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Hypobaric hypoxia
is not a direct dyspnoegenic factor
in healthy individuals at rest
(低圧低酸素は、安静時健常人の
呼吸困難の直接の原因とはならない)

指導 岩崎 正之 教授

東海大学大学院医学研究科

先端医科学専攻

中野 隆之

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Summary

Dyspnea is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”. Dyspnea is one of the most common complaints in patients with pulmonary disease. Not only patients, but also healthy people, can experience dyspnea. Despite its commonness, the exact mechanisms underlying dyspnea have not been fully elucidated. It is believed that hypoxia causes dyspnea, but whether hypoxia is a direct dyspnogenic factor remains uncertain in the previous studies. We investigated whether hypoxia has a direct dyspnogenic effect. We evaluated changes in vital signs, arterial blood gases, SaO₂, CaO₂, Borg scale score, and Mini-Mental State Examination score in seven mountain climbers at rest, by using a hypobaric hypoxic chamber in which the barometric pressure was lowered to the simulated altitude of 4500 m. PaO₂ and CaO₂ both decreased significantly as the simulated altitude increased. On the other hand, the Borg scale score, which reflects dyspnea, showed no significant difference. At a simulated altitude of 4500 m, the Borg scale score was 1.5 ± 1.2 (mean $\pm$ SD), despite the presence of absolute hypoxia (PaO₂, 46.8 ± 8.3 Torr; CaO₂, 16.4 ± 0.6 mL/dL). The MMSE score was 29.3 ± 0.8 , and the participants were judged as having no cognitive impairment. These results suggest that hypoxia is not a direct dyspnogenic factor in healthy individuals capable of breathing without restriction at rest.

Background and Introduction

1) Definition of dyspnea

Dyspnea is one of the most common complaints in patients with pulmonary disease. Not

only patients, but also healthy people without pulmonary disease, can experience dyspnea. Despite its commonness, the exact mechanisms underlying dyspnea have not been fully elucidated. Dyspnea is a subjective symptom that pertains to difficulty in breathing and discomfort associated with breathing. The American Thoracic Society defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”. Since dyspnea is a subjective symptom, it can be described only by the person who is experiencing it. Therefore, evaluation of dyspnea is difficult, except in humans in awaking state. Moreover, dyspnea comprises multiple complex sensations expressed by diverse words, such as “respiratory effort”, “air hunger”, and “tightness”, and involves multiple pathophysiological mechanisms, rather than a single mechanism. These factors complicate the study of dyspnea.

2) Qualities of dyspnea

Simon et al. conducted a study in which dyspnea was induced by different stimuli, including “breath holding”, “CO₂ inhalation”, and “exercise” in individuals who were then instructed to select descriptors that matched their experience of dyspnea from a randomly compiled list. In this way, these investigators statistically demonstrated the diversity of dyspnea symptoms and reported an association between certain descriptor groups and these stimuli. Their study showed that dyspnea involves various uncomfortable respiratory sensations and that different qualities of dyspnea may be mediated by different mechanisms. “Work/effort”, “air hunger/unsatisfied inspiration”, and “tightness” are commonly accepted characteristic qualities of dyspnea.

3) Receptors related to the onset of dyspnea

The mechanisms and pathways involved in dyspnea remain unclear, but it is generally accepted that the onset of dyspnea involves peripheral and central chemoreceptors, which detect changes in blood gases, as well as mechanoreceptors in the chest wall, lungs, and

upper airway, and central receptors, which detect the output of respiratory motions to the respiratory muscle (motor command).

Peripheral chemoreceptors are located in the carotid body and aortic body, and respond to changes in arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide (PaCO_2), and pH. Central chemoreceptors are located in the medulla oblongata, and respond to changes in PaCO_2 and pH. These chemoreceptors detect changes in arterial blood gases that reflect the result of ventilation. Information about blood gases obtained via chemoreceptors is sent to the respiratory center, resulting in formation of a corresponding motor command. By means of this feedback control, respiratory rate and tidal volume are adjusted reflexively so that blood gas may be maintained at suitable levels. In a hypoxic environment, ventilation is increased. In humans, this hypoxic ventilatory response depends completely on peripheral chemoreceptors, particularly the carotid body, and it is known that patients with bilateral carotid body resection lose the hypoxic ventilatory response. However, it is uncertain whether stimulation of peripheral chemoreceptors by hypoxia can directly generate dyspnea.

Muscle spindles and tendon organs in the chest wall act as mechanoreceptors, and sense muscle force, tension, and contraction. To investigate the role of these mechanoreceptors, studies of chest wall vibration have been performed. It has been reported that in-phase vibration (i.e., inspiratory intercostal muscles vibrated during inspiration and expiratory intercostal muscles vibrated during expiration) decreases dyspnea, whereas out-of-phase vibration (i.e., inspiratory intercostal muscles vibrated during expiration and expiratory intercostal muscles vibrated during inspiration) increases dyspnea.

Lung receptors consist of slowly adapting pulmonary stretch receptors, rapidly adapting pulmonary stretch receptors (or so-called irritant receptors), and C-fibers. Slowly adapting pulmonary stretch receptors are located in the smooth muscles of the large, central airways, and respond to lung inflation. Stimulation of these receptors decreases respiratory rate due to an increase in expiratory time, and mediates the Hering-Breuer inflation reflex.

Rapidly adapting pulmonary stretch receptors are located in the airway epithelium, and respond to both mechanical and chemical stimuli, including inhaled gaseous and particulate irritants, direct mechanical stimuli, pulmonary congestion, and histamine. Stimulation of these receptors causes cough and bronchoconstriction. C-fibers are unmyelinated afferent nerve fibers located within the alveolar septa in juxtaposition to the pulmonary capillaries of the lung, and respond to mechanical stimuli such as pulmonary edema, embolism, and congestive heart failure, and to chemical stimuli such as bradykinin and serotonin. Stimulation of C-fibers induces rapid and shallow breathing. Sensory information arising from these lung receptors is transmitted by the vagal nerves to the brainstem. Previous studies have shown that vagal nerve blockade or section decreases dyspnea, and inhaled furosemide suppresses the activity of rapidly adapting pulmonary stretch receptors and decreases dyspnea.

Upper airway receptors respond to mechanical and chemical stimuli. Nishino et al. reported that stimulation of the cold receptors in the upper airway by nasal inhalation of *L*-menthol reduces dyspnea. It is commonly found that patients who suffer from dyspnea experience relief when they sit near an open window and breathe cold air, which could be due to the effects of upper airway cold receptors.

A copy of the motor command is sent to the central receptor as a corollary discharge, and is projected to the perceptual areas in the cerebral cortex through this central receptor. The respiratory motor system has both automatic/non-voluntary (brainstem) and voluntary (cortical) sources of motor command, and corollary discharges from these different sources generate dyspnea with different qualities.

4) Mechanisms of dyspnea

From the 1960s through the 1980s, the sense of respiratory “work/effort” was widely believed to be responsible for all dyspnea; however, that concept was disproved by studies indicating that air hunger could be perceived in the absence of respiratory work. This

uncomfortable sensation may be caused by an excessive impedance to breathing (high airway resistance and stiff lungs or chest wall) or respiratory muscle weakness. This is commonly experienced by patients with asthma or chronic obstructive pulmonary disease. Today, it is known that the perception of work/effort may arise through not only mechanoreceptors in the respiratory muscles, but also through corollary discharge. Corollary discharge, as a copy of the motor command, could be sensed as work/effort. Mechanoreceptors in the respiratory muscles, which provide feedback to the central nervous system about muscle force and tension, could modify this sense.

“Air hunger/unsatisfied inspiration” could be induced by a mismatch between the motor command and the achieved ventilation. Information from various afferent sources, such as chemoreceptors, is sent to the brainstem to set the demand for ventilation so as to match metabolic need. This motor command is conveyed to the cerebral cortex as a corollary discharge. On the other hand, mechanoreceptors in the chest wall, lungs, and airway provide afferent feedback information about the achieved ventilation. When this does not match the motor command, it results in a perception of air hunger. In contrast, increased voluntary motor command from the cerebral cortex mainly causes a work/effort perception, which is not as unpleasant as that of air hunger.

“Tightness” is relatively specific for bronchoconstriction. In the study by Moy et al. , during methacholine-induced bronchoconstriction, patients with asthma perceived tightness, but when breathing against external resistors, they rather had a sense of work/effort. Tightness is experienced in the early stages of an asthma attack, but as airway resistance increases, work/effort perception also arises. Binks et al. reported that work/effort is significantly reduced by mechanical ventilation, although tightness remains unchanged.

Thus, different distinguishable sensations of dyspnea are mediated by different mechanisms. Nevertheless, these different sensations rarely arise as individual perceptions in real world. Various uncomfortable sensations are present at the same time and, together, produce the overall perception of dyspnea as complex sensations.

5) Central neural structures related to dyspnea

Little is known about the central neural processing of dyspnea. Recent neuroimaging studies have revealed the brain structures that are activated by dyspnea. Using positron emission tomography (PET), Banzett et al. showed that the right anterior insular cortex is activated during air hunger that is induced by restricting tidal volume. Evans et al. , using functional magnetic resonance imaging (fMRI), also detected right anterior insular activation, with additional limbic, paralimbic, and cerebellar activation, during similarly induced air hunger. The insula appears to be essential to the perception of dyspnea. The limbic/paralimbic system, including the insula, is thought to be related to the perception of primitive sensations, such as pain, hunger, and thirst.

6) Physiological and pathophysiological responses to acute hypoxia

The physiological responses to acute hypoxia serve to minimize the reduction in oxygen delivery to tissues. Under acute hypoxic conditions, ventilation, cardiac output, and hemoglobin concentration ([Hb]) increase in a process termed acclimatization. The most important acclimatization is increased ventilation. The receptors that are stimulated directly by hypoxia are the peripheral chemoreceptors. Afferent signals from the peripheral chemoreceptors are sent to the respiratory center in the brainstem and a motor command is built to promote ventilation. Simultaneously, this motor command is projected to the cerebral cortex as a corollary discharge. This is a possible mechanism by which dyspnea may be mediated, and is known as the "Motor Command Theory", as described above.

During mountain climbing, hypoxia induces neurohormonal and hemodynamic responses that sometimes result in regional overperfusion, with elevated hydrostatic pressure, increased capillary permeability, and consequent edema in the brain and the lungs. As a result, people who fail to acclimatize to hypoxia show symptoms of high altitude illness, such as high altitude cerebral edema and high altitude pulmonary edema.

7) The effect of hypoxia on dyspnea

In general, a lack of oxygen is believed to cause dyspnea, but no conclusion has yet been drawn about whether the effect of hypoxia on dyspnea is a direct effect of hypoxia itself, an indirect effect mediated by hyperventilation, or both of these. To date, several reports have discussed the relationship between hypoxia and dyspnea. Some reports have supported a direct dyspnogenic effect of hypoxia, while others have not. However, these previous reports have been based on the analysis of percutaneous oxygen saturation (SpO_2), measured with a pulse oximeter as an indicator of hypoxia. In general, the accuracy of pulse oximetry readings is not established during severe hypoxemia. Based on our literature search, there has been no published study examining the influence of hypoxia on dyspnea by directly measuring PaO_2 in serial arterial blood gas analysis. In the presence of hypoxia, the cognitive function of the cerebrum can be disturbed and can possibly result in an individual's inability to be aware of dyspnea. Therefore, when dyspnea is evaluated, cognitive function needs to be simultaneously evaluated. However, no study using this approach has been reported to date.

8) The aim of the present study

The aim of the present study was to investigate whether hypoxia has an independent, direct dyspnogenic effect. We analyzed changes in the vital signs, arterial blood gases, [Hb], arterial oxygen saturation (SaO_2), arterial oxygen concentration (CaO_2), intensity of dyspnea, and cognitive function in seven mountain climbers at rest, by using a hypobaric hypoxic chamber in which the barometric pressure was lowered to the simulated altitude of 4500 m.

Discussion

Meakins reported in 1923 that dyspnea arises from hypercapnia and hypoxia. These two

factors stimulate chemoreceptors, and hypercapnia may have a direct dyspnoenic effect. Some reports have also indicated that hypoxia has a direct dyspnoenic effect, whereas others have refuted this. Thus, whether hypoxia is a direct dyspnoenic factor remains uncertain. In the present study, both PaO_2 and CaO_2 decreased constantly and significantly as the simulated altitude increased. The lowest levels of PaO_2 were recorded at the highest simulated altitude of 4500 m, and resulted in severe hypoxemia. On the other hand, the Borg scale score, which reflects dyspnea, showed no significant difference in association with the various altitudes; at the highest altitude (4500 m), this score was 1.5 ± 1.2 . A Borg scale score of 1 corresponds to "very slight" and score of 2 corresponds to "slight" dyspnea. Thus, it is unlikely that the participants were feeling marked discomfort even in the presence of severe hypoxemia at the altitude of 4500 m. The Borg scale is widely used to evaluate dyspnea in both basic and clinical studies. Its sensitivity and reproducibility to change in the assessment of subjective symptoms have been confirmed in normal subjects. Even under the most hypobaric hypoxic conditions (simulated altitude of 4500 m), the participants in the present study did not complain of dyspnea. Instead, they enjoyed talking, reading cartoons, and other activities. They also maintained an MMSE score of 29.3 ± 0.8 at the altitude of 4500 m, and were judged as having no cognitive impairment. It has been reported that, when using MMSE for highly educated people, it is more useful to use a higher cut-off score. The MMSE score of participants in the present study was very close to the highest score of 30; thus, even if a higher cut-off score was used, the cognitive function of the participants was still considered normal, and it is unlikely that dyspnea would have been masked by hypoxia-induced cognitive impairment. Thus, these results suggest that severe hypoxia (equivalent to a PaO_2 of 46.8 ± 8.3 Torr) was not a direct dyspnoenic factor in healthy resting participants who were able to breathe without restriction.

Our results showed that PaCO_2 tended to decrease as the altitude increased, although the difference was not statistically significant ($p = 0.056$). This indicates a tendency toward hyperventilation at higher altitudes. Hypoxia stimulates peripheral chemoreceptors and

promotes ventilation, and hypoxic ventilatory response stimulates an increase in oxygen uptake in hypoxic environments. Schoene stated that it is a significantly excellent hypoxic ventilatory response that enables successful climbers to maintain adequate oxygenation in the presence of extreme environmental hypoxia at extreme altitudes. The work of Rahn and Otis was the first to describe the differences in alveolar PO_2 (P_{AO_2}) and PCO_2 (P_{ACO_2}) between those acutely exposed to hypoxia and those who have undergone a process of acclimatization. At each altitude, the P_{ACO_2} was consistently lower and the P_{AO_2} was higher in the acclimatized than in the unacclimatized individual. They described that the ventilatory response becomes sensitized following a period of acclimatization. They indicate that in people unacclimatized to high altitude, acute hypoxia failed to cause hyperventilation until P_{AO_2} fell below 50 to 60 Torr. Since ventilatory acclimatization had not occurred in participants of the present study, changes in $PaCO_2$ during decompression in a hypobaric chamber are in good agreement with these observations.

Our conclusions differ from past reports that have supported a direct dyspnoenic effect of hypoxia. Chronos et al. compared the effects of three different inspired gas compositions (100% O_2 , 15% O_2 , and air) on the intensity of dyspnea during exercise in normal individuals, and concluded that hypoxia itself could have a direct effect on dyspnea, because changes in the intensity of dyspnea preceded changes in ventilation and more closely reflected changes in SpO_2 . Ward and Whipp investigated the influence of both hypoxia and hypercapnea on the intensity of dyspnea during exercise at the same level of ventilation in normal subjects, and reported that hypoxia had a dyspnoenic effect, as the intensity of dyspnea was significantly greater in the presence of hypoxia. One substantial difference between the present study and these past reports lies in the stimuli used to induce dyspnea. The previous reports involved hypoxic exercise, whereas we performed the present study with participants at rest and involved only hypoxia-induced chemical stimuli as the dyspnea-inducing stimuli. In view of the possibility that different stimuli can induce different types of dyspnea, the use of exercise stimuli by Chronos et al. and Ward

and Whipp may have played an important role in the development of dyspnea. Another difference is that all of the participants in the present study were mountain climbers, which may be a possible limitation of the study. Sasao et al. stated that climbing experience may lead to significant differences in cardiopulmonary function under hypoxic conditions, and that the ventilatory response to hypoxia remains unchanged for years. The results of the present study may have been influenced by the participant's history of hypoxic exposure through their mountain climbing experience. In our previous study, non-climbers (i.e., scientists without mountain climbing experience) were exposed to hypobaric environments up to a simulated altitude of 5000 m, using the same protocol. They also enjoyed talking and reading books during the study without complaining of dyspnea (unpublished observation), although the study did not incorporate a quantitative evaluation of dyspnea. It is unclear whether the same results would be obtained in healthy subjects chosen from the general population. Therefore, further studies are needed to determine whether there are any significant differences in the intensity of dyspnea during hypoxia between climbers and non-climbers.

Previous reports that have denied a direct dyspnogenic effect of hypoxia have included studies by Adams et al. , Burki et al. , and Swinburn et al. . The results of the present study support these previous reports. Adams et al. used oscillatory hypoxic stimuli for normal subjects at rest, and denied a dyspnogenic effect of hypoxia because dyspnea was linked to the ventilatory response rather than the stimulus level. Burki et al. examined the effect of high altitude (4450 m)-induced hypoxia on exercise-induced dyspnea in normal subjects, and concluded that exercise-induced dyspnea is not related to the level of hypoxia per se, but rather to the level of reflexively increased ventilation. Swinburn et al. found that the relationship between ventilation and dyspnea remained the same during exercise, irrespective of the presence of hypoxia, in patients with chronic obstructive pulmonary disease, and concluded that hypoxia does not contribute to dyspnea by a mechanism distinct from its effect as ventilatory stimulus. These three reports described that

hypoxia-induced dyspnea could be explained by an indirect effect of the attendant increase in ventilation.

In the present study, the participants did not complain of dyspnea at all, despite the presence of absolute hypoxia. Because their cognitive function was normal, it is unlikely that dyspnea was masked by hypoxia-induced cognitive impairment. Previous reports that have denied a direct dyspnoegenic effect of hypoxia stated that it is increased ventilation that induces dyspnea. Participants in the present study tended to hyperventilate at higher altitudes, although the difference was not statistically significant. It remains unclear why they did not complain of dyspnea. In the study by Burki et al. , the relationship between hypoxia and dyspnea was examined using high altitude hypoxia, similar to the present study, although exercise was added as a dyspnea-inducing stimulus. In their study, healthy, normal men were taken from sea level to 4450 m over a period of 8 h, by car, and the changes in SpO_2 , RR, tidal volume, minute ventilation, and the intensity of exercise-induced dyspnea quantified by the Borg scale were evaluated. Participants in their study showed significant hyperventilation and significantly increased dyspnea. The RR of their participants was significantly increased while the tidal volume remained unchanged. They found that increased ventilation of their participants was primarily achieved by an increase in RR. Burki showed in another report that healthy normal lowlanders at rest also increased ventilation primarily due to a significant increase in RR, with no significant change in tidal volume, in response to high altitude (3940 m)-induced hypoxia; however, they did not evaluate dyspnea. In contrast, the RR of participants in the present study remained unchanged; hence, it is likely that increased ventilation might be primarily achieved by an increase in tidal volume, although the actual tidal volume was not measured. Unlike the present study, participants in the study by Burki were all lowlanders and had never been exposed to high altitudes. Thus, it is possible that this difference may have been due to the history of hypoxic exposure through the mountain climbing experience of participants in the present study. Some reports have indicated that tidal

volume is related to the intensity of dyspnea. Manning et al. showed a significant inverse correlation between tidal volume and air hunger at fixed end-tidal PCO_2 in ventilated quadriplegics. It is therefore possible that hyperventilation with unchanged RR and increased tidal volume may have resulted in the lack of perception of dyspnea in the present study. Further examination is required to confirm this.

Conclusions

The results of the present study suggest that hypoxia is not an independent direct dyspnoenic factor in healthy individuals capable of breathing without restriction at rest.