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Hypobaric hypoxia is not a direct dyspnogenic factor in healthy individuals at rest

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ABSTRACT

Dyspnea consists of various uncomfortable respiratory sensations. It is believed that hypoxia causes dyspnea, but whether hypoxia is a direct dyspnogenic factor remains uncertain. We investigated whether hypoxia has a direct dyspnogenic effect. We evaluated changes in vital signs, arterial blood gases, SaO_2, CaO_2, Borg scale, and Mini-Mental State Examination in seven mountain climbers by using a hypobaric hypoxic chamber in which the barometric pressure was lowered to the simulated altitude of 4500 m. PaO_2 and CaO_2 both decreased significantly as the simulated altitude increased. On the other hand, Borg scale score which reflects dyspnea showed no significant difference. At the simulated altitude of 4500 m, Borg scale score was 1.5 ± 1.2 (mean $\pm$ SD), despite the presence of absolute hypoxia (PaO_2, 46.8 ± 8.3 T; CaO_2, 16.4 ± 0.6 mL/dL). These results suggest that hypoxia is not a direct dyspnogenic factor in healthy individuals capable of breathing without restriction at rest.

1. Introduction

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" (Parshall et al., 2012). Dyspnea comprises multiple complex sensations expressed by diverse words such as "respiratory effort," "air hunger", and "tightness", and involves multiple pathophysiologic mechanisms rather than a single mechanism (Manning and Schwartzstein, 1997).

In general, a lack of oxygen is believed to cause dyspnea, but its exact mechanism has not been fully clarified. No conclusion has yet been obtained concerning whether the effect of hypoxia on dyspnea is a direct effect of hypoxia itself, an indirect effect mediated by hyperventilation, or both of these effects. To date, several reports that discuss the relationship between hypoxia and dyspnea have been published. 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 was no report that examined the influence of hypoxia on dyspnea through directly measuring the arterial partial pressure of oxygen (PaO_2) in serial arterial blood gas analysis. In the presence of hypoxia, the cognitive function of the cerebrum can be disturbed and 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 such evaluation has been performed in any study reported to date.

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

Abbreviations: BPsys, systolic blood pressure; BPdia, diastolic blood pressure; HR, heart rate; HVR, hypoxic ventilatory response; MMSE, Mini-Mental State Examination; RR, respiratory rate; SD, standard deviation.

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Table 1
Subject characteristics.

Participant number	Age	Sex	Height (cm)	Weight (kg)	Main history of climbing
1	21	F	156	49	Seoraksan (Korea, 1708 m) Japanese 3000 m class mountains × 10
2	20	M	160	54	Japanese 2500–3000 m class mountains × 5 No history of overseas climbing
3	19	M	171	68	Mount Fuji (Japan, 3776 m) Tsurugidake (Japan, 2999 m) no history of overseas climbing
4	46	M	162	67	Nepal Himalaya (Big White Peak, 6979 m) European Alps (Mont Blanc, 4810 m) Indian Himalaya (Barnaji, 6290 m) Pakistan Karakorum (Batura Glacier, 7795 m) Kula Kangri (Tibet, 7418 m)
5	19	M	177	66	Tsurugidake (Japan, 2999 m) No history of overseas climbing
6	20	M	168	61	Tsurugidake (Japan, 2999 m) No history of overseas climbing
7	19	M	181	65	Tsurugidake (Japan, 2999 m) No history of overseas climbing

2. Materials and methods

2.1. Study participants

Seven individuals (six males and one female) participated in the present study. They were all well-trained members of the Tokai University West Kunlun Expedition (altitude 6355 m). All participants were healthy climbers (19–46 years old). Prior to the expedition, their health conditions were evaluated at the simulated altitude of the base camp at 4500 m. Tokai University Research Ethics Committee approved this study. All participants gave written, informed consent.

2.2. Experimental protocol

Experiments were safely conducted in a hypobaric chamber (PHC-60; Tabai Manufacturing Co., Ltd., Osaka, Japan; size, 7.7 m long, 3.8 m wide, 2.8 m high; floor dimension, 18.0 m^2; accommodation, 13 people) at the Tokai University Hospital (Kanagawa, Japan) under the constant supervision of two medical doctors. The temperature and humidity inside the chamber were set at 22.0 °C–22.8 °C and 44–58%, respectively, for the entire experiment. The study participants sat in comfortable chairs and could breathe freely. A catheter was inserted in the radial artery to collect arterial blood samples at each simulated altitude. Once completing the control measurements at the sea level condition, the barometric pressure of the chamber was gradually lowered to the simulated altitudes of 2000 m, 3000 m, 4000 m, and 4500 m at a rate of 33 m/min (−2 T/min). The participants were maintained at each simulated altitude for 30 min. Arterial blood samples were collected by a medical doctor who was present in the chamber. Supplemental O_2 was available if a participant's PaO_2 decreased below 40 T, which corresponds to the level in mixed venous blood. The samples were removed through a service hatch of the chamber and analyzed immediately for blood gases, [Hb], and SaO_2 with a blood gas analyzer (IL-1304; Instrumentation Laboratory, Lexington, Massachusetts, USA) and a hemoximeter (OSM3; Radiometer, Copenhagen, Denmark). The CaO_2 was calculated as follows: $0.003 \times PaO_2 + [1.39 \times [Hb] \times SaO_2/100]$. Systolic blood pressure (BPsys), diastolic blood pressure (BPdia), heart rate (HR), and respiratory rate (RR) were also measured at each simulated altitude, and the magnitude of dyspnea at each altitude was quantified by the Borg scale (Borg, 1982). When the simulated altitude of 4500 m was reached, each participant's cognitive function was evaluated by the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). The MMSE consists of 11 questions with a total score of 30 and is designed to evaluate orientation, memory, attention, calculation, linguistic capability, graphic capability, and other cognitive factors. In the present study, the cut-off score was set at 23/24, which is consistent with the widely adopted method in clinical practice, and participants who scored 24 or higher were judged as having normal cognition.

2.3. Statistical analysis

Data analyses were performed using the IBM Statistical Package for the Social Science software (SPSS; IBM, Armonk, New York, USA). All values are expressed as mean ± standard deviation (SD). For each participant, repeated measures analysis of variance (ANOVA) with Bonferroni correction was used to compare the data obtained at each simulated altitude. A p value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

All experiments were performed safely. No study participant required supplemental O_2 inhalation during the experiments. All of the participants could reach the simulated altitude of 4500 m without problems. They had cyanosis of the lips and/or nails, but none of them complained of dyspnea under the hypobaric environments.

Table 1 shows the participants' profile and their primary history of climbing. Only one individual among the seven participants had experience of climbing to altitudes over 4000 m. The remaining six climbers had domestic mountain climbing experience up to approximately 3000 m.

Table 2 shows changes in barometric pressure and partial pressure of inspired oxygen (P_IO_2), and timetable of decompression.

Table 2
Changes in barometric pressure and partial pressure of inspired oxygen, and timetable of decompression.

Altitude	P_B (T)	P_IO_2 (T)	Arrival time	Departure time
Sea level	763	150		14:00
2000 m	600	116	15:00	15:30
3000 m	534	102	16:00	16:30
4000 m	477	90	17:00	17:30
4500 m	451	85	17:45	18:15 (to sea level)

P_B, barometric pressure; P_IO_2, partial pressure of inspired oxygen calculated as (P_B-47) x 0.21.