conclusion, a similar inhibition of pain perception was observed during both AIR HUNGER and WORK/EFFORT and it seems that C-fiber stimulation induced by the act of breathing may not be essential to the dyspnoea-induced analgesia.

Conflict of interest

The authors state that there are no conflicts of interest regarding this work.

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