Influence of Sustained Hypoxia on the Sensation of Dyspnea

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Abstract: We assessed the effect of sustained isocapnic hypoxia ($PCO_2=40$ Torr, $SaO_2=80\%$) on the sensation of dyspnea in 16 normal healthy males. Subjects rated the sensation of dyspnea ($\psi$) on 15 cm visual analog scales during 20 min of sustained hypoxia. Following this hypoxic period, 8 subjects undertook mild exercise (10–50 W on a bicycle ergometer for 3 min) under the continuation of hypoxia. During sustained hypoxia, $\psi$ increased initially with ventilation from 0.6±0.2 ($n=16$, mean±SE) to 2.9±0.6 at peak ventilation, but it decreased with ventilatory depression to 1.6±0.4. Dyspnea intensity during hypoxic exercise was significantly smaller than that at peak ventilation in the resting hypoxic period (2.3±0.7 vs. 3.9±1.0), although the ventilation was greater during exercise (24.0±3.0 vs. 19.7±1.4 l/min). These results indicate that sustained hypoxia has a biphasic, i.e., initial stimulatory and delayed depressant, effect on dyspnea and on ventilation. It is suggested that the dyspnea sensing mechanism is suppressed during mild exercise under sustained hypoxia. [Japanese Journal of Physiology, 48, 291–295, 1998]

Key words: hypoxic ventilatory depression, respiratory sensation, exercise.

It has been reported that in humans, the effect of sustained hypoxia on respiration is biphasic and is comprised of an initial stimulatory phase mediated by peripheral chemoreceptors and a following depressive phase caused by central and/or peripheral mechanisms [1–3]. On the other hand, hypoxia is known to impair neuropsychological performance [4, 5]. However, it is not clear how sustained hypoxia affects respiratory sensations. In this study we sought to determine whether sustained hypoxia has inhibitory effects on the sensation of dyspnea. For this purpose, the time course of the changes in the intensity of dyspnea was assessed during 20 min of isocapnic hypoxia ($SaO_2=80\%$) in normal volunteers. Furthermore, mild exercise was performed under continuation of sustained hypoxia to examine whether sustained hypoxia attenuates the accentuation of dyspnea induced by a moderate increase in respiratory motor output.

METHODS

Subjects. Studies were carried out in 16 healthy normal males who ranged in age from 26 to 45 year. All had previously participated in hypoxic studies using the same circuit employed in this study, but they had no knowledge of the hypothesis of the experiment. The protocol was approved by the Human Research Committee of our institution, and voluntary consent was obtained from each subject.

Sustained hypoxia. The breathing apparatus was similar to that reported previously [6] and consisted of a mouthpiece and a directional Hans-Rudolph low-resistance valve. The expiratory side of the directional valve was connected to a heated pneumotachograph and a pressure transducer (±5 cmH2O; Validyne, Northridge, CA) to measure expiratory airflow. Subjects wore a noseclip, and the airflow signal was integrated to obtain tidal volume ($VT$) and minute ventilation ($VE$). Mouth pressure was measured at the
mouthpiece by using a pressure transducer (±50 cmH₂O; Validyne). End-tidal PO₂ and PCO₂ were continuously monitored at the directional valve with a mass spectrometer (WSMR-1400; Westron, Chiba, Japan). Arterial oxygen saturation (SaO₂) was measured with a pulse oximeter (Biox 3700; Ohmeda, Boulder, CO). All variables were recorded with an eight-channel thermal recorder (model 360; NEC San-ei, Tokyo, Japan).

The inspiratory limb of the breathing apparatus could be switched from room air to a large reservoir of premixed gas with a low fractional concentration of O₂ (10%). Supplementary gas was continuously added to the reservoir from a gas blender (N3800, Bird, Palm Springs, CA), which mixes the air and N₂ at a variable ratio. Furthermore, CO₂ gas could be independently added to the outflow of the reservoir at a variably low rate, and a bypass circuit consisting of a CO₂ absorber and a variable fan was connected between the reservoir and the inspiratory line. With this apparatus being used, normocapnic hypoxia (PCO₂=40±3 Torr, SO₂=80±3%) was introduced, after 5–10 min of stable air breathing, by changing the mixing ratio of N₂ and O₂ and CO₂ inflow within 3 min and maintaining it for 20 min. The height of the whole breathing apparatus was made adjustable so that the subjects could breathe comfortably while sitting on a chair or riding a bicycle.

**Rating of dyspnea.** The sensation of dyspnea or difficulty in breathing (ψ) was rated by using 15 cm visual analog scales. The two ends of the scale were designated “none at all” and “most intense imaginable.” Subjects were simply instructed to consider the sensation of difficulty in breathing (dyspnea). No further clarification or definitions were given, and the subjects were not asked to distinguish different qualities or dimensions of the respiratory sensation. The intensity of dyspnea was rated every minute during sustained hypoxia and at the end of the protocol that followed.

**Exercise under sustained hypoxia.** Experiments were carried out in eight subjects while they were seated on a bicycle ergometer (Gould Godart BV, Bilthoven, Netherlands) throughout the study. Following 20 min of sustained hypoxia at rest, subjects performed mild exercise at a fixed work rate from 10 to 50 W for 3 min, during which the same isocapnic hypoxia was maintained. Subjects were allowed to select the actual work rate from 10 to 50 W to ensure that constant exercise was maintained without technical difficulty. Dyspnea intensity was rated at the end of the trial.

To assess the effects of sustained hypoxia on the respiratory mechanics in 8 subjects not involved in exercise protocol, spirometry was performed before and after sustained hypoxia, and VC and FEV₁ were obtained.

**Data analysis.** Statistical analysis was performed by using paired or unpaired t-tests and parametric or nonparametric analysis of variance, depending on whether the data of the two groups compared were related and whether population variances were equal [7, 8]. The results are given as means±SE.

**RESULTS**

Figure 1 shows an example of the changes in SaO₂, VE, and the intensity of dyspnea (VAS) during hypoxia in one subject. During sustained hypoxia, both VE and VAS increased initially and decreased after 7 min; SaO₂ was basically unchanged. The value of SaO₂ was maintained at 80±3% for 20 min in all subjects, and during that period the average level of SaO₂ did not change significantly. During sustained hypoxia, VE and VAS both showed a biphasic response that consisted of an early increase followed by a gradual de-
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Fig. 2. Average time course of changes in minute ventilation (VE) and the intensity of dyspnea (VAS) during sustained hypoxia in 16 subjects. Data are shown as means±SE. The data during the transitional period from normoxia to stable hypoxia are not shown. See text for details.

Table 1. Minute ventilation (VE) and the intensity of dyspnea (ψ) in the control state at peak ventilation during hypoxia and in the last minute of sustained hypoxia, while at rest.

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<th></th>
<th>Control</th>
<th>Peak</th>
<th>Last</th>
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<tbody>
<tr>
<td>VE (L/min)</td>
<td>10.1±0.6</td>
<td>18.5±0.9*</td>
<td>14.1±1.1*†</td>
</tr>
<tr>
<td>ψ (cm)</td>
<td>0.6±0.2</td>
<td>2.9±0.6*</td>
<td>1.6±0.4*†</td>
</tr>
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Values are means±SE. n=16. * Significantly different from the control value. † Significantly different from the value at peak VE.

crease. Times from the beginning of sustained hypoxia to reach the peak values for VE and VAS were 2.9±0.6 and 4.1±0.7 min, respectively, and they did not differ significantly. Table 1 indicates the value of VE and the intensity of dyspnea during control state, at ventilatory peak during hypoxia, and at the last minute of hypoxia, while at rest. During sustained hypoxia, VE and ψ significantly increased initially, then significantly decreased to levels higher than those in the control state.

Figure 3 shows an example of the changes in $S_{a}O_2$, VE, and VAS during sustained hypoxia at rest and during mild exercise (50 W). During the resting hypoxic period, VE and VAS increased initially and decreased gradually thereafter, as described above. The level of VE approximately doubled and reached the highest point with exercise, but the exercise-induced rise in VAS was less than 50%, and the intensity of dyspnea remained below the peak level of the initial resting hypoxic period.

The summarized data of exercise protocol are shown in Fig. 4. The level of $S_{a}O_2$ during exercise was maintained at 80±3%, and it was 78.9±0.5% at the end of exercise. The early increase and the late decrease in ventilation were associated with concomitant changes in the intensity of dyspnea during the resting hypoxic period. However, the exercise-induced sharp rise in VE was not accompanied by a similar sensory change that might have been expected from the relationship between VE and VAS during sustained hypoxia at rest.

Sustained hypoxia did not affect VC or FEV$_1$ significantly (prehypoxia: VC=4.77±0.22 l, FEV$_1$=3.86±
0.24 l; posthypoxia: VC = 4.75 ± 0.24 l, FEV₁ = 3.87 ± 0.23 l).

**DISCUSSION**

The results of the present study indicate that the sensation of dyspnea changes biphasically during a moderate degree of sustained hypoxia (SaO₂ = 80%), i.e., it increases initially and gradually decreases thereafter to a level greater than the control level. Moreover, during sustained hypoxia the exercise-induced accentuation of dyspnea is less than would be expected from the increase in ventilation.

The degree of hypoxia introduced in the present experiment seemed to have had no major effects on the respiratory mechanics because neither VC nor FEV₁ differed before and after hypoxic exposure. Therefore we believe that minute ventilation basically represents respiratory motor output in the present experiment.

Several reports have suggested that hypoxia accentuates dyspnea or breathlessness in normal subjects and in patients with chronic airway obstruction [9–11], although there seems to be an inconsistency whether hypoxia itself has additional effects on the sensation of dyspnea besides the mechanism that increase ventilation [12, 13]. In these reports, however, the magnitude of hypoxia was mild, and/or the duration was shorter, compared with the present study. The results of our experiment indicate that sustained hypoxia of a moderate degree (SaO₂ = 80%) has biphasic, i.e., initial stimulatory and delayed depressant, effects on the sensation of dyspnea.

Hypoxic ventilatory depression has been suggested to occur through inhibition of peripheral chemoreceptors and/or the central nervous system (CNS) [3, 14]. In the present study, the time course of changes in the respiratory sensation was similar to that of ventilation during sustained hypoxia at rest. Therefore it may be that the sensory reduction was simply a result of ventilatory depression. However, the increase in sensory intensity was unexpectedly small in contrast to the sharp rise in ventilation during exercise under sustained hypoxia. Consistent with this, Pandit and Robbins [15] recently reported that hypoxic ventilatory depression is less evident during exercise than at rest. This report and the results of our study suggest that sustained hypoxia has diverse effects on respiratory motor output and on respiratory sensation during exercise, and that the CNS mechanism, which assesses the intensity of exercise-induced dyspnea, may be more vulnerable than the mechanism that determines exercise hyperpnea. Alternatively, it could be argued that exercise-induced hyperpnea and hypoxia-induced hyperpnea evoke different degrees of dyspnea at a given level of ventilation; thus a direct comparison is difficult. However, Adams et al. [16] reported that the relationship between ventilation and the magnitude of breathlessness was not different between hypoxia and exercise. Moreover, the same group [13] reported that hypoxia induced less breathlessness than exercise did for a given ventilation. Therefore it seems more likely that exercise-induced dyspnea was underestimated during sustained hypoxia in our study.

The energy supply for the brain is intact in mild to moderate hypoxia, and it has been hypothesized that hypoxia impairs brain function by impairing the metabolism of central neurotransmitters [4]. In our study, normocapnia was maintained throughout the experiment; however, the sensory attenuation might have been greater if CO₂ had not been controlled because hypoxia-induced hyperpnea evokes respiratory alkalosis, which reduces cerebral blood flow [4, 17].

Mild hypoxia (alveolar Po₂ > 45 Torr) has been reported to impair the ability to concentrate and to learn complex tasks, and also to cause failures in short-term memory [4]. In more severe hypoxia, cognitive function and critical judgment fails before the loss of consciousness. Long-lasting neurobehavioral impairment may persist after returning to normoxia in severe cases [5]. The central mechanism that assesses the respiratory sensation also seems to be impaired during
sustained hypoxia because exercise-induced hyperventilation evoked only an unexpectedly mild accentuation of dyspnea. The sensory attenuation induced by sustained hypoxia could impair the behavioral control system of breathing, which maintains body homeostasis through the optimization of respiratory sensations [18–20]. An attenuation of dyspnea could worsen hypoxemia by preventing an increase in ventilation. Consistent with this hypothesis, Kikuchi et al. [21] have reported that most patients who experienced near-fatal asthmatic attacks had a blunted perception of dyspnea during resistive loading, and a decreased respiratory response to hypoxia. Many deaths from acute respiratory failure may involve an impairment of the respiratory sensing mechanism, resulting in the underestimation of dyspnea that is induced by mild physical activities.

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REFERENCES