Original Research

Acute intermittent hypoxia exposures enhance arterial oxygen delivery

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Abstract

Physiological adaptations to intermittent hypoxia (IH) conditioning are based on the cumulative effect of repeated IH exposures. The present study sought to test the hypothesis that acute IH exposures would promote arterial O_2 delivery and regional tissue oxygenation. Changes in arterial O_2 saturation (SaO_2, oximeter), forearm muscle and cerebral tissue oxygenations (SmO_2 and ScO_2, near-infrared spectroscopy) were compared during five repeated hypoxia exposures ($10 \pm 0.2\%$ O_2 for 5-min each) interposed with four-minute inhalation of room air in 11 healthy subjects (24 ± 0.9 y). Baseline, prehypoxia partial pressure of end-tidal O_2 ($P_{ET}O_2$, mass spectrometer) and SaO_2 (107 ± 2 mmHg and $97.3 \pm 0.3\%$) were decreased ($P < 0.05$) after the first bout as compared with those during normoxia prior to the second (94 ± 2 mmHg and $96.2 \pm 0.4\%$) and the fifth (92 ± 3 mmHg and $95.7 \pm 0.7\%$) episodes of IH exposures, whereas partial pressure of end-tidal CO_2, tidal volume and breathing frequency were similar. Arterial O_2 dissociation in terms of per unit decrease in $P_{ET}O_2$ during hypoxia, i.e. the slope of $SaO_2/P_{ET}O_2$, was augmented ($P = 0.0025$) from $0.71 \pm 0.09\%$/mmHg during the first hypoxia bout to $1.39 \pm 0.15\%$/mmHg and $1.47 \pm 0.16\%$/mmHg during the second and the fifth bouts, respectively. Fractional muscle tissue O_2 extraction rate (SmO_2D, i.e. normalized difference between SaO_2 and SmO_2) progressively decreased ($P < 0.01$) during IH; however, fractional cerebral tissue O_2 extraction rate (ScO_2D, i.e. normalized difference between SaO_2 and ScO_2) did not decrease during hypoxia ($P = 0.94$). ScO_2D during normoxia tended to increase ($P = 0.089$) following repeated IH exposures. We conclude that enhanced arterial O_2 delivery with repeated IH exposures serves as a compensatory mechanism to potentiate O_2 availability during hypoxia.

Keywords: chemoreflex, hyperventilation, hypocapnia, O_2 dissociation, tachycardia

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Introduction

Hypoxia decreases arterial O_2 saturation (SaO_2) and content. Consequently, it diminishes O_2 delivery to and utilization by body tissues. Previously, Henson *et al.*[1] documented that regional cerebral tissue O_2 saturation (ScO_2), monitored by near-infrared spectroscopy (NIRS), was diminished along with a decrease in partial pressure of end tidal O_2 ($P_{ET}O_2$) during acute hypoxia. This relationship between decreases in ScO_2 and in $P_{ET}O_2$ during hypoxia exposure was confirmed by Kolb *et al.*[2] despite an increase in middle cerebral arterial blood flow velocity (V_{MCA}). Although hypocapnia due to hyperventilation during hypoxia would increase vascular tone in the brain, these data indicate that a decrease in ScO_2 is not likely restricted by a reduction of cerebral blood flow, since V_{MCA} is augmented during acute hypoxia.[2,3] Recently, Peltonen *et al.*[3] reported that ScO_2 was diminished, while regional muscle tissue O_2 saturation (SmO_2) remained unchanged, during acute hypoxia. Their data[3] suggested a more sensitive response in ScO_2 than in SmO_2 to decreases in SaO_2 or $P_{ET}O_2$. We postulated that this difference between ScO_2 and SmO_2 would be attributed to tissue differences in O_2 extraction rate during acute hypoxia. Although NIRS measured tissue oxygenation[1–3] includes oxyhemoglobin within all vessels of the region, the hemoglobin volume in the venous bed or capacitance vessels is predominant as compared with that within the arterial bed or resistant vessels.[4] Furthermore, ScO_2 has been validated to be significantly correlated with jugular venous oxygenation.[1,5] Therefore, the difference between SaO_2 and tissue

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oxygenation (i.e. ScO_2 and SmO_2) is an estimate of regional tissue O_2 extraction rate.

Normobaric intermittent hypoxia (IH) conditioning using repeated, five-minute bouts of hypoxia exposures interposed with brief normoxia recovery periods for 14–21 d provide antioxidant defenses[6] and beneficial or protective influence on the heart[7,8] and brain.[9] While this IH conditioning has been adopted in the treatment of various pathological conditions[6,10–13] and for improvement of physical performance,[14–16] the acute impact of repeated IH exposures remains to be defined. Based on the previous observations that acute hypoxia reduced ScO_2, which was associated with a decrease in SaO_2 and with an increase in V_{MCA},[2,3] we hypothesized that repeated IH exposures could acutely enhance arterial O_2 delivery during repeated, moderate hypoxia. Since reduced ScO_2 during hypoxia was not due to reduced flow-mediated O_2 delivery,[2,3] we further postulated that cerebral tissue O_2 extraction rate could be improved in relation to a concurrently enhanced systemic arterial O_2 delivery. The present study focused on examining the responses in systemic arterial O_2 delivery and regional tissue oxygenation by comparing the acute changes in SaO_2, ScO_2 and SmO_2 before and after repeated IH exposures.

Methods

Subjects

Eleven healthy, young volunteer subjects (5 women and 6 men) participated in the study after having given a written informed consent and passed a physical examination. The group (mean ± standard error of the mean) age, body mass index, weight and height were 24.3 ± 0.9 y, 23.6 ± 1.05 U, 70.2 ± 4.5 kg and 172 ± 3 cm, respectively. The study protocol was reviewed and approved by the Institutional Review Board for the Protection of Human Subjects at UNT Health Science Center at Fort Worth. All subjects were clinically confirmed to be free of cardiovascular, metabolic, renal, or pulmonary diseases and symptoms. No subject was exposed to hypoxia or lived in high altitude area before. Prior to the experimental testing, all subjects had an orientation in the laboratory to familiarize them with the experimental procedure and measurements applied in the study.

Measurements

During the experiment, the subject's heart rate (HR) was beat-to-beat monitored from a standard lead of the electrocardiogram. Brachial arterial blood pressure (ABP) was manually measured using a brachial cuff controlled by a Tonometry machine (Colin Model 7000 Tonometry, San Antonio, TX, USA). SaO_2 and partial pressure of transcutaneous CO_2 ($P_{TC}CO_2$) were continuously monitored from the subject's earlobe by a radiometer sensor (TOSCA 500, Radiometer America Inc, Westlake, OH, USA). The temperature of the sensor was set and maintained at 42°C, which augmented the cutaneous blood flow of the earlobe and arterialized the dermal capillary blood. The radiometer sensor was calibrated against the standard gas prior to each use. Ipsilateral regional ScO_2 of the prefrontal cortex and regional forearm muscle oxygenation (SmO_2) were monitored using the technique of NIRS (Somanetics, 4100 INVOS Cerebral Oximeter, Troy, MI, USA) by the sensors placed on the right side of the forehead and on the right brachioradialis, respectively. In this technique, two light diodes generate low-intensity NIR light at 730 and 805 nm wavelengths that are emitted into the subject's prefrontal cerebral tissue and forearm muscle tissue, respectively. The light penetrates through the tissues up to ~2 cm in depth. The spectral absorptions of blood in the regions targeted by the light is determined by measuring the amount of light returned to two detectors positioned at distances of 3 and 4 cm from the light source.[17,18] This measurement and the technique of NIR spectroscopy have been repeatedly applied in our previous studies.[19,20] Breath-by-breath inspired and expired O_2 and CO_2 fractions were measured using a mass spectrometer (Perkin-Elmer, 1100 Medical Gas Analyzer, Saint Louis, MO, USA), which was calibrated against room air and medical gas containing 10% O_2 and 10% CO_2 balanced with N_2. Both inspiration and expiration tidal volumes were breath-by-breath monitored using a Universal Ventilation Meter (UVM VacuMed, Ventura, CA, USA) interfaced with a VacuMed disposable, air-cushioned face mask during the experiment. The UVM air flow volume was calibrated using a 3-L calibration syringe (VacuMed) before the experiment. Subject's inspired air (normobaric hypoxic air with 10.0 ± 0.2% O_2 or room air) was manually guided by a three-way T-shape stopcock control valve (Hans Rudolph 2100C, Shawnee, KS, USA). All these analog data were continuously digitized at 250 Hz by a computer interfaced with a data acquisition system (BIOPAC MP150, Santa Barbara, CA, USA). Continuous $P_{ET}O_2$ and partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) were calculated off-line using the product of ambient barometric pressure and the end-tidal fractions of O_2 and CO_2, respectively. Fractional O_2 extraction or the estimated O_2 extraction rate in regional cerebral tissue (ScO_2D) or regional muscle tissue (SmO_2D) was calculated from the ratio: $(SaO_2 - ScO_2)/SaO_2$ or the ratio: $(SaO_2 - SmO_2)/SaO_2$. Breathing frequency (f) was counted from the analog signals of the expiration tidal volume (V_T) and minute ventilation (V_E) was computed from the product of f and V_T.

Procedure

The experiment was carried out with the subject resting in a supine position at a room temperature of 24 ± 1°C. The subject wore the face mask during the entire period of the experiment. After ≥15 minutes of supine resting from the instrumentation, the subject's baseline SaO_2, ScO_2, SmO_2, $P_{ET}O_2$, $P_{ET}CO_2$, $P_{TC}CO_2$, V_E and HR were continuously recorded for five minutes; meanwhile, 2–3 ABP readings were collected using the standard brachial cuff controlled by the tonometry machine during inhalation of normoxia room air. Following the normoxia baseline data collection, the subject's inspiratory airflow was directed to a prefilled (and constantly being refilled) gas bag which was connected

to a gas tank with hypoxic air (10.0 ± 0.2% O_2). Each single bout of hypoxia exposure was five minutes followed by a four-minute recovery with breathing normoxia room air. During the hypoxia exposure and the normoxia recovery, SaO_2, ScO_2, SmO_2, $P_{ET}O_2$, $P_{ET}CO_2$, $P_{TC}CO_2$, V_E and HR were continuously monitored and ABP was manually collected. This five-minute hypoxia and four-minute room air cyclic bout was repeated five times during the experiment. All subjects tolerated hypoxia without any discomfort or irregular heart beat during the entire duration of the experiment. Figure 1 illustrates the experimental protocol carried out on a representative subject.

Data analyses

Data analyses were focused on comparison of the systemic arterial O_2 delivery and regional tissue oxygenation responses during the first, second and last (i.e. fifth) bouts of IH exposures. Minute data were averaged over 30 s continuous data from the second half of the minute during the baseline condition prior to hypoxia and during 5 min of hypoxia exposures. Two-way analysis of variance (ANOVA) with repeated measures was applied to test the significance of bout and minute (i.e. time) factors. *Post hoc* analysis was performed using Tukey's option if a significant effect ($P < 0.05$) was detected by ANOVA. Data recorded each minute during hypoxia were analyzed using simple linear regression to examine the effect of time on these variables. General linear model analysis was applied for the comparison of the difference between the slopes. All data were reported as group mean and the mean of standard error (SE). Statistical analyses were performed using Statistic Analysis System software (SAS; Cary, NC, USA).

Results

During normoxia with inhalation of room air, baseline SaO_2, $P_{ET}O_2$ and ScO_2 became smaller after repeated IH exposures (see Table 1). However, baseline $P_{ET}CO_2$, V_E and SmO_2 were not significantly different before and after repeated IH exposures. Hypoxia significantly decreased $P_{ET}O_2$, $P_{ET}CO_2$, SaO_2, ScO_2 and SmO_2, and significantly increased V_E (Table 1). During five-minute hypoxia exposure, the decrease in SaO_2 was significantly explained by the decrease in $P_{ET}O_2$ (Figure 2). In terms of per unit decrease in $P_{ET}O_2$, the rate of decrease in SaO_2 was significantly smaller ($P = 0.0025$) during the first bout ($0.71 \pm 0.09\%$/mmHg, $R^2 = 0.96$) as compared with those during the second ($1.39 \pm 0.15\%$/mmHg, $R^2 = 0.96$) and the fifth ($1.47 \pm 0.16\%$/mmHg, $R^2 = 0.97$) bouts of IH exposures.

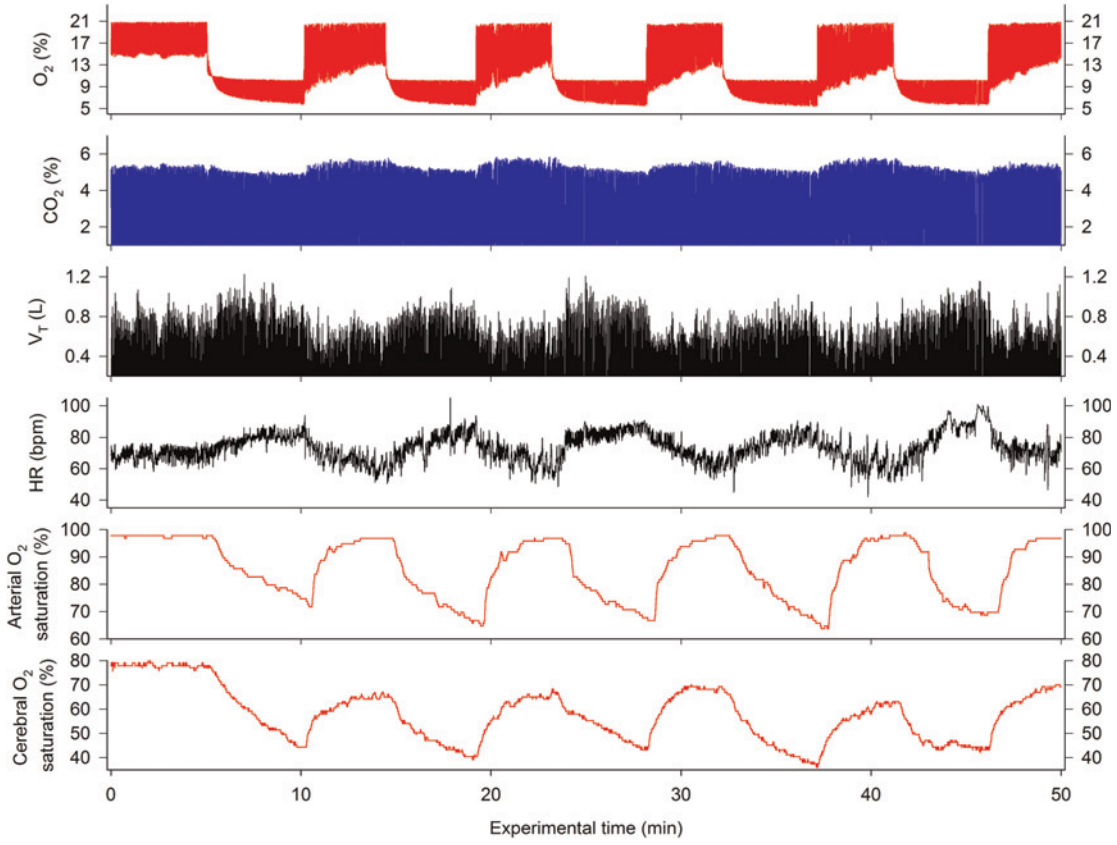

Figure 1 Experimental protocol: five bouts of cyclic intermittent hypoxia exposures (with 5-min inhalation of 10% O_2) interspersed with 4-min inhalation of room air. From top to bottom panels: continuous analog O_2, CO_2, expiratory tidal volume (V_T), heart rate (HR), arterial O_2 saturation (SaO_2) and cerebral tissue O_2 saturation (ScO_2). Hypoxia exposures elicit progressive decreases in the fraction of end tidal O_2 ($F_{ET}O_2$), in SaO_2 and in ScO_2. During normoxia recovery with inhalation of room air, $F_{ET}O_2$ gradually approach the baseline prior to hypoxia exposure. Tidal volume is increased immediately in response to hypoxia. This hypoxia stimulated increase in tidal volume or hyperventilation appears to be counteracted by hypocapnia, as indicated by gradual decrease in the fraction of end tidal CO_2. Heart rate is continuously increased in the entire duration of hypoxia exposure (A color version of this figure is available in the online journal)

Table 1 Group cardiorespiratory variables

		Time (min)					
Bout		**0**	**1**	**2**	**3**	**4**	**5**
SaO_2 (%)	1	97.31 ± 0.25	93.37 ± 0.83*	87.34 ± 0.67*†	84.31 ± 0.64*†	84.31 ± 0.79*†	78.78 ± 1.19*†
	2	96.23 ± 0.37	92.64 ± 0.92*	86.75 ± 1.18*†	80.70 ± 0.96*†‡	77.73 ± 1.17*†‡	74.25 ± 1.46*†‡
	5	95.74 ± 0.74‡	94.20 ± 1.23*	85.84 ± 1.31*	79.49 ± 1.18*†‡	76.63 ± 1.43*†‡	74.54 ± 1.70*†‡
		Time factor: $P < 0.0001$; bout factor: $P < 0.0001$					
$P_{ET}O_2$ (mmHg)	1	106.59 ± 1.66	62.67 ± 2.20*	51.25 ± 1.35*†	47.28 ± 1.12*†	45.25 ± 1.06*†	42.99 ± 1.08*†
	2	93.76 ± 2.29‡	54.48 ± 2.12*‡	48.44 ± 1.51*†	44.85 ± 1.47*†	42.51 ± 1.19*†	41.82 ± 1.32*†
	5	91.87 ± 2.71‡	54.11 ± 40.82*‡	46.04 ± 1.42*†‡	43.52 ± 1.24*†‡	41.78 ± 1.19*†‡	40.82 ± 1.09*†‡
		Time factor: $P < 0.0001$; bout factor: $P < 0.0001$					
$P_{ET}CO_2$ (mmHg)	1	40.88 ± 0.72	39.48 ± 0.71*	38.07 ± 0.60*†	37.37 ± 0.57*†	36.84 ± 0.60*†	36.93 ± 0.60*†
	2	41.34 ± 0.79	39.38 ± 0.72*	38.83 ± 0.73*	37.98 ± 0.78*†	37.73 ± 0.68*†	37.05 ± 0.79*†
	5	41.23 ± 0.69	39.27 ± 0.68*	37.94 ± 0.80*†	37.16 ± 0.77*†	37.00 ± 0.74*†	36.74 ± 0.69*†
		Time factor: $P < 0.0001$; bout factor: $P = 0.39$					
ScO_2 (%)	1	63.46 ± 3.02	60.45 ± 2.75	56.15 ± 2.59*	56.15 ± 2.59*†	51.54 ± 2.37*†	49.14 ± 2.33*†
	2	60.90 ± 1.50	56.66 ± 1.69*	53.77 ± 1.90*†	50.70 ± 1.85*†	48.72 ± 1.85*†	47.34 ± 1.98*†
	5	58.36 ± 2.25‡	55.35 ± 2.23	50.93 ± 2.14*	48.91 ± 2.16*†	47.90 ± 2.10*†	46.59 ± 2.02*†‡
		Time factor: $P < 0.0001$; bout factor: $P = 0.0012$					
SmO_2 (%)	1	65.78 ± 2.27	65.51 ± 2.64	63.73 ± 2.59	62.28 ± 2.56*	61.42 ± 2.3*†	60.70 ± 2.38*†
	2	63.06 ± 1.83	63.01 ± 2.07	62.38 ± 2.11	60.49 ± 2.42	59.07 ± 2.54*†	58.02 ± 2.31*†
	5	63.64 ± 1.88	64.51 ± 1.94	62.90 ± 2.20	61.13 ± 2.18*	60.12 ± 2.19*†	59.08 ± 2.25*†
		Time factor: $P = 0.02$; bout factor: $P = 0.22$					
ScO_2D	1	0.348 ± 0.031	0.354 ± 0.027	0.358 ± 0.027	0.366 ± 0.029	0.368 ± 0.029	0.377 ± 0.027
	2	0.367 ± 0.015	0.389 ± 0.017	0.380 ± 0.022	0.372 ± 0.022	0.373 ± 0.022	0.363 ± 0.023
	5	0.390 ± 0.023	0.414 ± 0.020	0.406 ± 0.025	0.386 ± 0.024	0.375 ± 0.025	0.374 ± 0.025
		Time factor: $P = 0.94$; bout factor: $P = 0.089$					
SmO_2D	1	0.322 ± 0.022	0.296 ± 0.028	0.269 ± 0.029	0.261 ± 0.030	0.245 ± 0.031	0.226 ± 0.035*
	2	0.345 ± 0.019	0.319 ± 0.021	0.277 ± 0.026*	0.247 ± 0.033*	0.236 ± 0.038*	0.213 ± 0.040*†
	5	0.335 ± 0.019	0.313 ± 0.020	0.265 ± 0.027*	0.227 ± 0.031*†	0.209 ± 0.036*†	0.201 ± 0.039*†
		Time factor: $P < 0.0001$; bout factor: $P = 0.66$					
V_E (L/min)	1	9.74 ± 0.68	12.95 ± 0.79*	13.71 = 1.12*	14.19 ± 1.22*	13.49 ± 0.96*	13.79 ± 1.06*
	2	9.31 ± 0.72	6.01 ± 0.47*‡	13.95 ± 1.56*†	12.72 ± 0.88*†	13.30 ± 1.08*†	6.23 ± 0.29*†
	5	8.93 ± 0.76	11.89 ± 1.53*	13.04 ± 0.88*	13.88 ± 1.20*	13.93 ± 1.14*	13.10 ± 0.81*
		Time factor: $P < 0.0001$; bout factor: $P < 0.0006$					
HR (bpm)	1	70.74 ± 4.21	75.86 ± 4.14*	80.84 ± 4.38*†	82.35 ± 4.04*†	85.39 ± 4.11*†	85.81 ± 4.15*†
	2	67.61 ± 3.93	73.11 ± 4.06*	77.75 ± 4.48*†	79.75 ± 4.69*†	82.92 ± 4.22*†	86.43 ± 4.28*†
	5	66.65 ± 3.46	69.40 ± 3.76	78.37 ± 4.80*†	83.01 ± 4.39*†	85.26 ± 4.26*†	88.12 ± 4.54*†
		Time factor: $P < 0.0001$; bout factor: $P = 0.61$					

Bouts 1, 2 and 5 indicate the first, second and fifth intermittent hypoxia exposures, respectively. Minute 0, baseline with inhalation of room air; minutes 1–5, time of hypoxia; SaO_2, arterial O_2 saturation; $P_{ET}O_2$, partial pressure of end tidal O_2; $P_{ET}CO_2$, partial pressure of end tidal CO_2; ScO_2, cerebral tissue oxygenation; SmO_2, muscle tissue oxygenation; ScO_2D, cerebral tissue O_2 extraction rate; SmO_2D, muscle tissue O_2 extraction rate; V_E, minute ventilation; HR, heart rate. *P* values indicate the outcome of two-way analysis of variance

*†Significant difference as compared with minute 0 and minute 1 data, respectively

‡A significant difference from the first bout of intermittent hypoxia in the same minute

There was no significant difference in the slopes between the second and the fifth bouts.

Although hypoxia significantly stimulated ventilation, hyperventilation during hypoxia was not linearly correlated with decreases in $P_{ET}O_2$ or SaO_2 either before or after repeated IH exposures, probably due to hypocapnia associated with the hyperventilation, which counteracted the hypoxia stimulus to ventilation. During five-minute hypoxia, graded hypocapnia, i.e. decrease in $P_{ET}CO_2$, was linearly associated with a progressive decrease in $P_{ET}O_2$. The magnitude of changes in $P_{ET}CO_2$ in relation to $P_{ET}O_2$ was not significantly ($P = 0.16$) different between the bouts, i.e. slope of $P_{ET}CO_2/P_{ET}O_2$ was 0.14 ± 0.01 mmHg/mmHg ($R^2 = 0.98$) in the first bout, 0.17 ± 0.03 mmHg/mmHg ($R^2 = 0.92$) in the second and 0.19 ± 0.01 mmHg/mmHg ($R^2 = 0.99$) in the fifth bouts of IH exposures (Figure 3, left panel). During hypoxia, hyperventilation elicited decreases in $P_{ET}CO_2$ were highly correlated ($R^2 = 0.90$, $P < 0.001$) with those in $P_{TC}CO_2$, with no significant difference between the bouts (Figure 3, right panel).

Decreases in both SmO_2 and ScO_2 were significantly associated with decreases in $P_{ET}O_2$ during hypoxia (Tables 1 and 2). The estimated O_2 extraction rate in forearm muscle (SmO_2D) was decreased with time ($P < 0.0001$) without differences between the bouts ($P = 0.66$), whereas directional change of the estimated O_2 extraction rate in cerebral tissue (ScO_2D) during hypoxia was not consistent ($P = 0.94$). There was a trend ($P = 0.089$) that ScO_2D became greater at minute zero and early minutes of hypoxia following acute, repeated bouts of hypoxia exposures (Table 1). Overall, the magnitude of the estimated tissue O_2 extraction rate was consistently greater in ScO_2D than in SmO_2D at rest ($P = 0.035$) and during hypoxia ($P = 0.0001$).

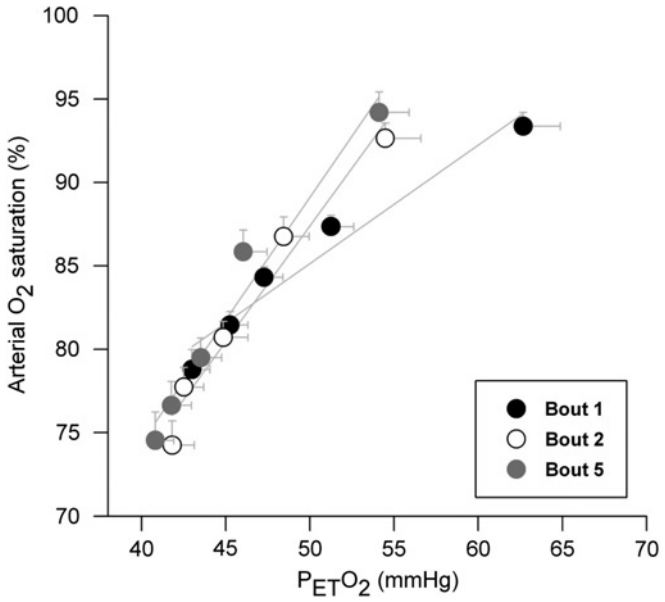

Figure 2 Decreases in arterial O_2 saturation in relation to partial pressure of end-tidal O_2 ($P_{ET}O_2$) during the first, second and fifth bouts of 5-min hypoxic exposures. The rate of decrease in SaO_2 in terms of per unit decrease in $P_{ET}O_2$ during hypoxia is significantly smaller ($P = 0.0025$) during the first bout (slope $= 0.71 \pm 0.09\%$/mmHg, $R^2 = 0.96$) as compared with those during the second (slope $= 1.39 \pm 0.15\%$/mmHg, $R^2 = 0.97$) and the fifth (slope $= 1.47 \pm 0.16\%$/mmHg, $R^2 = 0.97$) bouts of IH exposures. There is no slope difference between the second and the fifth hypoxia bouts

Table 2 Response to decreases in $P_{ET}O_2$ during 5-min intermittent hypoxia exposures

Bout	Slope	*r*	*P* value	Interaction
Muscle tissue oxygenation versus $P_{ET}O_2$				
1	0.24 ± 0.03	0.974	0.0001	$P = 0.184$
2	0.38 ± 0.09	0.931	0.0017	
5	0.39 ± 0.08	0.947	0.0010	
Cerebral tissue oxygenation versus $P_{ET}O_2$				
1	0.55 ± 0.08	0.972	0.0057	$P = 0.263$
2	0.72 ± 0.08	0.983	0.0026	
5	0.64 ± 0.04	0.993	0.0006	
Muscle tissue O_2 extraction rate versus $P_{ET}O_2$ ($\times 10^{-2}$)				
1	0.32 ± 0.06	0.949	0.0137	$P = 0.0008$
2	0.78 ± 0.07	0.987	0.0017	
5	0.85 ± 0.09	0.982	0.0028	
Cerebral tissue O_2 extraction rate versus $P_{ET}O_2$ ($\times 10^{-2}$)				
1	-0.10 ± 0.03	-0.893	0.0411	$P = 0.0004$
2	0.18 ± 0.04	0.945	0.0154	
5	0.31 ± 0.08	0.915	0.0293	

Interaction *P* value indicates whether a decrease in tissue oxygenation or O_2 extraction rate associated with decrease in $P_{ET}O_2$ is significantly affected by different IH bouts. A negative slope suggests an increase in O_2 extraction rate during hypoxia-induced decrease in $P_{ET}O_2$
$P_{ET}O_2$, partial pressure of end-tidal O_2; IH, intermittent hypoxia

HR and ABP

During normoxia, baseline HR was not affected by repeated IH exposures (Table 1). Hypoxia significantly augmented HR. Acute, repeated IH exposures significantly ($P = 0.0008$) augmented the rate of tachycardiac response during decrease in $P_{ET}O_2$, i.e. the slopes of $HR/P_{ET}O_2$ were -0.51 ± 0.06 ($R^2 = 0.96$), -0.96 ± 0.16 ($R^2 = 0.92$) and -1.36 ± 0.11 ($R^2 = 0.98$) bpm/mmHg during the first, second and fifth bouts, respectively (Figure 4). There was no significant difference in the slopes between the second and the fifth bouts. ABP was not different during normoxia before and after repeated IH exposures. Normobaric hypoxia did not significantly change ABP (Table 3).

Discussion

This study was first of this kind to examine the acute compensatory responses in arterial and tissue oxygenation dynamics during repeated IH exposures. The three novel findings of the study were as follows: first, repeated IH exposures significantly decreased SaO_2 during subsequent normoxia and hypoxia. In terms of per unit change in $P_{ET}O_2$, the rate of decrease in SaO_2 during hypoxia was significantly augmented following acute IH exposures, suggesting an enhanced hemoglobin–O_2 dissociation or increased tissue O_2 delivery. Second, cerebral tissue O_2 extraction rate was significantly

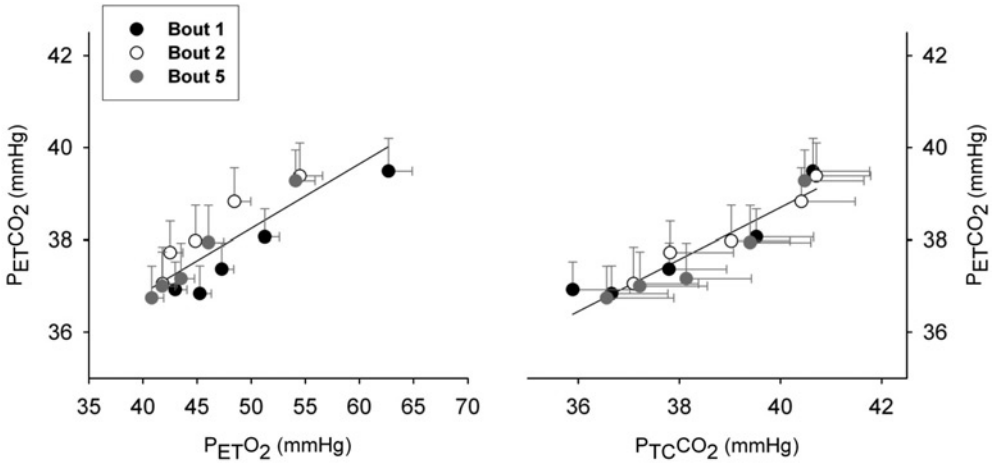

Figure 3 Overall slope of decreases in partial pressure of end tidal CO_2 during hypoxia (slope $= 0.14 \pm 0.02$ mmHg/mmHg, $R^2 = 0.77$, left panel). Acute, repeated intermittent hypoxia exposures have no significant effect on the rate of hypocapnia associated with decreases in partial pressure of end tidal O_2. During hypoxia, changes in $P_{ET}CO_2$ are highly ($P < 0.001$) correlated with changes in partial pressure of transcutaneous CO_2 ($R^2 = 0.90$, slope $= 0.56 \pm 0.05$ mmHg/mmHg) which is not affected by different bouts of intermittent hypoxia exposures

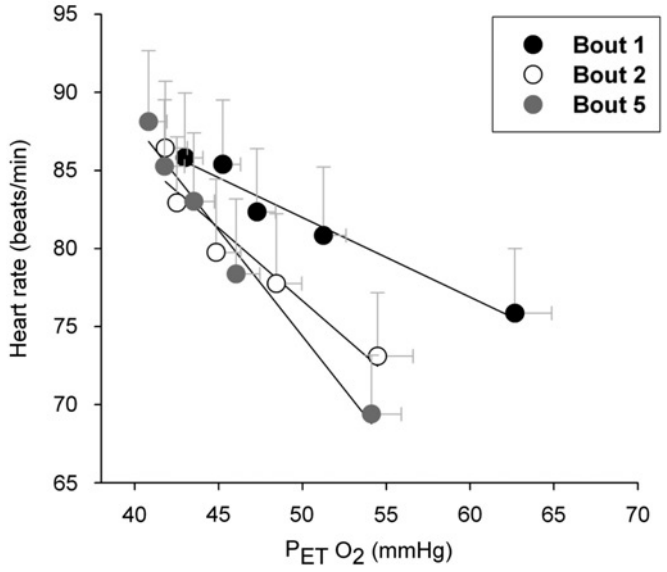

Figure 4 Tachycardiac responses are significantly stimulated by hypoxia. The rate of increase in heart rate in terms of per unit decrease in partial pressure of end tidal O_2 is significantly smaller in the first bout (-0.51 ± 0.06 bpm/mmHg, $R^2 = 0.96$) as compared with that during the second bout (-0.96 ± 0.16 bpm/mmHg, $R^2 = 0.92$) or the fifth bout (-1.36 ± 0.11 bpm/mmHg, $R^2 = 0.98$). There is no significant difference in the slopes between the second and the fifth bouts of hypoxia exposures

greater than muscle tissue O_2 extraction rate at rest and during hypoxia exposures. Repeated IH exposure showed a trend toward increased cerebral tissue O_2 extraction rate. Third, short duration of IH exposures did not change ABP, although HR was significantly increased during hypoxia. The chemoreflex-mediated tachycardiac response was significantly sensitized by acute IH exposures, which could help facilitate O_2 flux during hypoxia.

Repeated IH exposures enhance systemic O_2 delivery

During inhalation of normoxia room air, baseline $P_{ET}O_2$ was significantly decreased from 107 to 94 and 92 mmHg prior to the second and fifth bouts of IH exposures. This $P_{ET}O_2$ difference during normoxia between different bouts was not attributable to the different cardiovascular or ventilatory responses, because the baseline pulmonary ventilation, $P_{ET}CO_2$, HR and ABP during normoxia were all similar (see Tables 1 and 3). Therefore, a lower $P_{ET}O_2$ following the first IH exposure could not have fully resulted from incomplete recovery with four-minute inhalation of room air between the hypoxia episodes or the residual effect of IH exposures. It more likely resulted from enhanced systemic O_2 utilization with acute, repeated IH exposures.

During hypoxia, enhanced systemic O_2 delivery after repeated IH exposures was augmented in the presence of decreased $P_{ET}O_2$ (see Figure 2). This improved O_2 delivery might have resulted, at least in part, from a shift of the hemoglobin–O_2 dissociation curve. However, hyperventilation during repeated IH would reduce partial pressure of arterial CO_2 ($PaCO_2$) and increase pH, which would increase O_2 affinity with hemoglobin (the Bohr effect) and blunt O_2 delivery by the tissue. However, neither hyperventilation nor hypocapnia during hypoxia was significantly different between

Table 3 Arterial blood pressure during cyclic hypoxia interposed with inhalation of normoxia room air

	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia	Hypoxia	Normoxia
SBP (mmHg)	118.6 ± 6.8	116.2 ± 3.8	116.6 ± 5.2	118.3 ± 4.8	116.2 ± 5.2	116.1 ± 4.4	116.1 ± 4.2	115.6 ± 4.7	116.3 ± 4.7	117.3 ± 4.5	115.4 ± 5.9
DBP (mmHg)	63.8 ± 3.2	63.7 ± 2.5	64.5 ± 2.3	65.3 ± 2.9	63.7 ± 2.0	65.1 ± 2.5	65.3 ± 2.4	62.5 ± 1.8	61.5 ± 2.1	65.0 ± 2.2	64.4 ± 3.7
MAP (mmHg)	82.0 ± 4.3	81.2 ± 2.9	81.9 ± 3.1	83.0 ± 3.3	81.2 ± 2.8	82.1 ± 3.0	82.2 ± 2.9	80.2 ± 2.4	79.8 ± 2.8	82.4 ± 2.6	81.4 ± 4.4
PP (mmHg)	54.9 ± 4.0	52.6 ± 1.5	52.1 ± 3.8	53.0 ± 3.2	52.5 ± 4.2	51.0 ± 2.6	50.8 ± 2.7	53.1 ± 4.0	54.8 ± 3.4	52.3 ± 3.8	51.0 ± 2.9

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. Arterial blood pressure is not significantly altered during the experiment

the bouts (Table 1, Figure 3). Therefore, the Bohr effect should have been comparable during repeated hypoxia exposures. Although body temperature may also affect the O_2 association with hemoglobin, any change in blood temperature should have been insignificant in the current protocol. Therefore, the most likely explanation for the difference in the slopes of $SaO_2/P_{ET}O_2$ (a significant increase immediately following the initial bout of hypoxia exposure, see Figure 2) would be a difference in the intracellular hypoxia product of the erythrocyte 2,3-diphosphoglycerate (DPG). Diphosphoglycerate production would be stimulated by hypoxia,[21] and 2,3-DPG would accumulate during repeated IH exposures. Apparently, this change was able to serve as a rapid compensatory mechanism and to help increase O_2 availability with reduced blood O_2 content during hypoxia. Furthermore, increased 2,3-DPG could explain the lesser SaO_2 observed at the end of repeated five-minute hypoxia (Table 1 and Figure 2), suggesting an enhanced O_2 unloading in the presence of elevated 2,3-DPG.[22]

Repeated IH exposures and tissue O_2 extraction rate

Normobaric hypoxia has been proved to diminish ScO_2.[1–3] The present study confirmed that both ScO_2 and SmO_2 were linearly decreased with $P_{ET}O_2$ during five-minute hypoxia (Tables 1 and 2). However, the magnitude of decreases in ScO_2 was much greater as compared with that in SmO_2. This finding was consistent with a previous report by Peltonen *et al.*[3] in which they observed that cerebral tissue showed a greater deoxygenation during acute hypoxia as compared with muscle tissue. A low ScO_2 observed during hypoxia was probably related to the fact that the brain has high basal metabolic rate, i.e. high O_2 demand, while its O_2 reserve is limited. The present data indicated that the estimated O_2 extraction rate was constantly greater in cerebral than in muscle tissues during both normoxia and hypoxia conditions. This finding suggests that the brain compensates for hypoxic hypoxemia by increasing its O_2 extraction rate. This compensatory mechanism seems important and practical when systemic arterial O_2 content is diminished by hypoxia, and when the hypoxia-mediated vasodilation is counteracted by sympathoexcitation and hypocapnia due to the hypoxia stimulated hyperventilation.

The present data indicated that the O_2 extraction rate during hypoxia was well maintained in cerebral tissue as compared with muscle tissue, suggesting that regional cerebral tissue was protected during brief IH exposures. Repeated IH exposures showed a trend to increase baseline cerebral tissue O_2 extraction rate, which would likely explain higher ScO_2D during early minutes of hypoxia following repeated IH exposures. However, the estimated SmO_2D either during normoxia or during hypoxia was not increased by repeated IH exposures.

Repeated IH exposures sensitizes chemoreflex control of HR

The data of the present study demonstrated that ABP was well maintained at normal, baseline level during the entire duration of IH exposures (see Table 3). These data are consistent with previous observations[3,23,24] that acute hypoxia with poikilocapnia or isocapnia does not cause hypertensive response in healthy, young adults. Increased sympathetic nerve activity during hypoxia appears to be counterbalanced by the hypoxia-mediated systemic vasodilation.

Nonetheless, there was a significant tachycardiac response that progressed with the duration of hypoxia (Table 1 and Figure 4). This continuous increase in HR appeared not to be correlated with the mechanical action of the hyperventilation, which did not continuously increase during hypoxia due to the counter effect of hypocapnia. Since HR during the supine resting condition is primarily mediated by parasympathetic influence, and since ABP was maintained during IH exposures, this tachycardiac response during hypoxia was predominantly determined by the chemoreflex. Repeated IH exposures caused rapid reset of the tachycardiac responses. This chemoreflex-mediated tachycardia was significantly sensitized, as manifest by the greater magnitude of increases in HR driven by decreases in $P_{ET}O_2$ during repeated IH exposures. This rapid, augmented chemoreflex control of HR would help increase cardiac output and O_2 delivery while maintaining constant ABP during hypoxia.

Limitations of the study

Since all our subjects were healthy, young adults and they were exposed to short durations (5 min) of normobaric hypoxia, the outcome of the study may be not compatible with observations made on older subjects or patients in pathological conditions[25–27] or with data from longer hypoxic exposure.[28] Another limitation is that change in $P_{ET}O_2$, instead of alveolar or arterial PO_2, was measured in the present study. However, we believe that breath-by-breath measured $P_{ET}O_2$ should be faithfully related to continuous change in alveolar or arterial PO_2 in healthy, young subjects who have no problem with gas exchange. Finally, NIRS measured tissue oxygenation includes oxyhemoglobin in all regional vascular beds and this regional tissue oxygenation is predominantly determined by oxyhemoglobin in regional capacitance vessels.[1,4] Thus, estimated O_2 extraction based on the difference between arterial oxygenation and tissue oxygenation could have underestimated O_2 utilization. However, it seems unlikely that the proportional distribution of oxyhemoglobin in arterial, venous and microvascular beds would be significantly altered within a single session of IH exposures, so the ScO_2D and SmO_2D comparisons made between different bouts of IH exposures should be valid.

In summary, repeated short bouts of IH exposures acutely enhance systemic O_2 delivery or arterial hemoglobin–O_2 dissociation during hypoxia. This acute compensatory change shows a trend to help improve regional cerebral tissue O_2 extraction rate following repeated IH exposures.

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