Hypoxic Ventilatory Response to Acute and Prolonged Hypoxic Exposures in Subjects Susceptible to High-altitude Pulmonary Edema

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Background : The low hypoxic ventilatory response (HVR) has been suggested to be one of the pathophysiological features in high-altitude pulmonary edema (HAPE). Ventilatory responses to hypoxia vary widely depending on the length of hypoxic exposure. The pathophysiological role of HVR in the development of HAPE has not yet been well understood.

Methods : Isocapnic hypoxic exposure was induced to 12 Japanese HAPE susceptible subjects (HAPE-s) and 10 HAPE resistant subjects (HAPE-r) in Shinshu University at an altitude of 600 meters (m). A slope linear regression relating minute ventilation ($\dot{V}_E$, L/min) to oxygen saturation (SpO_2, %), $\dot{V}_E = \alpha * SpO_2 + \beta$, was obtained in each of the subjects of HAPE-s and HAPE-r after 10-minutes (min) and 30-min isocapnic hypoxic exposure, respectively. The slope α parameter was the ratio of change of $\dot{V}_E$ ($\Delta \dot{V}_E$) to change of SpO_2 (ΔSpO_2) and the absolute slope α value was used for evaluation of HVR. In addition, the hypoxic ventilation decline (HVD) was calculated in the later phase of hypoxic exposures.

Results : The HVR was significantly lower in the HAPE-s than the HAPE-r subjects at 10-min (0.29 ± 0.18 vs 1.13 ± 1.21, $p = 0.03$) and 30-min (0.16 ± 0.09 vs 1.01 ± 1.08, $p = 0.01$) hypoxic exposure. Moreover, the HVR continuously declined in the HAPE-s subjects over the prolonged hypoxic exposure from 0.29 ± 0.18 at 10-min hypoxic exposure to 0.16 ± 0.09 at 30-min hypoxic exposure, resulting in 29.3 % of HVD in HAPE-s, in contrast to 3.1 % of HVD in the HAPE-r subjects over the prolonged hypoxia.

Conclusion : The HVR was not only significantly blunted but also continuously declined in the HAPE-s over a prolonged hypoxic exposure, which contributed to the failure in acclimatization to high-altitude hypoxia.
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Key words : acclimatization, hypoxic ventilatory response, high-altitude pulmonary edema

I Introduction

Hypoxic ventilatory response (HVR), which is a measurement of ventilatory response to a reduced arterial blood oxygen tension (PaO_2) independent of the effect of carbon dioxide, increases in conscious humans after exposure to hypoxia to compensate for the loss of oxygen[1)-3)]. Under a sustained hypoxic condition at high altitudes, even if the PaO_2 related stimulus is diminished, ventilation remains stable or continues to increase. This phenomenon is known as ventilatory acclimatization that prevents high-altitude sicknesses[4)]. A blunted HVR was thought to be one of the pathophysiological features in high-altitude pulmonary edema (HAPE) susceptible individuals (HAPE-s) who develop this life-threatening disease after 4-6 hours of rapid exposure to altitudes over 2,500 meters (m) above sea level[4)-6)]. Reviewing the abundance of research literature regarding the HVR in HAPE-s, the published data were mostly obtained over a relatively short period of several minutes of hypoxia[4)-6)]. In fact, ventilatory responses to hypoxia vary widely depending on the length of

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hypoxic exposure[7]. HVR is time-dependent and the isocapnic HVR includes two phases, a first phase (0-10 minutes) of immediate ventilation increase, followed by a second phase (10-30 minutes) of slow ventilation decline[7)8)]. There is still a lack of data regarding the HVR of HAPE-s in a relatively prolonged hypoxic exposure. The pathophysiological roles of HVR including both the increase and decline phases have not yet been completely understood in the development of HAPE.

Thus, investigation of HVR over prolonged hypoxia is required for thoroughly understanding the role of HVR in the development of HAPE. For this reason, in order to illustrate the progress of HVR over a prolonged hypoxia in the development of HAPE, we extended the hypoxic course over more than 30 minutes and measured the HVR in the HAPE-s and HAPE-r subjects after 10-min and 30-min hypoxic exposures.

Ⅱ Subjects and Methods

This study and the investigational protocol were approved by the institutional ethics review board of Shinshu University for human study and written informed consent was obtained from each case and control subject after a full explanation of the study. The procedures used in this human study were in accordance with the principles found in the Helsinki Declaration[9].

A Study population

The HAPE-s and controls were recruited from Japanese residing in Japan.

The HAPE-s subjects in the present study were defined as individuals who had previously experienced HAPE at least one occasion while climbing the Japan Alps ranging from 2,758 to 3,190 m, and had been admitted to Shinshu University hospital. The diagnosis of HAPE was based upon the following criteria[10] : onset at a high altitude of the typical symptoms, including cough and dyspnea at rest ; absence of signs of infection ; presence of pulmonary rales and cyanosis ; disappearance of symptoms and signs within 3 days of the start of treatment with bed rest and supplemental oxygen at low altitudes ; and chest roentgenographic infiltrates consistent with pulmonary edema. All subjects with HAPE met the criteria at the onset of the disorder and recovered promptly and well with hospitalization. Examinations and cardiovascular tests were conducted in-hospital after their recovery to exclude any preexisting cardiopulmonary diseases. They were all completely recovered without any complications and discharged from the hospital after 7-14 days of hospitalization. We recruited them to participate in the current study on condition that the recovery from HAPE was over one year previously. None of them had traveled to high-altitude within six months of the present study.

The control group consisted of elite mountaineers who repeated alpine-style climbing to peaks above 2,800 m but did not have any symptoms of HAPE or acute mountain illnesses at high altitudes. They were defined as subjects with resistance to HAPE (HAPE-r) in this study. The physical examinations excluded any preexisting cardiopulmonary disorders in the HAPE-r group in the recruitment. They had done no mountaineering within six months of the present study.

B Isocapnic hypoxic exposure

The study was carried out in a respiratory institute in Shinshu University at an altitude of 600 m. To control the effect of $PaCO_2$ on HVR, a progressive isocapnic hypoxic exposure was applied to the current experiment with a computerized spirometer system (Duograph, Chest Inc., Tokyo, Japan, **Fig. 1A**). Subjects sat up right in a chair and spent a variable time breathing room air through a rebreathing valve with mouthpiece until steady ventilation was obtained **(Fig. 1A)**. The isocapnic hypoxic exposure was induced by switching the rebreathing valve to let it connect to a big balloon that contained hypoxic gas mixed with oxygen (O_2), nitrogen (N_2), and carbon dioxide (CO_2) in a closed circuit, so that the subjects started to breathe the hypoxic gas. Sensors in the rebreathing valve sensed signals of real-time partial pressure of end-tidal oxygen ($P_{ET}O_2$) and partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) breath-by-breath and all these data were input into the computerized spirometer (Duograph, Chest Inc., Tokyo, Japan)

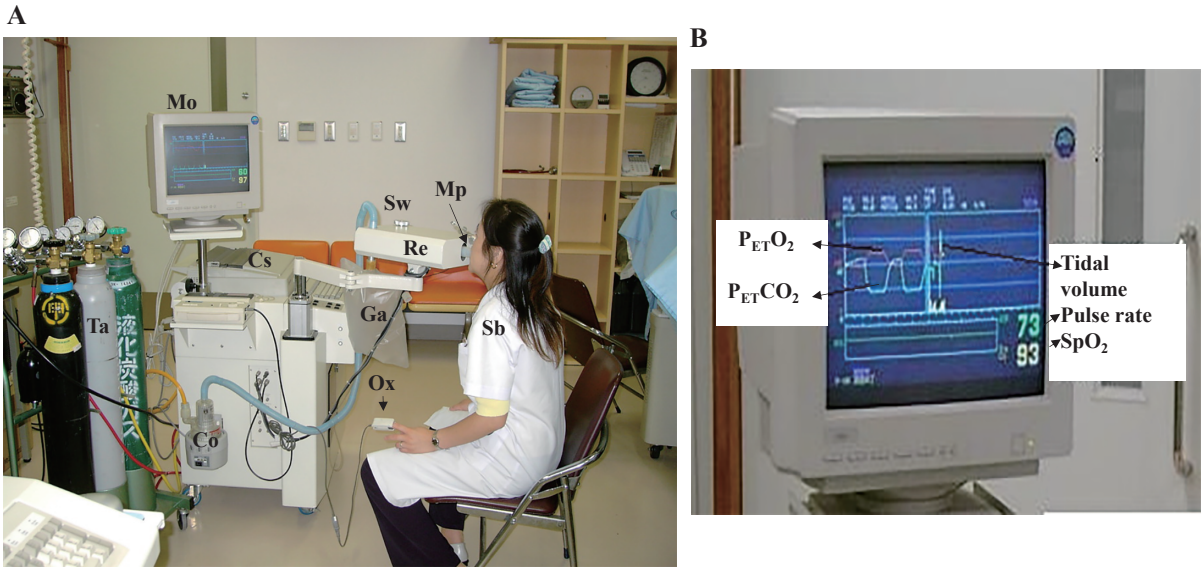

Fig. 1 Measurement of hypoxic ventilatory response (HVR) by the computerized spirometer system (Duograph, Chest Inc., Tokyo, Japan) in the current study. A : Subjects sat up right in a chair and breathed mixed hypoxic gas through a rebreathing valve with mouthpiece for the measurement of HVR ; B : The monitor of the computerized spirometer system displayed the real-time $P_{ET}O_2$, $P_{ET}CO_2$, tidal volume, pulse rate and SpO_2 during the isocapnic hypoxic exposure.

Abbreviations : Co, CO_2 absorber ; Cs, computerized spirometer system ; Ga, gas balloon ; Mo, monitor ; Mp, mouthpiece ; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide ; $P_{ET}O_2$, partial pressure of end-tidal oxygen ; Re, Rebreathing valve and oxygen sensor ; Sb, subject ; Ox, oxygen pulse oximeter ; SpO_2, oxygen saturation ; Sw, switch connecting hypoxic circuit ; Ta, gas tanks of oxygen, nitrogen and carbon dioxide.

that could regulate the breathing O_2 and CO_2 concentrations **(Fig. 1A, B)**. The current hypoxic protocol **(Fig. 2)** was designed as the $P_{ET}O_2$ reduced from 120 Torr at the beginning of the experiment to 60 Torr after 10 min of breathing hypoxic gas at a rate of 6 Torr/min resulting from the metabolic consumption of O_2 during rebreathing the mixed gas in the closed circuit. A CO_2-absorbing bypass was connected in the closed-circuit to adjust $P_{ET}CO_2$ constantly around 40 Torr within ± 2 Torr deviation. The SpO_2 (%) was monitored by a pulse oximeter via a finger probe on the subjects, which was set up around 80 % over the time course of hypoxia **(Fig. 1B)**, corresponding to an altitude of about 4,000 m. The rebreathing hypoxic gas was terminated within 40 min of hypoxic breathing. The hypoxic breathing could terminate at any time if the subjects showed signs of intolerance of the hypoxia. Careful observation was done for any unexpected acute hypoxic sicknesses in the subjects during and after the hypoxic exposure.

C Measurement of hypoxic ventilatory response

The measurements were adjusted for age, body weight, and gender based on equations formulated for Japanese by using the computerized spirometer system that recorded real-time of the tidal volume, SpO_2, $P_{ET}O_2$, and $P_{ET}CO_2$ in every 10 seconds of each rebreathing during hypoxic exposure **(Fig. 3)**. The linear regression in relating the $\dot{V}_E$ to SpO_2 of breath-by-breath, $\dot{V}_E = \alpha^* SpO_2 + \beta$, was obtained in each of the subjects after 10-min and 30-min hypoxic exposure, respectively **(Fig. 4A-D)**. The coefficient α was a slope parameter showing the ratio of change of $\dot{V}_E$ ($\Delta\dot{V}_E$) to change of SpO_2 (ΔSpO_2) between any two distinct points on this linear regression. As illustrated in **Fig. 4E**, supposing that the y axis represents $\dot{V}_E$ and x axis represents SpO_2, the coefficient α was a slope parameter representing the ratio of change of y or $\dot{V}_E$ (Δy or $\Delta\dot{V}_E$) to change of x or SpO_2 (Δx or ΔSpO_2) between any two distinct points along the linear regression ($\Delta y/\Delta x$ or $\Delta\dot{V}_E/\Delta SpO_2$), which determined the steepness of the line.

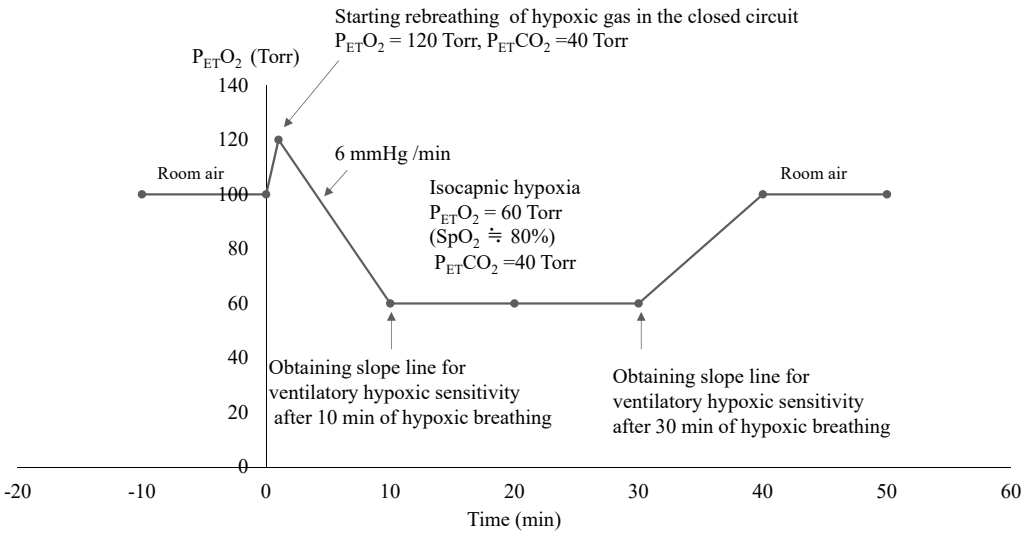

Fig. 2 The protocol of the current isocapnic hypoxic experiment. The hypoxic protocol was programmed as the partial pressure of end-tidal oxygen ($P_{ET}O_2$) reduced from 120 Torr at the beginning of the experiment to 60 Torr after 10 min of breathing hypoxic gas at a rate of 6 Torr/min resulting from the metabolic consumption of O_2 during rebreathing the mixed gas in the closed circuit. A CO_2-absorbing bypass was connected in the closed-circuit to adjust the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) constantly around 40 Torr within ± 2 Torr deviation. The percutaneous arterial oxygen saturation (SpO_2) was set up around 80 % over the time course of hypoxia, corresponding to an altitude of about 4,000 m.

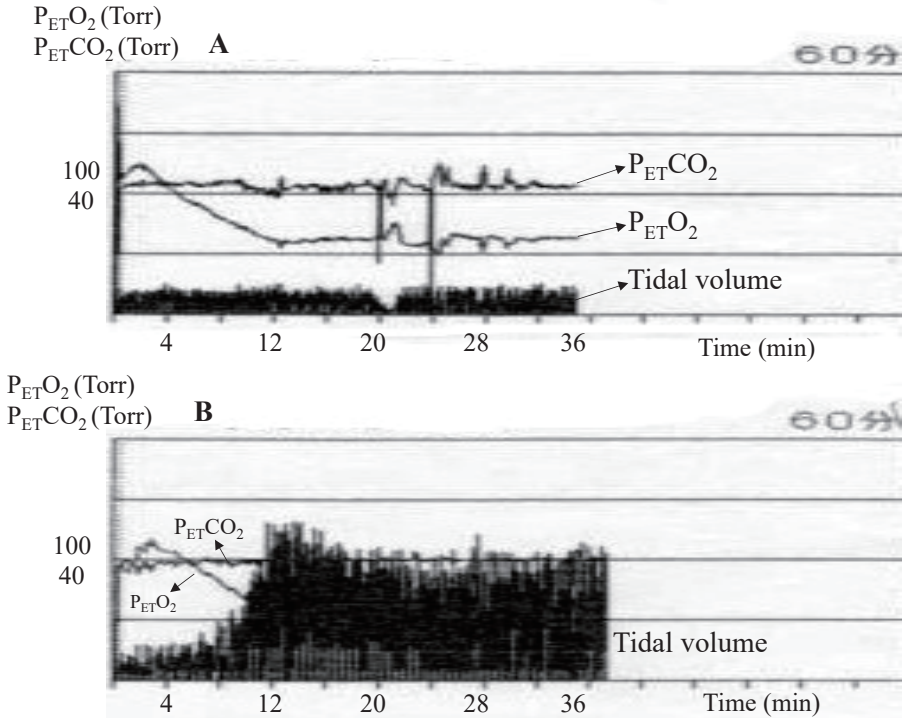

Fig. 3 Spirographs of the hypoxic response in subjects. A : a very weak hypoxic ventilatory response (HVR) in a HAPE-s subject (No. 1 of HAPE-s group in Table 1) ; B : a remarkable HVR in a HAPE-r subject (No. 4 of HAPE-r group in Table 1).

Abbreviations : $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide ; $P_{ET}O_2$, partial pressure of end-tidal oxygen.

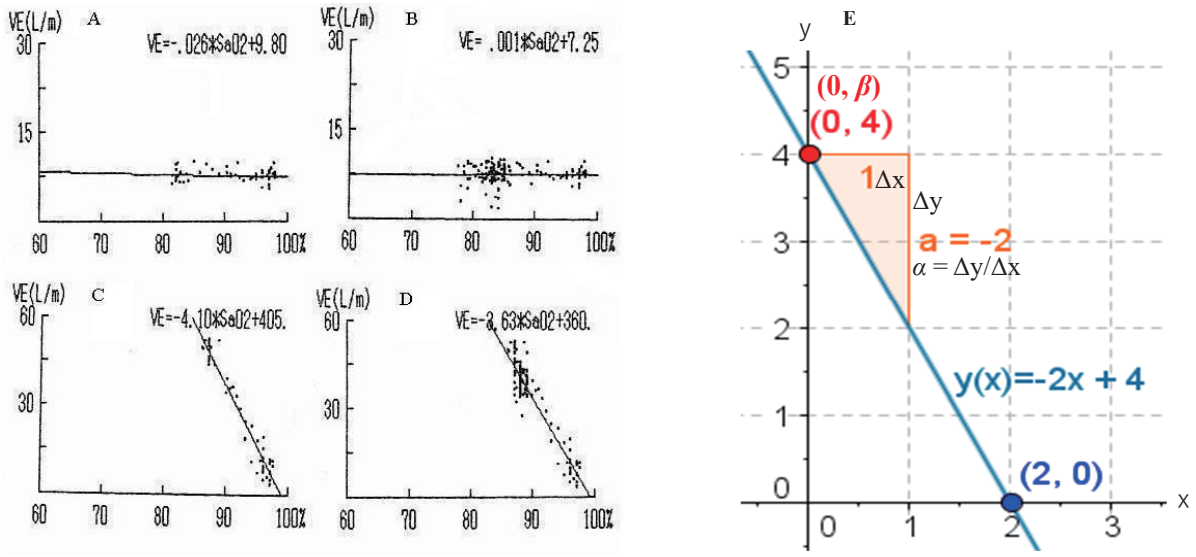

Fig. 4 The spirographs showed a typical response of $\dot{V}_E$ (L/min) to SpO_2 (%) in a HAPE-s subject (A-B) and in a HAPE-r subject (C-D). A : The $\dot{V}_E = -0.026^*SpO_2 + 9.80$ after 10-min hypoxic exposure in a HAPE-s subject (No. 1 of HAPE-s group in Table 1, absolute $\alpha = 0.026$) ; B : The $\dot{V}_E = 0.001^*SpO_2 + 7.25$ after 30-min hypoxic exposure in the same HAPE-s subject (No. 1 of HAPE-s group in Table 1, absolute $\alpha = 0.001$) ; C : The $\dot{V}_E = -4.10^*SpO_2 + 405$ after 10-min hypoxic exposure in a HAPE-r subject (No. 4 of HAPE-r group in Table 1, absolute $\alpha = 4.10$) ; D : The $\dot{V}_E = -3.63^*SpO_2 + 360$ after 30-min hypoxic exposure in the same HAPE-r subject (No. 4 of HAPE-r group in Table 1, absolute $\alpha = 3.63$) ; E : A mathematical illustration for understanding the slope linear regression relating minute ventilation ($\dot{V}_E$, L/min) to oxygen saturation (SpO_2, %), $\dot{V}_E = \alpha^*SpO_2 + \beta$. Supposing that the y axis represents $\dot{V}_E$ and x axis represents SpO_2, the coefficient α was a slope parameter representing the ratio of change of y or $\dot{V}_E$ (Δy or $\Delta \dot{V}_E$) to change of x or SpO_2 (Δx or ΔSpO_2) between any two distinct points along the linear regression ($\Delta y / \Delta x$ or $\Delta \dot{V}_E / \Delta SpO_2$), which determined the steepness of the line.

Thus, the absolute α value was used to indicate HVR based on the definition of $\Delta \dot{V}_E / \Delta SpO_2$. The negative value of slope α indicated decreasing direction of the line resulting from increasing $\dot{V}_E$ in relation to decreasing SpO_2. The β was a deduced vertical asymptote in $\dot{V}_E$ for infinitely responding to SpO_2 **(Fig. 4E)**.

D Evaluation of minute ventilation during hypoxic exposure

The $\dot{V}_E$ was estimated by the linear regression ($\dot{V}_E = \alpha^*SpO_2 + \beta$) at SpO_2 of 80 % after 10-min and 30-min hypoxic exposures in each subject, respectively **(Table 1)**. According to studies by Dahan et al.[11] and Teppema et al.[12], we defined the decline of $\dot{V}_E$ from 10-min to 30-min hypoxic exposures as hypoxic ventilation decline (HVD) during this period **(Table 1)**, which was estimated by the percentage of the $\dot{V}_E$ decline from 10-min to 30-min hypoxic exposures [HVD (%) = ($\dot{V}_{E\ \text{after 10-min hypoxia}} - \dot{V}_{E\ \text{after 30-min hypoxia}}$)/$\dot{V}_{E\ \text{after 10-min hypoxia}}$].

E Statistical analysis

The continuous variables were expressed as means ± standard deviation (SD). The differences of measurements between the HAPE-s and HAPE-r groups were compared using an unpaired Student's *t*-test. Meanwhile, the differences of measurements between 10-min and 30-min hypoxic exposure in each group were compared by paired Student's *t*-test. A two-tailed $p < 0.05$ indicated statistical significance.

Ⅲ Results

A Subjects

The case group consisted of 12 HAPE-s subjects including 10 males and 2 females with an average age of 50.7 ± 1.4 years old and the control group was composed of 10 HAPE-r subjects including 9 males and 1 female with an average of 50.9 ± 1.4 years old. The age, gender, ethnicity, and previous history of hypoxic exposure were comparable between the two groups. All subjects were unrelated Japanese, born

Table 1 Linear regressions of the ventilatory response to hypoxia in HAPE-s and HAPE-r subjects

	Over 10 minutes of hypoxia			Over 30 minutes of hypoxia			
No.	**[a] $\dot{V}_E$ (L/min) = α*SaO$_2$+β**	**Absolute slope α value ($\Delta\dot{V}_E/\Delta SpO_2$)**	**[b] $\dot{V}_E$ (L/min)**	**$\dot{V}_E$ (L/min) = α*SaO2+β [a]**	**Absolute slope α value ($\Delta\dot{V}_E/\Delta SpO_2$)**	**[b] $\dot{V}_E$ (L/min)**	**[c] HVD (%)**
HAPE-s							
1	−0.026*SaO2+9.80	0.026	9.8	0.001*SaO2+7.25	0.001	7.25	26.0
2	−0.14*SaO2+21.7	0.140	21.7	−0.106*SaO2+18.5	0.106	18.5	14.7
3	−0.137*SaO2+20.1	0.137	20.1	−0.079*SaO2+14.6	0.079	14.6	27.4
4	−0.2*SaO2+29.5	0.200	29.5	−0.201*SaO2+29.8	0.201	29.8	−1.0
5	−0.446*SaO2+52.3	0.446	52.3	−0.276*SaO2+36.2	0.276	36.2	30.8
6	−0.192*SaO2+29.6	0.192	29.6	−0.09*SaO2+20.2	0.090	20.2	31.8
7	−0.579*SaO2+65.1	0.579	65.1	−0.177*SaO2+27.4	0.177	27.4	57.9
8	−0.442*SaO2+58.8	0.442	58.8	−0.156*SaO2+24.8	0.156	24.8	57.8
9	−0.557*SaO2+62.0	0.557	62.0	−0.305*SaO2+38.5	0.305	38.5	37.9
10	−0.167*SaO2+31.1	0.167	31.1	−0.035*SaO2+18.3	0.035	18.3	41.2
11	−0.259*SaO2+31.6	0.259	31.6	−0.285*SaO2+34.1	0.285	34.1	−7.9
12	−0.327*SaO2+42.8	0.327	42.8	−0.168*SaO2+27.7	0.168	27.7	35.3
Mean±SD		**0.29±0.18**	**37.6±17.9**		**0.16±0.09 [d](P=0.004)**	**24.7±9.3 [d](P=0.005)**	**29.3**
HAPE-r							
1	−1.76*SaO2+179.0	1.760	179.0	−1.67*SaO2+170.0	1.670	170.0	5.0
2	−0.047*SaO2+12.6	0.047	12.6	−0.047*SaO2+3.98	0.047	3.98	68.4
3	−0.011*SaO2+10.8	0.011	10.8	−0.206*SaO2+31.3	0.206	31.3	−189.8
4	−4.10*SaO2+405.0	4.100	405.0	−3.63*SaO2+360.0	3.630	360.0	11.1
5	−0.673*SaO2+71.8	0.673	71.8	−0.623*SaO2+66.6	0.623	66.6	7.2
6	−1.35*SaO2+146.0	1.350	146.0	−1.01*SaO2+106.9	1.012	106.9	27.4
7	−1.15*SaO2+124.0	1.150	124.0	−1.34*SaO2+142.0	1.340	142.0	−14.5
8	−1.46*SaO2+158.0	1.460	158.0	−1.18*SaO2+131.0	1.180	131.0	17.1
9	−0.572*SaO2+65.8	0.572	65.8	−0.376*SaO2+47.1	0.376	47.1	28.4
10	−0.201*SaO2+32.4	0.201	32.4	−0.037*SaO2+9.98	0.037	9.98	69.2
	Mean±SD	**1.13±1.21**	**119.6±116.1**		**1.01±1.08 [d](P=0.11)**	**106.1±104.9 [d](P=0.07)**	**3.1**
	[e] P values (HAPE-s vs. HAPE-r)	**0.03**	**0.02**		**0.01**	**0.01**	

Abbreviations: HAPE-s, high-altitude pulmonary edema susceptible subjects; HAPE-r, high-altitude pulmonary edema resistant subjects; HVD, hypoxic ventilation decline; No., number of subjects; $\dot{V}_E$ (L/min), minute ventilation (litter/minute); SD, standard deviation.

[a]: This linear regression was expressed as $\dot{V}_E$ (L/min) = α*SaO$_2$+β, in which the slope parameter α value was the ratio of change of $\dot{V}_E$ ($\Delta\dot{V}_E$) to change of SpO$_2$ (ΔSpO_2).

[b]: The $\dot{V}_E$ was estimated by the linear regression ($\dot{V}_E = \alpha$*SpO$_2$+β) at SpO$_2$ of 80 % after 10-min and 30-min hypoxic exposures in each subject, respectively.

[c]: HVD (%) = ($\dot{V}_{E\ \text{after 10-min hypoxia}} - \dot{V}_{E\ \text{after 30-min hypoxia}}$)/$\dot{V}_{E\ \text{after 10-min hypoxia}}$).

[d]: P values were compared with 10-min hypoxic exposure by paired t-test in each group.

[e]: P values were compared between the HAPE-s and HAPE-r groups by unpaired t-test.

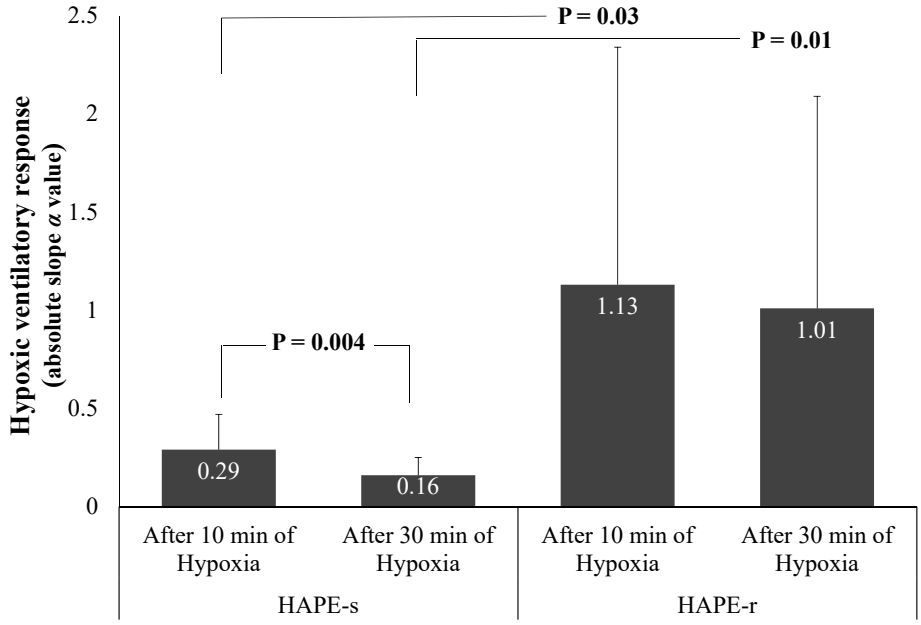

Fig. 5 The absolute slope α value was significantly lower in the HAPE-s than the HAPE-r groups both after 10-min (0.29 ± 0.18 vs. 1.13 ± 1.21, P = 0.03) and after 30-min hypoxic exposures (0.16 ± 0.09 vs. 1.01 ± 1.08, P = 0.01). The absolute slope α value was significantly reduced from 0.29 ± 0.18 after 10-min hypoxic exposure to 0.16 ± 0.09 after 30-min hypoxic exposure in the HAPE-s group (P = 0.004). There was no significant reduction of the absolute slope α value from 10-min to 30-min hypoxic exposures in the HAPE-r group (1.13 ± 1.21 vs. 1.01 ± 1.08, P = 0.11). The number in the bar was the mean value for each event.

and residing at low altitudes.

B Hypoxic status of the subjects

All subjects including HAPE-s and HAPE-r completed the present hypoxic experiment without severe hypoxic symptoms requiring termination of the hypoxic exposure. The SpO_2 was significantly reduced from 98.4 ± 0.9 % under normoxia to 79.6 ± 3.4 % after 30 min of isocapnic hypoxic exposure in the HAPE-s group ($p < 0.0001$), and from 98.4 ± 1.0 % to 80.8 ± 3.3 % in HAPE-r group ($p < 0.0001$). There were no significant differences of the SpO2 between the two groups either under normoxic or under hypoxic conditions ($P > 0.05$).

C Hypoxic ventilatory response

The linear regressions of $\dot{V}_E = \alpha^* SpO_2 + \beta$ in each subject of the two groups are shown in Table 1. The absolute slope α value was significantly lower in the HAPE-s than the HAPE-r groups both after 10-min (0.29 ± 0.18 vs. 1.13 ± 1.21) and 30-min (0.16 ± 0.09 vs. 1.01 ± 1.08) hypoxic exposures (P = 0.03 and P = 0.01, respectively, **Fig. 5**). Moreover, the absolute slope α value was significantly reduced from 0.29 ± 0.18 after 10-min hypoxic exposure to 0.16 ± 0.09 after 30-min hypoxic exposure in the HAPE-s group (P = 0.004, **Fig. 5**) with a reduced rate of 44.8 %. However, there was no significant reduction of the absolute slope α value from 10-min to 30-min hypoxic exposures in the HAPE-r group (P = 0.11, **Fig. 5**) with a reduced rate of 10.6 %. As a result, the declines of $\dot{V}_E$ from 10-min to 30-min hypoxic exposures (HVD) were 29.3 % in the HAPE-s and 3.1 % in the HAPE-r subjects **(Table 1)**.

Ⅳ Discussion

By the property of linear regression of $\dot{V}_E = \alpha^* SpO_2 + \beta$, the absolute slope α value determined the steepness of the line in a ratio of change of $\dot{V}_E$ ($\Delta \dot{V}_E$) to change of SpO_2 (ΔSpO_2) between any two distinct points on this line. Thus, the absolute slope α value was used to quantitatively express the ratio of $\Delta \dot{V}_E / \Delta SpO_2$ in the line obtaining at any time-domain throughout the hypoxic exposure. The HVR was usu-

ally calculated by dividing the change of ventilation ($\Delta \dot{V}_E$) by the change of SpO_2 (ΔSpO_2) in a hypoxic exposure ($\Delta \dot{V}_E / \Delta SpO_2$)[4)-6)]. In agreement with this definition, the absolute slope α value was used to quantitatively evaluate HVR in the present study.

The remarkable findings demonstrated that in addition to the significantly lower HVR in HAPE-s than HAPE-r over the 10-min hypoxic exposure, the HVR constantly declined at a reduction rate of 44.8 % over 30-min hypoxic exposure in the HAPE-s group, resulting in a significantly lower ventilation in HAPE-s than HAPE-r over the prolonged hypoxic exposures. To our knowledge, this was the first extended model of hypoxic study to investigate the HVR over a prolonged hypoxic exposure in HAPE-s subjects.

The HVR is a quick compensation for challenging oxygen deprivation by attempting to increase alveolar ventilation to overcome the hypoxic breathing[1)]. Matsuzawa and coworkers[6)] found that the HVR was lower in 8 out of 10 HAPE-s subjects than in HAPE-r subjects, while 2 out of the HAPE-s did not show the reduction of the HVR over 10 minutes of hypoxic exposure. Hohenhaus and colleagues[5)] reported that there was minimal overlap of the HVR in the HAPE-s and healthy controls within 10 minutes of hypoxic exposure. On the other hand, Selland and associates[13)] stated that HAPE occurred in susceptible individuals despite the presence of normal or high HVR. However, these studies did not investigate the HVR in HAPE-s subjects over a long-term of hypoxia. Easton and coworkers[1)] demonstrated that isocapnic hypoxia caused an initial increase of ventilation to 161 % of baseline with a significant fall after 25 minutes to 121 %. This hypoxic ventilatory decline (HVD) is a reduction of $\dot{V}_E$ in the second phase of a hypoxic exposure[12)] and it can be sustained for prolonged hypoxia in adult humans at high altitudes[14)]. The present results revealed that the HVD was indeed significantly present in the HAPE-s in the later phase of prolonged hypoxic exposure, probably due to the continuously low HVR in that group. We propose that the blunted HVR following significant HVD in the later phase of prolonged hypoxic exposure is an additionally essential element for further understanding of the role of HVR in the development of HAPE.

The significant HVD might be involved with the continuously blunted HVR over prolonged hypoxia. However, the HVR and HVD are highly variable between species, gender, genetic factors, and experiments[15)]. The roles of up-regulation inhibitory (i.e., dopaminergic) and down-regulation excitatory (i.e., glutamatergic) signaling in the carotid body chemoreceptors for responding to hypoxia are thought to be involved in the mechanisms of HVR and HVD over prolonged hypoxic exposure[15)16)]. The present results suggested that the ventilatory depression dominated in HAPE-s while counterbalanced in HAPE-r in the prolonged acute hypoxia. Taken together, the constantly low HVR with significant HVD over prolonged hypoxia contributes to the development of HAPE.

The major limitation of this human hypoxic study was the small sample size that might cause type I error in statistical analysis. The present method of measurement of HVR was novel, thus there was less opportunity to compare the current results with other related results for deep discussion of the issues of HVR and HVD over prolonged hypoxia. Replication studies elsewhere are required to confirm the present results. In addition, the neurotransmitters of carotid body chemoreceptors in responding to hypoxia were not analyzed in the present study due to the small sample size. Nevertheless, a significant constant reduction of HVR with significant HVD over prolonged hypoxia in the HAPE-s subjects was originally found in the present study. Further investigation is necessary for elucidating the pathophysiological roles of HVR and HVD exposed to high-altitude hypoxia in the development of HAPE.

In conclusion, in addition to the blunted HVR, the constantly declined HVR with remarkable HVD over a prolonged hypoxic exposure was one of the contributing elements in the development of HAPE.

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