The effects of two paradigms of intermittent hypoxia on human cardio-ventilatory responses and cerebral tissue oxygenation.

by

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ABSTRACT

The purpose of this study was to determine the ventilatory, cardiovascular, and cerebral tissue oxygen responses to two paradigms of normobaric, isocapnic, intermittent hypoxia (IH). Eighteen male subjects were randomly assigned to one of two IH groups; short duration IH (SDIH) was exposed to 5 minutes of 12% O_2 separated by 5 minutes of normoxia for one hour, and long duration IH (LDIH) was exposed to 30 minutes of 12% O_2. Both groups had 10 daily exposures over a twelve day period. The isocapnic hypoxic ventilatory response was measured before (preHVR) and after (postHVR) each daily exposure on day 1, 3, 5, 8, 10, 12 and again 3 and 5 days following the end of IH. The hyperoxic hypercapnic ventilatory response (HCVR) was determined following rest on days 1, 12, 15, and 17. During all procedures, ventilation, beat-by-beat blood pressure, heart rate (HR) arterial oxyhemoglobin saturation (SaO_2), and cerebral tissue oxygenation (ScO_2) were measured. The preHVR increased throughout IH exposure regardless of paradigm and returned to resting levels by day 17 (Day 1: 0.84 ± 0.50; Day 12: 1.20 ± 1.01; Day 17: 0.95 ± 0.58 l min^{-1} $\%SaO_2^{-1}$; p= 0.002). The HCVR did not change throughout IH. The postHVR was blunted compared with the preHVR (p= 0.02). There were no differences in the change in systolic blood pressure sensitivity ($\Delta SBP/\Delta SaO_2$), diastolic blood pressure sensitivity ($\Delta DBP/\Delta SaO_2$), heart rate sensitivity ($\Delta HR/\Delta SaO_2$), cardiac output sensitivity ($\Delta CO/\Delta SaO_2$), stroke volume sensitivity ($\Delta SV/\Delta SaO_2$), and total peripheral resistance sensitivity ($\Delta TPR/\Delta SaO_2$) to hypoxia following IH. The change in cerebral tissue oxygen saturation sensitivity to hypoxia ($\Delta ScO_2/\Delta SaO_2$) was less on day 12 (Day 1: -0.51 ± 0.13; Day 12: -0.64 ± 0.18l p= 0.0002) and the change in cerebral tissue deoxyhemoglobin concentration ($\Delta HHb/\Delta SaO_2$)

was more on day 12 (Day 1: 0.34 ± 0.21; Day 12: 0.44 ± 0.14 uM $\%SaO_2^{-1}$; p= 0.007). These differences had returned to baseline by day 17. Acute exposure to SDIH increased mean arterial pressure (MAP; p= 0.005) but LDIH did not (p>0.05). Intermittent hypoxia did not improve exercise ventilatory efficiency during exercise. In conclusion, exposures to SDIH and LDIH have similar effects on the ventilatory, cardiovascular, and cerebral oxygen responses to acute progressive hypoxia. However, acute exposure to SDIH increases MAP while LDIH does not.

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INTRODUCTION

Exposure to hypoxia affects animal and human physiology in numerous ways. In response to acute isocapnic hypoxia, ventilation, blood pressure and muscle sympathetic nerve activity increase (Xie *et al.*, 2000). Two types of hypoxic exposure can be distinguished: continuous hypoxia (CH) and intermittent hypoxia (IH). Continuous hypoxia can be described as a single exposure to a sustained hypoxic stimulus over a prolonged period. There are two forms of IH: long duration intermittent hypoxia (LDIH) and short duration intermittent hypoxia (SDIH) (Peng & Prabhakar, 2004). From the available studies, LDIH is typically defined as a single daily episode of hypoxia lasting 30 minutes to five hours that occurs every day for more than five days, while SDIH typically involves several daily bouts of hypoxia (3-12 bouts) lasting less than 5-7 minutes with each bout of hypoxia being separated by normoxia. Like LDIH, SDIH involves daily exposures that continue for more than five days. Continuous hypoxia typically occurs in individuals who inhabit environments at high-altitude, while IH seems to occur more frequently in daily life, as in situations of brief episodic sojourns to high-altitude or during repeated apneas, such as in sleep apnea.

In both animal and human studies, LDIH and SDIH affect the control of breathing (Gozal & Gozal, 2001; Mitchell *et al.*, 2001; Prabhakar, 2001; Mitchell & Johnson, 2003; Morris *et al.*, 2003), the cardiovascular system (Earley & Walker, 2002; Gonzales & Walker, 2002; Jernigan & Resta, 2002), and the autonomic nervous system (Morgan *et al.*, 1995; Smith & Muenter, 2000; Yasuma & Hayano, 2000). Unlike CH, IH may contribute to the effects of pathological conditions, such as sleep apnea and chronic obstructive pulmonary disease (Prabhakar, 2001). Intermittent exposure to hypoxia for a prolonged period of time (i.e. several years) is associated with secondary conditions including systemic hypertension, myocardial and brain infarctions, and cognitive dysfunction (Prabhakar, 2001). Recurrent episodes of hypoxia are also common in humans without pathophysiologies, such as those who voluntarily engage in breath-holding

activities (i.e. breath-hold diving) (Andersson *et al.*, 2002) or travel to high altitude regularly (Powell & Garcia, 2000). These individuals display characteristics in respiratory and cardiovascular control that may be advantageous to them. Breath-hold divers demonstrate a reduced ventilatory response to hypoxia and have an enhanced diving response that allows them to sustain longer breath-hold dives and conserve oxygen (Lindholm *et al.*, 1999; Andersson *et al.*, 2002). On the contrary, individuals who travel to high altitude regularly demonstrate an enhanced ventilatory response to hypoxia; this quality has been suggested to reduce the incidence of acute mountain sickness (Beidleman *et al.*, 2004). It is important to note that individuals with sleep apnea or breath-hold divers are not exposed exclusively to hypoxia. The physiological outcomes of their activities, whether pathological or not, are complicated by marked hypercapnia. However, several animal studies do show that exposure to SDIH, modeled after sleep apnea, leads to secondary hypertension and that hypercapnia is not necessary [reviews: (Fletcher, 2001; Neubauer, 2001; Prabhakar *et al.*, 2001)].

Respiratory function is altered following exposure to hypoxia and is referred to as respiratory neural plasticity (Powell *et al.*, 1998). Various animal studies have demonstrated respiratory neural plasticity within the central nervous system in response to hypoxia (Morris *et al.*, 2003). Interestingly, the response to CH is different from IH. In the rodent model, chronic IH enhances hypoxic sensitivity and leads to sensory long-term facilitation in the carotid body (Peng *et al.*, 2001; Prabhakar, 2001), while sustained hypoxia does not (Mitchell *et al.*, 2001). The study of the control of breathing in humans is ethically limited; as a result, animal models play a major role in the interpretation and analysis of human studies. Studies involving normal human subjects also demonstrate respiratory neural plasticity. As in the rodent model, human hypoxic sensitivity increases with repeated exposure to hypoxia (Katayama *et al.*, 1998; Tansley *et al.*, 1998; Katayama *et al.*, 1999; Garcia *et al.*, 2000b; Katayama *et al.*, 2001a; Katayama *et al.*, 2001b; Mahamed & Duffin, 2001; Katayama *et al.*, 2002; Mateika *et al.*, 2004) although long

term facilitation cannot be detected (Mateika *et al.*, 2004). Other human studies involving patients who have undergone carotid body resection as a treatment for asthma or carotid body tumors (Gross *et al.*, 1976; Honda *et al.*, 1988; Timmers *et al.*, 2003) indicate that the carotid body plays an inhibitory role for the heart rate response and an excitatory role for the ventilatory response to hypoxia. Timmers *et al.* (2003) reported an abolished ventilatory response to hypoxia following bilateral carotid body resection. Similarly, Honda *et al.* (1988) noted the absence of the ventilatory response to progressive eucapnic hypoxia in bilateral carotid body resected subjects; an enhanced tachycardic heart rate response was also seen in these patients.

Making direct comparisons between studies is difficult as there appears to be no standard IH protocol. Some studies expose human subjects to isocapnic hypoxia [controlled end-tidal partial pressure of CO_2 ($PetCO_2$)] (Garcia *et al.*, 2000a) while others expose subjects to poikilocapnic hypoxia (uncontrolled $PetCO_2$) (Tansley *et al.*, 1998; Katayama *et al.*, 2001b). Patterns, durations, and hypoxic intensities vary throughout all IH studies and may involve normobaria (Serebrovskaya *et al.*, 1999; Mahamed & Duffin, 2001; Ainslie *et al.*, 2003; Mateika *et al.*, 2004) or hypobaria (Sato *et al.*, 1992; Sato *et al.*, 1994; Katayama *et al.*, 1998; Katayama *et al.*, 1999; Garcia *et al.*, 2000c; Katayama *et al.*, 2001a; Katayama *et al.*, 2001b). Intermittent hypoxic studies have even involved simultaneous exercise training (Levine *et al.*, 1992; Katayama *et al.*, 1998; Katayama *et al.*, 1999, 2001a). Whether or not the changes in respiratory and cardiovascular physiologies are similar among all of these conditions is unknown and requires further study. In contrast to the rodent model, human studies involving high altitude CH for a week or more have demonstrated an increase in the hypoxic ventilatory response (HVR) that subsequently returns to normal within a week of descent to sea-level (Sato *et al.*, 1992; Sato *et al.*, 1994). More similar to the rodent model are the human studies involving both LDIH and SDIH and equivocally demonstrate increases in HVR (Katayama *et al.*, 1998; Garcia *et al.*, 2000b, 2000c; Katayama *et al.*, 2001b; Katayama *et al.*, 2002). Garcia *et al.* (2000c) compared

five days of hypobaric IH at rest (two hours daily at 3800m) with eight weeks of CH (also at 3800m). Both LDIH and CH induced similar changes in magnitude of HVR; however, two weeks of CH were necessary to reach the same change in HVR seen after only five days of LDIH.

Most paradigms of IH in humans evoke an increase in HVR; however, the available data on the HCVR is not so clear. The HCVR has been reported to either remain unchanged (Katayama *et al.*, 1998; Katayama *et al.*, 1999, 2001a; Mahamed & Duffin, 2001) or increase following IH (Ainslie *et al.*, 2003). Several studies involve IH with concurrent exercise training (Katayama *et al.*, 1998; Katayama *et al.*, 1999) and each study involves a different method for determining HCVR making it difficult to directly compare studies. The first and most common method of determining HCVR is the rebreathing method (Read, 1967) which is thought to be a measure of CO_2 sensitivity at the central chemoreceptor (Mohan *et al.*, 1999). Using this method and exercise training during IH, 30 min of hypobaric hypoxia at 432 mmHg for either six days or two weeks, shows no change in the central chemoreceptor response to CO_2 (Katayama *et al.*, 1998; Katayama *et al.*, 1999). However, Ainslie *et al.* (2003) showed an increase in the hypercapnic ventilatory response following five nights of normobaric poikilocapnic hypoxia (13.8% O_2) using the rebreathing method. Other investigators have used the single breath CO_2 response test (HCVRsb), which is thought to be a measure of the peripheral chemoreceptor response to CO_2 (McClean *et al.*, 1988). No change in HCVRsb was seen following 30 minutes of hypobaric hypoxia at 432 mmHg for six days with concurrent exercise training (Katayama *et al.*, 1999) and also following 1 hour of hypobaric hypoxia at 432 mmHg for two weeks without exercise training (Katayama *et al.*, 2002). Finally, a novel approach of determining the central chemoreceptor response to CO_2 has been employed by Mahamed *et al.* (2001). This method involves prior hyperventilation before commencing the rebreathe at different iso-oxic levels and allows for the determination of the chemoreflex threshold to CO_2. Using the modified

rebreathing technique, changes in the peripheral chemoreflex to CO_2 were measured in hyperoxia and in hypoxia. Following twenty minutes of isocapnic hypoxia daily for 14 consecutive days, an increase in the CO_2 threshold occurred only in the presence of hypoxia, but not hyperoxia (Mahamed & Duffin, 2001). The authors interpreted this result as indicating changes in the peripheral chemoreflex and not the central chemoreflex.

The acute cardiovascular response to hypoxia involves an increase in cardiac output (CO), systemic arterial vasodilation, and pulmonary arterial vasoconstriction (Semenza, 1999). Cerebral blood flow velocity (Vovk *et al.*, 2002), heart rate (HR), and arterial blood pressure increase with progressive isocapnic hypoxia and hyperoxic hypercapnia (Yasuma & Hayano, 2000). Twenty minutes of sustained isocapnic hypoxia elicits increases in heart rate, limb blood flow, blood pressure, and muscle sympathetic nerve activity (Morgan *et al.*, 1995; Xie *et al.*, 2000). Intact peripheral chemoreceptors appear to be necessary for the blood pressure in rats to increase in response to SDIH patterned after that of sleep apnea in humans (Fletcher *et al.*, 1992). Few studies have examined the cardiovascular response to intermittent hypoxic exposure in humans. Katayama *et al.* (2001b) studied the cardio-ventilatory response to progressive isocapnic hypoxia before and after one hour of daily exposure to 4,500 m (~12 % O_2) for 7 days. Resting ventilation, blood pressure, and heart rate did not change after IH. There was, however, an increase in the systolic (SBP) and diastolic (DBP) blood pressure response to progressive hypoxia. These changes in cardiovascular sensitivity were accompanied by an increase in HVR. Alternatively, in a cat model, no changes in the blood pressure response to hypoxia were present following four days of chronic intermittent hypoxia (hypoxic episodes lasting for ~ 90s, 8 hours/day, inspired PO_2 ~ 75 mmHg) (Rey *et al.*, 2004).

Recently published animal work suggests IH may alter both peripheral and cerebrovascular vasomotor activity as a result of a hypoxia associated endothelial dysfunction (Earley & Walker, 2002; Gonzales & Walker, 2002; Jernigan & Resta, 2002; Altay *et al.*, 2004;

Phillips *et al.*, 2004). These alterations in vasomotor activity may differ depending on the location of the vascular bed. Mesenteric resistance arteries isolated from rats exposed to 48 hours of hypobaric hypoxia (380 mmHg) have attenuated vasoconstrictor reactivity (Earley & Walker, 2002; Gonzales & Walker, 2002). On the other hand, rats exposed to a similar level of hypobaric hypoxia for four weeks have an attenuated endothelium-derived nitric oxide-dependent pulmonary vasodilation (Jernigan & Resta, 2002). Another study exposed rats to SDIH and assessed endothelial function of resistance vessels in skeletal muscle and cerebral circulations and found that exposure to chronic IH severely blunts vasodilator responsiveness to acute hypoxia (Phillips *et al.*, 2004). Impaired blood flow regulation caused by endothelial dysfunction could limit oxygen delivery during acute episodes of hypoxia. No similar studies have been performed in humans. One study does assess, however, the effects of five consecutive nocturnal hypoxic exposures in humans (Kolb *et al.*, 2004). Using an end-tidal forcing technique, cerebral blood flow velocity responses to acute variations in O_2 and CO_2 were determined before and after the nocturnal hypoxic episode. Their results show that discontinuous hypoxia (nocturnal hypoxia separated by daytime normoxia) elicits an increase in the sensitivity of cerebral blood flow velocity to acute variations in O_2 and CO_2. In another study, the cerebral blood flow velocity response to 5-minute steps of isocapnic hypoxia and hyperoxic hypercapnia were measured before and during a 5-day sojourn at 3,810 m altitude (Jensen *et al.*, 1996). The results from this study indicate that the cerebral vascular response to acute isocapnic hypoxia may increase during acclimatization at high altitude. However, it is unknown if IH affects cerebral oxygenation.

Hypothesis

The primary purpose of this study was to compare normobaric, isocapnic SDIH with LDIH exposure and to follow changes in ventilatory, cardiovascular, and cerebral tissue oxygen responses over a twelve-day period and again over a five-day period after hypoxic exposure had ended. It was hypothesized that IH would increase the cardio-ventilatory responses to acute hypoxia, but not to hypercapnia, and that those individuals exposed to SDIH would have a greater response than those exposed to LDIH. It was further hypothesized that the change in cerebral oxygenation during acute hypoxia would increase over the twelve-day period and would remain increased for at least five days after hypoxic exposure had been completed.

MATERIALS AND METHODS

All procedures and methods were approved by the clinical research ethics board of the University of British Columbia and conformed to the Declaration of Helsinki. All testing occurred within the Health and Integrative Physiology Laboratory at the University of British Columbia.

Subjects

Eighteen active, healthy male volunteers were randomly assigned to one of two intermittent hypoxia groups. All subjects had normal cardiopulmonary function and were excluded from participation if they had been diagnosed with sleep apnea, had a history of smoking, or if they were hypertensive (systolic>140mmHg; diastolic>90mmHg). All subjects were life-long residents at sea-level and had not sojourned to altitude (>3,000m) in the year prior to testing. None of the subjects participated in breath-hold diving or trained/competed as endurance athletes, as this has been known to affect ventilatory responses (Byrne-Quinn *et al.*, 1971; Ferretti, 2001).

Experimental Protocol

The experimental protocol is displayed in Figure 1. Subjects reported to the laboratory on the first day of testing when procedures were explained and informed consent was obtained. Anthropometric measures and pulmonary function tests were determined on Day 1 prior to ventilatory response testing and IH. Subjects were exposed to a total of ten intermittent hypoxic exposures throughout a twelve-day period. Following the twelve-day IH period, subjects returned three and five days later to determine the time course of recovery for the cardio-ventilatory responses. The HCVR was determined after ten minutes of rest (eupnea) on Days 1, 12, 15, and 17. The HVR was determined immediately before intermittent hypoxic exposure

(preHVR) and five minutes following exposure (postHVR) on Days 1, 3, 5, 8, 10, 12, 15, and 17. On Days 1, 12, 15, and 17 the HCVR preceded the preHVR test by a minimum of five minutes or until cardio-ventilatory parameters returned to eupneic levels. A maximal cycle exercise test occurred on Days 1 and 12 to determine the subjects' maximal oxygen consumption ($\dot{V}O_{2max}$) and to determine if intermittent hypoxia improves ventilatory efficiency during submaximal and maximal exercise. For both experimental groups, IH exposure involved isocapnic exposure to a fraction of inspired O_2 (FiO_2) of 12% (balance N_2) for a total duration of 30 minutes. The SDIH group (n=9) was exposed to a five-minute hypoxia to five-minute normoxia cycle for one hour, while the LDIH group (n=9) was exposed to 30 minutes of sustained hypoxia.

Measurements and Procedures

All data was acquired in real-time using an analog-to-digital converter (Powerlab/16SP ML 795, ADInstruments, Colorado Springs, CO, USA) interfaced with a personal laptop computer (Satellite, Toshiba, Irvine, CA, USA). During the measurement of heart rate variability all data was sampled at 1000 Hz; during all other procedures data was sampled at 200 Hz and stored for subsequent analysis. Commercially available software was used to analyze ventilatory and near-infrared spectroscopy variables (Powerlab V5.02, ADInstruments, Colorado Springs, CO, USA) and cardiovascular variables (Beatscope V1.1, FMS, Arnhem, Netherlands).

Pulmonary Function Testing. Subjects performed three forced vital capacity (FVC) maneuvers using a calibrated spirometer (Spirolab II, Medical International Research, Via del Maggiolino, Roma, Italy). Recorded parameters included FVC, forced expiratory volume in one second ($FEV_{1.0}$), and the ratio of $FEV_{1.0}$ to FVC ($FEV_{1.0}$/FVC). The above parameters were tested in accordance with the procedures outlined by the American Thoracic Society (1995). Predicted

values were determined for each individual based on European Respiratory Society prediction equations for adult men (Quanjer *et al.*, 1993).

Maximal Cycle Exercise Test. Maximal oxygen consumption was determined using a ramped exercise test on an electronically braked cycle ergometer (Excalibur, Lode, Groningen, Netherlands). Workload was increased in a ramped fashion (30-watts/min) until subjects reached volitional fatigue. Metabolic and ventilatory parameters were recorded using a calibrated open-circuit system (Physio-Dyne, Max-1, Fitness Instrument Tech., NY, USA). Heart rate was obtained using a telemetric HR monitoring system (S410, Polar Electro Inc., Kempele, Finland). In addition to volitional exhaustion, all subjects fulfilled at least two of the following criteria for $\dot{V}O_{2\,max}$: 1) heart rate $\geq$ 220-age, 2) respiratory exchange ratio $\geq$ 1.10, 3) no further increase in $\dot{V}O_2$ with increasing workload.

Hyperoxic Hypercapnic Ventilatory Response (HCVR). HCVR was assessed by a modified rebreathing technique (Read, 1967). Subjects were asked to maximally expire and were then switched to a rebreathing bag (6% CO_2; 94% O_2) and took three full breaths to facilitate mixing between the lungs and bag (Rebuck, 1976), after which they were asked to "breathe as you feel necessary". Rebreathing continued until $PetCO_2$ reached 60-65 mmHg or for a maximal duration of five minutes. Gas was sampled at the mouth and analyzed using an infrared CO_2 analyzer (CD-3A, AEI, Pittsburgh, Pennsylvania, USA). Inspired minute ventilation ($\dot{V}_I$) was plotted as a function of $PetCO_2$ and the linear regression relating these two variables was used to represent the HCVR (i.e. the slope of the line expressed as l min^{-1} $mmHg^{-1}$). $\dot{V}_I$ and $PetCO_2$ were averaged over 10 second intervals prior to plotting HCVR.

Isocapnic Hypoxic Ventilatory Response (HVR). HVR was assessed by modifications of a method previously described (Weil *et al.*, 1970; Harms & Stager, 1995; Derchak *et al.*, 2000; Guenette *et al.*, 2004; Koehle *et al.*, In Press). Subjects breathed room air from a mixing chamber (13.5 liters) and 100% N_2 was gradually added to the inspiratory circuit to evoke a gradual drop in SaO_2 to 75% over an approximate 5 minute period. SaO_2 was measured at the finger using a pulse oximeter (3740, Ohmeda, Louisville, CO, USA). Isocapnia was maintained during the test by the addition of 100% CO_2 through a 25 gauge needle inserted into the inspiratory circuit 30 cm from the inspiratory valve. Resting $PetCO_2$ was determined during a ten-minute rest period which occurred at the beginning of each day. The FiO_2 was determined by analyzing gas sampled from the proximal side of the inspiratory valve (S-3A, AEI, Pittsburgh, Pennsylvania, USA). CO_2 was sampled at the mouth and analyzed as described above. $\dot{V}_I$ was plotted as a function of SaO_2 and the slope of this line was taken to represent the HVR (expressed as $l\ min^{-1}\ \%SaO_2^{-1}$). $\dot{V}_I$ and SaO_2 were averaged over 10 second intervals prior to plotting HVR.

Cardiovascular Parameters. Beat-by-beat SBP, DBP, and mean arterial pressure (MAP) were obtained during rest, HCVR, HVR, and IH using finger pulse photoplethysmography (Finometer, FMS, Arnhem, Netherlands). MAP was calculated from SBP and DBP using the following formula: MAP = DBP + 1/3(SBP-DBP). The photoplethysmograph was placed on the mid-phalanx of the middle digit of the left hand. Beat-by-beat blood pressure was calibrated against an automated blood pressure measurement (BPM-100, VSM Medtech Ltd., Vancouver, Canada) taken from the right arm at the level of the heart every three minutes. Cardiovascular analysis included determination of heart rate (HR), cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR), all obtained from arterial pressure using a three-element model of

arterial input impedance (Wesseling *et al.*, 1993; Harms *et al.*, 1999; Houtman *et al.*, 1999; Remmen *et al.*, 2002; Van Lieshout *et al.*, 2003). Cardiovascular sensitivity to hypoxia was determined as per previously published studies and was expressed as $\Delta SBP/\Delta SaO_2$, $\Delta DBP/\Delta SaO_2$, $\Delta MAP/SaO_2$, $\Delta HR/\Delta SaO_2$, $\Delta CO/\Delta SaO_2$, $\Delta SV/\Delta SaO_2$, and $\Delta TPR/\Delta SaO_2$ (Insalaco *et al.*, 1996; Katayama *et al.*, 2001b). Similar analyses during hypercapnia were not undertaken because of the inability to demonstrate linearity of the cardiovascular variables and $PetCO_2$. All cardiovascular parameters were averaged over 10 second intervals.

Near-infrared Spectroscopy (NIRS). Cerebral tissue oxygen saturation (ScO_2) and changes in oxyhemoglobin concentration (O_2Hb), deoxyhemoglobin concentration (HHb), and total hemoglobin concentration (cHb) were determined using near-infrared spectroscopy at a sampling rate of 2 Hz (Niro 300, Hamamatsu Phototonics K. K., Sunayama-Cho, Hamamatsu-city, Japan). The cerebral optodes were applied so that the detection probe sat toward the middle of the forehead and the emission probe was 4-5 cm away, towards the right side, avoiding the temporal muscles, sinuses, and the hairline as previously described (Madsen & Secher, 1999). Optodes were placed in a black plastic holder and applied to the head with a bandage to shield the light and maintain optode separation. The path-length value was determined as the product of the source-detector probe spacing (in cm) multiplied by the differential path-length factor (DPF) for the brain (Madsen & Secher, 1999). A DPF of 5.92 was used for the brain as determined by Van der Zee *et al.* (1992) where a 4 or 5 cm probe spacing would have a pathlength of 23.7 cm or 29.6 cm respectively. Like the other cardiovascular parameters, ScO_2, O_2Hb, HHb, and cHb sensitivity to hypoxia was expressed as $\Delta ScO_2/\Delta SaO_2$, $\Delta O_2Hb/\Delta SaO_2$, $\Delta HHb/\Delta SaO_2$, and $\Delta cHb/\Delta SaO_2$.

Heart Rate Variability (HRV). Heart rate variability was determined during the ten-minute resting (normoxia) period on days 1, 12, 15, and 17. HRV was measured in order to determine if resting shifts in autonomic function occurred through intermittent hypoxia exposure. Subjects were monitored via an ECG (ML 132, ADInstruments, Colorado Springs, CO, USA), configured in the standard bipolar limb lead I and sampled at 1 kHz. Analysis occurred off-line as described previously (Task Force, 1996). Measured R-R intervals were determined from the electrocardiogram and the resulting tachogram was fast Fourier transformed (FFT). The high frequency (HF), low frequency (LF), and very low frequency (VLF) bands were defined as 0.15-0.4 Hz, 0.04-0.15 Hz, and <0.04 Hz respectively. HRV calculations were performed on normal R-R intervals and ectopic intervals. If it was too difficult to accurately select the R-wave from the ECG signal, then a 45 Hz low pass filter was applied. In addition, a derivative function was applied when necessary to correct for shifts in the ECG baseline.

Statistical Analysis

All data are expressed as means ± SD unless otherwise indicated. Statistical software (Statistica V.6.1, Statsoft Inc., Tulsa, OK, USA) was applied to detect differences between groups, between subjects, and between pre and post measures using repeated measures MANOVA. When significant F-ratios were detected, Tukey's post hoc analysis was applied to determine where the differences lay. Pearson product moment correlations were implemented to determine relationships between selected dependent variables. Statistical significance was set at $p<0.05$.

RESULTS

Subject Characteristics

All eighteen subjects completed 10 intermittent hypoxic exposures over the twelve-day period. One subject did not complete the final day 17 ventilatory response testing and another subject did not complete either maximal exercise test. Missing (incomplete) data on day 17 for this one subject was replaced with the group mean. Mean subject characteristics are displayed in Table 1. Subjects were not statistically different from each other based on age, mass, or pulmonary function; however, the SDIH group was slightly taller than the LDIH group ($F= 7.17$; $df= 16$; $p= 0.01$).

Effects of IH on maximal exercise performance and on the ventilatory response to exercise

Maximal exercise data is displayed in Table 2. There were no differences in any maximal or submaximal exercise data between SDIH and LDIH conditioned individuals. Therefore, all data was pooled together. Maximal $\dot{V}O_2$, $\dot{V}CO_2$, RER, and the ventilatory equivalents for oxygen and CO_2 were not affected by exposure to LDIH or SDIH. In addition, peak power, maximal ventilation and heart rate were also unaffected by exposure to either paradigm of intermittent hypoxia. The ventilatory response to exercise was determined at 20, 40, 60, 80, and 100% of maximal oxygen uptake and CO_2 production and is displayed in Table 3. $\dot{V}_I$, tidal volume (V_t), and breathing frequency (F_b) were not affected at any exercise intensity.

Effects of IH on basal ventilatory and cardiovascular variables

Basal ventilatory and cardiovascular variables measured during eupnea are displayed in Table 4. Also displayed in Table 4 are the coefficients of variation for each variable across 8

days. There were no differences between groups for any resting ventilatory or cardiovascular variable. Slight increases in resting breathing frequency (+2-3 breaths min^{-1}) were detected on day 8 and 10 ($F= 2.44$; $df= 1, 112$; $p= 0.02$), but tidal volume and overall minute ventilation were not different ($p>0.05$). Furthermore, $PetCO_2$ was not different on any day and the mean coefficient of variation was 3.2 %. Basal blood pressure did not differ on each experimental day; however, resting HR was slightly elevated (+7 bpm) at day 10 compared to days 1 and 3 ($F= 2.34$; $df= 7, 112$; $p= 0.03$). Although HR was slightly elevated, there was no difference in CO, suggesting that SV was slightly reduced even though not detectable by statistical analysis. In addition, heart rate variability did not change over the course of the intermittent hypoxic exposures. The HF and LF spectral components of HRV normalized to total power and the LF/HF ratio are displayed in Table 5. Resting TPR and ScO_2 did not change throughout the course of the experiment.

Effects of IH on the ventilatory response to hyperoxic progressive hypercapnia

Raw data traces for selected variables are shown in Figure 2a and 2b for the duration of the first experimental day for one representative subject from the SDIH group and one subject from the LDIH group. During the HCVR procedure, inspiratory flow increases with increasing $PetCO_2$ and the relationship between $PetCO_2$ and $\dot{V}_I$ is linear. A typical HCVR is plotted in Figure 3 for one representative subject. This ventilatory response is mediated largely by an increase in V_t while F_b remains relatively unchanged. The means for each group is displayed in Figure 4. The HCVR was not different on days 1, 12, 15, or 17 and was not different between SDIH conditioned individuals or LDIH conditioned individuals. The means ± SD for all subjects pooled together on day 1, 12, 15, and 17 were 2.49 ± 1.49, 1.74 ± 2.37, 2.35 ± 1.88, and 2.12 ± 1.15 l min^{-1} $mmHg^{-1}$ respectively.

Effects of IH on the ventilatory response to progressive isocapnic hypoxia

During the HVR procedure, the FiO_2 was reduced from 21% to approximately 5 % over approximately a 5-minute period, thus evoking an increase in inspiratory flow (Figure 2a and 2b). The increase in ventilation is mediated largely by increases in V_t and is linearly related to the reduction in SaO_2. Displayed in Figure 5 is an example of the preHVR for one subject on day 1 prior to intermittent hypoxic exposure and again on day 12 on the last day of exposure to IH.

The preHVR and postHVR were not different between groups on any day of its measurement. Therefore, the HVR data for all subjects was pooled together. Displayed in Figure 6 is the mean preHVR data for all subjects. There were significant increases in preHVR following 10 intermittent hypoxic exposures over a twelve-day period ($F= 3.42$; $df= 7, 112$; $p= 0.002$). This increase in preHVR was at a maximum by day 12 and subsequently returned to baseline by five days after the exposure to IH had ended. Figure 5 shows the preHVR for one individual subject on day 1 and again on day 12. This subject's preHVR had nearly doubled by day 12, increasing from 1.01 on day 1 to 1.99 on day 12. Several of the subjects ($n = 4$) involved in this study took part in another study completed in our laboratory 4 -6 months earlier (Koehle *et al.*, In Press). During that study, the subject's HVR was measured during an isolated occasion, and then five days later, the HVR was measured repeatedly over five consecutive days. The methods used in that study are identical to the method used during this study. Displayed in Figure 7 are the HVR's for one subject who took part in both studies. In this Figure the dotted trace indicates the repeated HVR measurements and the solid trace indicates the preHVR for each day of its measurement throughout and following exposure to LDIH. This subject does not display a peak in his HVR on day 12 and instead the HVR reaches a maximum on day 15. This

was true for several subjects. Not all subjects display a peak in their preHVR on day 12. Instead some show a peak on day 10 (n = 3) or 15 (n = 1).

The increase in preHVR at day 12 was mediated by a greater increase in V_t (F= 2.44; df= 7, 112; p= 0.02); on day 1, V_t increased by 0.74 ± 0.38 liters but on day 12, the change in V_t was 0.92 ± 0.41 liters at identical levels of SaO_2. The F_b did not change over the course of IH. The average $PetCO_2$ at which each preHVR was maintained was not different throughout the course of the study (Table 6).

Displayed in Figure 8 are the mean preHVR and postHVR for all subjects throughout the 12-day IH protocol. The postHVR measured five minutes following each IH exposure was significantly less than the preHVR (F=13.99; df= 1, 16; p=0.02). The $\dot{V}_I$ occurring immediately before the preHVR and the postHVR were not different. Also, the average levels of isocapnia that were maintained during each preHVR and each postHVR were the same (Table 6). Accompanying the blunted postHVR was a blunted V_t response (F= 5.27; df= 1, 16; p= 0.04). On day 1 the change in V_t during the preHVR was 0.74 ± 0.38 liters and during the postHVR it was 0.60 ± 0.42 liters. Similarly, on day 12 the change in V_t during the preHVR was 0.92 ± 0.41 liters and during the postHVR it was 0.79 ± 0.45 liters.

Effects of IH on the cardiovascular response to progressive isocapnic hypoxia

Displayed in Figure 9 are the cardiovascular sensitivities to hypoxia for one individual subject on the first day of study. There were no differences between the SDIH and LDIH conditioned individuals for any cardiovascular sensitivity to hypoxia; therefore, all subjects will be discussed as one group throughout this section.

Shown in Table 7 are the sensitivities to hypoxia for SBP, DBP, and MAP during both the preHVR and the postHVR. During the HVR, as FiO_2 is progressively lowered there is an increase in both systolic and diastolic blood pressures. This increase in blood pressure was

linearly related to the change in SaO_2 (Figure 9). The mean $\Delta SBP/\Delta SaO_2$ and the mean $\Delta DBP/\Delta SaO_2$ during the preHVR are displayed in Figure 10. The $\Delta SBP/\Delta SaO_2$ was not significantly different on day 12; nor was the $\Delta DBP/\Delta SaO_2$. As shown in Table 7, the $\Delta SBP/\Delta SaO_2$ and $\Delta DBP/\Delta SaO_2$ during the postHVR were significantly less than that occurring during the preHVR (SBP: $F= 28.38$; $df= 1, 16$; $p= 0.0007$, DBP: $F= 37.73$; $df= 1, 16$; $p= 0.00001$). The SBP and DBP immediately prior to each postHVR were greater than immediately before the preHVR (SBP: $F= 25.67$; $df= 1, 16$; $p= 0.0001$, DBP: $F= 58.40$; $df= 1, 16$; $p= 0.000001$). The mean SBP occurring prior to the preHVR on day 1 was 125 ± 8 mmHg and prior to the postHVR it was 132 ± 7 mmHg; and on Day 12 it was 123 ± 7 and 132 ± 11 respectively. The mean DBP occurring prior to the preHVR on day 1 was 73 ± 7 mmHg and on day 12 was 72 ± 7; prior to the postHVR it was 78 ± 6 mmHg on day 1 and 76 ± 8 on day 12. The change in $\Delta SBP/\Delta SaO_2$ (δ: day 12- day 1) and the change in $\Delta DBP/\Delta SaO_2$ (δ: day 12- day 1) were correlated to the change in HVR and are displayed in Table 8. The change in $\Delta SBP/\Delta SaO_2$ and HVR was positively correlated ($r = 0.68$; $p<0.05$) as was the change in $\Delta DBP/\Delta SaO_2$ and HVR ($r = 0.73$; $p<0.05$). When the relationships were analyzed separately as SDIH and LDIH groups the significant correlations remained for SDIH but not LDIH (Table 8).

During progressive hypoxia, cardiac output increases with SaO_2 in a linear manner (Figure 9). The $\Delta CO/\Delta SaO_2$ during both the preHVR and the postHVR on each day is displayed in Table 9. In addition, the $\Delta CO/\Delta SaO_2$ during the preHVR was not significantly different from the $\Delta CO/\Delta SaO_2$ occurring during the postHVR.

Heart rate increased linearly with decreasing SaO_2 as displayed in Figure 9. The $\Delta HR/\Delta SaO_2$ during the preHVR was not different from the postHVR and was not affected by intermittent hypoxia (Table 9). The change in $\Delta HR/\Delta SaO_2$ was not significantly correlated to the change in HVR (Table 8).

The SV response to progressive hypoxia was variable; some subjects show a linear increase in SV when plotted against SaO_2 (as displayed in Figure 9), while others show a decrease or no change at all. The mean $\Delta SV/\Delta SaO_2$ during the preHVR was not different from the postHVR and was not affected by intermittent hypoxia (Table 9).

Total peripheral resistance decreases linearly with decreasing SaO_2 (Figure 9). The mean $\Delta TPR/\Delta SaO_2$ during the preHVR and during the postHVR on each day of measurement is displayed in Table 9. The $\Delta TPR/\Delta SaO_2$ during the preHVR was unaffected by intermittent hypoxia; however, the $\Delta TPR/\Delta SaO_2$ during the postHVR was much less than the $\Delta TPR/\Delta SaO_2$ during the preHVR ($F= 7.08$; $df= 1, 16$; $p= 0.02$). The TPR occurring immediately prior to the postHVR was greater than the TPR occurring prior to the preHVR ($F= 16.34$; $df= 1, 16$; $p= 0.0009$). On day 1 the TPR prior to the preHVR was 0.87 ± 0.18 PRU but immediately prior to the postHVR it was 0.94 ± 0.25 PRU. Similarly, on day 12 the TPR prior to the preHVR was 0.77 ± 0.14 PRU; but, immediately before the postHVR it was 0.91 ± 0.21 PRU.

Effects of IH on cerebral tissue oxygenation

As arterial oxyhemoglobin saturation decreased so did ScO_2 (Figure 2a and b) and O_2Hb, while both HHb and cHb increased. The relationships for each of these variables for one individual subject are displayed in Figure 11. There were no differences between the LDIH and SDIH conditioned individuals for the following variables: $\Delta ScO_2/\Delta SaO_2$, $\Delta O_2Hb/\Delta SaO_2$, $\Delta HHb/\Delta SaO_2$, and $\Delta cHb/\Delta SaO_2$. As a result, the NIRS data for all subjects was pooled together.

Displayed in Figure 12 is the group mean $\Delta ScO_2/\Delta SaO_2$ during the preHVR for each day of its measurement. The $\Delta ScO_2/\Delta SaO_2$ during the preHVR was significantly less on day 12 and subsequently returned to baseline by day 17 ($F= 4.44$; $df= 7, 112$; $p= 0.0002$). This change in $\Delta ScO_2/\Delta SaO_2$ corresponds to a reduction in ScO_2 (at similar levels of SaO_2) of -8.4 ± 2.8 % on day 1, -10.0 ± 2.7 % on day 12, and -8.3 ± 2.3 % on day 17. As displayed in Figure 13, a greater

reduction in ScO_2 on day 12 was consistent for 8 of 9 subjects in the SDIH group and 5 of 9 subjects in the LDIH group.

The $\Delta ScO_2/\Delta SaO_2$ during the preHVR tended to be greater during the preHVR than during the postHVR; however, this difference was not significant ($p=0.06$). The ScO_2 prior to the preHVR was not different than immediately prior to the postHVR.

The $\Delta O_2Hb/\Delta SaO_2$ during the preHVR was not different from the postHVR and did not change over the course of intermittent hypoxia. On the other hand, the $\Delta HHb/\Delta SaO_2$ during the preHVR (Table 10) became progressively greater throughout exposure to intermittent hypoxia and was significantly different on day 12 compared with days 1 and 3 ($F= 2.94$; $df= 7, 112$; $p= 0.007$). In addition, the $\Delta HHb/\Delta SaO_2$ during the postHVR was significantly greater than the $\Delta HHb/\Delta SaO_2$ during the preHVR ($F= 6.32$; $df= 1, 16$; $p= 0.02$) (Table 10). The $\Delta cHb/\Delta SaO_2$ during the preHVR was not different from the postHVR and did not display significant changes over the course of intermittent hypoxia.

Effects of ventilatory and cardiovascular variables in hypoxia to IH exposure

During each exposure, ventilation, blood pressure, heart rate, cerebral oxygen saturation, and arterial oxyhemoglobin saturation were averaged over a three-minute period at the end of the first 5 minutes of hypoxia (H-1) and at the end of the last 5 minutes of hypoxia (H-2). Displayed in Table 11 are the ventilatory variables and, in Table 12, the cardiovascular variables for the SDIH and LDIH group during H-1 and H-2 for each day of its measurement. None of the ventilatory or cardiovascular variables on day 12 was different from those on day 1.

Ventilation was not different between the SDIH and the LDIH conditioned individuals. In addition, ventilation during H-1 was not significantly different than that of H-2. Breathing frequency was, however, significantly less during H-2 for both groups of IH ($F= 7.82$; $df= 1, 16$;

p= 0.01). Tidal volume tended to be greater during H-2 when compared with the first 5 minutes, although this difference was not statistically significant (p= 0.16).

Mean arterial pressure was not different between groups during H-1. During H-2, MAP was significantly greater than during H-1 for SDIH conditioned individuals, but not for LDIH conditioned individuals (F= 10.87; df= 1, 16; p= 0.005).

Heart rate was not different between groups during H-1 or during H-2. But, heart rate did increase significantly throughout exposure (F= 13.5; df= 1, 16; p= 0.002).

Arterial oxyhemoglobin saturation was not different between conditions during H-1; however, during H-2, the LDIH group had an SaO_2 that was significantly less than that of the SDIH conditioned group (F=21.74; df= 1,16; p=0.0003). The SaO_2 during each exposure was unaffected by IH even though there were large increases in the HVR.

During H-1, ScO_2 was similar between conditions; but, during H-2, the LDIH conditioned individuals had an ScO_2 that was significantly less than the SDIH conditioned individuals (F= 32.75; df= 1,16; p= 0.00003). The ScO_2 during hypoxic exposure was unaffected by 12 days of IH.

DISCUSSION

This is the first study to compare ventilatory, cardiovascular, and cerebral tissue oxygen responses to SDIH and LDIH in humans. The principal findings of this study are five-fold: (1) twelve days of exposure to isocapnic intermittent hypoxia reversibly enhanced the hypoxic ventilatory response, regardless of paradigm, and had no effect on the hypercapnic ventilatory response; (2) following acute exposure to SDIH and LDIH, the hypoxic ventilatory response is blunted compared to immediately before exposure; (3) cardiovascular sensitivity to hypoxia was not affected by exposure to either SDIH or LDIH; however, during exposure to SDIH, MAP was significantly greater than during LDIH; (4) exposure to intermittent hypoxia resulted in a greater reduction in cerebral tissue oxygenation compared to baseline measures and (5) no differences occur in submaximal or maximal exercise ventilatory efficiency following intermittent hypoxia.

Ventilatory Effects of Intermittent Hypoxia. The hypoxic ventilatory response was significantly increased on day 12. This increase in HVR occurred regardless of the intermittent hypoxic paradigm (i.e. LDIH or SDIH). Five days following the end of intermittent hypoxia, the HVR had returned to baseline, indicating that the change in HVR is transient. The increase in HVR is attributed to an enhanced tidal volume response to hypoxia. On day 1, V_t increased by 0.74 ± 0.38 liters (~ +52%) but on day 12, the change in V_t was 0.92 ± 0.41 liters (~ +57%) at identical levels of SaO_2. Other studies involving human subjects have reported results similar to this study (Katayama *et al.*, 1998; Katayama *et al.*, 1999; Garcia *et al.*, 2000b, 2000c; Katayama *et al.*, 2001a; Katayama *et al.*, 2001b; Mahamed & Duffin, 2001; Mateika *et al.*, 2004). Katayama *et al.* (2001b) exposed human subjects to an hour daily of hypobaric hypoxia (432 mmHg) and demonstrated a 62% increase in HVR after 7 days. In the current study, subjects were exposed to thirty minutes of a similar level of isocapnic hypoxia for 10 episodes

(over 12 days) and improved their HVR by 70% (range: -42%-108%). Several human studies have used similar SDIH methods to ours and have also reported increases in HVR (Serebrovskaya *et al.*, 1999; Bernardi *et al.*, 2001). In contrast to the results from the current study are the findings from Peng and Prabhakar (2004) who clearly showed in the rat that LDIH does not enhance carotid body chemosensitivity, while SDIH does. A possible explanation for the differences in results is that the rats in Peng and Prabhakar's study were exposed to a substantially greater hypoxic stimulus (5% O_2 versus 12% O_2). In addition, the rats in the SDIH group were exposed to hypoxia for 15 seconds every 5 minutes, 8 hours per day, while the rats in the LDIH group received 4 hours of hypoxia per day (0.4 atm). In the present study, human subjects were exposed to either 30 minutes of sustained normobaric isocapnic hypoxia (LDIH; 12% O_2) or 5 minutes of normobaric isocapnic hypoxia separated by 5 minutes of normoxia for an hour (SDIH; 12% O_2).

In this study, the HVR was measured immediately before each exposure to intermittent hypoxia and again 5 minutes following each exposure. The HVR occurring after each exposure was significantly less than the HVR occurring immediately prior to, indicating a form of hypoxic desensitization (Figure 8). Similar results were found in other human studies (Easton *et al.*, 1986, 1988) and cat studies (Long *et al.*, 1994). In these studies, an initial exposure to isocapnic hypoxia decreased the ventilatory response to a subsequent hypoxic exposure. The results from the current study agree with these studies and indicate that the reduced ventilatory response to hypoxia was largely due to alterations in the tidal volume response to hypoxia. On day 1 the change in V_t during the preHVR was 0.74 ± 0.38 liters and, during the postHVR, it was 0.60 ± 0.42 liters. From the data obtained throughout this study, it is difficult to discern the mechanism responsible for the apparent hypoxic desensitization; however, others suggest that the hypoxic ventilatory depression is mediated by relatively slowly reversible neurochemical

events that are specific to the central neural structures concerned with the hypoxic ventilatory response (Long *et al.*, 1994).

While the results indicate an increase in HVR following intermittent hypoxia, no change in the hypercapnic ventilatory response was evident. This finding is similar to the results of almost all other studies which have measured the HCVR using the Read rebreathing method and the single breath CO_2 response test (Katayama *et al.*, 1998; Katayama *et al.*, 1999; Katayama *et al.*, 2002). However, some studies have found increases in HCVR following intermittent hypoxia (Mahamed & Duffin, 2001; Ainslie *et al.*, 2003). Ainslie *et al.* (2003) showed an increase in the hypercapnic ventilatory response following five nights of normobaric hypoxia (13.8% O_2). A novel approach of determining the central chemoreceptor response to CO_2 has been employed by Mahamed *et al.* (2001). This method involves prior hyperventilation before commencing the rebreathe at different iso-oxic levels and allows for the determination of the chemoreflex threshold to CO_2. Using the modified rebreathing technique, changes in the peripheral chemoreflex to CO_2 were measured in hyperoxia and in hypoxia. Following twenty minutes of isocapnic hypoxia daily for 14 consecutive days, an increase in the CO_2 threshold occurs only in the presence of hypoxia, but not hyperoxia (Mahamed & Duffin, 2001). The authors interpreted this result as indicating changes in the peripheral chemoreflex and not the central chemoreflex. It may be that marked respiratory alkalosis is necessary to elicit changes in HCVR. In the majority of the studies that measure HCVR, the hypoxic exposure is usually no more than an hour per day for less than two weeks. In the current study, it may be no surprise that the HCVR did not change; our subjects were exposed to isocapnic hypoxia and, thus, no respiratory alkalosis occurred.

During acute exposure to sustained hypoxia (similar to LDIH) and during several short repeated bouts of hypoxia (similar to SDIH), several phenomena are known to occur. At the onset of hypoxia there is an immediate increase in ventilation. Following 5-30 minutes of

sustained hypoxia, a decrease in ventilation is observed and is referred to as hypoxic ventilatory decline (HVD) (Powell *et al.*, 1998). HVD occurs even during isocapnic hypoxia. In contrast, during short repeated bouts of hypoxia (similar to SDIH), progressive augmentation is known to occur (Powell *et al.*, 1998). Progressive augmentation refers to the increase in the magnitude of the hypoxic ventilatory response seen in each successive episodes of an identical hypoxic stimulus. Following exposures to successive episodes of hypoxia, respiratory motor output progressively increases during the normoxic intervals and is referred to as long term facilitation (Powell *et al.*, 1998). This condition can last for many minutes to several hours after the final stimulus episode. The results from this study suggest that, during exposures to SDIH and LDIH, HVD, progressive augmentation, and long term facilitation did not occur or were undetectable. During exposure to LDIH, there was no difference in ventilation during H-1 when compared with H-2 (Day 1: 14 ± 2 and 13 ± 2 l min^{-1} respectively). During SDIH, ventilation during the first bout of hypoxia was not different from the final bout of hypoxia (Day1: 14 ± 3 and 13 ± 3 l min^{-1} respectively). This was true for all days of exposure. While overall minute ventilation did not change throughout exposure, our results do indicate a small but significant increase in F_b (+ ~1 breaths min^{-1}; $p<0.05$) during H-2 of both LDIH and SDIH. Tidal volume did not change significantly. The results from the present study suggest that long term facilitation did not occur. There was no difference in resting ventilation nor in the ventilation occurring in normoxia immediately prior to the final HVR procedure of each day. If long term facilitation did occur, any increase in ventilation should have returned to resting levels within the five-minute period prior to the postHVR measurement. This study is not the first study to suggest that long-term facilitation does not occur in human subjects following exposure to successive episodes of hypoxia (McEvoy *et al.*, 1996; Jordan *et al.*, 2002; Mateika *et al.*, 2004).

Cardiovascular Sensitivity to Intermittent Hypoxia. The results showed a transient increase in resting heart rate on day 10 (+7 bpm), although there were no concomitant changes in cardiac output or stroke volume. Our subjects, resting in a supine position, had a mean CO of 6.88 l min^{-1} (range: 4.7-9.0 l min^{-1}). This result is similar to other studies which have determined cardiac output using the thermodilution technique during supine rest and found it to range from 5.3-8.7 l min^{-1} (Harms *et al.*, 2003). Blood pressure and total peripheral resistance did not systematically change throughout the intermittent hypoxic protocol. While there were fluctuations in resting normoxic heart rate, we did not detect any changes in the high and low frequency spectral components of heart rate variability, indicating that baseline autonomic control of the heart did not change throughout experimentation and that all subjects were in a comparable autonomic state prior to each hypoxic trial. There were no changes in the sensitivity to hypoxia for any cardiovascular variables including: systolic, diastolic, and mean arterial pressure, and cardiac output, stroke volume, and total peripheral resistance. Very few studies have studied cardiovascular sensitivity and intermittent hypoxia. In contrast to the results found here, Katayama *et al.* (2001b) found a 68% increase in systolic blood pressure sensitivity and a 44% increase in diastolic blood pressure sensitivity. The results from the present study are comparable, but did not show statistically significant differences. In this study, systolic blood pressure sensitivity increased by 70% and diastolic blood pressure sensitivity increased by 67%. Katayama *et al.* (2001b) also showed a significant relationship between the change in SBP ($r = 0.66$) and DBP ($r = 0.62$) sensitivity and the change in HVR (Table 8). Interestingly, the data from the present study showed similar significant relationships between the same variables. Our data suggests that the increase in SBP and DBP are positively related to the increase in HVR ($r = 0.68$ and $r = 0.73$ respectively). Our correlational coefficients are very similar to those of Katayama *et al.* (2001b) but, appear to only be significant and comparable for either all subjects or only those exposed SDIH. In agreement

with the study of Katayama *et al.* (2001b), the present study's results did not illustrate changes in the heart rate sensitivity to hypoxia or a relationship to the change in HVR. There are several differences between the methods used in this study and the methods used by Katayama *et al.* (2001b). While the hypoxic intensity was similar for both studies (12% O_2 vs. a simulated altitude of 4,500 m), the subjects in the present study were exposed to thirty minutes of normobaric, isocapnic hypoxia while the subjects in the study by Katayama *et al.* (2001b) were exposed to an hour of poikilocapnic, hypobaric hypoxia. The results of a study by Insalaco *et al.* (1996) also differ from this study's results; however, their results involved exposure to 24 days of continuous hypoxia. They found increases in blood pressure sensitivity following one day at 5,050m that continued to increase by the 24th day at high-altitude. In their study they found a slight reduction in heart rate sensitivity. In support of our findings are two studies, both involving exposure to a variant of SDIH. In one study, humans were exposed to 3-4 periods of 7 minutes of isocapnic progressive hypoxia (end-tidal PO_2 was allowed to drop to 35-40 mmHg) in 1 hour each day for 14 days; no changes in the blood pressure or heart rate sensitivity to hypoxia occurred (Bernardi *et al.*, 2001). Similarly, in another study, cats were exposed to a cyclic hypoxic episode (~ 2 min each; inspired PO_2 ~ 75 mmHg) repeated during 8 hours for 2-4 days; no changes in arterial pressure or heart rate during acute hypoxia were found (Rey *et al.*, 2004). Interestingly, Rey *et al.* (2004) also found a marked increase in the resting, normoxic LF/HF ratio and an increase of the power spectral distribution toward the LF spectral component of heart rate variability indicating sympathetic predominance. In our study there was no change in the resting HF, LF, or the LF/HF ratio, indicating that there was no change in autonomic control of the heart throughout intermittent hypoxia. Clearly, the daily exposure to hypoxia used for this study (30 minutes) was much less than that displayed in the study by Rey *et al.* (2004); therefore, direct comparisons are difficult.

Cardiovascular sensitivity measures occurred during both the preHVR and the postHVR procedure (Table 7). When the $\Delta SBP/\Delta SaO_2$ during the preHVR are compared with the postHVR, our results indicate a reduction in the SBP sensitivity to hypoxia following the daily acute exposure to LDIH or SDIH. This was true for the $\Delta DBP/\Delta SaO_2$ and the $\Delta MAP/\Delta SaO_2$. No other study has done a similar comparison. This blunted blood pressure sensitivity can be explained by the increase in normoxic SBP, DBP, or MAP during the five-minute period following the daily acute exposure to hypoxia. The SBP, DBP, and MAP were significantly greater immediately before the postHVR compared with those before the preHVR. In addition, the peak increase in SBP, DBP, and MAP at similar levels of SaO_2 during the postHVR were not different from the preHVR. The results can, therefore, not be interpreted as indicating a reduction in blood pressure sensitivity to hypoxia following exposure to an acute episode of hypoxia. Similar analysis was undertaken for the CO, HR, SV, and TPR sensitivity to hypoxia (Table 9). Cardiac output, HR, and SV sensitivity were not different during the postHVR when compared with the preHVR. The $\Delta TPR/\Delta SaO_2$ during the preHVR was significantly less during the postHVR. Like the blood pressure sensitivities, this can be explained by an increase in the normoxic TPR occurring immediately prior to the postHVR when compared with the preHVR.

Cardiovascular Function during Exposure to Intermittent Hypoxia. A significant increase in mean arterial pressure (+ ~5 mmHg; $p<0.05$) was found throughout acute exposure to SDIH. This increase in MAP did not occur during acute exposure to LDIH (+ ~ 2 mmHg; $p>0.05$). The change in MAP was not greater following 12 days of exposure to intermittent hypoxia. Heart rate was similar between both groups throughout exposure to either LDIH or SDIH. There were small but significant increases in HR over the duration of exposure (+ ~1 bpm; $p= 0.002$). No previous study has documented a similar finding. It is not understood why

SDIH results in a rise in MAP while LDIH does not. It may be that exposure to SDIH resulted in a greater carotid body stimulation. While the repeated deoxygenation-reoxygenation states may have provided increased carotid body stimulation, the subjects in the SDIH group were exposed to significantly less hypoxaemia. During the first 5 minutes of hypoxic exposure, SaO_2 was similar between both intermittent hypoxic groups (SDIH = 92%; LDIH = 91%); but, during the final 5 minutes of hypoxia, SaO_2 was significantly less for those subjects exposed to LDIH (SDIH = 91%; LDIH = 87%). It is possible that repeated states of deoxygenation-reoxygenation are more important than sustained hypoxemia for increasing blood pressure. Furthermore, this phenomenon may relate to the secondary hypertension that is present in patients with obstructive sleep apnea (Morgan & Joyner, 2002). Although under somewhat different circumstances, Fletcher and colleagues (1992), using a rat model, demonstrated increases in resting, normoxic daytime blood pressure following exposure to 35 days of SDIH patterned after that of sleep apnea. This increase in resting daytime blood pressure was dependent upon intact carotid chemoreceptors. In a different study, sympathetic responsiveness to hypoxia and hypercapnia were increased following 30 days of SDIH, also modeled after sleep apnea syndrome (Greenberg *et al.*, 1999). Or perhaps more simply, LDIH conditioned individuals did not display an increase in MAP because the sustained systemic hypoxia experienced by them mediated a local vasodilatory response that prevented the increase in blood pressure (Doherty & Liang, 1984; Blauw *et al.*, 1995).

Effects of Intermittent Hypoxia on Cerebral Tissue Oxygenation. During acute exposure to progressive hypoxia, cerebral tissue oxygen saturation decreases. This includes an increase in oxyhemoglobin concentration and total hemoglobin concentration, while deoxyhemoglobin concentration decreases. The change in each variable is linearly related to the change in arterial oxyhemoglobin saturation (Figure 11). In the cerebral circulation,

vascular autoregulation is responsible for the vasodilator response to hypoxia. Several lines of evidence suggest that exposure to intermittent hypoxia affects vascular function negatively (Earley & Walker, 2002; Gonzales & Walker, 2002; Jernigan & Resta, 2002; Altay *et al.*, 2004; Phillips *et al.*, 2004). Exposure to chronic intermittent hypoxia markedly attenuates the acute vasodilator responses to hypoxia in isolated vessels (Phillips *et al.*, 2004). Phillips *et al.* (2004) exposed rats (n = 6) to chronic intermittent hypoxia (FiO_2 = 10% for 1 min at 4-min intervals, 12h/day) for 14 days. After 14 days the middle cerebral arteries were isolated and placed in a tissue bath. The arteries were pressurized to 90 mmHg, and vessel diameters were measured via a video micrometer before and after exposure to acetylcholine (ACh) (10^{-7}-10^{-4} M) and acute reduction of PO_2 in the perfusate and superfusate (from 140 to 40 mmHg). Dilation of the middle cerebral artery induced by ACh was greatly attenuated while dilation-induced by acute reductions in PO_2 was virtually abolished in animals exposed to chronic intermittent hypoxia. These results suggest that vascular regulation is altered following intermittent hypoxia and may affect the ability to oxygenate cerebral tissue. In the current human study, the sensitivity of the cerebral vasculature was assessed by determining the ability to oxygenate cerebral tissue during acute exposure to progressive hypoxia using near-infrared spectroscopy. Changes in ScO_2, O_2Hb, HHb, and cHb per change in SaO_2 were used to represent the sensitivity of the cerebral vasculature to hypoxia (Table 10). The results indicate that the $\Delta ScO_2/\Delta SaO_2$ became significantly less following exposure to both SDIH and LDIH (Day 1 = -0.51 ± 0.13; Day 12 = -0.64 ± 0.18). This change in ScO_2 sensitivity was mediated by an increase in the $\Delta HHb/\Delta SaO_2$ (Day 1 = 0.34 ± 0.21; Day 12 = 0.44 ± 0.12). These changes in the ability to oxygenate the brain were reversible and, following the end of exposure to intermittent hypoxia, had returned to baseline. There were no differences in the $\Delta O_2Hb/\Delta SaO_2$ or the $\Delta cHb/\Delta SaO_2$ response. In addition, the change in ScO_2 sensitivity throughout intermittent hypoxia cannot be explained by shifts in resting ScO_2, as it did not change. The resting ScO_2 was very reproducible and the

mean coefficient of variation was 4.7 ± 2.1 %. Taken together, the results indicate that there was a greater reduction in cerebral tissue oxygen saturation following exposure to both SDIH and LDIH. This was a consistent observation where 8 of 9 subjects in the SDIH group and 5 of 9 subjects in the LDIH group demonstrate a greater reduction in cerebral tissue oxygen saturation (Figure 13). To more fully understand what this means in terms of % change, we determined the change in ScO_2 for each subject at an SaO_2 that was similar on each day (i.e. iso-SaO_2). On day 1 the subjects demonstrate a -8 ± 3 % change in ScO_2 and on day 12 the change in ScO_2 is -10 ± 3 %. From the experimental design used here it is difficult to understand the mechanism leading to the greater reduction in ScO_2. While the results seem to suggest cerebral vascular dysregulation in the human subject following exposure to SDIH and LDIH and support the findings of results seen in the rat model (Phillips *et al.*, 2004), the results of this study differ from two human studies of the cerebral blood flow velocity response to acute hypoxia (Jensen *et al.*, 1996; Kolb *et al.*, 2004). Jensen *et al.* (1996) studied the cerebral blood flow velocity response from the control value with 5-minute steps of isocapnic hypoxia and hyperoxic hypercapnia before and during a 5-day sojourn at 3,810 m altitude. Their results indicate an increase in the cerebral vascular response to acute isocapnic hypoxia. Similarly, Kolb *et al.* (2004) studied the cerebral blood flow responses to acute variations in O_2 and CO_2 prior to, immediately after, and five days following exposure to five consecutive nocturnal exposures of 13.8 % O_2 (8 hours during the night). Their results also indicate an increase in the sensitivity of cerebral blood flow velocity to acute variations in O_2 and CO_2. Several key differences may account for the variations between the results of the current study and the results from Jensen *et al.* (1996) and Kolb *et al.* (2004). The hypoxic exposure used in the present study was more intense (12% O_2) and involved isocapnia. In addition, the hypoxic protocol lasted for 12 days while it lasted only 5 days during the other two studies. In fact, following the 3rd and 5th day of this study's protocol there were no significant decreases in ScO_2 sensitivity to hypoxia; if

anything, there was an increase in $\Delta ScO_2/\Delta SaO_2$ on day 3 (not significant) (Figure 12). Furthermore, fourteen days of intermittent hypoxia were needed to demonstrate vascular dysfunction in the rat model (Phillips *et al.*, 2004). It is possible that had these researchers (*Jensen et al.*, 1996; *Kolb et al.*, 2004) continued their hypoxic protocol for 5 more days they may have discovered decrements in cerebral blood flow sensitivity.

The change in cerebral tissue oxygen sensitivity was measured during the HVR and, therefore, the results also include the cerebral tissue oxygen sensitivity during the postHVR. The results from this analysis indicate that the $\Delta ScO_2/\Delta SaO_2$ was less and the $\Delta HHb/\Delta SaO_2$ was greater on each day of measurement during the postHVR (Table 10). The change in ScO_2 sensitivity cannot be explained by an increase in normoxic ScO_2 immediately prior to the postHVR when compared with immediately prior to the preHVR, as it was not different. It is more likely that the blunted postHVR (Figure 8) is the cause of the cerebral tissue oxygen sensitivity being less following hypoxic exposure.

Effects of Intermittent Hypoxia on Submaximal and Maximal Exercise. Several studies suggest that exposure to intermittent hypoxia during rest improves exercise efficiency (Katayama *et al.*, 2001a; Katayama *et al.*, 2003; Katayama *et al.*, 2004); others do not (Katayama *et al.*, 2002). The results from this study do not indicate any improvement in maximal or submaximal exercise ventilatory efficiency. Maximal $\dot{V}O_2$, $\dot{V}CO_2$, ventilatory equivalents for O_2 and CO_2, $\dot{V}_I$, peak power, and HR were not different following intermittent hypoxia compared with immediately before (Table 2). In addition, there were no differences in $\dot{V}_I$, F_b, or V_t at 20, 40, 60, 80, or 100 % of maximal $\dot{V}O_2$ and $\dot{V}CO_2$ (Table 3). Katayama *et al.* (2002) found similar results; there was no change in either minute ventilation or the ventilatory equivalent for oxygen during maximal and submaximal exercise following intermittent hypoxia.

In other studies, submaximal $\dot{V}O_2$, and 3,000m running time improved (Katayama *et al.*, 2003; Katayama *et al.*, 2004). In these studies, intermittent hypoxia involved either hypobaric hypoxia at 4,500 m for 90 minutes, 3 days a week for 3 weeks (Katayama *et al.*, 2003), or normobaric hypoxia (12.3 % O_2) for 3 hours per day for 14 consecutive days (Katayama *et al.*, 2004). While the hypoxic intensity is similar to the current study, the total time in hypoxia is significantly greater and may account for the discrepancy between studies. Furthermore, the subjects involved in both of these studies were trained athletes continued to train throughout participation in the study. Katayama *et al.* (2002) used active healthy subjects with similar peak exercise values to our subjects; they also used a similar IH protocol. Their protocol involved 1 hour daily of exposure to hypobaric hypoxia (4,500m) for 7 days while our protocol involved 30 minutes exposure to normobaric isocapnic hypoxia (12% O_2).

Critique of Methods. The HVR measurement can be associated with large day-to-day variability (Sahn *et al.*, 1977; Beidleman *et al.*, 1999). The coefficient of variation for HVR can range from 26% to 76% (Zhang & Robbins, 2000; Fahlman *et al.*, 2002). Using similar methods described in this study, repeated HVR measurements were performed in our laboratory over 5 consecutive days (n = 8; male subjects) and the mean individual CV was found to be 27 ± 4 % (Koehle *et al.*, In Press). This coefficient of variation is identical to that of Zhang and Robbins (2000) who found a CV of 26%. In addition to having a low coefficient of variation, several subjects involved in the current study also took part in our repeated HVR study (Koehle *et al.*, In Press). As a result, there is additional reassurance that the increase in HVR seen throughout this study was not due to either the repeated measure of HVR or day-to-day variability.

Arterial oxygen saturation was measured by pulse oximetry and not determined from arterial blood. Changes in arterial pH and body temperature affect the haemoglobin-oxygen

dissociation curve. Pulse oximetry fails to account for this. During this study subjects were at rest, so there were not likely changes in temperature during the experiment and changes in pH were minimized by maintaining subjects' isocapnic throughout all hypoxic exposures.

The measurement of cardiac output and stroke volume was evaluated using a pulse wave analysis method that calculates beat-to-beat flow from non-invasive arterial pressure by simulating a non-linear, time-varying model of human aortic input impedance (Van Lieshout *et al.*, 2003). This model incorporates three elements to calculate aortic flow: aortic impedance, aortic compliance, and total peripheral resistance (Wesseling *et al.*, 1993). Using this method for obtaining continuous cardiac output and stroke volume has not been embraced by clinical studies because its methods, although based on strong physical principles, are also based on some weaker physiological models (Van Lieshout & Wesseling, 2001). Some major concerns include a non-linear aortic compliance, using finger pressure to determine stroke volume instead of proximal aortic pressure, inadequate pulse detection, and an inability to accurately obtain an absolute cardiac output (Van Lieshout & Wesseling, 2001). This method has now been compared with thermodilution, whole-body impedance cardiography, CO_2 rebreathing, and Doppler ultrasound techniques for determining cardiac output. Generally, the studies have determined that pulse wave analysis may not be appropriate for determining absolute values of cardiac output (Hirschl *et al.*, 1997; Houtman *et al.*, 1999; Nieminen *et al.*, 2000; Remmen *et al.*, 2002). However, if calibrated against an invasive method, pulse wave analysis can produce accurate measurements (Jansen *et al.*, 2001; Remmen *et al.*, 2002). Pulse wave analysis calibrated against thermodilution measures accurately reflects changes in cardiac output over a range of cardiac output values when compared with thermodilution techniques in mechanically ventilated patients with septic shock (Jellema *et al.*, 1999). A study which tracked the changes in stroke volume and cardiac output during different phases of a tilt-table test determined that pulse wave analysis can track the changes in cardiac output and stroke volume but, for absolute values,

is not appropriate (Nieminen *et al.*, 2000). Changes in stroke volume can be adequately assessed using pulse wave analysis when compared with stroke volume obtained by Doppler ultrasound during tilt-table testing (Van Lieshout *et al.*, 2003). Houtman *et al.* (1999) showed that pulse wave analysis derived cardiac output reflects the cardiac output determined using the CO_2 rebreathing method at rest and during exercise up to 60% of the individual peak power output. Unfortunately, the methods used in this study do not involve calibrating our pulse wave analysis derived cardiac output with an invasive method. However, our measurements were performed during supine rest and are within the range of resting cardiac output determined using the thermodilution technique in other supine resting individuals (5.3 – 8.7 l min^{-1}) (Harms *et al.*, 2003). The range of cardiac output values in our study was 4.7-9.0 l min^{-1}.

Near-infrared spectroscopy provides a unique and detailed measurement of cerebral oxygenation. NIRS reflects cerebral oxygenation during arterial hypotension, hypoxic hypoxemia, and hypo- and hypercapnia (Madsen & Secher, 1999). Some important limitations to NIRS include insufficient light shielding, optode displacement, and a sample volume that includes muscle or the frontal sinus mucous membrane (Madsen & Secher, 1999). During this study, optodes were placed just below the hairline in the center of the forehead to ensure that the sample volume was not affected by the frontal sinus or temporal muscles. Contained within the sampled volume is information about the hemoglobin contained within arterioles, capillaries, and venules, and the relative position of pigments determined by NIRS cannot be determined. In the brain, approximately 5% of the blood is situated in the capillaries, 20% in the arteries, and the remainder is in the venous circulation (Madsen & Secher, 1999). The hemoglobin measured by NIRS is therefore 'post cellular' and it can be argued that NIRS determines local venous oxygen saturation rather than tissue oxygen content. While some degree of co-variation is present between regional cerebral oxygen saturation and internal jugular venous oxygen content, the

contribution from capillaries and arterioles is significant and the NIRS signal provides the best non-invasive method of monitoring cerebral tissue oxygenation (Madsen & Secher, 1999).

Another limitation to this study is that the methods did not include a control group that was exposed to the experimental set-up but not to intermittent hypoxic exposure. While this does provide a limitation, it is unlikely that the results of this study would be different. As described earlier in a previous study, HVR was measured in subjects over five consecutive days (Koehle *et al.*, In Press). Four subjects involved in the current study also were involved in this repeated HVR study. These subjects had, therefore, been previously exposed to the identical experimental setup without exposure to intermittent hypoxia. During this repeated HVR study, there was no effect of measuring HVR over 5 consecutive days. In addition, several other investigations have studied the effects of intermittent hypoxia on HVR and on cardiovascular responses and have included a control group (Bernardi *et al.*, 2001; Katayama *et al.*, 2001b; Mahamed & Duffin, 2001; Katayama *et al.*, 2002; Katayama *et al.*, 2003; Katayama *et al.*, 2004). In these studies, having a control group had no effect on the outcome of their studies.

Conclusion. The results from this study indicate that exposure to twelve days of isocapnic intermittent hypoxia will transiently increase hypoxic chemosensitivity regardless of how the hypoxic stimulus is patterned (i.e. SDIH or LDIH), when the hypoxic intensity and total duration are the same. The increase in hypoxic chemosensitivity is short-lived as HVR returns to baseline 5 days after intermittent hypoxia has ended. Hypercapnic chemosensitivity is not altered following isocapnic intermittent hypoxia, likely because respiratory alkalosis is necessary to evoke changes in hypercapnic chemosensitivity. The HVR that occurrs following acute exposure to hypoxia was blunted and suggests hypoxic desensitization. The mechanism leading to hypoxic desensitization is unknown and requires further study. While intermittent hypoxia led to increases in hypoxic chemosensitivity, the cardiovascular sensitivity to hypoxia (SBP, DBP,

CO, SV, HR, and TPR) was not affected. This finding is in contrast with other studies and it is suspected that a longer duration of exposure is necessary to evoke changes in cardiovascular sensitivity to hypoxia. Several animal studies have suggested that intermittent hypoxia may affect the ability to oxygenate cerebral tissue due to vascular dysregulation. The results from this study suggest that the vascular processes required to control blood flow and to oxygenate cerebral tissue in the human have been affected in a way that inhibits the ability to oxygenate the cerebral tissue in response to progressive isocapnic hypoxia following exposure to twelve days of isocapnic intermittent hypoxia. This is the first study to show that acute exposure to SDIH results in a rise in MAP that is not present during acute exposure to LDIH. This suggests that exposure to SDIH may be a useful model when studying the effects of sleep-disordered breathing and intermittent hypoxia on the cardiovascular system, including systemic hypertension.

Table 1. Descriptive and resting pulmonary function data. Percent of predicted values are contained within parentheses. Values are means ± SD. Definitions of abbreviations: FVC = forced vital capacity; $FEV_{1.0}$ = forced expired volume in 1 second. *Significantly different from SDIH ($p<0.05$).

	SDIH (n=9)		LDIH (n=9)	
Age (years)	25.8 ± 4.3		25.6 ± 4.5	
Height (cm)	177.9 ± 7.0		174.0 ± 18.7*	
Mass (kg)	81.3 ± 7.4		81.4 ± 10.9	
FVC (liters)	4.99 ± 0.83	(95 ± 12)	4.96 ± 0.51	(107 ± 43)
$FEV_{1.0}$ (liters)	4.14 ± 0.47	(94 ± 9)	4.16 ± 0.50	(105 ± 40)
$FEV_{1.0}$/FVC (%)	84.25 ± 5.92	(102 ± 7)	83.49 ± 5.67	(101 ± 7)

Table 2. Peak exercise values during maximal cycle ergometry tests. Values are means ± SD. Definition of abbreviations: $\dot{V}O_2$ = maximal oxygen consumption; $\dot{V}CO_2$ = maximal CO_2 production; RER = respiratory exchange ratio; $\dot{V}_I / \dot{V}O_2$ = ventilatory equivalent for oxygen; $\dot{V}_I / \dot{V}CO_2$ = ventilatory equivalent for CO_2; $\dot{V}_I$ = ventilation; HR = heart rate.

	Day 1 (n = 17)	Day 12 (n = 17)
$\dot{V}O_2$ (ml kg^{-1} min^{-1})	42.2 ± 7.5	42.9 ± 7.5
$\dot{V}O_2$ (l min^{-1})	3.47 ± 0.59	3.53 ± 0.66
$\dot{V}CO_2$ (l min^{-1})	4.31 ± 0.68	4.32 ± 0.74
RER	1.25 ± 0.07	1.24 ± 0.08
$\dot{V}_I / \dot{V}O_2$	34.02 ± 4.81	33.83 ± 4.95
$\dot{V}_I / \dot{V}CO_2$	26.75 ± 1.72	27.37 ± 3.08
$\dot{V}_I$ (l min^{-1})	118.3 ± 21.9	115.1 ± 23.4
Power (watts)	322 ± 67	327 ± 67
HR (bpm)	179 ± 10	181 ± 10

Table 3. Ventilatory efficiency at submaximal exercise intensities. Values are means ± SD. Definition of abbreviations: $\dot{V}_I$ = ventilation; F_b = breathing frequency; V_t = tidal volume; $\dot{V}O_2$ = % of maximal oxygen consumption; $\dot{V}CO_2$ = % of maximal CO_2 production.

		$\dot{V}O_2$		$\dot{V}CO_2$	
Variable	Intensity (%)	Day 1	Day 12	Day 1	Day 12
$\dot{V}_I$ (liters min^{-1})	20	17.3 ± 1.0	17.1 ± 1.1	21.8 ± 1.1	22.0 ± 1.0
	40	29.2 ± 1.7	29.0 ± 1.7	38.3 ± 2.1	40.0 ± 2.0
	60	47.3 ± 3.4	47.7 ± 2.6	58.8 ± 3.2	60.1 ± 3.3
	80	69.9 ± 5.4	73.5 ± 3.5	83.2 ± 4.9	84.7 ± 4.6
	100	116.3 ± 5.4	116.0 ± 5.4	117.3 ± 5.2	117.2 ± 5.4
F_b (breaths min^{-1})	20	18 ± 1	18 ± 1	19 ± 1	20 ± 1
	40	22 ± 1	21 ± 1	24 ± 1	22 ± 1
	60	27 ± 2	27 ± 2	30 ± 1	31 ± 2
	80	33 ± 3	35 ± 2	37 ± 3	38 ± 2
	100	52 ± 3	53 ± 3	54 ± 4	52 ± 3
V_t (liters)	20	0.99 ± 0.05	0.99 ± 0.07	1.24 ± 0.10	1.14 ± 0.08
	40	1.40 ± 0.06	1.43 ± 0.09	1.62 ± 0.06	1.82 ± 0.08
	60	1.78 ± 0.06	1.82 ± 0.09	2.02 ± 0.07	1.98 ± 0.09
	80	2.13 ± 0.07	2.16 ± 0.09	2.31 ± 0.09	2.27 ± 0.11
	100	2.37 ± 0.09	2.34 ± 0.10	2.30 ± 0.10	2.29 ± 0.09

Table 4. Effects of intermittent hypoxia on basal ventilatory and cardiovascular variables during eupnea. Values are means ± SD. *Significantly different from day 1 ($p<0.05$). † Significantly different from day 3 ($p<0.05$). Definition of abbreviations: $\dot{V}_I$ = ventilation; F_b= breathing frequency; V_t= tidal volume; $PetCO_2$= end-tidal partial pressure of CO_2; SBP= systolic blood pressure; DBP= diastolic blood pressure; MAP= mean arterial pressure; CO= cardiac output; HR= heart rate; SV= stroke volume; TPR= total peripheral resistance; ScO_2= cerebral oxygen saturation.

	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	CV (%)
$\dot{V}_I$ (l min^{-1})	11.1 ± 2.4	11.8 ± 2.1	11.9 ± 2.3	12.4 ± 2.4	12.1 ± 2.6	11.7 ± 2.2	11.7 ± 1.9	11.8 ± 1.9	9.7 ± 0.5
F_b (breaths min^{-1})	16.8 ± 3.8	18.1 ± 3.6	17.8 ± 4.0	18.4 ± 3.2*	18.7 ± 3.4*	17.7 ± 2.7	17.6 ± 3.1	17.9 ± 3.0	8.6 ± 4.5
V_t (liters)	0.69 ± 0.12	0.67 ± 0.11	0.69 ± 0.10	0.69 ± 0.11	0.67 ± 0.13	0.68 ± 0.12	0.69 ± 0.07	0.68 ± 0.10	10.6 ± 0.7
$PetCO_2$ (mmHg)	43.6 ± 3.8	43.2 ± 3.0	43.6 ± 3.6	43.0 ± 3.3	42.4 ± 2.6	43.6 ± 3.3	43.6 ± 3.1	43.1 ± 3.0	3.2 ± 1.2
SBP (mmHg)	124 ± 9	120 ± 11	121 ± 9	121 ± 10	118 ± 9	122 ± 7	123 ± 11	121 ± 12	5.4 ± 2.0
DBP (mmHg)	71 ± 7	70 ± 7	71 ± 6	71 ± 8	70 ± 8	70 ± 6	70 ± 9	70 ± 9	6.5 ± 1.9
MAP (mmHg)	89 ± 7	87 ± 8	87 ± 6	88 ± 9	86 ± 8	88 ± 6	88 ± 9	87 ± 10	5.7 ± 1.8
CO (l min^{-1})	6.88 ± 1.10	6.64 ± 1.26	6.61 ± 1.46	6.70 ± 1.40	6.91 ± 1.12	7.33 ± 1.21	7.02 ± 1.19	6.94 ± 1.34	10.6 ± 3.8
HR (bpm)	66 ± 11	66 ± 12	68 ± 13	67 ± 13	73 ± 15*†	70 ± 12	68 ± 13	68 ± 11	8.9 ± 3.2
SV (ml)	106 ± 17	101 ± 19	101 ± 18	101 ± 19	99 ± 19	106 ± 15	106 ± 18	104 ± 18	7.6 ± 3.6
TPR (PRU)	0.83 ± 0.14	0.84 ± 0.17	0.86 ± 0.21	0.86 ± 0.27	0.79 ± 0.15	0.76 ± 0.15	0.79 ± 0.16	0.81 ± 0.23	13.0 ± 1.2
ScO_2 (%)	70 ± 5	68 ± 7	69 ± 4	69 ± 5	69 ± 6	70 ± 6	70 ± 5	69 ± 4	4.7 ± 2.1

Table 5. Heart rate variability data throughout intermittent hypoxia. Values are means ± SD. Definition of abbreviations: HF = high frequency power normalized to total power; LF = low frequency power normalized to total power; n.u.= normalized units (HF/total power).

	Day 1	Day 12	Day 15	Day 17
HF (n.u.)	44.7 ± 15.2	47.3 ± 15.4	45.5 ± 18.8	54.34 ± 20.5
LF (n.u.)	45.9 ± 15.3	32.2 ± 17.4	31.8 ± 19.1	37.7 ± 12.7
LF/HF	1.06 ± 0.55	0.83 ± 1.12	0.85 ± 0.86	0.83 ± 0.44

Table 6. Average level of isocapnia maintained throughout each preHVR and postHVR. Values are means ± SD. Definition of abbreviations: $PetCO_2$ = end-tidal partial pressure of CO_2; preHVR = hypoxic ventilatory response occurring prior to each intermittent hypoxic exposure; postHVR = hypoxic ventilatory response occurring following each intermittent hypoxic exposure.

$PetCO_2$ (mmHg)	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17
preHVR	42.4 ± 3.4	42.7 ± 2.8	42.8 ± 3.4	42.5 ± 2.9	42.0 ± 2.3	42.3 ± 2.9	42.4 ± 2.7	42.2 ± 2.9
postHVR	42.8 ± 3.5	42.4 ± 3.1	42.9 ± 3.3	42.5 ± 2.9	42.2 ± 2.0	42.8 ± 2.7		

Table 7. Effects of intermittent hypoxia on systolic, diastolic, and mean arterial blood pressure sensitivity to hypoxia. Values are means ± SD. * Significantly different from preHVR ($p<0.05$). Definition of abbreviations: $\Delta SBP/\Delta SaO_2$ = change in systolic blood pressure per change in arterial oxyhemoglobin saturation; $\Delta DBP/\Delta SaO_2$ = change in diastolic blood pressure per change in arterial oxyhemoglobin saturation; $\Delta MAP/\Delta SaO_2$ = change in mean arterial pressure per change in arterial oxyhemoglobin saturation; preHVR = hypoxic ventilatory response prior to each hypoxic exposure; postHVR = hypoxic ventilatory response following each hypoxic exposure.

Variable	HVR	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17
$\Delta SBP/\Delta SaO_2$	preHVR	0.74 ± 0.44	0.77 ± 0.70	0.76 ± 0.64	0.92 ± 0.57	0.83 ± 0.44	1.05 ± 0.98	0.74 ± 0.88	0.85 ± 0.62
(mmHg $\%SaO_2^{-1}$)	postHVR	0.46 ± 0.59*	0.47 ± 0.42*	0.69 ± 0.74*	0.39 ± 0.37*	0.45 ± 0.47*	0.50 ± 0.49*		
$\Delta DBP/\Delta SaO_2$	preHVR	0.32 ± 0.20	0.35 ± 0.38	0.34 ± 0.38	0.45 ± 0.36	0.35 ± 0.29	0.48 ± 0.50	0.32 ± 0.40	0.37 ± 0.29
(mmHg $\%SaO_2^{-1}$)	postHVR	0.16 ± 0.28*	0.20 ± 0.24*	0.25 ± 0.32*	0.14 ± 0.22*	0.18 ± 0.25*	0.22 ± 0.31*		
$\Delta MAP/\Delta SaO_2$	preHVR	0.47 ± 0.26	0.49 ± 0.47	0.48 ± 0.45	0.60 ± 0.42	0.51 ± 0.33	0.67 ± 0.65	0.45 ± 0.55	0.53 ± 0.38
(mmHg $\%SaO_2^{-1}$)	postHVR	0.26 ± 0.37*	0.29 ± 0.26*	0.40 ± 0.45*	0.22 ± 0.24*	0.27 ± 0.32*	0.31 ± 0.35*		

Table 8. Relationship between the changes in cardiovascular responses and changes in the ventilatory response to hypoxia for all subject, SDIH, LDIH, and that reported by Katayama *et al.* (2001).

Variable vs. δHVR	All (n=18)	SDIH (n = 9)	LDIH (n = 9)	Katayama *et al.*, (2001)
$\delta\Delta SBP/\Delta SaO_2$	r = 0.68*	r = 0.93*	r = -0.05	r = 0.66*
$\delta\Delta DBP/\Delta SaO_2$	r = 0.73*	r = 0.85*	r = 0.09	r = 0.62*
$\delta\Delta HR/\Delta SaO_2$	r = 0.32	r = 0.49	r = -0.05	r = 0.11

δ = Day 12 – Day 1, * $p<0.05$.

Table 9. Effects of intermittent hypoxia on cardiac output, heart rate, stroke volume, and total peripheral resistance sensitivity to hypoxia. Values are means ± SD. * Significantly different from preHVR ($p<0.05$). Definition of abbreviations: $\Delta CO/\Delta SaO_2$ = change in cardiac output per change in arterial oxyhemoglobin saturation; $\Delta HR/\Delta SaO_2$ = change in heart rate per change in arterial oxyhemoglobin saturation; $\Delta SV/\Delta SaO_2$ = change in stroke volume per change in arterial oxyhemoglobin saturation; $\Delta TPR/\Delta SaO_2$ = change in total peripheral resistance per change in arterial oxyhemoglobin saturation; preHVR = hypoxic ventilatory response occurring immediately prior to each hypoxic exposure; postHVR = hypoxic ventilatory response occurring following each hypoxic exposure.

Variable	HVR	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17
$\Delta CO/\Delta SaO_2$	preHVR	0.12 ± 0.05	0.10 ± 0.04	0.12 ± 0.05	0.11 ± 0.06	0.12 ± 0.06	0.11 ± 0.09	0.13 ± 0.09	0.11 ± 0.06
($l\ min^{-1}\ \%SaO_2^{-1}$)	postHVR	0.13 ± 0.08	0.09 ± 0.06	0.12 ± 0.06	0.11 ± 0.06	0.11 ± 0.06	0.12 ± 0.08		
$\Delta HR/\Delta SaO_2$	preHVR	1.11 ± 0.36	1.02 ± 0.46	1.15 ± 0.45	1.10 ± 0.53	1.08 ± 0.46	1.13 ± 0.54	1.16 ± 0.16	0.96 ± 0.70
($bpm\ \%SaO_2^{-1}$)	postHVR	1.16 ± 0.79	1.06 ± 0.34	0.97 ± 0.74	1.06 ± 0.56	1.02 ± 0.57	1.18 ± 0.61		
$\Delta SV/\Delta SaO_2$	preHVR	-0.02 ± 0.52	-0.11 ± 0.64	0.06 ± 0.49	-0.07 ± 0.44	0.24 ± 0.49	0.02 ± 0.48	0.03 ± 0.54	0.14 ± 0.58
($ml\ \%SaO_2^{-1}$)	postHVR	-0.07 ± 0.37	-0.13 ± 0.63	0.07 ± 0.48	0.06 ± 0.51	0.07 ± 0.39	-0.04 ± 0.57		
$\Delta TPR/\Delta SaO_2$	preHVR	-0.007 ±	-0.006 ±	-0.008 ±	-0.006 ±	-0.009 ± 0.007	-0.005 ±	-0.007 ±	-0.006 ±
($PRU\ \%SaO_2^{-1}$)		0.007	0.004	0.005	0.008		0.006	0.009	0.007
	postHVR	-0.022 ±	-0.010 ±	-0.010 ±	-0.010 ±	-0.008 ±	-0.009 ±		
		0.043*	0.011*	0.005*	0.007*	0.014*	0.006*		

Table 10. Effects of intermittent hypoxia on near-infrared spectroscopy variables. Values are means ± SD. * Significantly different from preHVR. † Significantly different from day 1 and 3. Definition of abbreviations: $\Delta ScO_2/\Delta SaO_2$ = change in cerebral oxygen saturation per change in arterial oxyhemoglobin saturation; $\Delta O_2Hb/\Delta SaO_2$ = change in oxyhemoglobin concentration per change in arterial oxyhemoglobin saturation; $\Delta HHb/\Delta SaO_2$ = change in deoxyhemoglobin concentration per change in arterial oxyhemoglobin saturation; $\Delta cHb/\Delta SaO_2$ = change in total hemoglobin concentration per change in arterial oxyhemoglobin saturation; preHVR = hypoxic ventilatory response occurring prior to hypoxic exposure; postHVR = hypoxic ventilatory response occurring following each hypoxic exposure.

Variable	HVR	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17
$\Delta ScO_2/\Delta SaO_2$	preHVR	-0.51 ± 0.13	-0.44 ± 0.19	-0.53 ± 0.12	-0.55 ± 0.15	-0.55 ± 0.15	-0.64 ± 0.18†	-0.59 ± 0.11	-0.51 ± 0.13
(%ScO_2 %SaO_2^{-1})	postHVR	-0.58 ± 0.15*	-0.50 ± 0.18*	-0.56 ± 0.15*	-0.52 ± 0.14*	-0.60 ± 0.13*	-0.64 ± 0.19*		
$\Delta O_2Hb/\Delta SaO_2$	preHVR	-0.29 ± 0.08	-0.22 ± 0.13	-0.25 ± 0.08	-0.27 ± 0.13	-0.27 ± 0.12	-0.26 ± 0.19	-0.28 ± 0.13	-0.25 ± 0.15
(μM% SaO_2^{-1})	postHVR	-0.22 ± 0.18	-0.26 ± 0.12	-0.29 ± 0.12	-0.26 ± 0.11	-0.27 ± 0.09	-0.33 ± 0.14		
$\Delta HHb/\Delta SaO_2$	preHVR	0.34 ± 0.21	0.34 ± 0.09	0.38 ± 0.09	0.39 ± 0.11	0.36 ± 0.10	0.44 ± 0.12†	0.43 ± 0.11	0.38 ± 0.10
(μM %SaO_2^{-1})	postHVR	0.43 ± 0.11*	0.38 ± 0.09*	0.40 ± 0.11*	0.39 ± 0.09*	0.41 ± 0.09*	0.43 ± 0.09*		
$\Delta cHb/\Delta SaO_2$	preHVR	0.10 ± 0.07	0.12 ± 0.14	0.12 ± 0.07	0.12 ± 0.10	0.08 ± 0.09	0.18 ± 0.24	0.15 ± 0.14	0.13 ± 0.12
(μM %SaO_2^{-1})	postHVR	0.17 ± 0.13	0.11 ± 0.10	0.11 ± 0.09	0.13 ± 0.09	0.14 ± 0.11	0.10 ± 0.14		

Table 11. Effects of exposure to SDIH and LDIH on respiratory variables during hypoxia. Values are means ± SD. * Significantly different from H-1 ($p<0.05$). Definition of abbreviations: $\dot{V}_I$ = ventilation; F_b = breathing frequency; V_t = tidal volume; H-1 = average over the last 3 minutes of the first 5 minute period of hypoxic exposure; H-2 = average over the last 3 minutes of the last 5 minute period of hypoxic exposure.

		Day 1		Day 3		Day 5		Day 8		Day 10		Day 12	
Variable	Group	H-1	H-2	H-1	H-2	H-1	H-2	H-1	H-2	H-1	H-2	H-1	H-2
$\dot{V}_I$	SDIH	13.6 ±	13.1 ±	12.5 ±	12.6 ±	13.6 ±	13.7 ±	13.0 ±	12.7 ±	13.7 ±	13.6 ±	13.9 ±	14.0 ±
(l min^{-1})		3.1	2.5	2.6	2.4	3.2	2.5	3.0	4.3	3.3	2.1	2.8	2.3
	LDIH	14.0 ±	13.3 ±	13.9 ±	13.2 ±	13.8 ±	13.7 ±	15.1 ±	14.2 ±	13.2 ±	13.3 ±	14.8 ±	13.5 ±
		2.0	2.3	1.9	2.3	2.2	2.0	2.8	2.4	2.4	2.9	2.4	2.4
F_b	SDIH	18.0 ±	17.0 ±	18.6 ±	17.5 ±	18.1 ±	17.7 ±	17.7 ±	16.5 ±	18.8 ±	18.0 ±	17.9 ±	17.4 ±
(breaths		3.8	4.4*	4.2	3.7*	4.8	4.3*	4.1	4.7*	4.1	3.4*	3.4	3.8*
min^{-1})	LDIH	18.4 ±	18.0 ±	19.1 ±	17.9 ±	18.6 ±	18.2 ±	19.6 ±	18.9 ±	19.8 ±	17.6 ±	19.4 ±	17.9 ±
		2.0	2.9*	2.7	3.5*	2.4	2.6*	2.1	3.6*	2.9	4.3*	2.7	2.9*
V_t (liters)	SDIH	0.80 ±	0.83 ±	0.70 ±	0.75 ±	0.80 ±	0.84 ±	0.76 ±	0.81 ±	0.75 ±	0.80 ±	0.81 ±	0.85 ±
		0.12	0.18	0.13	0.17	0.20	0.27	0.16	0.31	0.18	0.21	0.21	0.19
	LDIH	0.81 ±	0.77 ±	0.75 ±	0.77 ±	0.76 ±	0.78 ±	0.79 ±	0.79 ±	0.70 ±	0.86 ±	0.78 ±	0.78 ±
		0.14	0.11	0.06	0.21	0.07	0.11	0.14	0.25	0.14	0.45	0.11	0.17

Table 12. Effects of exposure to SDIH and LDIH on cardiovascular function during hypoxia. Values are means ± SD. * Significantly different from H-1 ($p<0.05$). Definition of abbreviations: MAP = mean arterial pressure; HR = heart rate; SaO_2 = arterial oxyhemoglobin saturation; ScO_2 = cerebral oxygen saturation.

		Day 1		Day 3		Day 5		Day 8		Day 10		Day 12	
Variable	Group	H-1	H-2	H-1	H-2	H-1	H-2	H-1	H-2	H-1	H-2	H-1	H-2
MAP	SDIH	94.6 ±	99.8 ±	89.7 ±	96.7 ±	94.0 ±	99.4 ±	90.1 ±	97.7 ±	91.4 ±	98.0 ±	96.4 ±	99.4 ±
(mmHg)		9.3	9.5*	8.3	5.9*	6.8	8.6*	7.2	7.6*	10.3	8.4*	8.5	11.9*
	LDIH	95.1 ±	98.5 ±	88.8 ±	91.8 ±	87.0 ±	90.2 ±	90.8 ±	91.9 ±	89.2 ±	89.3 ±	91.3 ±	92.9 ± 6.2
		11.3	15.4	10.5	10.6	8.0	6.6	11.4	13.1	6.6	9.0	7.6	
HR (bpm)	SDIH	68.1 ±	71.2 ±	67.0 ±	72.5 ±	71.1 ±	73.1 ±	68.0 ±	70.2 ±	69.8 ±	69.4 ±	69.6 ±	70.8 ±
		14.2	17.5	14.3	21.6	17.1	13.3	12.2	13.2	11.5	11.5	13.4	12.1
	LDIH	72.9 ±	73.9 ±	71.7 ±	70.6 ±	70.1 ±	72.4 ±	71.5 ±	73.7 ±	78.4 ±	81.6 ±	76.4 ±	77.2 ±
		9.2	10.6	10.7	10.2	9.8	11.5	13.4	12.6	14.1	15.1	9.4	12.7
SaO_2 (%)	SDIH	91.4 ±	89.9 ±	92.2 ±	90.8 ±	92.1 ±	91.8 ±	91.6 ±	91.4 ±	92.5 ±	92.7 ±	92.0 ±	92.2 ± 2.1
		3.7	4.7	2.7	3.7	1.9	2.2	2.1	2.2	1.5	2.1	1.6	
	LDIH	91.1 ±	87.1 ±	91.1 ±	86.9 ±	91.3 ±	87.3 ±	92.2 ±	89.1 ±	90.6 ±	84.8 ±	91.6 ±	87.3 ±
		2.1	6.1*	2.5	3.0*	1.9	3.8*	2.0	3.8*	1.1	2.4*	1.2	4.3*
ScO_2 (%)	SDIH	67.9 ±	67.6 ±	65.3 ±	67.0 ±	66.4 ±	67.9 ±	65.1 ±	65.7 ±	68.1 ±	69.1 ±	67.8 ±	68.1 ± 7.0
		5.9	6.5	6.4	8.1	5.2	5.0	5.7	6.2	6.0	6.0	5.9	
	LDIH	65.1 ±	62.6 ±	62.3 ±	60.1 ±	63.6 ±	61.9 ±	65.0 ±	63.1 ±	62.3 ±	59.1 ±	63.7 ±	61.3 ±
		6.9	8.0*	6.3	7.2*	5.3	5.4*	3.6	4.8*	4.7	6.7*	6.4	6.7*

Figure 1. Displays the experimental protocol. Each day of measurement is indicated along the top bar.

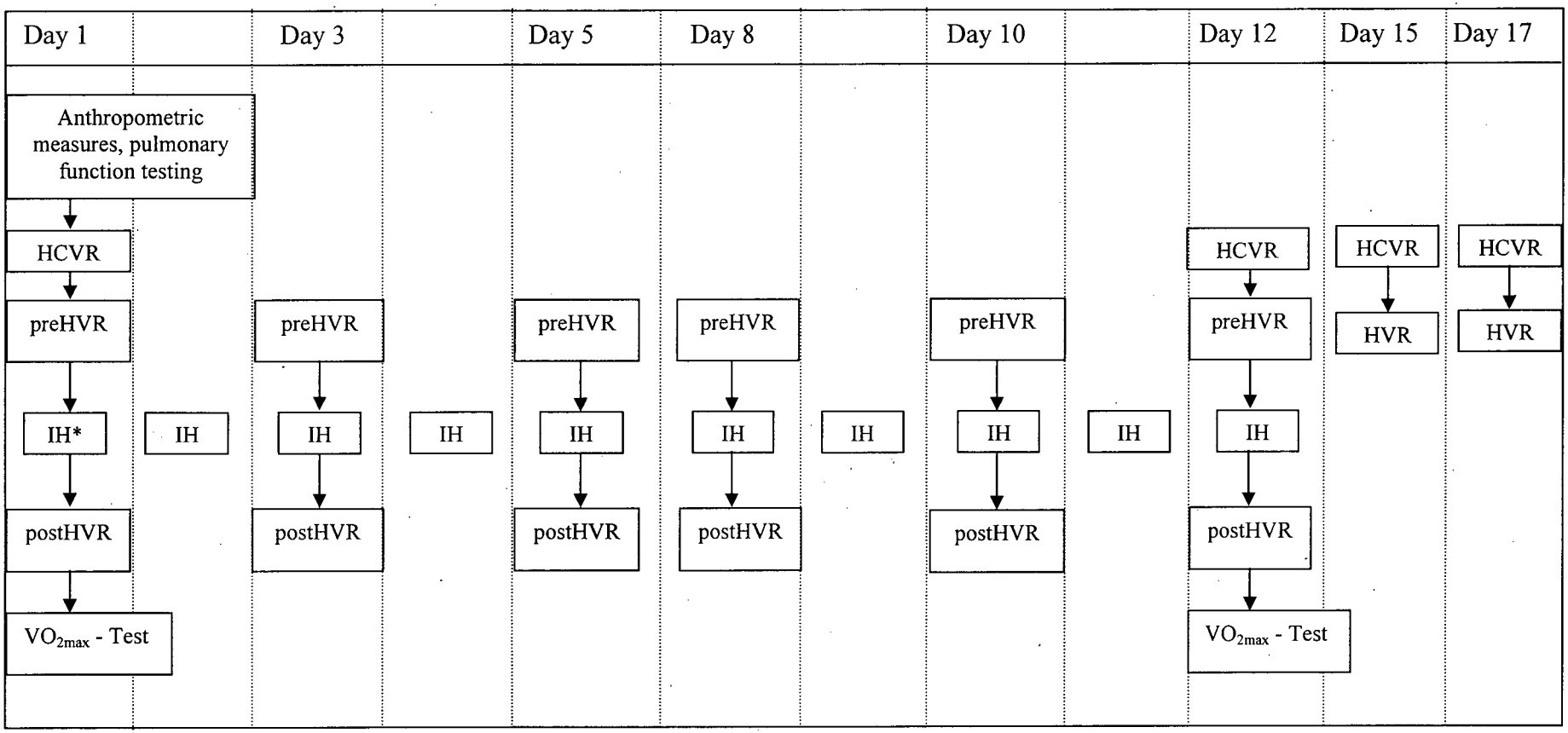


Figure 2a. Raw data trace of one individual subject from the LDIH group on the first day of the experimental protocol. Data was sampled at 1000Hz. Definition of abbreviations: FiO_2 = fraction of inspired oxygen; SaO_2 = arterial oxyhemoglobin saturation; ScO_2 = cerebral oxygen saturation; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response.

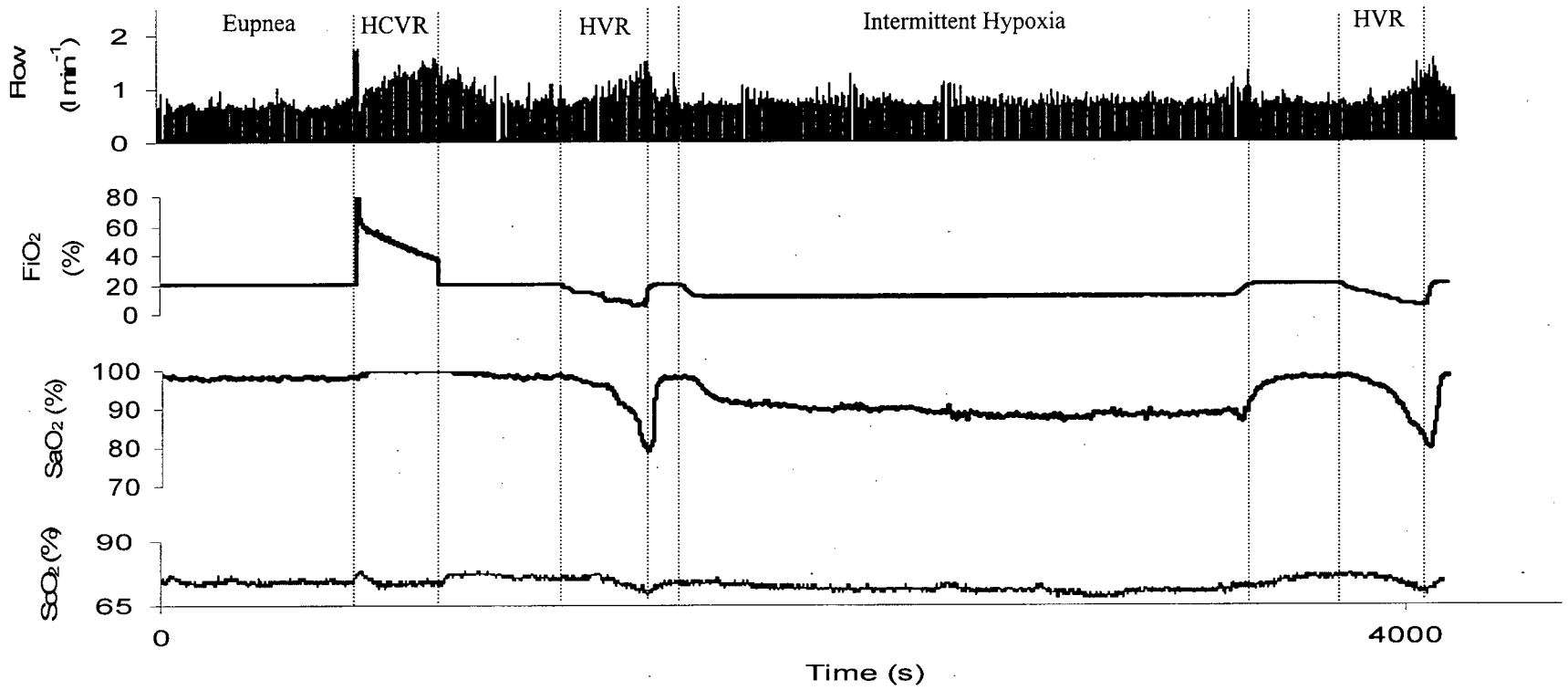


Figure 2b. Raw data trace of one individual subject from the SDIH group on the first day of the experimental protocol. Data was sampled at 1000Hz. Definition of abbreviations: FiO_2 = fraction of inspired oxygen; SaO_2 = arterial oxyhemoglobin saturation; ScO_2 = cerebral oxygen saturation; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response.

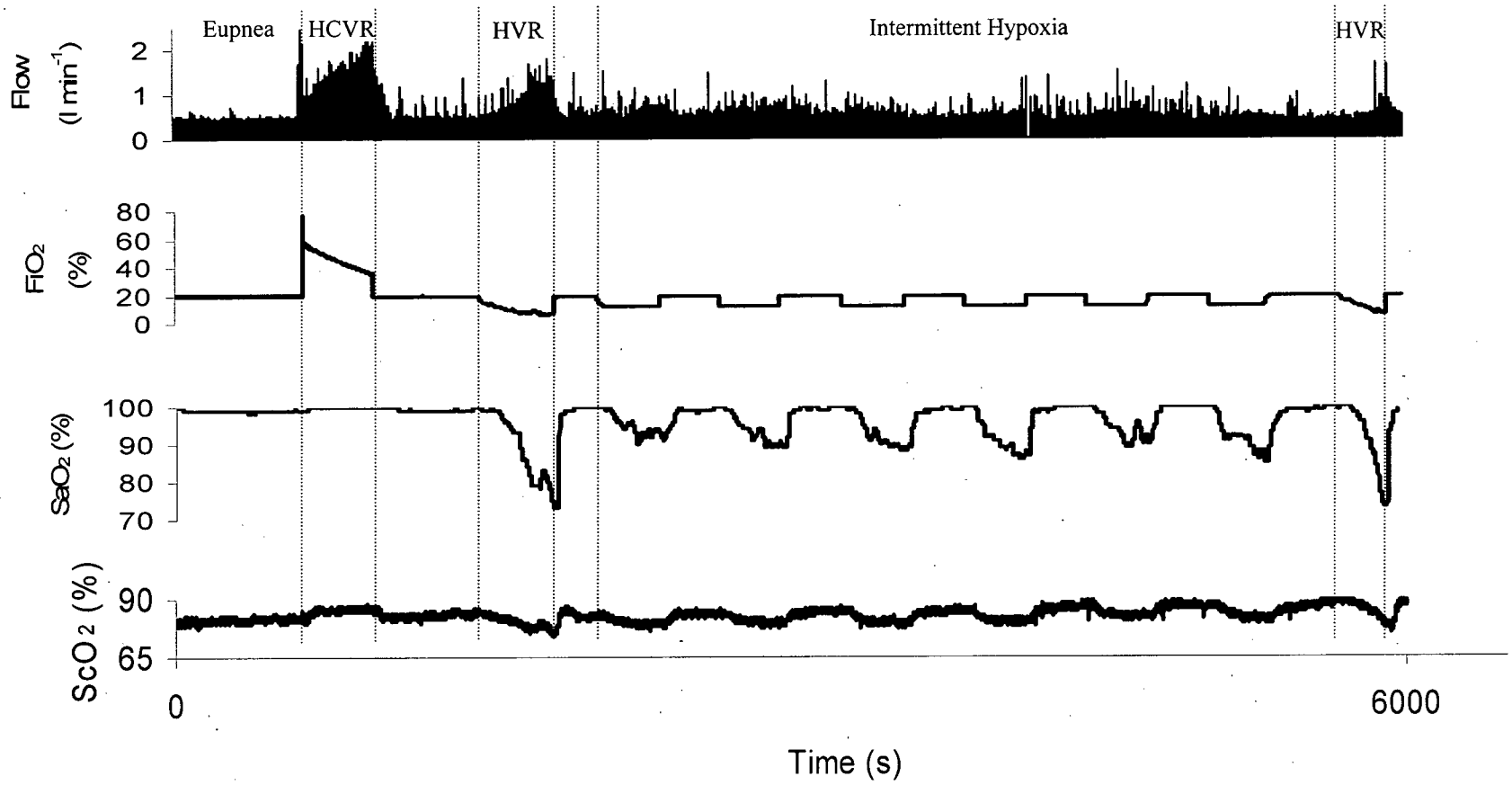


Figure 3. A typical hypercapnic ventilatory response (HCVR) for one representative subject. Data points are 10-second averages. Definition of abbreviations: V_I = minute ventilation; $PetCO_2$ = end-tidal partial pressure of CO_2.

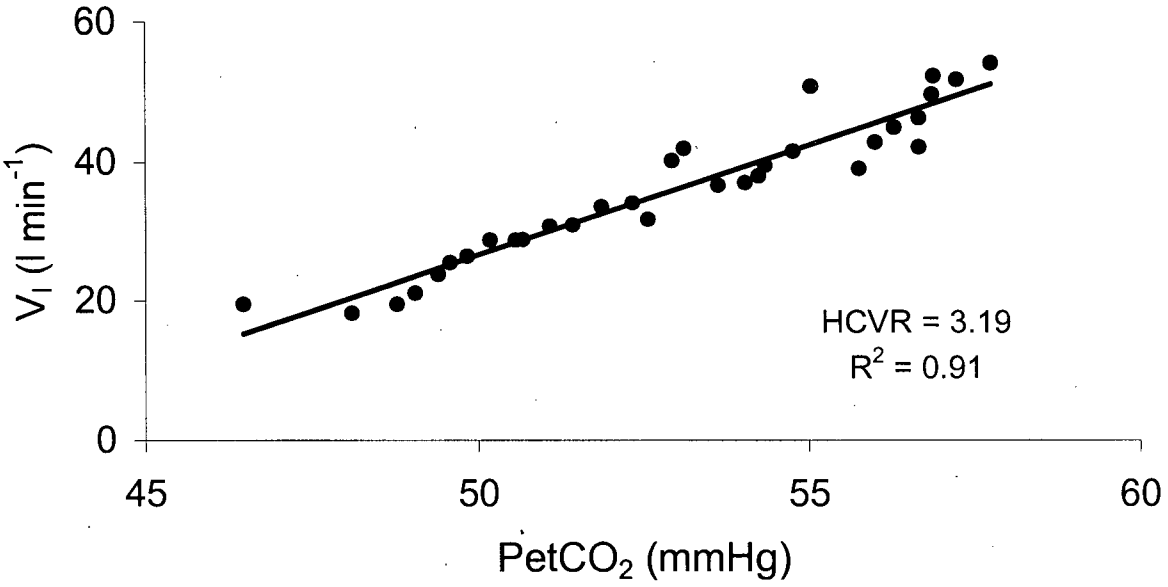


Figure 4. Effects of intermittent hypoxia on the hypercapnic ventilatory response (HCVR) for subjects in the SDIH group (n=9) and subjects in the LDIH group (n=9). Data points are means ± S.E.

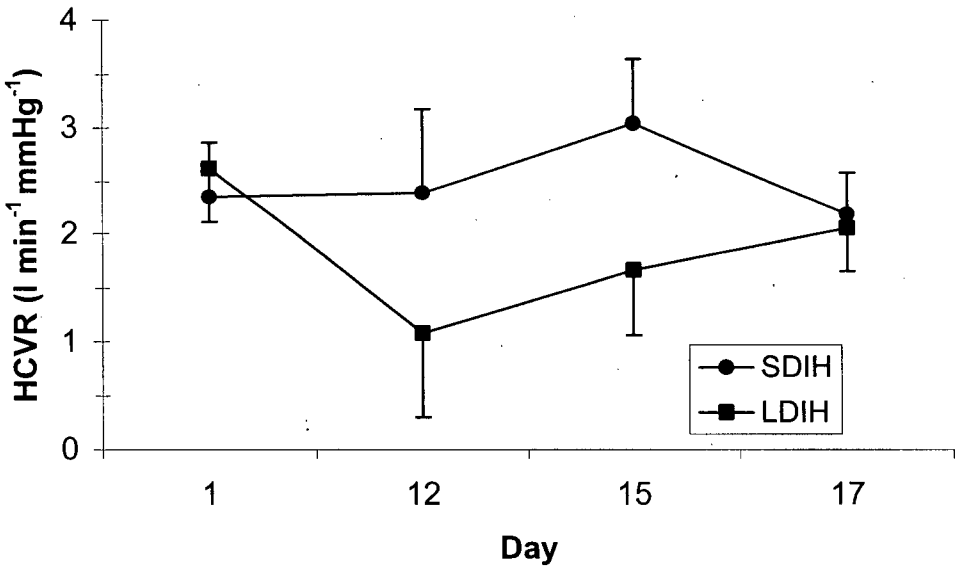


Figure 5. Displays the hypoxic ventilatory response (preHVR) for one individual subject on day 1 (pre-IH) prior to intermittent hypoxic exposure and again on day 12 (post-IH) on the last day of intermittent hypoxic exposure. Definition of abbreviations: V_I = minute ventilation; SaO_2 = arterial oxyhemoglobin saturation.

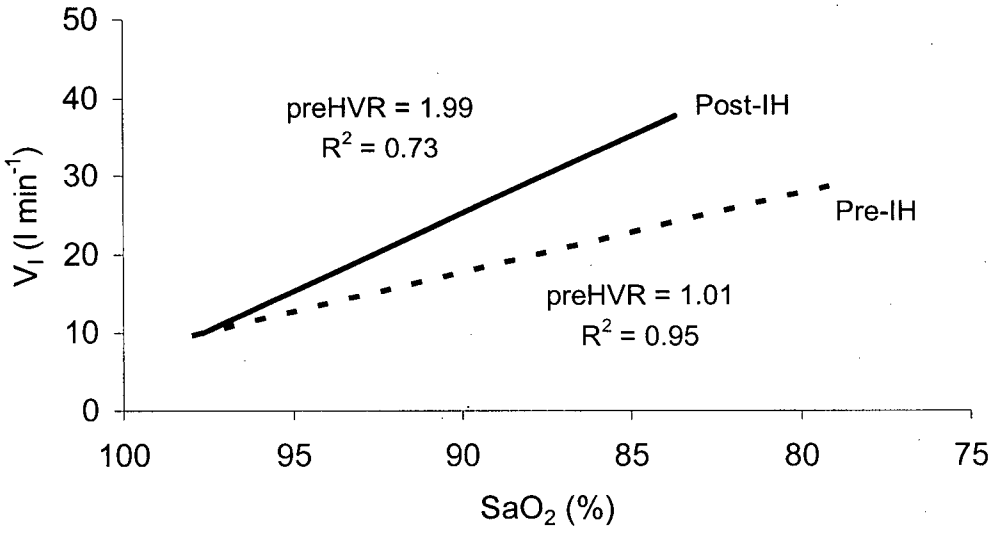


Figure 6. Effects of intermittent hypoxia on the hypoxic ventilatory response occurring prior to each hypoxic exposure (preHVR) for all subjects. Data points are means ± SE. * Significantly different from day 1 and day 3.

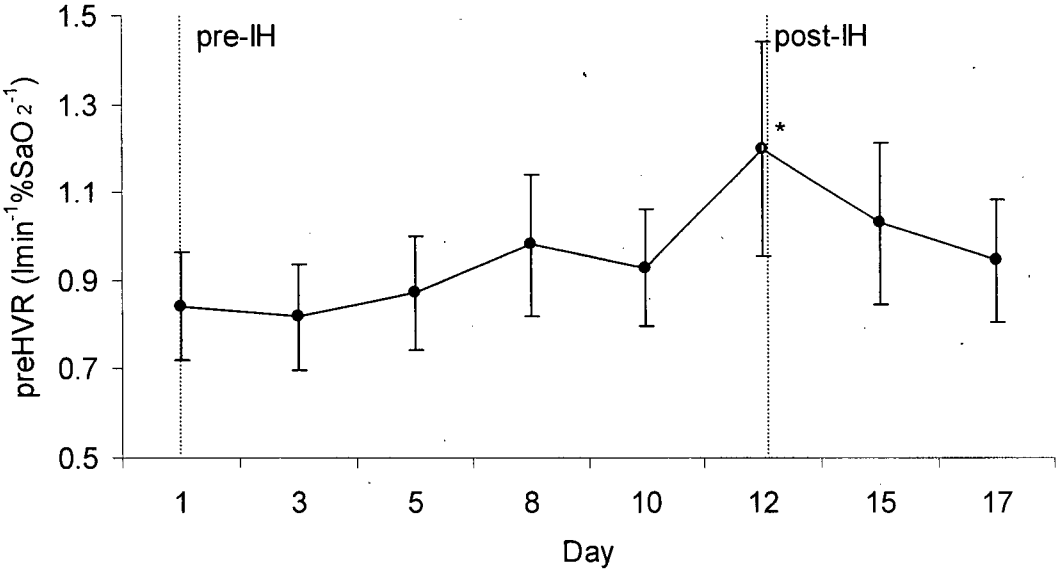


Figure 7. Displays the hypoxic ventilatory response (preHVR) for one individual subject prior to each exposure throughout intermittent hypoxia and the HVR measured on one occasion and 5 days later for 5 consecutive days for the same subject during a different study (Koehle *et al.*, In press).

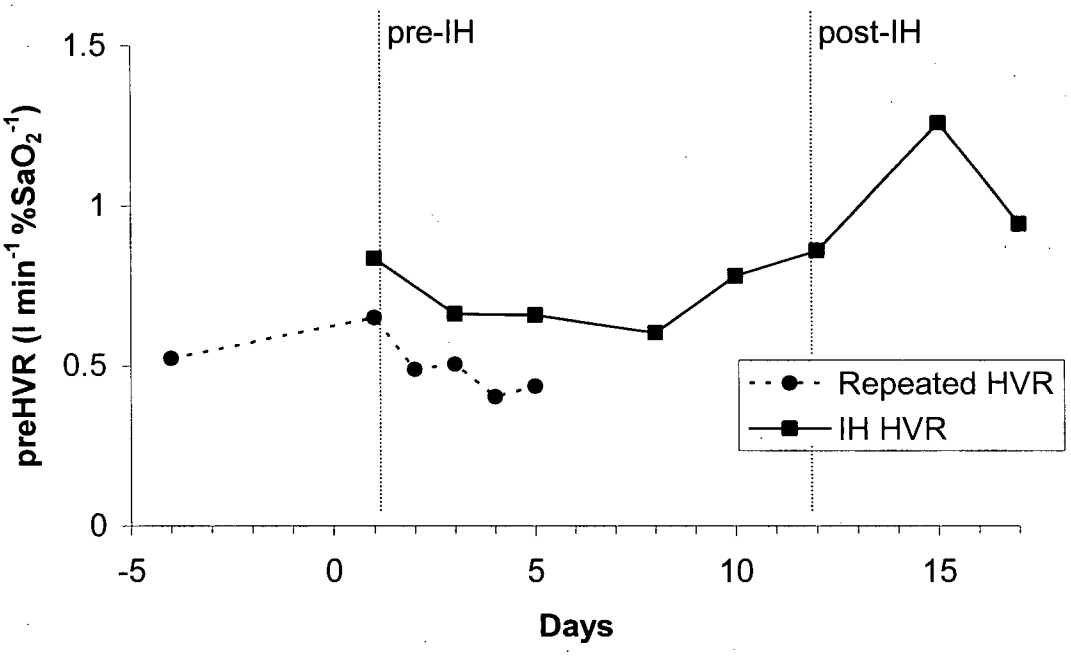


Figure 8. Displays the effects of intermittent hypoxia on preHVR and postHVR for all subjects. Data points are means ± SE. * Significantly different from postHVR ($p<0.01$). Definition of abbreviations: HVR = hypoxic ventilatory response; preHVR = HVR occurring prior to each hypoxic exposure; postHVR = HVR occurring following each hypoxic exposure.

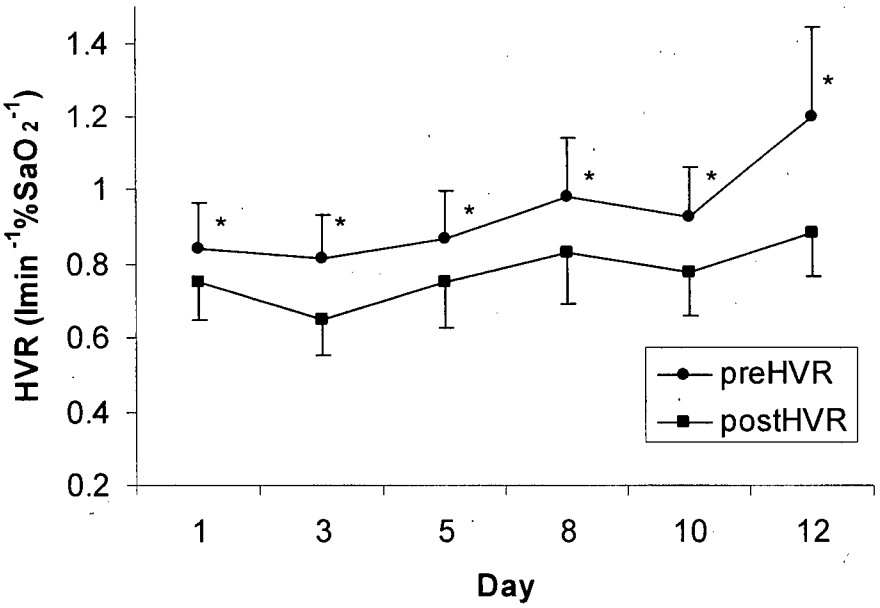


Figure 9. Displays the relationships and sensitivities to hypoxia of (A) systolic (SBP) and (B) diastolic blood pressure (SBP), (C) heart rate (HR), (D) stroke volume (SV), (E) cardiac output (CO), and (F) total peripheral resistance (TPR) for one individual subject during a hypoxic ventilatory response on the first day of its measurement. Data points are 10-second averages. Definition of abbreviations: SBP/SaO_2 = change in systolic blood pressure per change in arterial oxyhemoglobin saturation; DBP/SaO_2 = change in diastolic blood pressure per change in arterial oxyhemoglobin saturation; HR/SaO_2 = change in heart rate per change in arterial oxyhemoglobin saturation; SV/SaO_2 = change in stroke volume per change in arterial oxyhemoglobin saturation; CO/SaO_2 = change in cardiac output per change in arterial oxyhemoglobin saturation; TPR/SaO_2 = change in total peripheral resistance per change in arterial oxyhemoglobin saturation.

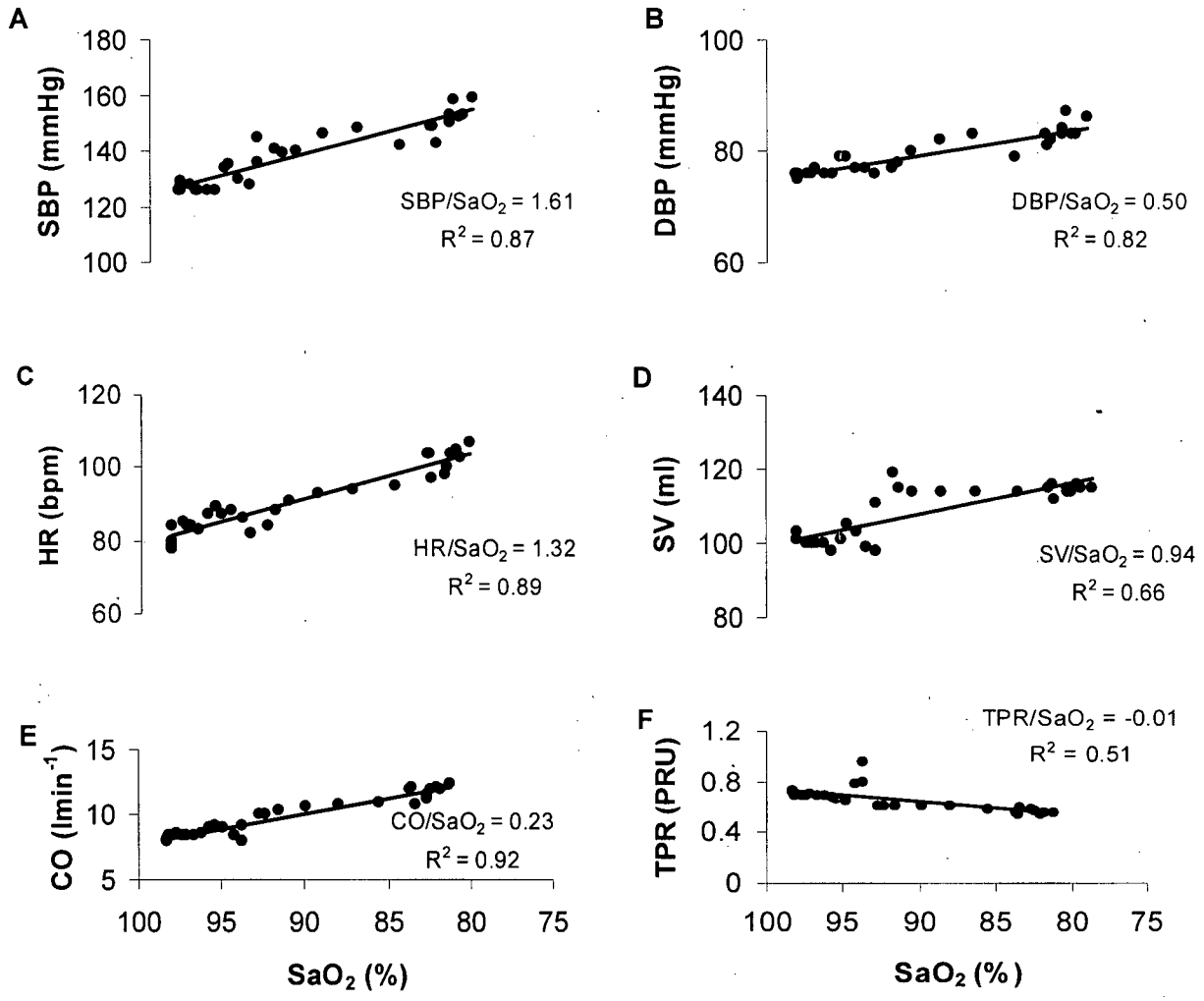


Figure 10. The effects of intermittent hypoxia on systolic blood pressure sensitivity and on diastolic blood pressure sensitivity for all subjects. Data points are means ± SE. Definition of abbreviations: BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; pre-IH = pre intermittent hypoxia; post-IH = post intermittent hypoxia.

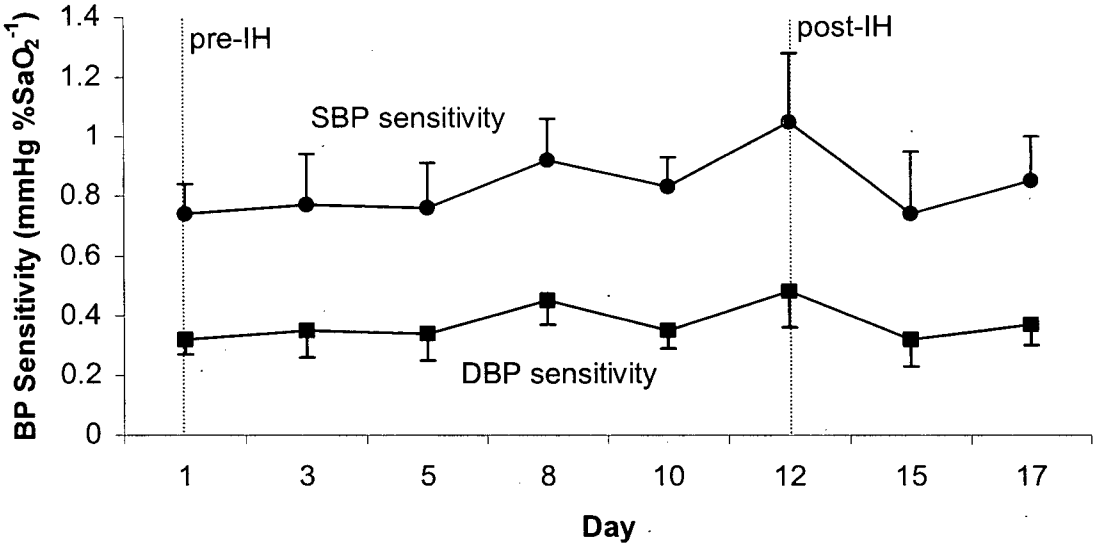


Figure 11. Displays the relationship and sensitivity to hypoxia of cerebral (A) oxygen saturation (ScO_2), (B) oxyhemoglobin concentration (uM), (C) deoxyhemoglobin concentration (HHb), and (D) total hemoglobin concentration (cHb) during a hypoxic ventilatory response for one individual subject. Data points are 10-second averages. Definition of abbreviations: $dScO_2/dSaO_2$ = the change in cerebral oxygen saturation per change in arterial oxyhemoglobin saturation.; $dO_2Hb/dSaO_2$ = change in oxyhemoglobin concentration per change in arterial oxyhemoglobin saturation; $dHHb/dSaO_2$ = change in deoxyhemoglobin saturation per change in arterial oxyhemoglobin saturation; $dcHb/dSaO_2$ = change in total hemoglobin concentration per change in arterial oxyhemoglobin saturation; SaO_2 = arterial oxyhemoglobin saturation.

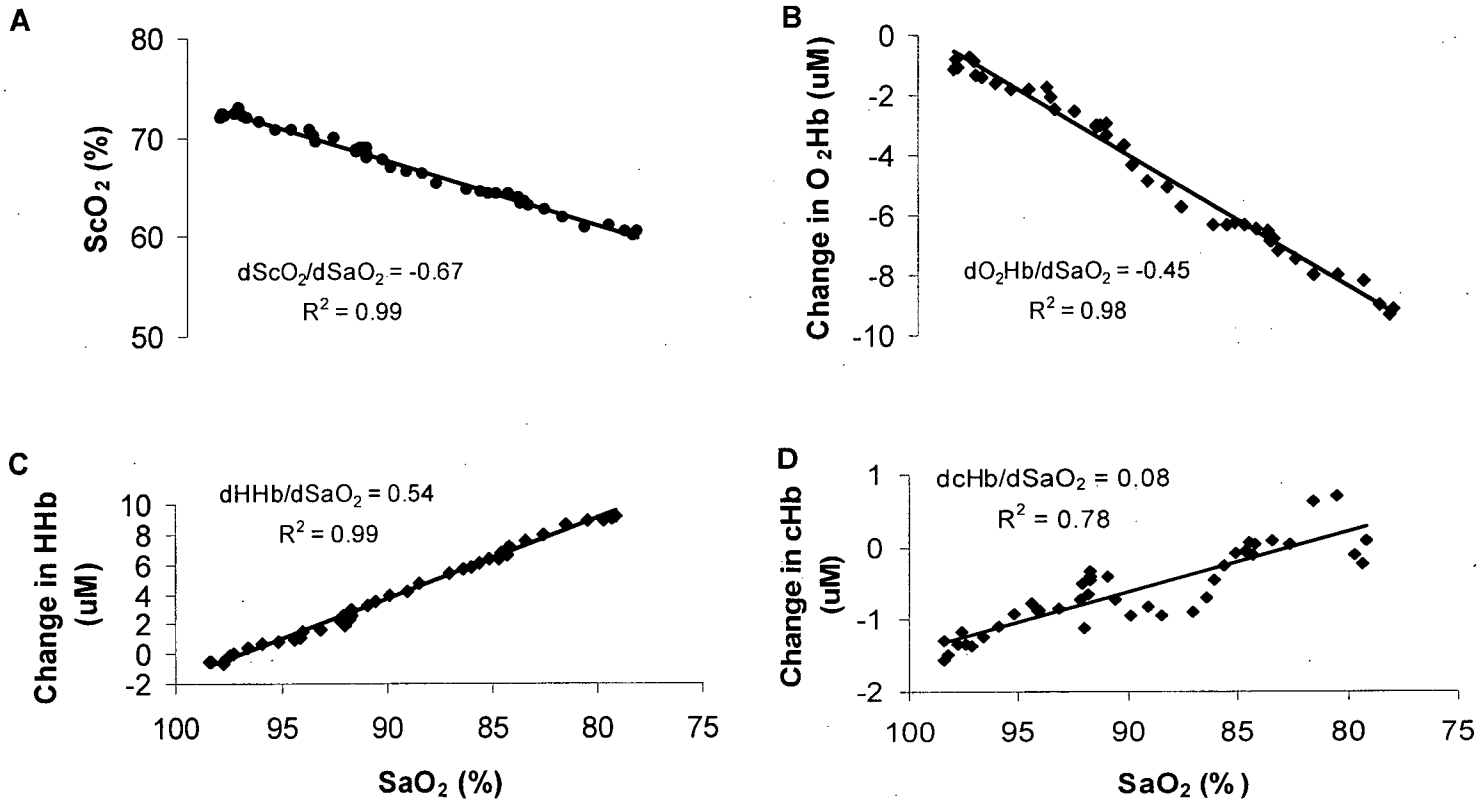


Figure 12. The effects of intermittent hypoxia on cerebral oxygen saturation sensitivity ($dScO_2/dSaO_2$) to hypoxia for all subjects. Cerebral oxygen saturation sensitivity is the change in cerebral oxygen saturation ($dScO_2$) per change in arterial oxygen saturation ($dSaO_2$). Data points are means ± SE. * Significantly different from day 1 and day 3 ($p<0.05$). Definition of abbreviations: pre-IH = pre intermittent hypoxia; post-IH = post intermittent hypoxia.

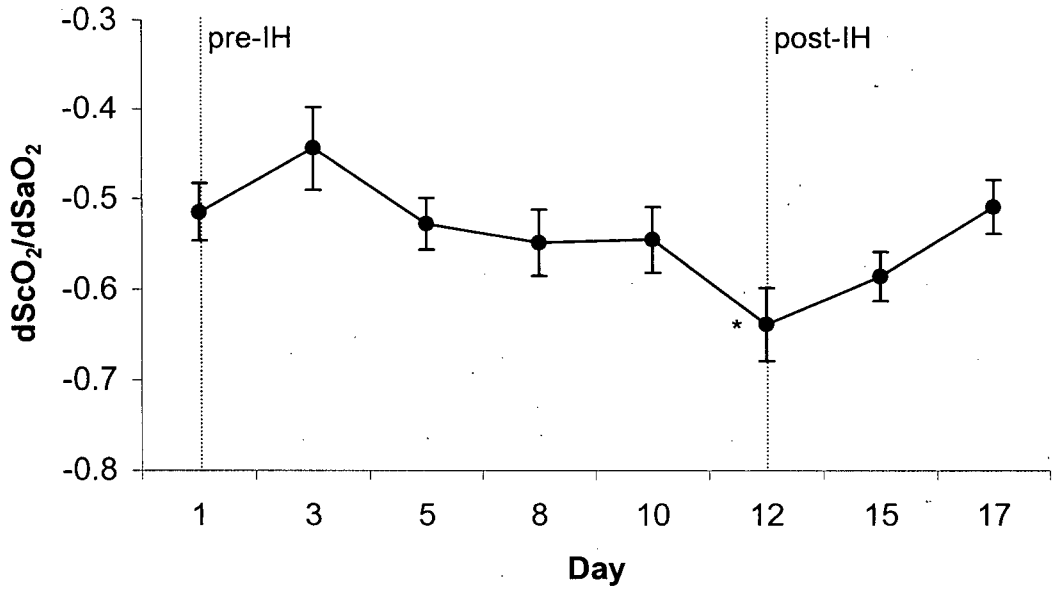
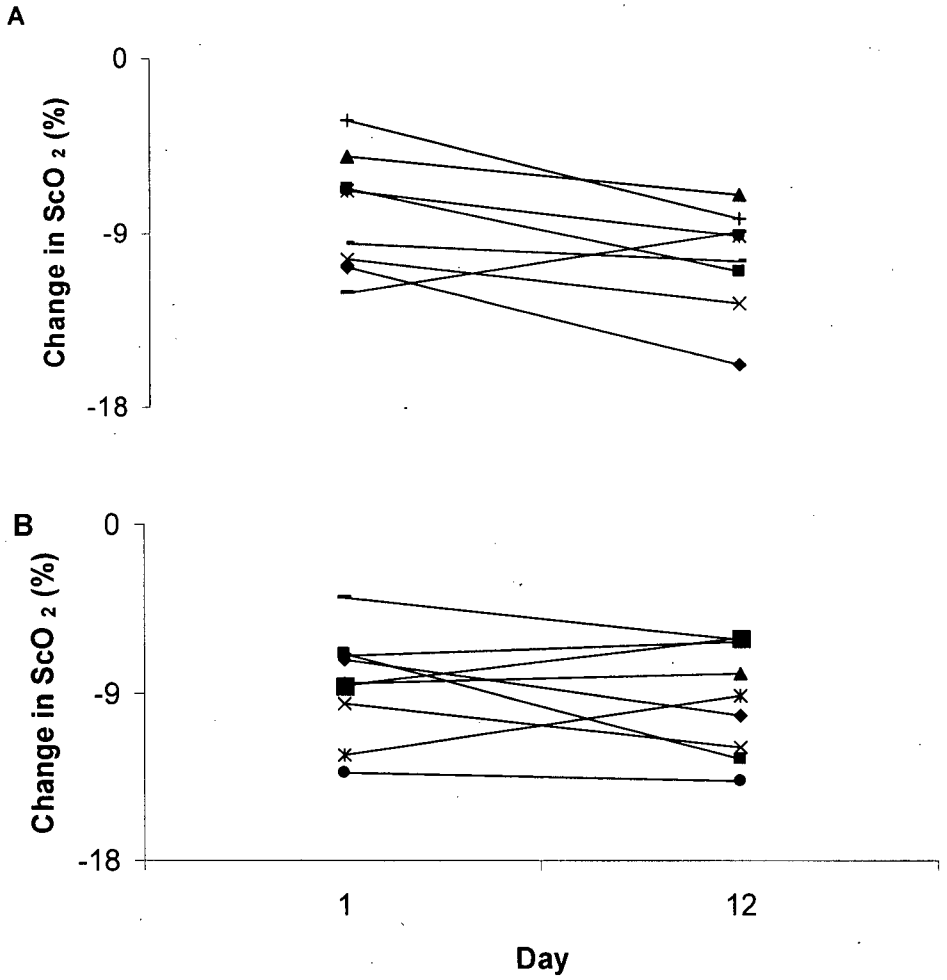


Figure 13. Displays the change in cerebral oxygen saturation (ScO_2) during the preHVR on day 1 and on day 12 for all subjects in (A) SDIH and (B) LDIH. The preHVR is the hypoxic ventilatory response occurring prior to exposure to daily hypoxia.



APPENDIX A

Review of Literature – Intermittent Hypoxia

Introduction

Intermittent exposure to hypoxia has been shown to affect the control of breathing (Gozal & Gozal, 2001; Mitchell *et al.*, 2001; Prabhakar, 2001; Mitchell & Johnson, 2003; Morris *et al.*, 2003), the cardiovascular system (Earley & Walker, 2002; Gonzales & Walker, 2002; Jernigan & Resta, 2002), and the autonomic nervous system (MacDonald *et al.*, 1992; Morgan *et al.*, 1995; Smith & Muenter, 2000; Yasuma & Hayano, 2000). Unlike continuous hypoxia (CH), intermittent hypoxia (IH) may contribute to the effects of certain pathological conditions, such as sleep apnea and chronic obstructive pulmonary disease. Chronic exposure to IH can lead to secondary conditions including systemic hypertension, myocardial and brain infarctions, and cognitive dysfunction (Prabhakar, 2001). Recurrent episodes of hypoxia are also common in individuals who do not display pathophysiologies. This includes individuals who voluntarily engage in breath-holding activities (i.e. breath-hold diving) (Andersson *et al.*, 2002) or sojourn to altitude (Powell & Garcia, 2000). These healthy individuals display adaptations as a result of repetitive hypoxemia (Ferretti, 2001). The purpose of this review is to examine the consequences of IH on ventilatory, cardiovascular, and autonomic systems in healthy humans and to compare these findings to animal models and to individuals who have been exposed to IH as a result of disease. Several extensive reviews already exist which describe intermittent hypoxia in the animal model (Fletcher *et al.*, 1992; Fletcher, 2001; Gozal & Gozal, 2001; Mitchell *et al.*, 2001; Prabhakar, 2001; Prabhakar *et al.*, 2001); the reader is referred to them as a supplement to this review.

For the purpose of this review, three types of exposure to hypoxia are distinguished. Continuous hypoxia is defined as a single exposure to a sustained hypoxic stimulus for a

duration greater than 48 hours with no subsequent exposure to hypoxia. Continuous hypoxia is contrasted to two forms of IH: long duration intermittent hypoxia (LDIH) and short duration intermittent hypoxia (SDIH) (Peng & Prabhakar, 2004). LDIH is defined as exposure to a single daily episode of hypoxia for 30 minutes to five hours that occurs every day for 5 days or more, while SDIH is several daily exposures (3-12 bouts) to less than five minutes of hypoxia separated by normoxia. Like LDIH, SDIH involves daily exposures that continue for 5 days or more.

This review is divided into three sections. The first section describes the ventilatory consequences of IH with particular emphasis on the acute ventilatory response to hypoxia and hypercapnia. The subsequent section describes the cardiovascular consequences of IH and discusses changes in blood pressure, cardiac output, stroke volume, heart rate, and total peripheral resistance. This section also describes changes in endothelial function in response to hypoxia. The final section discusses the consequences of IH on autonomic function.

Ventilatory Consequences of Intermittent Hypoxia

The control of breathing in humans is often studied by quantifying the ventilatory response to chemical stimuli. The hypoxic ventilatory response (HVR) is measured by progressively reducing the inspired fraction of oxygen to evoke a change in the partial pressure of oxygen in arterial blood (PaO_2) and, thus, an increase in minute ventilation (Weil *et al.*, 1970). Using this method, the HVR is the slope of the linear regression relating ventilation and arterial oxygen saturation (Harms & Stager, 1995; Derchak *et al.*, 2000; Guenette *et al.*, 2004; Koehle *et al.*, In Press). Another method of assessing HVR involves plotting the hyperbolic curve that results when the partial pressure of oxygen is related to ventilation (Weil *et al.*, 1970; Byrne-Quinn *et al.*, 1971). These two methods of assessing HVR are qualitatively similar but quantitatively different. The hypercapnic ventilatory response (HCVR) is measured by

quantifying the increase in ventilation as the individual's end-tidal partial pressure of CO2 is increased (Read, 1967). A linear regression relates the change in ventilation to the change in end-tidal partial pressure of CO_2; the slope of this line is termed the HCVR. Various methods exist for measuring the HCVR; however, the rebreathing method developed by Read (Read, 1967) is the most common. Other methods are simply variations of this method that may involve previous hyperventilation and varying levels of oxygen (hyperoxic, normoxic, or hypoxic) (Mohan & Duffin, 1997; Mohan *et al.*, 1999; Mahamed & Duffin, 2001; Duffin & Mahamed, 2003; Mateika *et al.*, 2004). The mechanisms are qualitatively similar for both responses; changes in the partial pressure of oxygen and CO2 are sensed by the peripheral chemoreceptor and a ventilatory correction is made reflexively to maintain homeostasis (Duffin & Mahamed, 2003). Changes in HVR and HCVR (i.e. changes in slope) indicate changes in the sensitivity of the respiratory control system to hypoxia and hypercapnia respectively.

Ventilatory responses have been determined in a broad spectrum of individuals. In comparison to healthy normal controls, endurance athletes (Martin *et al.*, 1979; Mahler *et al.*, 1982; Miyamura & Ishida, 1990; Harms & Stager, 1995), breath-hold divers (Masuda *et al.*, 1981; Grassi *et al.*, 1994; Delapille *et al.*, 2001), and sleep apnea patients (Garcia-Rio *et al.*, 2002) have a reduced ventilatory response to hypercapnia and hypoxia. Blunted ventilatory responses in breath-hold divers and sleep apnea patients might be explained by their chronic exposure to intermittent hypoxic conditions; however, individuals involved in mountain climbing who repeatedly sojourn to altitude demonstrate an enhanced ventilatory response to hypoxia (Powell & Garcia, 2000). Also, in healthy humans with no breath-holding experience and no previous exposure to altitude, intermittent hypoxic exposure for a duration of one to two weeks increases the ventilatory response to hypoxia (Prabhakar & Kline, 2002).

Respiratory control in the animal model is similar in that chemical stimuli may be used to evoke respiratory compensation; however, direct nerve recordings can be obtained from either

the carotid sinus nerve or the phrenic nerve rather than quantifying ventilation itself (Daly, 1997). Chemical stimuli include changes in the partial pressures of oxygen and CO2, changes in pH and application of pharmacological agents. Direct electrical stimulation of the carotid sinus nerve is also a popular method for evoking respiratory changes in the animal model. For the purpose of this review only those respiratory responses that result from changes in oxygen and CO2 partial pressures will be discussed.

Various studies on the control of breathing using animal models have demonstrated respiratory neural plasticity within the central nervous system in response to hypoxia (Mitchell & Johnson, 2003; Morris *et al.*, 2003). Long term facilitation occurs following exposure to successive episodes of hypoxia and is characterized by a progressive increase in respiratory motor output during the normoxic intervals (Powell *et al.*, 1998). Respiratory motor output can remain elevated for many minutes to several hours following the final stimulus episode (Powell *et al.*, 1998). In the rodent model, SDIH enhances hypoxic sensitivity and leads to long-term facilitation in the sensory discharge of the carotid nerve while continuous hypoxia does not (Peng *et al.*, 2001; Prabhakar, 2001; Peng & Prabhakar, 2004). Peng and Prabhakar (2004) exposed rats to SDIH and LDIH for ten days and determined carotid body sensory activity *in vivo* and *ex vivo* to graded isocapnic hypoxia. The hypoxic sensory activity was enhanced in SDIH animals but not in LDIH animals.

Studies involving normal human subjects also demonstrate respiratory plasticity. As in the rodent model, human hypoxic sensitivity increases with repeated exposure to hypoxia (Katayama *et al.*, 1998; Katayama *et al.*, 1999; Garcia *et al.*, 2000b; Katayama *et al.*, 2001a; Katayama *et al.*, 2001b); but, long term facilitation does not occur. Other human studies involve patients who have undergone carotid body resection as a treatment for asthma or carotid body tumors (Gross *et al.*, 1976; Honda *et al.*, 1988; Timmers *et al.*, 2003). From these studies it appears that the carotid body plays an obligatory, excitatory role in the ventilatory response to

hypoxia. Bilateral carotid body resected patients have no ventilatory response to progressive hypoxia (Honda *et al.*, 1988; Timmers *et al.*, 2003).

Making direct comparisons between studies is difficult as there appears to be no standard method of intermittent hypoxia protocols. Some studies expose human subjects to isocapnic hypoxia (controlled $PetCO_2$) (Garcia *et al.*, 2000a), while others expose subjects to poikilocapnic hypoxia (uncontrolled $PetCO_2$) (Tansley *et al.*, 1998; Katayama *et al.*, 2001b). Patterns, durations, and hypoxic intensities vary throughout many IH studies and may involve normobaria (Serebrovskaya *et al.*, 1999; Mahamed & Duffin, 2001; Ainslie *et al.*, 2003; Mateika *et al.*, 2004) or hypobaria (Sato *et al.*, 1992; Sato *et al.*, 1994; Katayama *et al.*, 1998; Katayama *et al.*, 1999; Garcia *et al.*, 2000c; Katayama *et al.*, 2001a; Katayama *et al.*, 2001b). Some intermittent hypoxic studies have involved simultaneous exercise training (Levine *et al.*, 1992; Katayama *et al.*, 1998; Katayama *et al.*, 1999, 2001a). Whether or not the changes in respiratory and cardiovascular physiologies are similar among all of these conditions is unknown and requires further study. In contrast to the rodent model, human studies involving CH for a week or more have demonstrated an increase in the HVR that subsequently returns to normal within a week of descent to sea-level (Sato *et al.*, 1992; Sato *et al.*, 1994). More similar to the rodent model are the human studies involving both LDIH and SDIH which equivocally demonstrate increases in HVR (Katayama *et al.*, 1998; Garcia *et al.*, 2000b, 2000c; Katayama *et al.*, 2001b; Katayama *et al.*, 2002). Garcia *et al.* (2000c) compared five days of hypobaric IH at rest (two hours daily at 3800m) with eight weeks of CH (also at 3800m). Both LDIH and CH induced similar changes in magnitude of HVR; however, two weeks of CH were necessary to reach the same change in HVR seen after only five days of LDIH.

Most paradigms of IH in humans evoke an increase in HVR; the available data on the HCVR is not so clear. The HCVR has been reported to either stay the same or increase following IH (Katayama *et al.*, 1998; Katayama *et al.*, 1999, 2001a; Mahamed & Duffin, 2001;

Ainslie *et al.*, 2003). Some of these studies involve IH with concurrent exercise training and involve three different methods for determining HCVR, making it difficult to compare studies. The first and most common method of determining HCVR is the rebreathing method (Read, 1967) which is thought to be a measure of CO_2 sensitivity at the central chemoreceptor (Mohan *et al.*, 1999). Using this method and exercise training during IH, 30 min of hypobaric hypoxia at 432 mmHg for either six days or two weeks shows no change in the central chemoreceptor response to CO_2 (Katayama *et al.*, 1998; Katayama *et al.*, 1999). However, Ainslie *et al.* (2003) showed an increase in the hypercapnic ventilatory response following five nights of normobaric hypoxia (13.8% O_2) using the rebreathing method. Other investigators have used the single breath CO_2 response test (HCVRsb) which is thought to be a measure of the peripheral chemoreceptor response to CO_2 (McClean *et al.*, 1988). No change in HCVRsb was seen following 30 minutes of hypobaric hypoxia at 432 mmHg for six days with concurrent exercise training (Katayama *et al.*, 1999) and also following 1 hour of hypobaric hypoxia at 432 mmHg for two weeks without exercise training (Katayama *et al.*, 2002). Finally, a novel approach of determining the central chemoreceptor response to CO2 has been employed by Mahamed *et al.* (2001). This method involves prior hyperventilation before commencing the rebreathe at different iso-oxic levels and allows for the determination of the chemoreflex threshold to CO_2. Using the modified rebreathing technique, changes in the peripheral chemoreflex to CO2 were measured in hyperoxia and in hypoxia. Following twenty minutes of isocapnic hypoxia daily for 14 consecutive days, an increase in the CO2 threshold occurs but only in the presence of hypoxia, not hyperoxia (Mahamed & Duffin, 2001). The authors interpreted this result as indicating changes in the peripheral chemoreflex and not the central chemoreflex. It may be that marked respiratory alkalosis is necessary to elicit changes in HCVR. In the majority of the studies that measure HCVR, the hypoxic exposure is usually no more than an hour per day for

less than two weeks. Furthermore, it is likely that no change in HCVR occurs in studies where the subjects are exposed to isocapnic hypoxia because no respiratory alkalosis occurs.

Cardiovascular Consequences of Intermittent Hypoxia

The acute cardiovascular response to hypoxia involves an increase in cardiac output (CO), systemic arterial vasodilation, and pulmonary arterial vasoconstriction (Semenza, 1999). Cerebral blood flow (Vovk *et al.*, 2002), heart rate (HR), and arterial blood pressure increase with progressive isocapnic hypoxia and hyperoxic hypercapnia (Yasuma & Hayano, 2000). Twenty minutes of isocapnic hypoxia elicits increases in heart rate, limb blood flow, blood pressure, and muscle sympathetic nerve activity (Morgan *et al.*, 1995; Xie *et al.*, 2000). Intact peripheral chemoreceptors are necessary for arterial blood pressure in rats to increase in response to SDIH patterned after that of sleep apnea in humans (Fletcher *et al.*, 1992). Few studies have examined the cardiovascular response to intermittent hypoxic exposure in humans. Katayama *et al.* (2001b) studied the cardio-ventilatory response to progressive isocapnic hypoxia before and after one hour of daily exposure to 4,500 m for 7 days. Resting ventilation, blood pressure, and heart rate did not change after IH. There was, however, an increase in the systolic (SBP) and diastolic (DBP) blood pressure response to progressive hypoxia. These changes in cardiovascular sensitivity were accompanied by an increase in HVR. Similar results were found in men at high-altitude (5,050M) for 24 days (Insalaco *et al.*, 1996). They found increases in blood pressure sensitivity following one day at high-altitude that continued to increase by the 24^{th} day at high-altitude. They also observed a slight reduction in heart rate sensitivity. In contrast to these studies, several studies using SDIH did not observe changes in cardiovascular function (Bernardi *et al.*, 2001; Rey *et al.*, 2004). Bernardi *et al.* (2001) studied the change in SBP and DBP in response to progressive hypoxia before and after 14 days of exposure to three to four 7-minute isocapnic rebreathing sessions daily (PO_2 was progressively reduced to ~35-40

mmHg). They found no changes in SBP or DBP sensitivity to isocapnic hypoxia. Similarly, in another study, cats were exposed to cyclic hypoxic episodes (PO2 ~ 75 mmHg) repeated during 8 hours for 2 to 4 days; no changes in arterial pressure or heart rate sensitivity during acute hypoxia were found (Rey *et al.*, 2004). Studies involving sleep apnea patients show that an elevated resting normoxic blood pressure and, in many cases, a hypertensive condition are present (Fletcher, 2001).

Recently published animal work suggests IH may alter both peripheral and cerebrovascular vasomotor activity as a result of a hypoxia associated endothelial dysfunction (Earley & Walker, 2002; Gonzales & Walker, 2002; Jernigan & Resta, 2002; Altay *et al.*, 2004; Phillips *et al.*, 2004). These alterations in vasomotor activity may differ depending on the location of the vascular bed. Mesenteric resistance arteries isolated from rats exposed to 48 hours of hypobaric hypoxia (380 mmHg) have an attenuated vasoconstrictor reactivity (Earley & Walker, 2002; Gonzales & Walker, 2002). On the other hand, rats exposed to a similar level of hypobaric hypoxia for four weeks have an attenuated pulmonary vasodilation (Jernigan & Resta, 2002). Another study exposed rats to SDIH and assessed endothelial function of resistance vessels in skeletal muscle and cerebral circulations and found that exposure to chronic IH severely blunts vasodilator responsiveness to acute hypoxia (Phillips *et al.*, 2004). None of the above studies have determined if blood flow or tissue oxygenation is affected by the altered endothelial function. No similar studies have been performed in humans. One study does assess, however, the effects of five consecutive nocturnal hypoxic exposures in humans (Kolb *et al.*, 2004). Using an end-tidal forcing technique, cerebral blood flow responses to acute variations in O_2 and CO_2 were determined before and after the nocturnal hypoxic episode. Their results show that discontinuous hypoxia elicits an increase in the sensitivity of cerebral blood flow to acute variations in oxygen and CO_2. In a similar study where cerebral blood flow responses to 5-min steps of isocapnic hypoxia were measured before and during 5 days at 3, 810 m, increases in

cerebral blood flow responses occurred (Jernigan & Resta, 2002). Perhaps maladaptive effects occur following a greater duration of intermittent hypoxia.

Autonomic Consequences of Intermittent Hypoxia

Intermittent exposure to hypoxia produces sustained systemic hypertension in a rat model that is preventable by denervating the carotid body (Fletcher *et al.*, 1992). Researchers have hypothesized that long-term exposure to intermittent hypoxia increases sympathetic responsivity to chemoreflex stimulation and leads to long-lasting sympathetic activation and vasoconstriction in sleep apnea patients (Morgan & Joyner, 2002). This was true following a simple acute exposure to combined hypoxia (SaO_2 = 80%) and hypercapnia ($PetCO_2$ + 5 mmHg) (Morgan *et al.*, 1995). Muscle sympathetic nerve activity increased in response to the asphyxic exposure and about 2/3 of the sympathetic activation persisted in excess of twenty minutes (Morgan *et al.*, 1995). The exposure was repeated with hyperoxic hypercapnia and also caused an increase in sympathetic activity; but, unlike the asphyxic exposure, there was no after-effect. This study demonstrates that even relatively brief periods of asphyxic stimulation can cause a substantial increase in sympathetic vasomotor outflow that outlasts the chemical stimuli. Following this study, the researchers looked at the effects of intermittent asphyxia on sympathetic activation (Xie *et al.*, 2000). In this study, healthy subjects (n=7) were exposed to an intermittent asphyxic (SaO_2 = 79-85%; $PetCO_2$ = +3-5 mmHg) intervention consisting of 20-second asphyxic periods alternating with 40-second periods of room-air breathing for a total of 20 minutes. Like 20 minutes of sustained asphyxia, 20 minutes of intermittent asphyxia resulted in MSNA activity that remained elevated for at least 20 minutes after the removal of the chemical stimuli. While both these studies show an elevated sympathetic activation after exposure to combined hypoxia and hypercapnia, it is not known whether hypoxia alone would have similar results. Therefore, Xie *et al.* (2001) performed a study to determine the relative contributions of hypoxia and

hypercapnia in causing persistent sympathoexcitation. In this study, healthy subjects (n=9) were exposed to 20 minutes of isocapnic hypoxia (SaO_2 = 77-87%) or twenty minutes of normoxic hypercapnia ($PetCO_2$ = +5.3-8.6 mmHg) in random order on two separate days. The results indicated that both hypoxia and hypercapnia cause substantial increases in sympathetic outflow to skeletal muscle; but, hypercapnia-evoked sympathetic activation is short-lived, whereas hypoxia-induced sympathetic activation outlasts the chemical stimuli. To more clearly understand if this response is true for intermittent exposure and not just sustained exposure, Cutler *et al.* (2004) undertook a study. In this study, the effects of 20 minutes of intermittent voluntary hypoxic apneas (30-second hypoxic apnea performed every minute) on MSNA during 180 minutes of recovery were determined. In addition, the effects of 20 minutes of intermittent hypercapnic hypoxia (30-seconds hypercapnic hypoxia every minute), and isocapnic hypoxia (30-seconds isocapnic hypoxia every minute) on MSNA during 180 minutes of recovery were determined. The results indicate that short-term exposure to intermittent hypoxic apnea results in sustained elevation of MSNA and that hypoxia is the primary mediator of this response. It is now well documented that hypoxic exposure, whether intermittent or sustained, can induce sympathetic activation that remains elevated following the removal of the chemical stimuli. This response is not dependent on the presence of hypercapnia.

To date no long-term intermittent hypoxia studies have assessed sympathetic activity in humans. An animal study does, however, assess the sympathetic response to chronic intermittent hypoxia (FiO_2 nadir = 6.5-7% each minute separated by 1-minute of 21% O_2 occurring 8 hours/day during the night for 30 days) (Greenberg *et al.*, 1999). Preganglionic cervical sympathetic activity was measured directly in rats spontaneously breathing 100% O_2, room air, 10% O_2, 12%CO_2, and 10% O_2-12% CO_2. In addition, baroreceptor function was assessed during phenylephrine infusion. The results indicate that baroreceptor function was not different; but, the chronic intermittent hypoxia led to increased sympathetic responsiveness to chemoreflex

stimulation. In addition, there was an increase in resting normoxic mean arterial pressure. This is the first study to indicate that exposure to chronic intermittent hypoxia leads to systemic hypertension that may have been mediated by increased sympathetic responsiveness to chemoreflex stimulation.

Summary

In summary, the hypoxic ventilatory response increases following both SDIH and LDIH in human subjects (Katayama *et al.*, 1998; Katayama *et al.*, 1999; Garcia *et al.*, 2000b; Katayama *et al.*, 2001b); but in the animal model, only SDIH leads to enhanced chemosensitivity (Peng & Prabhakar, 2004). The hypercapnic ventilatory response has been described to either stay the same or increase (Katayama *et al.*, 1998; Katayama *et al.*, 1999; Mahamed & Duffin, 2001; Ainslie *et al.*, 2003). It is likely that marked respiratory alkalosis is necessary for changes in the hypercapnic ventilatory response to occur. The blood pressure response to isocapnic hypoxia has been reported to increase following both LDIH and sustained high altitude human studies, while the heart rate response is unaltered (Insalaco *et al.*, 1996; Katayama *et al.*, 2001b). This is not true for SDIH exposure in the human or the cat (Bernardi *et al.*, 2001; Rey *et al.*, 2004), even though SDIH in the rat for 30-35 days results in systemic hypertension (Fletcher *et al.*, 1992; Rey *et al.*, 2004). Several recent rat studies have suggested that exposure to SDIH leads to vasomotor dysfunction in cerebral, skeletal, and mesenteric resistance arteries (Gonzales & Walker, 2002; Phillips *et al.*, 2004). This is true for the pulmonary circulation as well (Jernigan & Resta, 2002). Human studies, however, suggest that hypoxic exposure leads to an increase in the blood flow response to both hypoxia and hypercapnia following 5 days of intermittent or sustained hypoxia (Jensen *et al.*, 1996; Kolb *et al.*, 2004). It is likely that longer exposures are necessary to evoke the maladaptive effects of SDIH. Elevated sympathetic activity is apparent for a short time following exposure to short sustained periods of isocapnic hypoxia and

intermittent isocapnic hypoxia, and is not present following similar exposures to normoxic hypercapnia (Morgan *et al.*, 1995; Xie *et al.*, 2000; Xie *et al.*, 2001; Cutler *et al.*, 2004). In addition, the sympathetic response to hypoxia is elevated following 30 days of exposure to SDIH (Greenberg *et al.*, 1999). Intermittent hypoxic exposure is a powerful stimulus to the ventilatory, cardiovascular, and autonomic system. The effects of intermittent hypoxia are still not fully understood.

APPENDIX B – Individual Raw Data

Subject characteristics and resting pulmonary function.

Subject	Age (years)	Height (cm)	Mass (kg)	Forced vital capacity (FVC, liters)	Forced expired volume in 1 second (FEV_1, liters)	FEV_1/FVC (%)
SDIH 01	23	172	90	4.27	3.79	88.8
SDIH 02	24	170	76	3.88	3.48	92.7
SDIH 03	23	170	72	4.21	3.62	86.1
SDIH 04	22	181	79	4.46	3.89	87.2
SDIH 05	23	182	70	5.81	4.81	82.8
SDIH 06	23	172	90	4.77	4.39	88.0
SDIH 07	33	186	84	5.93	4.25	76.0
SDIH 08	32	188	86	5.80	4.34	75.0
SDIH 09	29	181	85	5.74	4.69	81.7
LDIH 01	21	185	93	5.24	4.00	76.4
LDIH 02	23	126	69	5.10	4.64	91.0
LDIH 03	26	186	86	4.56	3.38	74.1
LDIH 04	33	177	76	5.08	4.34	85.3
LDIH 05	23	177	67	4.28	3.52	82.2
LDIH 06	28	182	96	5.12	4.25	82.0
LDIH 07	21	177	76	5.40	4.60	85.0
LDIH 08	32	171	93	4.20	3.92	90.6
LDIH 09	23	186	77	5.68	4.82	84.9

Maximal exercise data day 1.

Subject	VO_2 (ml kg^{-1} min^{-1})	Predicted VO_2 (ml kg^{-1} min^{-1})	VO_2 (l min^{-1})	VCO_2 (l min^{-1})	RER	V_I/VO_2	V_I/VCO_2	Power (watts)	V_I (liters)	HR (bpm)
SDIH 01	37.1	41.2	4.20	5.28	1.29	33.3	26.5	255	140.0	158
SDIH 02	39.4	39.1	3.77	4.65	1.25	35.7	28.9	230	134.5	192
SDIH 03	44.3	42.3	3.19	3.87	1.21	29.1	24.0	305	94.8	169
SDIH 04	36.4	45.1	2.93	3.75	1.28	34.0	26.6	283	97.6	172
SDIH 05	52.1	43.7	3.61	4.52	1.25	34.3	27.4	364	136.3	189
SDIH 06	27.6	34.2	2.56	3.60	1.40	37.4	26.7	257	86.1	188
SDIH 07	56.1	51.0	4.72	5.63	1.19	30.3	25.4	486	148.2	182
SDIH 08	48.7	48.2	4.19	4.85	1.16	30.0	25.9	412	139.1	175
SDIH 09	37.7	43.9	3.20	4.08	1.27	35.8	28.2	341	114.8	193
LDIH 01	41.8	42.9	2.87	3.72	1.31	48.5	29.0	279	139.2	180
LDIH 02	41.8	28.4	2.88	3.56	1.23	31.6	25.6	265	91.0	191
LDIH 03	42.8	43.5	3.69	4.20	1.14	26.7	23.5	337	97.9	168
LDIH 04	---	43.8	---	---	---	---	---	---	---	---
LDIH 05	48.5	44.8	3.38	4.09	1.21	36.0	29.8	294	116.7	187
LDIH 06	39.2	42.1	3.74	5.12	1.37	37.7	27.5	388	141.1	176
LDIH 07	38.4	44.8	2.92	3.53	1.21	30.8	25.4	287	89.8	179
LDIH 08	33.0	35.7	3.07	3.75	1.22	34.0	27.8	315	110.2	172
LDIH 09	52.5	50.8	4.04	5.05	1.25	33.2	26.5	381	133.9	176

Maximal exercise data day 12.

Subject	VO_2 (ml kg^{-1} min^{-1})	VO_2 (l min^{-1})	VCO_2 (l min^{-1})	RER	V_I/VO_2	V_I/VCO_2	Power (watts)	V_I (liters)	HR (bpm)
SDIH 01	40.5	4.62	5.35	1.20	29.7	25.6	256	137.2	165
SDIH 02	35.3	2.69	3.40	1.31	43.6	34.5	256	117.4	208
SDIH 03	44.5	3.17	3.89	1.23	29.9	24.3	300	95.6	173
SDIH 04	43.5	3.18	3.54	1.14	27.1	23.7	286	88.9	171
SDIH 05	52.5	3.49	4.75	1.36	41.0	30.2	353	143.8	184
SDIH 06	30.0	2.70	3.80	1.41	37.1	26.3	275	110.3	190
SDIH 07	58.1	4.88	5.70	1.17	30.0	25.7	504	146.3	185
SDIH 08	48.7	4.19	5.12	1.22	32.3	26.4	426	144.5	180
SDIH 09	39.7	3.43	4.05	1.18	38.2	32.4	340	129.4	183
LDIH 01	---	---	---	---	---	---	---	---	---
LDIH 02	---	---	---	---	---	---	---	---	---
LDIH 03	40.9	3.52	3.90	1.11	26.3	23.7	355	97.2	173
LDIH 04	---	---	---	---	---	---	---	---	---
LDIH 05	44.2	2.94	3.53	1.20	33.2	27.7	295	97.7	184
LDIH 06	40.7	3.85	4.84	1.26	32.4	25.8	380	125.5	172
LDIH 07	36.9	2.95	3.87	1.31	36.9	28.1	285	102.7	177
LDIH 08	36.4	3.39	4.09	1.21	34.3	28.4	317	116.8	173
LDIH 09	52.4	3.95	5.04	1.28	35.5	27.8	383	142.8	186

Normoxic resting ventilation (V_I) and coefficient of variation (CV).

	V_I ($l\ min^{-1}$)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	8.43	9.13	8.77	8.64	9.64	8.45	10.37	9.99	8.07
SDIH 02	9.12	10.80	11.50	9.31	7.32	9.10	9.20	9.93	13.17
SDIH 03	9.27	9.69	7.98	10.62	8.76	9.20	9.59	9.08	8.22
SDIH 04	14.86	14.00	12.66	15.29	11.48	11.42	12.44	13.31	11.02
SDIH 05	10.96	11.33	12.53	13.17	13.05	12.00	13.30	12.63	7.01
SDIH 06	11.39	12.22	14.32	10.26	11.55	14.91	14.66	11.60	13.97
SDIH 07	12.34	10.79	13.04	13.75	14.54	13.82	13.05	11.79	9.41
SDIH 08	12.24	11.50	13.70	13.52	15.64	12.55	11.63	12.39	10.54
SDIH 09	6.26	7.91	7.13	9.10	8.84	7.56	7.32	7.79	11.83
LDIH 01	13.126	13.71	12.95	13.56	11.71	12.83	11.78	13.30	5.85
LDIH 02	7.89	10.52	9.61	9.62	10.10	10.39	10.40	10.55	9.00
LDIH 03	14.04	10.82	11.77	13.84	10.78	13.51	12.12	11.90	10.52
LDIH 04	9.80	10.63	12.20	10.90	10.74	10.23	10.80	10.68	6.41
LDIH 05	10.69	14.75	13.64	15.73	14.58	12.77	12.31	12.69	12.02
LDIH 06	14.51	14.25	12.81	15.98	14.96	11.80	14.67	14.69	9.21
LDIH 07	9.91	11.00	11.06	12.96	13.74	12.69	11.93	11.77	11.18
LDIH 08	12.58	13.97	12.08	13.14	15.37	11.86	12.44	12.98	8.78
LDIH 09	12.18	15.08	16.09	14.60	15.47	15.24	13.13	14.84	8.86

Normoxic resting breathing frequency (F_b) and coefficient of variation (CV).

	F_b (breaths min^{-1})								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	14.6	14.8	14.9	14.6	15.3	14.8	14.6	14.7	1.6
SDIH 02	20.2	21.3	21.5	19.3	20.2	18.7	17.8	18.8	6.6
SDIH 03	10.1	11.9	10.4	12.4	11.1	13.4	12.4	11.6	9.5
SDIH 04	22.5	24.1	22.8	22.6	23.2	22.2	22.8	22.8	2.5
SDIH 05	15.7	16.1	18.5	17.5	15.8	17.0	19.5	18.6	8.2
SDIH 06	18.7	17.5	17.9	15.0	18.9	15.8	19.1	17.4	8.4
SDIH 07	18.4	19.2	18.6	17.9	20.3	18.9	19.3	19.0	3.9
SDIH 08	19.6	20.5	22.0	23.0	21.7	17.4	18.5	19.1	9.5
SDIH 09	7.3	11.3	7.8	12.7	13.3	11.4	10.2	11.8	20.2
LDIH 01	17.7	20.0	19.1	20.7	20.1	17.2	16.6	18.6	7.8
LDIH 02	11.6	17.7	13.3	17.3	17.3	17.8	16.7	17.1	14.3
LDIH 03	20.4	14.9	15.3	18.1	16.4	17.4	17.8	16.1	10.4
LDIH 04	17.9	20.9	20.6	18.7	19.0	17.6	15.5	17.7	9.4
LDIH 05	17.2	15.9	19.2	18.4	23.2	19.7	17.8	19.8	11.5
LDIH 06	20.0	20.1	19.8	22.5	21.8	21.7	22.3	21.6	5.2
LDIH 07	16.9	15.6	18.0	19.7	17.2	19.3	17.7	17.9	7.8
LDIH 08	17.2	20.9	18.0	20.0	22.6	18.8	19.7	22.0	8.9
LDIH 09	17.1	22.6	21.6	21.2	19.1	19.5	18.0	18.5	9.9

Normoxic resting tidal volume (V_t) and coefficient of variation (CV).

	V_t (liters)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	0.59	0.62	0.59	0.49	0.63	0.57	0.71	0.68	10.96
SDIH 02	0.45	0.54	0.53	0.48	0.36	0.49	0.52	0.53	11.82
SDIH 03	0.94	0.82	0.77	0.86	0.79	0.69	0.78	0.79	9.03
SDIH 04	0.67	0.59	0.56	0.71	0.50	0.52	0.55	0.59	12.26
SDIH 05	0.71	0.71	0.69	0.76	0.84	0.71	0.69	0.68	7.31
SDIH 06	0.62	0.71	0.83	0.69	0.62	0.99	0.80	0.68	16.88
SDIH 07	0.68	0.56	0.71	0.78	0.74	0.74	0.68	0.62	10.34
SDIH 08	0.63	0.56	0.62	0.59	0.73	0.73	0.63	0.65	9.44
SDIH 09	0.89	0.71	0.92	0.75	0.67	0.67	0.73	0.67	13.28
LDIH 01	0.75	0.69	0.68	0.66	0.58	0.76	0.71	0.72	8.19
LDIH 02	0.71	0.60	0.73	0.56	0.60	0.59	0.63	0.63	9.33
LDIH 03	0.69	0.73	0.77	0.77	0.66	0.78	0.69	0.74	6.11
LDIH 04	0.56	0.52	0.61	0.60	0.58	0.59	0.72	0.62	9.65
LDIH 05	0.64	0.94	0.76	0.93	0.63	0.67	0.71	0.66	16.94
LDIH 06	0.77	0.76	0.66	0.75	0.75	0.54	0.69	0.71	10.85
LDIH 07	0.59	0.71	0.61	0.67	0.80	0.66	0.68	0.67	10.23
LDIH 08	0.75	0.68	0.64	0.67	0.69	0.64	0.63	0.60	6.93
LDIH 09	0.77	0.70	0.81	0.70	0.87	0.84	0.80	0.98	11.38

Normoxic resting end-tidal partial pressure of CO_2 ($PetCO_2$) and coefficient of variation (CV).

	$PetCO_2$ (mmHg)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	46.18	44.63	44.88	44.03	47.20	45.76	46.10	45.36	2.21
SDIH 02	43.13	43.80	45.11	45.05	44.17	43.71	42.06	43.32	2.31
SDIH 03	42.42	43.18	44.71	43.97	43.22	45.04	43.72	42.98	2.04
SDIH 04	42.11	43.49	43.17	46.18	45.31	44.90	45.17	43.63	3.06
SDIH 05	42.85	44.20	42.80	44.52	43.42	42.36	43.30	41.46	2.28
SDIH 06	43.95	44.76	43.98	41.40	40.30	44.28	46.04	41.52	4.56
SDIH 07	41.80	41.56	42.23	43.14	40.71	43.21	42.49	42.21	1.96
SDIH 08	38.31	39.06	38.55	35.42	41.75	39.14	39.89	40.03	4.64
SDIH 09	53.74	50.54	51.17	48.86	47.73	48.82	49.72	47.93	3.98
LDIH 01	42.68	42.89	41.64	45.32	40.70	41.86	41.03	42.55	3.40
LDIH 02	47.36	46.78	50.54	45.09	43.26	51.83	48.76	49.81	5.99
LDIH 03	40.97	42.13	45.46	41.72	40.00	41.46	42.60	40.73	3.96
LDIH 04	45.23	44.52	44.48	45.33	44.44	45.37	45.58	44.64	1.05
LDIH 05	43.50	43.51	43.03	40.13	40.27	41.02	42.75	43.18	3.44
LDIH 06	49.04	45.40	44.82	45.52	42.76	46.20	45.16	46.85	3.93
LDIH 07	44.18	41.39	42.05	40.77	39.32	41.52	43.57	43.13	3.94
LDIH 08	37.08	38.25	37.43	38.59	38.92	39.35	38.08	37.67	2.01
LDIH 09	40.91	38.17	37.89	39.04	40.28	39.75	39.32	39.34	2.56

Normoxic resting cardiac output (CO) and coefficient of variation (CV).

	Cardiac Output ($l\ min^{-1}$)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	6.34	6.28	6.31	6.11	7.16	7.62	7.00	7.10	8.12
SDIH 02	6.68	7.42	7.53	6.47	7.50	7.84	6.40	6.89	7.72
SDIH 03	5.48	4.66	4.10	6.15	5.11	6.67	5.72	5.55	14.96
SDIH 04	6.42	7.22	6.64	6.45	6.16	6.02	6.06	7.01	6.75
SDIH 05	6.24	6.59	7.28	9.31	6.62	7.25	7.80	8.21	13.60
SDIH 06	8.16	8.68	8.75	7.79	7.45	8.76	9.59	8.31	7.86
SDIH 07	4.73	4.71	4.90	5.75	5.12	5.00	5.74	4.03	11.30
SDIH 08	5.86	5.75	5.41	5.52	6.67	6.68	6.20	6.28	8.09
SDIH 09	8.15	7.73	8.08	7.59	7.52	7.55	7.55	8.04	3.46
LDIH 01	9.01	9.25	9.12	9.37	8.19	9.82	8.77	8.28	6.12
LDIH 02	5.96	4.86	5.86	4.13	5.13	5.52	5.98	4.37	13.88
LDIH 03	7.27	6.36	8.39	6.56	7.91	7.08	7.40	7.21	9.08
LDIH 04	6.65	5.74	6.06	6.60	5.88	7.37	8.88	6.63	15.10
LDIH 05	7.01	7.11	5.78	7.28	6.67	8.68	7.57	7.55	11.49
LDIH 06	6.40	6.49	5.88	4.18	6.75	7.79	5.83	6.70	16.56
LDIH 07	8.20	6.20	7.00	6.92	8.88	7.92	6.85	6.94	12.57
LDIH 08	7.54	7.01	4.39	6.63	7.20	6.05	5.77	6.48	15.58
LDIH 09	7.79	7.51	7.48	7.72	8.38	8.27	7.26	9.37	8.57

Normoxic resting heart rate (HR) and coefficient of variation.

	Heart Rate (bpm)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	64.9	62.0	62.9	59.4	64.3	61.08	64.27	71.77	5.80
SDIH 02	69.8	86.2	91.9	72.4	89.1	90.16	71.93	78.79	11.23
SDIH 03	64.4	62.1	66.5	70.6	67.8	71.83	65.66	67.19	4.72
SDIH 04	66.1	71.4	64.5	66.0	65.1	63.21	62.10	65.28	4.23
SDIH 05	65.7	71.7	76.5	84.7	69.0	72.12	76.21	81.67	8.36
SDIH 06	79.1	78.0	76.5	71.8	69.1	76.36	88.94	76.17	7.58
SDIH 07	46.6	44.9	44.3	52.5	53.1	45.88	46.60	40.86	8.79
SDIH 08	41.6	41.1	44.1	43.9	47.6	52.38	42.19	45.78	8.37
SDIH 09	69.3	64.5	63.5	62.7	90.5	59.88	63.26	64.19	14.49
LDIH 01	69.5	85.3	82.2	98.3	83.4	90.52	84.14	82.32	9.62
LDIH 02	87.5	73.6	80.4	74.3	81.9	78.97	81.50	75.16	5.96
LDIH 03	62.6	53.7	68.1	55.5	69.4	65.86	60.79	57.21	9.51
LDIH 04	59.3	52.9	58.6	56.3	66.5	64.66	77.05	62.12	11.97
LDIH 05	68.0	69.5	55.5	67.9	67.5	81.14	66.62	67.29	10.15
LDIH 06	64.2	67.9	62.0	65.7	70.3	70.67	65.72	74.43	5.98
LDIH 07	86.6	73.0	84.5	81.1	115.1	86.67	86.10	68.06	14.94
LDIH 08	64.3	61.9	51.1	58.1	76.2	60.59	55.26	68.33	12.63
LDIH 09	64.4	75.0	67.9	73.9	72.8	73.03	66.48	78.45	6.70

Normoxic resting stroke volume (SV) and coefficient of variation (CV).

	Stroke Volume (ml)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	98.0	103.5	101.1	103.7	112.1	126.1	109.6	99.3	8.6
SDIH 02	96.3	86.4	81.9	89.5	84.4	87.1	89.1	87.6	4.8
SDIH 03	85.6	75.5	62.2	87.3	75.9	92.8	87.5	83.0	11.9
SDIH 04	97.3	101.2	103.2	97.8	95.0	95.4	97.7	107.6	4.3
SDIH 05	95.5	92.2	95.6	110.1	95.0	100.9	102.4	100.8	5.8
SDIH 06	103.5	111.6	114.7	108.9	108.2	115.0	108.3	109.5	3.4
SDIH 07	101.8	105.4	110.7	110.2	97.0	109.3	123.5	99.4	7.8
SDIH 08	140.9	139.8	122.5	125.9	140.4	127.9	147.1	137.5	6.4
SDIH 09	118.2	120.3	128.1	121.6	126.1	126.6	119.8	125.7	3.0
LDIH 01	130.1	108.9	111.3	95.6	98.4	108.7	104.6	101.1	10.0
LDIH 02	68.4	66.3	73.0	55.7	62.7	69.9	73.5	58.2	10.0
LDIH 03	116.7	119.6	123.9	118.6	114.4	107.9	122.1	126.7	5.0
LDIH 04	112.5	109.3	103.9	117.6	88.5	114.4	115.4	107.1	8.6
LDIH 05	103.3	102.4	104.8	107.7	99.1	107.2	114.1	112.4	4.8
LDIH 06	99.8	67.9	95.1	63.9	96.3	110.5	89.1	90.1	17.7
LDIH 07	95.1	85.1	83.3	85.6	77.3	91.7	79.8	103.6	7.3
LDIH 08	117.6	113.6	86.1	114.1	94.5	100.1	104.5	95.0	10.9
LDIH 09	122.0	100.3	110.6	104.8	115.6	113.7	110.0	119.8	6.5

Normoxic resting mean arterial pressure (MAP) and coefficient of variation (CV).

	Mean arterial pressure (mmHg)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	92.1	89.0	87.3	85.0	85.4	91.4	93.3	87.9	3.5
SDIH 02	84.6	82.1	86.9	88.2	84.9	98.4	87.0	90.5	5.7
SDIH 03	87.8	92.3	86.3	86.7	86.1	91.8	83.7	87.7	3.3
SDIH 04	90.9	89.8	90.9	85.8	81.0	84.2	87.2	88.3	4.0
SDIH 05	81.4	92.2	86.0	84.3	85.1	84.8	84.1	79.9	4.3
SDIH 06	92.9	85.1	91.2	89.8	95.1	83.0	99.6	86.7	6.1
SDIH 07	78.0	74.6	87.7	81.7	72.9	85.4	79.2	81.0	6.3
SDIH 08	83.6	74.1	83.1	81.7	76.0	82.1	74.1	80.1	5.1
SDIH 09	96.1	94.2	88.5	98.8	90.4	95.8	95.2	91.3	3.6
LDIH 01	95.7	94.5	93.6	83.2	90.2	81.2	85.8	79.5	7.3
LDIH 02	95.6	91.9	80.1	93.8	94.8	88.6	90.5	92.0	5.4
LDIH 03	84.2	83.5	83.9	85.6	82.7	85.1	82.6	73.9	4.5
LDIH 04	77.8	79.4	82.5	85.0	84.4	78.7	76.7	77.5	4.1
LDIH 05	96.7	88.3	80.3	83.1	73.0	84.3	84.1	81.1	8.1
LDIH 06	97.6	100.2	104.1	116.9	100.7	89.9	107.1	105.7	7.6
LDIH 07	92.7	74.9	77.0	78.4	86.1	82.1	87.7	87.1	7.8
LDIH 08	94.9	98.7	95.3	82.8	98.5	100.1	104.6	114.7	9.2
LDIH 09	79.2	81.1	90.0	92.9	80.2	92.0	80.4	82.2	6.9

Normoxic resting total peripheral resistance (TPR) and coefficient of variation (CV).

	Total peripheral resistance (PRU)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	1.08	0.87	0.86	0.88	0.73	0.74	0.77	0.71	14.72
SDIH 02	0.80	0.69	0.71	0.84	0.70	0.78	0.85	0.82	8.46
SDIH 03	0.99	1.21	1.28	0.88	1.04	0.86	0.90	0.97	15.20
SDIH 04	0.92	0.74	0.87	0.81	0.80	0.84	0.87	0.75	7.53
SDIH 05	0.80	0.85	0.72	0.55	0.77	0.72	0.66	0.60	14.28
SDIH 06	0.71	0.61	0.66	0.74	0.80	0.59	0.65	0.65	10.30
SDIH 07	1.00	0.98	1.08	0.86	0.89	1.04	0.82	1.23	13.49
SDIH 08	0.87	0.82	0.94	0.93	0.71	0.74	0.73	0.8	10.94
SDIH 09	0.73	0.75	0.68	0.81	0.75	0.79	0.79	0.70	6.09
LDIH 01	0.66	0.63	0.63	0.55	0.68	0.51	0.60	0.59	9.25
LDIH 02	1.03	1.22	0.85	1.38	1.18	0.99	0.93	1.36	17.63
LDIH 03	0.71	0.83	0.63	0.82	0.64	0.74	0.70	0.64	11.06
LDIH 04	0.71	0.86	0.83	0.80	0.87	0.66	0.53	0.72	15.55
LDIH 05	0.83	0.77	0.87	0.71	0.68	0.60	0.69	0.66	12.47
LDIH 06	0.94	0.93	1.06	1.71	0.97	0.71	1.10	0.95	27.90
LDIH 07	0.70	0.75	0.69	0.70	0.60	0.64	0.79	0.81	9.12
LDIH 08	0.78	0.87	1.34	0.77	0.84	1.03	1.12	1.10	20.45
LDIH 09	0.63	0.66	0.74	0.74	0.60	0.69	0.69	0.55	10.07

Normoxic resting cerebral saturation of oxygen (ScO_2) and coefficient of variation (CV).

	ScO_2 (%)								CV (%)
Subject	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17	
SDIH 01	72.2	69.0	67.9	65.8	67.3	83.7	71.8	63.4	8.8
SDIH 02	69.2	66.1	68.3	67.8	67.7	69.5	69.5	68.8	1.7
SDIH 03	69.2	68.0	67.9	72.9	74.5	71.7	73.8	68.9	3.8
SDIH 04	71.1	70.1	70.5	71.5	71.9	73.8	71.8	71.0	1.5
SDIH 05	81.3	78.8	72.1	68.9	81.7	66.0	74.8	74.0	7.6
SDIH 06	68.0	69.6	71.3	70.4	65.4	67.5	72.6	68.2	3.3
SDIH 07	67.6	60.0	66.1	69.1	72.2	71.6	69.0	67.0	5.6
SDIH 08	76.1	78.3	79.4	79.0	76.7	77.4	73.7	77.9	2.4
SDIH 09	65.3	58.2	63.4	58.4	61.3	63.8	61.4	62.3	4.0
LDIH 01	66.5	69.1	70.7	70.7	67.5	69.1	69.3	67.9	2.1
LDIH 02	71.6	73.9	71.2	69.3	67.4	67.5	73.1	76.0	4.3
LDIH 03	71.4	63.4	64.5	66.0	70.8	74.0	67.8	70.6	5.4
LDIH 04	63.7	65.8	65.5	69.4	59.2	56.5	64.5	65.2	6.3
LDIH 05	58.4	54.5	59.0	62.1	60.4	67.0	59.9	61.9	5.9
LDIH 06	74.6	71.8	73.5	69.3	68.4	73.1	72.1	71.8	2.9
LDIH 07	73.2	65.4	67.0	66.1	72.0	62.1	74.0	69.0	6.6
LDIH 08	67.3	73.2	70.4	74.2	73.5	68.0	76.8	67.2	5.1
LDIH 09	74.3	60.5	70.0	74.6	68.6	73.2	69.5	70.5	6.4

Change in cerebral tissue oxygen saturation (ScO_2) per change in arterial oxyhemoglobin saturation (SaO_2) during both the preHVR and the postHVR.

	$\Delta ScO_2/\Delta SaO_2$													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	-0.62	-0.69	-0.46	-0.42	-0.63	-0.42	-0.45	-0.40	-0.50	-0.67	-0.83	-1.26	-0.63	-0.57
SDIH 02	-0.52	-0.84	-0.42	-0.49	-0.51	-0.43	-0.44	-0.51	-0.62	-0.64	-0.79	-0.80	-0.60	-0.35
SDIH 03	-0.40	-0.39	-0.44	-0.40	-0.41	-0.48	-0.67	-0.52	-0.49	-0.56	-0.41	-0.40	-0.48	-0.46
SDIH 04	-0.51	-0.82	-0.32	-0.67	-0.54	-0.79	-0.62	-0.58	-0.65	-0.59	-0.74	-0.64	-0.63	-0.63
SDIH 05	-0.28	-0.49	-0.27	-0.49	-0.42	-0.49	-0.35	-0.36	-0.26	-0.45	-0.65	-0.72	-0.54	-0.57
SDIH 06	-0.55	-0.65	-0.50	-0.51	-0.65	-0.75	-0.71	-0.55	-0.50	-0.65	-0.51	-0.62	-0.62	-0.60
SDIH 07	-0.39	-0.39	-0.32	-0.62	-0.40	-0.54	-0.71	-0.84	-0.57	-0.79	-1.16	-0.58	-0.76	-0.41
SDIH 08	-0.70	-0.74	-0.62	-0.77	-0.70	-0.75	-0.72	-0.64	-0.63	-0.64	-0.71	-0.76	-0.53	-0.76
SDIH 09	-0.65	-0.50	-0.59	-0.50	-0.54	-0.54	-0.52	-0.53	-0.53	-0.55	-0.61	-0.64	-0.60	-0.54
LDIH 01	-0.41	-0.64	-0.42	-0.44	-0.63	-0.57	-0.49	-0.54	-0.54	-0.60	-0.57	-0.55	-0.51	-0.35
LDIH 02	-0.38	-0.54	-0.36	-0.39	-0.37	-0.40	-0.27	-0.32	-0.27	-0.65	-0.46	-0.53	-0.56	-0.35
LDIH 03	-0.52	-0.49	-0.38	-0.48	-0.49	-0.57	-0.51	-0.61	-0.46	-0.47	-0.51	-0.66	-0.33	-0.45
LDIH 04	-0.51	-0.40	-0.32	-0.30	-0.42	-0.24	-0.40	-0.31	-0.49	-0.46	-0.49	-0.38	-0.53	-0.30
LDIH 05	-0.57	-0.66	-0.52	-0.44	-0.65	-0.62	-0.42	-0.44	-0.55	-0.43	-0.76	-0.51	-0.62	-0.67
LDIH 06	-0.74	-0.73	-0.75	-0.86	-0.62	-0.71	-0.57	-0.65	-0.61	-0.62	-0.71	-0.67	-0.69	-0.65
LDIH 07	-0.67	-0.60	-0.69	-0.57	-0.64	-0.61	-0.82	-0.64	-0.96	-0.90	-0.63	-0.69	-0.81	-0.51
LDIH 08	-0.53	-0.53	-0.68	-0.57	-0.61	-0.71	-0.74	-0.64	-0.67	-0.72	-0.52	-0.52	-0.66	-0.46
LDIH 09	-0.32	-0.33	-0.06	-0.04	-0.30	-0.39	-0.48	-0.34	-0.54	-0.39	-0.43	-0.60	-0.46	-0.55

Change in cerebral oxyhemoglobin concentration (O_2Hb) per change in arterial oxyhemoglobin saturation (SaO_2) during both the preHVR and the postHVR.

	$\Delta O_2Hb/\Delta SaO_2$ (uM $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	-0.33	-0.15	-0.19	-0.04	-0.30	-0.24	-0.20	-0.18	-0.24	-0.16	-0.12	-0.21	-0.12	-0.28
SDIH 02	-0.24	-0.28	-0.27	-0.40	-0.26	-0.17	-0.21	-0.05	-0.31	-0.29	-0.30	-0.42	-0.31	-0.14
SDIH 03	-0.30	-0.31	-0.28	-0.19	-0.29	-0.46	-0.27	-0.29	-0.33	-0.33	-0.24	-0.23	-0.32	-0.32
SDIH 04	-0.23	0.36	-0.22	-0.40	-0.19	-0.55	-0.34	-0.37	-0.36	-0.40	-0.45	-0.46	-0.26	-0.36
SDIH 05	-0.25	-0.20	-0.20	-0.21	-0.20	-0.27	-0.24	-0.22	-0.33	-0.27	-0.36	-0.37	-0.41	-0.41
SDIH 06	-0.26	-0.30	-0.32	-0.20	-0.33	-0.35	-0.24	-0.42	-0.26	-0.38	-0.05	-0.00	-0.45	-0.42
SDIH 07	-0.16	-0.05	0.16	-0.28	-0.20	-0.20	-0.39	-0.20	-0.20	-0.15	0.27	-0.34	0.00	-0.04
SDIH 08	-0.20	-0.30	-0.24	-0.35	-0.23	-0.23	-0.23	-0.21	-0.14	-0.28	-0.35	-0.41	-0.36	-0.43
SDIH 09	-0.41	-0.29	-0.31	-0.18	-0.22	-0.27	-0.26	-0.26	-0.24	-0.22	-0.29	-0.33	-0.28	-0.18
LDIH 01	-0.35	-0.35	-0.20	-0.41	-0.38	-0.43	-0.20	-0.39	-0.25	-0.28	-0.30	-0.29	-0.23	-0.18
LDIH 02	-0.23	-0.09	-0.13	-0.09	-0.04	-0.18	0.00	-0.08	-0.00	-0.16	0.02	-0.22	-0.15	0.15
LDIH 03	-0.18	-0.19	-0.16	-0.19	-0.16	-0.17	-0.12	-0.18	-0.15	-0.18	-0.17	-0.24	-0.16	-0.18
LDIH 04	-0.27	-0.16	-0.16	-0.13	-0.25	-0.07	-0.27	-0.18	-0.19	-0.18	-0.29	-0.24	-0.33	-0.23
LDIH 05	-0.36	-0.44	-0.30	-0.23	-0.32	-0.42	-0.45	-0.36	-0.53	-0.36	-0.57	-0.56	-0.45	-0.37
LDIH 06	-0.32	-0.41	-0.39	-0.48	-0.34	-0.37	-0.26	-0.35	-0.29	-0.32	-0.41	-0.39	-0.43	-0.29
LDIH 07	-0.45	-0.35	-0.42	-0.38	-0.34	-0.35	-0.58	-0.39	-0.46	-0.44	-0.40	-0.51	-0.39	-0.25
LDIH 08	-0.28	-0.27	-0.19	-0.22	-0.23	-0.33	-0.33	-0.19	-0.30	-0.30	-0.28	-0.26	-0.16	-0.22
LDIH 09	-0.35	-0.22	-0.18	-0.30	-0.29	-0.24	-0.37	-0.30	-0.36	-0.24	-0.32	-0.52	-0.32	-0.38

Change in cerebral deoxyhemoglobin concentration (HHb) per change in arterial oxyhemoglobin saturation (SaO_2) during both the preHVR and the postHVR.

	$\Delta HHb/\Delta SaO_2$ (uM $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	0.40	0.57	0.42	0.36	0.41	0.35	0.33	0.31	0.35	0.41	0.35	0.49	0.40	0.52
SDIH 02	0.30	0.42	0.37	0.43	0.35	0.28	0.29	0.32	0.36	0.34	0.43	0.45	0.34	0.25
SDIH 03	0.34	0.37	0.32	0.35	0.33	0.34	0.35	0.32	0.35	0.35	0.32	0.28	0.29	0.32
SDIH 04	0.32	0.54	0.24	0.38	0.43	0.47	0.32	0.36	0.33	0.36	0.43	0.40	0.41	0.32
SDIH 05	0.22	0.24	0.25	0.34	0.29	0.32	0.25	0.30	0.22	0.36	0.42	0.48	0.41	0.43
SDIH 06	0.42	0.53	0.32	0.41	0.57	0.61	0.56	0.47	0.32	0.49	0.45	0.57	0.46	0.49
SDIH 07	0.45	0.40	0.46	0.56	0.34	0.47	0.47	0.51	0.40	0.57	0.77	0.33	0.54	0.40
SDIH 08	0.37	0.36	0.34	0.48	0.39	0.41	0.37	0.42	0.38	0.41	0.44	0.51	0.49	0.42
SDIH 09	0.41	0.46	0.36	0.37	0.39	0.41	0.37	0.35	0.32	0.36	0.37	0.40	0.37	0.35
LDIH 01	0.45	0.52	0.35	0.36	0.47	0.44	0.47	0.49	0.43	0.48	0.48	0.42	0.42	0.25
LDIH 02	0.27	0.53	0.26	0.31	0.28	0.29	0.29	0.30	0.20	0.46	0.33	0.37	0.33	0.26
LDIH 03	0.28	0.26	0.25	0.31	0.23	0.29	0.22	0.24	0.23	0.24	0.28	0.41	0.23	0.25
LDIH 04	0.34	0.26	0.22	0.19	0.30	0.20	0.30	0.26	0.29	0.25	0.36	0.28	0.40	0.32
LDIH 05	0.52	0.54	0.37	0.29	0.47	0.54	0.58	0.46	0.57	0.49	0.65	0.52	0.68	0.59
LDIH 06	0.50	0.48	0.47	0.52	0.43	0.48	0.43	0.45	0.43	0.48	0.48	0.49	0.49	0.46
LDIH 07	0.54	0.49	0.54	0.45	0.47	0.45	0.61	0.50	0.56	0.54	0.47	0.51	0.61	0.38
LDIH 08	0.38	0.33	0.35	0.33	0.41	0.54	0.45	0.44	0.38	0.42	0.39	0.35	0.41	0.32
LDIH 09	0.45	0.54	0.32	0.31	0.27	0.33	0.44	0.44	0.45	0.44	0.48	0.52	0.42	0.47

Change in cerebral total hemoglobin concentration (cHb) per change in arterial oxyhemoglobin saturation (SaO_2) during both the preHVR and the postHVR.

	$\Delta cHb/\Delta SaO_2$ (uM $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	0.07	0.42	0.23	0.33	0.11	0.11	0.13	0.13	0.11	0.25	0.23	0.28	0.28	0.24
SDIH 02	0.06	0.14	0.10	0.03	0.09	0.11	0.08	0.27	0.05	0.05	0.13	0.02	0.03	0.11
SDIH 03	0.04	0.06	0.03	0.15	0.03	-0.12	0.08	0.03	0.03	0.02	0.08	0.05	-0.02	-0.00
SDIH 04	0.09	0.18	0.02	-0.02	0.24	0.08	-0.03	-0.01	-0.03	-0.04	-0.02	-0.06	0.15	-0.04
SDIH 05	-0.03	0.04	0.06	0.13	0.08	0.05	0.01	0.08	-0.12	0.09	0.05	0.11	-0.01	0.02
SDIH 06	0.17	0.23	0.00	0.20	0.24	0.26	0.32	0.05	0.05	0.10	0.40	0.57	0.01	0.07
SDIH 07	0.29	0.35	0.61	0.28	0.14	0.27	0.08	0.31	0.20	0.42	1.04	-0.00	0.55	0.36
SDIH 08	0.17	0.06	0.10	0.13	0.16	0.18	0.14	0.21	0.24	0.12	0.09	0.09	0.13	-0.01
SDIH 09	0.06	0.17	0.05	0.19	0.17	0.14	0.11	0.09	0.09	0.13	0.08	0.07	0.09	0.17
LDIH 01	0.10	0.16	0.15	-0.04	0.09	0.00	0.27	0.10	0.18	0.20	0.17	0.13	0.19	0.07
LDIH 02	0.03	0.44	0.13	0.22	0.23	0.11	0.29	0.22	0.20	0.29	0.35	0.15	0.18	0.41
LDIH 03	0.10	0.07	0.09	0.12	0.07	0.11	0.10	0.05	0.07	0.06	0.11	0.16	0.07	0.07
LDIH 04	0.07	0.09	0.07	0.06	0.05	0.13	0.02	0.08	0.11	0.07	0.07	0.03	0.06	0.09
LDIH 05	0.16	0.10	0.07	0.06	0.15	0.11	0.13	0.10	0.04	0.14	0.08	-0.04	0.23	0.22
LDIH 06	0.17	0.07	0.08	0.04	0.08	0.11	0.16	0.11	0.14	0.16	0.06	0.11	0.06	0.17
LDIH 07	0.08	0.14	0.11	0.07	0.13	0.09	0.03	0.10	0.10	0.10	0.06	0.01	0.22	0.13
LDIH 08	0.10	0.06	0.16	0.10	0.19	0.21	0.11	0.24	-0.08	0.12	0.11	0.09	0.35	0.11
LDIH 09	0.09	0.32	0.14	0.00	-0.02	0.09	0.07	0.14	0.09	0.19	0.16	0.00	0.11	0.09

Hypercapnic ventilatory response (HCVR).

	HCVR ($l\ min^{-1}\ mmHg^{-1}$)			
Subject	Day 1	Day 12	Day 15	Day 17
SDIH 01	1.71	1.31	1.49	1.53
SDIH 02	1.26	0.12	0.75	0.80
SDIH 03	1.26	1.25	1.66	1.48
SDIH 04	2.74	2.07	1.63	3.24
SDIH 05	3.19	3.89	5.51	4.93
SDIH 06	1.02	1.32	1.51	1.26
SDIH 07	4.71	4.12	5.87	1.38
SDIH 08	2.60	3.88	5.56	3.80
SDIH 09	2.70	3.57	3.40	1.22
LDIH 01	2.07	2.13	1.99	2.02
LDIH 02	0.62	1.16	0.52	0.76
LDIH 03	3.05	3.60	2.81	1.92
LDIH 04	1.91	1.62	2.15	2.06
LDIH 05	0.89	1.62	0.88	1.74
LDIH 06	1.91	0.29	1.89	1.20
LDIH 07	6.74	6.15	1.39	2.12
LDIH 08	3.45	3.05	3.37	2.90
LDIH 09	2.96	3.02	2.75	3.73

The hypoxic ventilatory response (HVR) prior to acute intermittent hypoxia (preHVR) and following acute intermittent hypoxia (postHVR).

	HVR ($l\ min^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	0.67	0.82	1.10	0.83	1.12	1.15	0.89	0.90	0.96	1.14	1.26	1.13	1.14	1.57
SDIH 02	0.48	0.51	0.24	0.36	0.55	0.12	0.20	0.28	0.65	0.44	0.28	0.70	0.52	0.26
SDIH 03	0.31	0.31	0.10	0.21	0.50	0.44	0.74	0.48	0.82	0.44	0.56	0.42	0.37	0.30
SDIH 04	0.43	0.33	0.25	0.27	0.39	0.31	0.38	0.29	0.46	0.44	0.49	0.30	0.31	0.36
SDIH 05	0.84	0.50	0.66	0.67	0.66	0.59	0.60	0.72	0.78	0.63	0.86	1.07	1.26	0.94
SDIH 06	0.60	0.58	0.56	0.69	0.69	0.45	0.64	0.65	0.67	0.80	0.60	0.78	0.44	0.46
SDIH 07	2.39	1.61	2.04	1.97	2.33	2.11	2.57	2.50	2.76	2.10	4.78	2.15	3.61	2.32
SDIH 08	0.71	1.52	1.31	0.86	1.59	0.77	1.60	0.92	1.47	1.43	1.26	0.95	1.34	1.70
SDIH 09	1.00	0.68	1.01	0.76	1.09	1.05	0.91	0.91	0.95	0.82	1.26	1.11	1.10	1.18
LDIH 01	0.53	0.55	0.52	0.24	0.32	0.23	0.70	0.79	0.52	0.29	1.10	0.52	0.81	0.65
LDIH 02	0.76	1.12	0.73	0.66	0.79	0.70	0.84	0.53	0.76	0.85	0.95	0.87	0.62	0.99
LDIH 03	0.61	0.35	0.72	0.53	0.51	0.79	0.50	0.22	0.65	0.26	0.76	0.76	0.62	0.49
LDIH 04	0.63	0.39	0.84	0.59	0.63	0.35	0.68	0.49	0.64	0.32	0.93	0.62	0.89	0.65
LDIH 05	0.36	0.23	0.21	0.24	0.07	0.16	0.24	0.28	0.25	0.20	0.39	0.03	0.37	0.31
LDIH 06	1.05	1.21	0.84	0.79	0.78	0.68	0.86	0.79	0.73	0.45	1.13	0.57	1.00	0.99
LDIH 07	1.01	0.76	1.20	0.80	1.18	1.36	2.12	1.11	0.83	0.97	1.99	1.07	1.66	0.95
LDIH 08	1.61	0.94	1.19	0.72	1.33	1.42	1.83	1.78	1.47	1.27	1.91	1.45	1.63	1.47
LDIH 09	1.14	1.15	1.16	0.44	1.14	0.84	1.34	1.31	1.31	1.14	1.08	1.45	0.85	1.42

Ventilation (V_I) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	V_I (l min^{-1})													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	8.59	9.71	9.11	10.97	10.14	10.85	9.99	6.73	9.54	8.11	7.96	7.73	10.49	8.91
SDIH 02	8.49	11.91	8.73	10.19	11.31	15.11	8.03	11.28	7.42	10.51	10.13	11.76	10.82	10.63
SDIH 03	9.19	9.97	10.74	12.10	8.61	9.48	11.31	9.37	8.91	12.37	6.77	9.22	9.61	9.44
SDIH 04	10.14	11.73	10.92	11.57	11.76	11.11	15.03	13.78	10.46	9.65	10.95	11.51	12.42	11.67
SDIH 05	9.57	10.54	11.83	10.58	11.88	11.18	13.00	10.75	11.46	10.94	11.60	10.48	12.28	13.32
SDIH 06	11.49	9.05	11.52	10.68	13.61	11.12	10.20	13.15	9.93	11.89	13.21	15.10	12.17	13.26
SDIH 07	14.29	13.04	11.41	10.94	20.25	12.24	11.88	10.16	22.35	12.05	12.12	14.51	14.64	10.66
SDIH 08	13.61	15.29	10.25	22.64	12.90	17.21	15.36	14.52	16.58	12.32	12.67	12.33	12.21	11.49
SDIH 09	6.54	7.03	7.86	6.28	5.80	10.70	9.76	7.66	6.16	8.91	7.99	8.78	9.27	9.38
LDIH 01	11.87	9.61	14.16	14.21	14.22	14.83	13.37	15.12	11.51	10.47	12.65	11.48	13.12	13.29
LDIH 02	8.53	9.77	9.71	7.97	8.53	9.46	8.15	9.14	10.57	7.65	10.52	11.30	8.26	11.50
LDIH 03	13.90	11.63	9.86	10.43	11.47	8.29	12.70	12.82	10.45	11.67	6.67	9.32	13.30	11.73
LDIH 04	11.70	11.50	12.13	12.11	12.08	11.88	10.55	11.60	11.09	16.24	9.51	10.53	9.67	9.68
LDIH 05	11.01	8.62	15.31	13.66	12.35	11.79	15.93	10.24	13.36	12.27	11.04	10.73	12.21	11.50
LDIH 06	16.78	15.75	11.74	11.03	11.32	9.73	14.27	11.86	13.28	12.52	14.17	13.34	13.40	12.41
LDIH 07	7.44	9.87	10.24	9.10	9.81	9.89	11.35	14.19	13.85	12.34	9.99	11.16	10.20	11.28
LDIH 08	12.38	14.70	14.53	10.38	13.19	9.94	10.71	11.26	13.62	13.22	11.02	8.40	11.47	9.59
LDIH 09	12.39	12.96	14.83	18.81	11.66	13.33	14.22	15.13	17.49	15.12	15.96	12.83	13.12	13.36

Change in heart rate (HR) per change in arterial oxyhemoglobin saturation (SaO_2) during preHVR and postHVR.

	$\Delta HR/\Delta SaO_2$ (bpm $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	1.39	0.22	1.33	1.37	1.30	1.10	1.52	-0.23	1.03	0.90	1.47	1.56	0.97	1.06
SDIH 02	1.07	1.66	0.69	1.08	0.53	1.07	0.77	0.76	1.01	0.76	0.55	1.08	0.94	0.64
SDIH 03	0.60	0.53	0.31	0.84	0.78	0.61	0.54	0.72	0.78	0.55	0.53	0.06	0.50	0.44
SDIH 04	0.66	0.83	0.47	0.84	0.81	1.12	0.87	0.79	0.81	0.87	0.52	0.67	0.60	0.81
SDIH 05	0.78	0.81	0.64	0.62	0.71	0.57	0.71	0.80	1.02	0.83	0.93	0.99	1.08	1.00
SDIH 06	1.32	1.27	0.98	1.56	1.32	1.28	1.16	1.65	1.24	1.50	0.93	1.48	0.92	1.24
SDIH 07	1.92	1.74	1.50	1.19	1.85	1.35	1.80	1.91	2.38	1.92	2.24	1.37	2.99	1.52
SDIH 08	1.46	2.69	1.99	1.74	1.89	2.06	2.09	1.70	1.94	2.34	2.26	2.95	2.31	2.78
SDIH 09	1.25	1.46	1.76	0.96	1.37	1.45	1.82	1.50	1.15	1.19	1.34	1.51	1.26	1.20
LDIH 01	1.06	1.47	0.84	0.66	0.93	0.94	0.79	0.82	1.00	0.84	0.96	1.12	0.83	0.77
LDIH 02	1.22	2.29	1.08	1.48	1.06	1.04	0.81	1.25	0.85	1.80	0.99	1.25	1.22	1.11
LDIH 03	0.97	0.66	0.73	0.72	0.45	0.80	0.62	0.48	0.63	0.59	0.79	1.55	0.81	-0.77
LDIH 04	1.05	1.15	1.45	1.45	1.75	1.48	1.53	1.45	1.34	1.17	1.40	1.33	1.31	1.23
LDIH 05	1.47	1.66	1.14	0.82	1.65	1.52	1.30	1.36	1.15	0.09	0.97	0.59	1.55	1.38
LDIH 06	0.40	0.82	0.46	0.74	0.67	0.59	0.03	0.20	0.52	0.37	0.47	0.43	0.01	0.14
LDIH 07	1.20	1.01	1.15	1.21	1.35	1.57	1.38	1.16	0.75	1.14	1.33	0.98	1.46	0.96
LDIH 08	1.12	0.84	0.80	0.79	0.93	1.26	1.12	1.35	0.63	0.61	0.86	0.97	0.94	0.63
LDIH 09	0.97	1.42	0.95	1.07	1.28	0.88	0.95	1.34	1.18	0.90	1.75	1.25	1.15	1.07

Heart rate (HR) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	HR (bpm)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	67.00	78.95	62.41	60.24	75.12	58.08	60.47	62.44	65.97	59.73	55.65	57.94	69.18	64.59
SDIH 02	70.76	80.42	83.80	77.62	88.33	90.33	73.67	78.33	84.33	84.67	90.00	85.33	72.33	81.33
SDIH 03	64.00	62.00	65.00	62.33	67.00	69.00	70.67	63.67	65.33	61.00	70.67	65.33	63.67	62.67
SDIH 04	62.00	84.00	72.67	73.67	64.00	65.00	64.67	62.67	65.00	63.67	67.00	57.33	64.33	66.67
SDIH 05	63.67	66.67	69.67	68.00	75.00	79.33	85.00	80.67	65.33	75.00	74.00	69.00	77.00	83.33
SDIH 06	79.00	80.67	77.33	78.00	77.67	79.33	72.00	77.00	64.00	68.67	77.00	78.33	93.00	74.67
SDIH 07	42.67	39.00	43.33	47.33	47.00	48.00	49.67	48.33	52.67	50.33	48.33	45.33	53.00	41.33
SDIH 08	42.33	46.00	40.67	47.00	50.67	44.67	50.33	43.00	52.00	48.33	52.00	41.67	42.00	44.67
SDIH 09	69.67	71.00	63.67	69.00	63.00	63.00	62.00	59.67	59.00	61.00	64.00	63.67	65.33	69.33
LDIH 01	71.53	73.14	89.91	78.40	82.67	82.33	96.67	100.33	80.67	80.00	91.67	83.00	91.00	78.00
LDIH 02	80.33	69.00	72.00	67.00	78.33	73.67	81.00	72.33	82.67	68.00	81.00	77.33	78.33	70.00
LDIH 03	63.00	61.33	57.00	54.33	68.00	59.67	60.00	55.67	65.00	53.67	65.00	52.00	60.33	54.33
LDIH 04	63.33	50.00	55.33	47.33	55.00	59.00	51.00	51.00	65.33	53.67	61.67	54.00	65.00	64.00
LDIH 05	66.00	53.33	69.33	58.00	52.00	56.67	72.00	55.00	65.67	55.00	78.00	70.33	61.67	61.00
LDIH 06	62.33	62.00	64.67	61.67	64.67	61.33	66.00	67.67	68.00	67.67	75.67	71.33	67.33	73.33
LDIH 07	85.67	86.00	70.67	66.00	85.00	72.67	80.33	76.00	113.00	110.33	85.33	83.00	83.33	66.74
LDIH 08	62.67	62.33	62.67	60.67	52.00	49.67	58.33	54.33	75.67	72.67	61.33	61.67	57.00	66.00
LDIH 09	65.67	63.67	77.00	69.67	68.33	66.67	75.67	72.67	75.00	77.33	72.67	74.00	69.33	79.33

Change in cardiac output (CO) per change in arterial oxyhemoglobin saturation (SaO_2) during preHVR and postHVR.

	$\Delta CO/\Delta SaO_2$ ($l\ min^{-1}\ \%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	0.08	0.02	0.09	-0.05	0.10	-0.06	0.13	-0.03	0.03	0.11	0.15	0.17	0.13	0.21
SDIH 02	0.11	0.15	0.07	0.11	0.04	0.17	0.08	0.06	0.11	0.09	0.02	0.02	0.12	0.06
SDIH 03	0.05	0.05	0.01	0.04	0.07	0.05	0.00	0.05	0.07	0.04	0.06	0.05	0.05	0.03
SDIH 04	0.07	0.09	0.07	0.08	0.11	0.13	0.12	0.09	0.11	0.11	0.06	0.08	0.07	0.12
SDIH 05	0.09	0.09	0.09	0.08	0.09	0.09	0.12	0.10	0.14	0.11	0.11	0.12	0.13	0.12
SDIH 06	0.23	0.13	0.19	0.22	0.11	0.14	0.12	0.25	0.18	0.18	0.15	0.17	0.11	0.16
SDIH 07	0.17	0.16	0.14	0.12	0.14	0.15	0.19	0.16	0.26	0.16	0.24	0.09	0.42	0.09
SDIH 08	0.16	0.35	0.15	0.10	0.16	0.20	0.20	0.17	0.18	0.25	0.31	0.36	0.25	0.23
SDIH 09	0.14	0.17	0.12	0.15	0.19	0.16	0.14	0.13	0.07	0.11	0.07	0.08	0.11	0.15
LDIH 01	0.02	0.06	0.11	0.02	0.06	0.09	0.08	0.07	0.10	0.08	0.14	0.14	0.09	0.10
LDIH 02	0.11	0.19	0.10	0.10	0.13	0.09	0.07	0.11	0.07	0.15	0.09	0.11	0.11	0.10
LDIH 03	0.10	0.07	0.04	0.07	0.03	0.07	0.06	0.06	0.05	0.05	0.07	0.14	0.06	0.06
LDIH 04	0.12	0.12	0.14	0.17	0.22	0.19	0.18	0.18	0.17	0.15	0.18	0.13	0.17	0.17
LDIH 05	0.17	0.16	0.09	0.10	0.18	0.12	0.15	0.12	0.15	0.06	-0.07	0.05	0.16	0.12
LDIH 06	0.05	0.07	0.12	0.11	0.10	0.14	0.01	0.05	0.15	-0.01	0.13	0.08	0.01	0.03
LDIH 07	0.14	0.11	0.08	0.06	0.09	0.12	0.15	0.09	0.06	0.06	0.05	0.06	0.12	0.11
LDIH 08	0.11	0.07	0.05	0.05	0.09	0.13	0.10	0.10	0.09	0.07	0.04	0.06	0.05	0.03
LDIH 09	0.18	0.23	0.15	0.14	0.20	0.11	0.14	0.17	0.16	0.15	0.21	0.22	0.19	0.17

Cardiac output (CO) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	CO ($l\ min^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	6.44	8.01	6.95	7.02	7.79	6.91	6.30	6.54	7.27	7.07	7.11	7.79	8.98	6.17
SDIH 02	6.59	7.91	7.00	6.37	7.99	7.54	6.43	7.00	7.30	6.99	7.30	6.76	6.22	7.18
SDIH 03	5.64	5.37	5.22	5.09	4.78	5.05	6.06	4.76	4.87	5.00	6.74	5.71	5.50	5.75
SDIH 04	5.82	8.58	7.37	7.68	6.35	6.82	6.23	5.86	6.26	5.93	6.47	5.29	6.36	7.41
SDIH 05	5.94	6.05	6.68	6.39	7.39	7.72	9.78	8.38	6.28	7.37	7.80	6.35	7.80	8.49
SDIH 06	8.02	8.95	8.89	9.22	9.01	9.93	8.00	7.45	7.63	7.54	8.43	8.41	9.34	7.68
SDIH 07	4.24	3.60	4.54	4.49	5.39	5.28	5.54	5.16	5.17	4.33	5.29	4.82	5.86	4.12
SDIH 08	6.25	6.96	5.56	6.84	6.15	6.27	6.14	6.27	7.09	6.50	6.78	6.14	6.22	5.67
SDIH 09	7.78	7.31	7.48	7.02	7.93	7.65	7.47	7.06	7.43	7.56	7.46	6.98	7.81	7.97
LDIH 01	9.57	6.53	9.50	8.40	9.61	8.37	9.69	10.31	7.72	8.15	10.56	11.02	9.53	7.98
LDIH 02	4.98	4.22	4.96	4.03	5.66	5.10	4.88	4.39	5.33	4.55	5.60	4.63	5.64	4.38
LDIH 03	7.22	7.63	6.89	6.28	8.30	7.23	6.78	6.54	7.31	6.50	7.07	5.65	7.49	6.35
LDIH 04	6.75	5.94	6.21	5.71	5.75	6.65	6.01	6.20	6.22	5.22	6.67	6.58	7.66	7.24
LDIH 05	7.49	6.85	7.53	6.06	5.88	6.39	7.70	5.81	6.71	5.36	8.08	7.54	7.65	7.38
LDIH 06	6.11	6.53	6.31	5.94	6.19	6.44	4.42	4.90	6.30	5.79	7.75	8.34	6.01	5.71
LDIH 07	7.81	8.09	6.31	5.70	7.25	6.42	6.77	6.63	8.45	7.96	7.70	8.23	6.55	6.78
LDIH 08	7.10	6.97	7.07	7.12	4.62	4.63	6.56	6.26	7.12	7.43	5.82	5.50	5.86	6.40
LDIH 09	7.91	7.58	7.46	6.41	7.51	6.89	7.90	6.73	8.45	7.88	8.09	7.41	7.96	9.38

Change in stroke volume (SV) per change in arterial oxyhemoglobin saturation (SaO_2) during preHVR and postHVR.

	$\Delta SV/\Delta SaO_2$ (ml $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	-0.58	-0.02	-0.60	0.06	-0.37	-0.16	-0.29	-0.16	-0.14	-0.17	-0.50	0.44	-0.03	1.23
SDIH 02	0.14	0.05	0.09	0.23	-0.04	0.75	0.19	-0.01	0.20	0.27	-0.22	-0.67	0.41	0.02
SDIH 03	0.00	-0.02	-0.18	-0.44	0.12	0.02	-0.58	-0.05	0.08	-0.14	0.06	-0.00	0.09	-0.14
SDIH 04	0.06	0.08	0.22	-0.05	0.42	0.13	0.51	0.18	0.37	0.27	0.17	0.28	0.14	0.40
SDIH 05	0.17	0.20	0.40	0.23	0.19	0.35	0.46	0.22	0.49	0.35	0.12	0.31	0.22	0.18
SDIH 06	0.94	-0.09	0.85	0.35	0.43	0.18	-0.10	0.92	0.43	0.16	0.55	0.01	0.10	0.24
SDIH 07	-0.25	-0.15	-0.18	-0.01	-1.07	0.03	-0.23	-0.70	0.22	-0.18	0.01	-1.00	1.21	-0.97
SDIH 08	-0.80	-0.72	-1.51	-2.23	-0.94	-0.98	-0.84	1.14	1.15	-0.84	0.14	0.88	-1.12	1.47
SDIH 09	-0.03	0.19	-1.09	0.59	0.18	0.20	-0.98	-0.64	-0.91	0.43	-0.99	-1.00	-0.48	0.09
LDIH 01	-1.28	-0.78	0.16	-0.51	-0.52	-0.10	0.00	-0.09	-0.01	-0.06	0.23	-0.09	-0.05	0.25
LDIH 02	0.37	0.44	0.25	0.12	0.53	0.22	0.23	0.30	0.12	0.31	0.22	0.31	0.19	0.30
LDIH 03	-0.20	-0.27	-0.65	-0.13	0.36	-0.38	-0.27	0.12	-0.31	-0.28	-0.23	-0.36	-0.49	-0.45
LDIH 04	0.09	-0.19	-0.24	-0.02	0.41	0.28	-0.06	-0.03	0.35	0.35	0.20	-0.33	0.14	0.27
LDIH 05	-0.03	-0.50	-0.36	0.23	-0.10	-0.71	0.10	-0.23	0.38	-0.41	-0.37	-0.20	-0.38	-0.65
LDIH 06	0.15	-0.18	1.01	0.60	0.51	1.13	0.17	0.46	1.32	0.61	1.08	0.46	0.43	0.06
LDIH 07	0.30	0.19	-0.25	-0.50	0.23	-0.26	0.39	-0.12	-0.01	-0.23	-0.74	-0.37	0.05	0.14
LDIH 08	-0.16	-0.26	-0.46	-0.60	0.16	0.21	-0.40	-0.73	0.37	0.13	0.45	-0.39	-0.68	-0.36
LDIH 09	0.77	0.71	0.57	-0.19	0.62	0.26	0.49	0.59	0.26	0.66	0.14	1.02	0.77	0.45

Stroke volume (SV) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	SV (ml)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	96.33	101.70	112.13	117.42	104.52	119.86	104.93	105.72	111.06	118.93	129.22	134.61	130.52	96.26
SDIH 02	93.70	98.39	83.87	82.38	91.00	84.00	87.67	89.67	86.67	83.00	81.67	79.33	86.67	88.67
SDIH 03	88.33	87.33	80.67	82.33	72.00	73.33	85.67	75.00	74.67	82.33	95.00	87.33	86.33	92.00
SDIH 04	94.00	102.00	101.67	104.67	99.00	105.33	97.00	93.33	96.67	93.67	97.00	93.00	98.33	112.00
SDIH 05	93.67	91.33	96.33	94.33	98.67	98.00	115.33	104.67	96.67	99.50	106.00	92.33	101.33	102.67
SDIH 06	101.67	111.33	115.67	119.00	116.33	125.67	111.67	97.67	119.67	110.33	109.33	108.00	100.67	103.33
SDIH 07	99.67	93.33	105.67	98.00	114.33	110.67	112.67	107.00	98.33	86.33	110.33	107.00	111.00	100.67
SDIH 08	147.33	151.33	136.33	146.67	121.33	140.33	122.33	144.67	136.33	135.00	130.00	147.00	148.67	127.33
SDIH 09	112.33	103.67	117.67	101.67	126.67	122.00	121.00	118.33	127.00	124.00	116.67	109.67	120.00	115.33
LDIH 01	134.33	89.42	106.07	107.43	115.67	101.67	100.00	103.00	96.00	102.33	115.33	133.67	105.00	103.00
LDIH 02	62.00	61.33	69.00	61.00	72.67	69.67	60.33	60.67	64.67	67.00	69.33	60.00	72.00	63.00
LDIH 03	115.00	125.33	122.33	117.00	122.67	122.33	113.33	117.33	113.00	121.33	109.00	110.00	124.67	118.00
LDIH 04	106.67	119.67	112.67	120.33	105.00	113.00	118.67	121.33	95.67	99.33	109.33	123.33	118.33	113.67
LDIH 05	114.33	128.67	109.33	105.00	113.67	113.00	107.33	105.67	102.00	97.33	103.33	107.67	124.67	122.00
LDIH 06	99.00	106.33	98.00	97.00	95.67	106.00	67.67	72.33	92.00	86.00	102.33	117.00	89.33	77.67
LDIH 07	91.67	94.67	89.33	87.00	86.00	89.00	84.33	88.00	75.00	72.33	90.33	99.33	78.33	103.01
LDIH 08	113.00	112.67	113.67	118.67	89.00	93.00	112.67	115.33	94.67	102.67	94.67	89.67	102.00	97.33
LDIH 09	121.00	119.33	97.33	93.00	110.67	104.00	104.33	92.67	113.33	103.33	112.00	100.33	115.33	118.33

Change in total peripheral resistance (TPR) per change in arterial oxyhemoglobin saturation (SaO_2) during preHVR and postHVR.

	$\Delta TPR/\Delta SaO_2$ (PRU $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	-0.007	0.000	-0.010	0.010	0.000	0.000	-0.010	0.008	-0.004	-0.010	0.006	-0.012	-0.005	-0.010
SDIH 02	-0.008	-0.189	-0.004	-0.012	-0.003	-0.005	-0.008	-0.009	-0.006	-0.007	-0.002	0.001	-0.012	-0.003
SDIH 03	-0.007	-0.011	-0.003	-0.007	-0.014	-0.010	0.002	-0.010	-0.010	-0.006	-0.005	-0.006	-0.005	-0.004
SDIH 04	-0.008	-0.008	-0.005	-0.007	-0.012	-0.012	-0.010	-0.010	-0.009	-0.013	-0.007	-0.010	-0.007	-0.008
SDIH 05	-0.008	-0.011	-0.008	-0.011	-0.005	-0.007	-0.004	-0.006	-0.010	-0.009	-0.007	-0.013	-0.007	-0.006
SDIH 06	-0.010	-0.008	-0.005	-0.010	-0.004	-0.004	-0.005	-0.018	-0.010	-0.013	-0.005	-0.008	-0.002	-0.005
SDIH 07	-0.024	-0.037	-0.013	-0.045	-0.012	-0.016	-0.014	-0.024	-0.021	-0.025	-0.015	-0.006	-0.026	-0.008
SDIH 08	-0.011	-0.025	-0.009	-0.006	-0.013	-0.016	-0.016	-0.015	-0.009	-0.017	-0.015	-0.022	-0.016	-0.019
SDIH 09	-0.005	-0.011	0.002	-0.012	-0.005	-0.009	-0.003	-0.006	0.002	-0.003	0.004	-0.006	-0.002	-0.006
LDIH 01	0.000	-0.008	-0.002	0.002	-0.004	-0.007	0.001	-0.003	-0.005	-0.005	-0.002	-0.005	-0.006	-0.005
LDIH 02	-0.015	-0.028	-0.009	-0.021	-0.007	-0.007	-0.006	-0.016	-0.005	-0.023	-0.002	-0.017	-0.009	-0.011
LDIH 03	-0.004	-0.006	-0.002	-0.007	0.000	-0.005	-0.005	-0.008	-0.002	-0.005	-0.004	-0.018	-0.003	-0.004
LDIH 04	-0.007	-0.013	-0.013	-0.016	-0.016	-0.015	-0.012	-0.016	-0.013	-0.015	-0.010	-0.010	-0.006	-0.008
LDIH 05	-0.011	-0.012	-0.007	-0.011	-0.016	-0.014	-0.010	-0.014	-0.010	-0.009	-0.003	-0.005	-0.015	-0.009
LDIH 06	0.015	-0.006	-0.002	-0.011	-0.005	-0.012	0.021	-0.001	-0.030	0.041	-0.004	-0.005	0.020	0.017
LDIH 07	-0.010	-0.009	-0.008	-0.009	-0.008	-0.011	-0.011	-0.010	-0.003	-0.004	-0.004	-0.006	-0.011	-0.006
LDIH 08	-0.006	-0.005	-0.002	-0.001	-0.012	-0.021	-0.003	-0.007	-0.004	-0.005	0.004	-0.002	-0.000	0.000
LDIH 09	-0.007	-0.011	-0.007	-0.014	-0.011	-0.009	-0.008	-0.015	-0.005	-0.008	-0.014	-0.013	-0.011	-0.006

Total peripheral resistance (TPR) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	TPR (PRU)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	1.06	0.81	0.79	0.90	0.76	0.88	0.87	1.01	0.71	0.90	0.80	0.94	0.69	0.85
SDIH 02	0.79	0.79	0.71	0.91	0.73	0.70	0.88	0.90	0.72	0.86	0.88	1.02	0.87	0.80
SDIH 03	1.03	1.16	1.13	1.16	1.12	1.02	0.88	1.21	1.06	1.23	0.82	0.98	0.96	0.97
SDIH 04	1.03	0.80	0.73	0.75	0.92	0.90	0.83	0.95	0.79	0.96	0.83	0.99	0.88	0.69
SDIH 05	0.88	0.96	0.85	0.99	0.71	0.80	0.53	0.74	0.80	0.78	0.69	0.96	0.66	0.59
SDIH 06	0.72	0.67	0.60	0.65	0.67	0.67	0.72	0.85	0.84	0.88	0.69	0.79	0.71	0.71
SDIH 07	1.14	1.47	1.02	1.91	0.95	1.01	0.88	1.04	0.89	1.24	0.94	1.10	0.88	1.14
SDIH 08	0.82	0.77	0.83	0.82	0.87	0.90	0.81	0.85	0.70	0.78	0.73	0.83	0.80	0.94
SDIH 09	0.77	0.86	0.77	0.97	0.69	0.82	0.82	0.83	0.76	0.80	0.72	0.98	0.76	0.74
LDIH 01	0.73	1.28	0.60	0.73	0.59	0.74	0.55	0.57	0.70	0.69	0.48	0.51	0.65	0.64
LDIH 02	1.28	1.52	1.20	1.66	0.86	1.12	1.22	1.32	1.14	1.38	1.05	1.41	0.98	1.38
LDIH 03	0.72	0.78	0.79	0.90	0.64	0.80	0.80	0.86	0.71	0.89	0.77	1.02	0.72	0.77
LDIH 04	0.74	0.93	0.81	0.91	0.83	0.84	0.85	0.82	0.84	1.04	0.73	0.85	0.60	0.68
LDIH 05	0.79	0.90	0.78	0.93	0.89	0.91	0.65	0.93	0.68	0.94	0.63	0.69	0.75	0.72
LDIH 06	1.00	0.93	0.92	0.99	0.98	0.89	1.66	1.43	1.52	0.95	0.71	0.72	1.06	1.12
LDIH 07	0.72	0.69	0.78	0.90	0.70	0.76	0.73	0.74	0.63	0.66	0.67	0.65	0.86	0.84
LDIH 08	0.83	0.85	0.89	0.82	1.26	1.31	0.77	0.85	0.87	0.88	1.05	1.13	1.12	1.05
LDIH 09	0.63	0.71	0.70	0.84	0.74	0.82	0.71	0.82	0.58	0.68	0.73	0.80	0.69	0.55

Change in systolic blood pressure (SBP) per change in arterial oxyhemoglobin saturation (SaO_2) during preHVR and postHVR.

	$\Delta SBP/\Delta SaO_2$ (mmHg $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	0.68	0.23	0.06	1.02	1.87	2.02	1.62	0.22	1.08	0.69	1.17	0.52	0.11	2.43
SDIH 02	0.45	-0.03	0.47	0.41	0.47	2.24	0.35	-0.04	0.88	0.64	0.22	0.15	0.24	0.71
SDIH 03	0.35	-0.39	0.10	-0.15	0.03	0.02	0.09	0.14	0.38	0.08	0.21	0.27	0.46	0.07
SDIH 04	0.34	-0.19	0.40	0.09	0.31	0.45	0.68	0.28	0.63	0.05	0.16	0.44	0.31	0.62
SDIH 05	0.21	0.12	0.24	0.11	0.34	0.22	0.81	0.49	0.50	0.24	0.31	0.09	0.59	0.59
SDIH 06	1.61	0.18	1.45	0.91	1.09	1.07	1.16	0.89	1.16	0.80	1.40	1.09	1.44	1.40
SDIH 07	1.14	0.60	1.19	0.78	1.49	1.32	1.64	0.11	1.66	1.26	3.62	0.88	3.15	0.88
SDIH 08	0.52	0.81	1.45	0.09	0.78	0.67	1.71	0.21	0.77	0.51	1.09	0.90	0.74	1.08
SDIH 09	1.71	1.24	2.57	1.02	2.05	1.09	2.21	1.26	1.82	1.34	2.69	1.06	1.77	1.31
LDIH 01	0.20	0.19	1.07	0.76	0.23	-0.23	1.22	0.54	0.71	0.02	1.46	0.16	0.27	0.56
LDIH 02	0.85	1.86	1.33	0.43	1.27	1.26	0.84	0.60	0.86	0.96	1.30	0.69	0.93	1.22
LDIH 03	0.98	0.11	0.32	0.41	0.45	0.31	0.20	0.11	0.23	0.04	0.32	0.28	0.71	0.35
LDIH 04	0.43	-0.07	0.29	0.18	0.49	-0.01	0.59	0.06	0.16	0.17	0.30	0.30	0.55	0.42
LDIH 05	0.62	0.24	0.05	0.32	0.58	-0.46	0.47	0.21	0.73	-0.38	0.25	-0.26	0.90	0.41
LDIH 06	0.85	0.81	1.41	1.17	0.77	0.78	0.76	0.84	1.06	0.27	1.76	0.58	1.58	1.56
LDIH 07	0.41	0.49	0.08	-0.05	0.12	0.14	0.61	-0.14	0.40	-0.02	0.11	-0.52	0.19	0.85
LDIH 08	0.98	0.68	0.72	0.81	1.18	1.06	1.04	0.61	1.03	0.60	1.54	1.29	1.02	0.86
LDIH 09	1.03	1.39	0.88	0.07	0.80	0.52	0.55	0.57	0.91	0.84	1.13	1.06	0.73	0.74

Systolic blood pressure (SBP) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	SBP (mmHg)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	125	133	135	125	140	117	113	113	126	131	114	138	126	117
SDIH 02	112	134	109	125	124	113	124	136	116	128	138	147	114	126
SDIH 03	120	123	132	132	118	113	116	127	109	127	124	120	118	125
SDIH 04	120	140	128	120	125	125	119	125	112	124	125	121	125	124
SDIH 05	119	129	131	124	121	123	127	125	119	121	126	122	120	117
SDIH 06	126	139	122	138	133	138	120	144	145	149	130	150	136	120
SDIH 07	112	120	109	127	123	127	114	126	107	122	116	129	126	107
SDIH 08	124	127	103	134	130	131	115	122	114	122	120	125	121	121
SDIH 09	135	142	135	154	126	146	138	133	130	139	118	157	134	134
LDIH 01	139	138	121	124	129	135	115	128	117	123	114	134	124	114
LDIH 02	127	121	116	131	113	124	132	130	122	116	122	117	129	124
LDIH 03	120	137	123	124	118	133	123	129	118	130	125	127	122	110
LDIH 04	117	131	118	115	113	128	122	122	122	126	117	136	113	119
LDIH 05	134	136	136	131	121	133	115	125	107	118	118	124	140	130
LDIH 06	136	135	134	133	140	131	159	158	136	122	125	140	146	143
LDIH 07	126	125	106	110	110	106	108	108	113	109	112	120	120	123
LDIH 08	132	131	143	130	128	134	115	121	136	149	132	132	146	147
LDIH 09	119	122	117	119	125	125	124	120	112	120	131	131	126	118

Change in diastolic blood pressure (DBP) per change in arterial oxyhemoglobin saturation (SaO_2) during preHVR and postHVR.

	$\Delta DBP/\Delta SaO_2$ (mmHg $\%SaO_2^{-1}$)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	0.48	0.18	0.19	0.50	0.88	0.81	1.05	0.21	0.51	0.33	0.69	0.19	0.27	0.76
SDIH 02	0.30	-0.16	0.17	0.01	0.24	0.79	0.09	-0.08	0.29	0.21	0.12	0.38	0.24	0.30
SDIH 03	0.17	-0.23	-0.07	0.08	-0.11	-0.04	0.19	0.02	0.04	0.07	0.05	0.07	0.20	0.07
SDIH 04	0.10	-0.16	0.03	-0.01	-0.06	-0.02	0.20	-0.00	0.20	-0.17	-0.01	0.09	-0.01	-0.03
SDIH 05	0.06	-0.03	-0.01	-0.10	0.11	-0.04	0.26	0.09	0.09	-0.03	0.06	-0.09	0.20	0.13
SDIH 06	0.50	0.08	0.50	0.18	0.54	0.46	0.48	0.21	0.40	0.20	0.55	0.50	0.43	0.61
SDIH 07	0.65	0.44	0.80	0.52	1.06	0.63	0.82	0.35	0.95	0.77	1.88	0.96	1.39	0.91
SDIH 08	0.42	0.39	0.74	0.59	0.64	0.35	0.89	0.22	0.60	0.43	0.43	0.38	0.52	0.75
SDIH 09	0.63	0.38	1.45	0.20	0.98	0.53	1.20	0.71	0.98	0.62	1.32	0.55	0.78	0.57
LDIH 01	0.37	0.37	0.49	0.52	-0.08	-0.12	0.73	0.14	0.28	-0.05	0.45	-0.00	-0.08	0.24
LDIH 02	0.31	0.89	0.61	0.26	0.56	0.51	0.46	0.26	0.57	0.36	0.88	0.27	0.45	0.63
LDIH 03	0.42	0.02	0.31	0.19	0.32	0.17	0.16	-0.04	0.19	0.01	0.26	0.04	0.40	0.24
LDIH 04	0.19	-0.05	0.17	0.09	0.17	-0.03	0.24	-0.03	0.00	-0.04	0.04	0.09	0.24	0.13
LDIH 05	0.19	0.04	0.05	0.02	0.27	-0.16	0.11	-0.01	0.10	-0.08	0.23	-0.06	-0.50	-0.12
LDIH 06	0.29	0.24	0.17	0.17	0.07	0.11	0.19	0.06	0.25	0.06	0.41	-0.00	0.40	0.39
LDIH 07	-0.07	-0.11	-0.04	-0.01	-0.14	-0.01	0.18	-0.17	0.12	0.03	0.10	-0.30	0.03	0.37
LDIH 08	0.52	0.31	0.47	0.51	0.57	0.41	0.68	0.49	0.36	0.26	0.87	0.73	0.69	0.49
LDIH 09	0.32	0.36	0.34	-0.19	0.16	0.09	0.11	0.08	0.45	0.22	0.40	0.19	0.14	0.22

Diastolic blood pressure (DBP) occurring in normoxia immediately before each preHVR and postHVR. Values are 30 second averages.

	DBP (mmHg)													
Day	1		3		5		8		10		12		15	17
HVR	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
SDIH 01	74	80	70	76	78	78	67	86	77	90	77	80	76	73
SDIH 02	68	79	67	78	76	70	75	83	70	81	86	93	72	76
SDIH 03	78	78	81	80	73	71	71	79	70	89	74	68	71	74
SDIH 04	81	85	72	73	79	76	69	76	65	78	73	72	75	66
SDIH 05	69	77	75	91	69	80	67	82	67	75	70	83	68	65
SDIH 06	76	78	68	77	77	88	74	85	83	87	76	88	79	71
SDIH 07	65	72	61	73	67	70	63	71	60	75	65	71	69	62
SDIH 08	64	67	58	69	70	72	64	67	62	64	63	64	62	68
SDIH 09	78	83	74	89	69	81	78	76	72	77	69	89	76	77
LDIH 01	90	93	76	74	75	84	72	79	73	77	66	72	80	69
LDIH 02	83	83	77	92	61	75	81	79	81	83	78	76	72	76
LDIH 03	68	75	70	73	68	75	70	73	68	75	72	76	69	63
LDIH 04	63	69	63	60	61	56	64	63	69	70	62	69	57	62
LDIH 05	75	76	75	73	66	74	63	69	57	66	66	68	72	67
LDIH 06	78	80	79	80	83	77	99	98	81	75	72	78	87	87
LDIH 07	75	74	65	69	68	64	66	65	73	73	68	70	91	71
LDIH 08	76	78	81	75	80	82	66	69	83	86	81	84	87	88
LDIH 09	62	69	69	72	72	74	73	74	62	70	77	77	71	64

Ventilation during the first (H_1) and last (H_2) 5 minutes of hypoxic exposure to SDIH and LDIH. Values are 3-minute averages of the end of each 5-minute period.

	V_I ($l\ min^{-1}$)											
Day	1		3		5		8		10		12	
HVR	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2
SDIH 01	14.98	14.16	13.38	16.69	10.64	14.97	9.60	9.63	10.75	12.92	10.39	13.74
SDIH 02	11.19	11.00	8.60	11.21	12.24	12.20	10.12	10.61	10.32	10.42	13.38	14.02
SDIH 03	11.59	10.95	10.30	11.30	13.43	11.32	13.60	12.60	13.59	15.28	12.52	11.97
SDIH 04	14.11	13.10	16.75	13.46	13.59	12.02	15.26	15.06	11.29	12.79	13.42	13.39
SDIH 05	13.98	12.64	13.21	12.63	13.62	14.89	13.61	14.53	14.29	14.38	13.23	12.99
SDIH 06	12.45	12.98	12.49	15.22	18.23	18.97	13.24	16.24	15.06	13.40	16.46	16.52
SDIH 07	19.74	16.81	14.53	11.04	18.29	15.05	17.37	17.72	20.59	16.85	19.31	18.02
SDIH 08	15.54	16.59	13.75	12.84	14.12	13.51	15.66	14.40	16.05	15.61	15.41	15.04
SDIH 09	9.04	9.26	9.77	8.72	8.20	10.79	8.58	3.55	11.11	11.15	11.15	10.27
LDIH 01	10.77	11.90	14.23	12.71	10.46	11.08	14.72	15.18	10.25	10.55	14.73	12.59
LDIH 02	11.84	10.52	11.33	11.68	13.82	13.93	10.44	11.87	9.71	10.31	12.53	13.22
LDIH 03	14.24	11.00	11.80	9.59	12.16	11.42	14.75	12.45	11.66	10.75	12.34	10.78
LDIH 04	15.68	17.50	16.26	15.52	17.53	15.42	15.41	14.38	14.35	12.81	17.65	15.76
LDIH 05	13.02	12.17	14.18	13.79	13.80	15.94	16.68	13.44	13.52	12.44	11.12	10.31
LDIH 06	16.37	16.14	15.88	14.01	14.86	14.47	20.23	18.39	15.30	17.42	16.79	16.25
LDIH 07	13.33	13.18	11.42	10.46	11.94	11.91	12.31	12.48	12.15	12.03	14.39	15.77
LDIH 08	16.54	14.23	15.08	14.16	13.23	12.42	14.53	12.15	14.69	17.06	15.71	11.16
LDIH 09	14.17	13.39	15.12	16.61	16.56	16.26	16.50	17.32	16.91	16.41	17.82	15.60

Mean arterial pressure (MAP) during the first (H_1) and last (H_2) 5 minutes of hypoxic exposure to SDIH and LDIH. Values are 3-minute averages of the end of each 5-minute period.

	MAP (mmHg)											
Day	1		3		5		8		10		12	
HVR	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2
SDIH 01	111.47	109.76	95.55	103.73	101.11	105.89	98.74	109.11	97.53	107.47	106.84	117.63
SDIH 02	86.95	107.24	88.12	90.32	101.63	98.95	98.16	102.95	89.42	104.00	108.68	115.58
SDIH 03	96.65	97.56	95.37	96.28	94.49	87.37	86.54	94.89	103.96	103.63	102.51	90.61
SDIH 04	100.46	112.70	97.63	98.89	99.40	109.91	87.47	94.02	85.00	94.33	87.46	87.26
SDIH 05	92.35	93.42	90.35	101.82	86.82	101.82	81.54	101.07	88.65	90.75	91.96	97.00
SDIH 06	98.21	102.77	92.19	97.35	98.40	110.09	95.40	100.96	108.51	108.53	94.05	105.42
SDIH 07	83.96	86.11	76.16	93.05	85.05	89.30	86.33	88.68	79.70	89.96	95.77	92.07
SDIH 08	82.14	87.47	75.91	86.12	85.02	91.12	80.12	85.21	78.11	85.21	83.42	85.09
SDIH 09	98.79	101.60	95.81	102.39	94.11	100.54	96.70	102.70	91.35	97.67	97.14	103.49
LDIH 01	115.17	134.82	100.49	110.70	91.84	91.00	92.16	87.68	92.53	98.26	90.37	89.74
LDIH 02	108.05	105.32	103.21	104.56	84.28	90.18	99.00	101.42	99.00	101.42	100.75	98.70
LDIH 03	87.28	90.88	78.35	83.14	83.89	87.70	87.35	87.42	78.46	79.04	89.14	88.11
LDIH 04	84.55	90.16	84.07	87.33	89.00	88.82	84.58	91.33	86.26	87.74	88.82	97.58
LDIH 05	96.02	94.82	84.46	85.18	80.96	95.19	87.16	90.74	85.88	80.47	82.04	85.72
LDIH 06	98.54	101.95	98.54	96.07	100.33	95.88	117.21	121.42	95.16	95.16	89.86	90.44
LDIH 07	95.58	95.30	73.44	78.30	72.70	75.54	77.72	76.70	84.84	82.39	80.93	85.74
LDIH 08	92.14	93.09	93.53	94.88	93.68	98.12	85.21	79.93	95.05	98.56	103.18	99.60
LDIH 09	78.98	79.86	82.74	86.42	86.35	89.51	86.88	90.02	85.25	80.95	96.19	100.67

Heart rate (HR) during the first (H_1) and last (H_2) 5 minutes of hypoxic exposure to SDIH and LDIH. Values are 3-minute averages of the end of each 5-minute period.

	HR (bpm)											
Day	1		3		5		8		10		12	
HVR	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2
SDIH 01	75.47	76.83	66.34	71.05	72.00	69.84	62.89	63.58	64.95	66.24	70.68	68.53
SDIH 02	80.15	81.47	83.76	80.86	95.11	90.05	78.37	79.47	89.84	89.84	95.63	95.05
SDIH 03	65.79	60.21	62.05	68.00	74.00	77.37	72.05	77.32	74.42	68.26	75.79	71.89
SDIH 04	70.21	94.21	82.32	79.11	74.00	78.68	71.05	73.63	68.95	74.16	64.68	61.58
SDIH 05	68.89	68.63	70.07	74.84	80.63	79.32	83.11	89.53	74.00	73.32	72.79	70.05
SDIH 06	89.74	89.16	81.32	119.05	86.95	87.47	75.74	77.42	81.32	77.68	78.26	80.74
SDIH 07	50.84	42.84	50.16	41.37	44.74	53.32	55.89	52.95	60.68	55.11	50.37	72.74
SDIH 08	42.95	49.32	42.89	51.53	44.89	52.89	43.47	48.53	51.79	51.68	56.00	52.05
SDIH 09	68.95	77.68	64.37	67.05	67.32	68.74	69.26	69.42	62.00	68.00	62.00	64.95
LDIH 01	77.81	81.70	88.49	83.73	79.68	87.63	101.11	98.63	85.32	89.63	92.21	96.47
LDIH 02	77.84	76.16	78.37	75.11	81.29	83.89	72.47	82.05	72.47	82.05	73.37	71.68
LDIH 03	67.79	65.42	53.95	54.63	63.37	59.68	63.84	67.84	67.16	64.14	61.00	59.26
LDIH 04	66.11	68.53	64.74	62.79	70.11	75.74	63.26	62.68	62.63	70.00	76.89	75.37
LDIH 05	74.00	83.84	73.53	72.79	65.79	73.05	67.68	70.00	79.05	78.16	80.11	83.00
LDIH 06	62.84	62.74	69.26	65.26	65.32	66.26	59.74	65.26	71.16	72.32	74.11	69.63
LDIH 07	92.79	92.79	72.95	70.89	79.37	77.58	76.58	79.11	110.58	116.26	85.53	91.37
LDIH 08	64.89	61.84	61.58	63.68	51.21	51.37	58.42	57.21	74.00	77.00	66.11	62.63
LDIH 09	71.89	71.63	82.37	86.42	75.16	76.05	80.53	80.53	83.11	85.00	78.47	85.16

Cerebral tissue oxygen saturation (ScO_2) during the first (H_1) and last (H_2) 5 minutes of hypoxic exposure to SDIH and LDIH. Values are 3-minute averages of the end of each 5-minute period.

	ScO_2 (%)											
Day	1		3		5		8		10		12	
HVR	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2
SDIH 01	70.3	68.4	67.0	70.8	64.8	66.9	63.0	64.9	64.1	67.5	80.1	83.4
SDIH 02	61.1	66.4	65.2	64.2	67.5	68.5	61.7	64.5	65.2	66.7	65.7	66.1
SDIH 03	64.2	64.1	64.7	66.2	64.1	65.3	66.1	66.0	70.6	73.8	68.0	68.4
SDIH 04	67.9	64.5	65.8	63.3	66.7	66.7	67.0	66.1	66.7	66.3	68.5	66.9
SDIH 05	79.5	81.7	74.5	81.8	66.4	67.3	63.9	65.2	79.5	79.7	60.9	59.6
SDIH 06	67.9	67.3	64.8	66.8	69.5	71.5	65.3	66.3	63.9	63.6	64.8	66.1
SDIH 07	64.6	62.6	58.3	60.3	62.5	64.8	65.8	64.6	69.9	70.3	67.5	67.0
SDIH 08	73.5	73.4	73.5	75.0	77.4	78.9	77.4	78.9	73.5	73.8	72.9	73.7
SDIH 09	61.8	60.1	54.2	54.4	58.6	61.0	55.7	54.6	59.6	59.9	61.9	61.7
LDIH 01	61.8	60.5	64.5	62.5	64.7	59.9	66.1	66.3	63.2	62.3	66.7	61.8
LDIH 02	70.9	68.2	70.2	68.7	68.4	67.9	67.2	66.6	63.6	62.0	66.0	65.8
LDIH 03	63.8	61.7	60.4	57.5	60.3	57.8	61.2	54.4	64.5	60.1	65.7	62.4
LDIH 04	58.4	55.5	60.0	59.7	61.4	58.7	63.4	62.7	52.9	46.3	51.8	50.5
LDIH 05	52.1	46.5	48.7	43.3	52.9	52.6	59.8	56.8	56.4	50.4	58.3	51.4
LDIH 06	72.0	72.3	68.2	66.0	70.8	70.1	67.1	67.5	65.8	64.3	70.9	68.9
LDIH 07	68.4	65.3	60.9	59.3	61.9	61.9	61.5	61.0	63.0	58.9	57.0	58.8
LDIH 08	65.1	62.9	66.3	63.2	65.0	63.0	69.5	66.5	68.4	67.2	66.3	63.2
LDIH 09	73.0	70.5	61.8	60.9	66.7	65.4	69.3	66.7	63.1	60.2	70.0	69.0

Arterial oxygen saturation (SaO_2) during the first (H_1) and last (H_2) 5 minutes of hypoxic exposure to SDIH and LDIH. Values are 3-minute averages of the end of each 5-minute period.

	SaO_2 (%)											
Day	1		3		5		8		10		12	
HVR	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2	H_1	H_2
SDIH 01	93.8	90.8	93.5	94.5	93.6	94.3	91.1	93.6	91.2	94.9	93.8	94.9
SDIH 02	81.8	89.2	96.5	92.9	93.9	91.5	87.9	90.6	94.1	94.0	90.3	89.7
SDIH 03	91.4	90.9	92.6	89.1	93.4	90.6	93.3	90.5	91.8	95.1	91.6	90.3
SDIH 04	92.3	91.7	87.4	82.1	88.4	88.4	89.4	89.0	89.6	90.0	90.1	90.4
SDIH 05	93.4	77.8	91.2	91.1	90.4	88.8	91.5	88.7	93.2	89.3	92.1	90.8
SDIH 06	91.3	91.4	89.5	90.5	93.3	94.3	91.7	92.6	93.8	92.2	92.2	93.4
SDIH 07	92.6	91.9	94.3	93.7	92.4	93.1	93.4	92.1	94.0	94.5	94.5	95.5
SDIH 08	93.2	93.8	92.9	92.3	93.1	93.6	94.8	95.5	93.0	92.9	90.5	91.9
SDIH 09	93.0	92.0	91.7	90.7	90.2	92.2	91.4	90.4	91.9	91.5	93.0	93.0
LDIH 01	89.5	86.7	88.3	84.1	88.8	80.2	88.6	88.8	90.2	86.1	90.5	82.7
LDIH 02	94.7	91.0	93.6	88.3	93.4	88.8	94.5	91.6	91.1	84.8	94.0	93.7
LDIH 03	89.0	87.6	94.8	88.1	92.8	89.2	90.8	80.4	89.0	81.3	90.1	80.5
LDIH 04	90.0	87.5	88.9	88.5	88.8	81.7	93.0	90.8	92.0	82.0	91.3	89.5
LDIH 05	88.2	71.9	88.0	80.3	89.2	86.8	95.0	91.8	91.2	83.2	91.4	82.8
LDIH 06	93.4	93.6	93.5	88.9	93.1	90.5	92.7	91.6	90.5	85.9	92.0	88.5
LDIH 07	91.6	87.4	91.6	90.2	91.0	90.5	91.6	91.2	88.8	85.1	90.4	88.9
LDIH 08	92.2	89.2	90.4	85.9	92.6	90.3	93.1	90.2	91.6	89.2	92.4	90.0
LDIH 09	91.4	88.5	90.6	87.4	91.8	87.4	90.6	85.3	90.9	85.2	92.2	89.5

REFERENCES

AINSLIE PN, KOLB JC, IDE K & POULIN MJ. (2003). Effects of five nights of normobaric hypoxia on the ventilatory responses to acute hypoxia and hypercapnia. *Respiratory Physiology and Neurobiology* **138**, 193-204.

ALTAY T, GONZALES ER, PARK TS & GIDDAY JM. (2004). Cerebrovascular inflammation after brief episodic hypoxia: modulation by neuronal and endothelial nitric oxide synthase. *Journal of Applied Physiology* **96**, 1223-1230.

AMERICAN THORACIC SOCIETY. (1995). Standardization of Spirometry. *American Journal of Respiratory and Critical Care Medicine* **152**, 1107-1136.

ANDERSSON JP, LINER MH, RUNOW E & SCHAGATAY EK. (2002). Diving response and arterial oxygen saturation during apnea and exercise in breath-hold divers. *Journal of Applied Physiology* **93**, 882-886.

BEIDLEMAN BA, MUZA SR, FULCO CS, CYMERMAN A, DITZLER D, STULZ D, STAAB JE, SKRINAR GS, LEWIS SF & SAWKA MN. (2004). Intermittent altitude exposures reduce acute mountain sickness at 4300 m. *Clinical Science (London)* **106**, 321-328.

BEIDLEMAN BA, ROCK PB, MUZA SR, FULCO CS, FORTE VA, JR. & CYMERMAN A. (1999). Exercise VE and physical performance at altitude are not affected by menstrual cycle phase. *Journal of Applied Physiology* **86**, 1519-1526.

BERNARDI L, PASSINO C, SEREBROVSKAYA Z, SEREBROVSKAYA TV & APPENZELLER O. (2001). Respiratory and Cardiovascular adaptations to progressive hypoxia. *European Heart Journal* **22**, 879-886.

BLAUW GJ, WESTENDORP RG, SIMONS M, CHANG PC, FROLICH M & MEINDERS AE. (1995). beta-Adrenergic receptors contribute to hypoxaemia induced vasodilation in man. *British Journal of Clinical Pharmacology* **40**, 453-458.

BYRNE-QUINN E, WEIL JV, SODAL IE, FILLEY GF & GROVER RF. (1971). Ventilatory control in the athlete. *Journal of Applied Physiology* **30**, 91-98.

CUTLER MJ, SWIFT NM, KELLER DM, WASMUD WL & SMITH ML. (2004). Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea. *Journal of Applied Physiology* **96**, 754-761.

DALY MDB. (1997). Peripheral arterial chemoreceptors and respiratory-cardiovascular integration. *Monographs of the Physiological Society* **46**.

DELAPILLE P, VERIN E, TOURNY-CHOLLET C & PASQUIS P. (2001). Ventilatory responses to hypercapnia in divers and non-divers: effects of posture and immersion. *European Journal of Applied Physiology* **86**, 97-103.

DERCHAK PA, STAGER JM, TANNER DA & CHAPMAN RF. (2000). Expiratory flow limitation confounds ventilatory response during exercise in athletes. *Medicine and Science in Sports and Exercise* **32**, 1873-1879.

DOHERTY JU & LIANG CS. (1984). Arterial hypoxemia in awake dogs. Role of the sympathetic nervous system in mediating the systemic hemodynamic and regional blood flow responses. *Journal of Laboratory and Clinical Medicine* **104**, 665-677.

DUFFIN J & MAHAMED S. (2003). Adaptation in the respiratory control system. *Canadian Journal of Applied Physiology and Pharmacology* **81**, 765-773.

EARLEY S & WALKER BR. (2002). Endothelium-dependent blunting of myogenic responsiveness after chronic hypoxia. *American Journal of Physiology* **283**, H2202-2209.

EASTON PA, SLYKERMAN LJ & ANTHONISEN NR. (1986). Ventilatory response to sustained hypoxia in normal adults. *Journal of Applied Physiology* **61**, 906-911.

EASTON PA, SLYKERMAN LJ & ANTHONISEN NR. (1988). Recovery of the ventilatory response to hypoxia in normal adults. *Journal of Applied Physiology* **64**, 521-528.

FAHLMAN A, JACKSON S, TERBLANCHE J, FISHER JA, VESELY A, SASANO H & MYBURGH KH. (2002). A simple breathing circuit to maintain isocapnia during measurements of the hypoxic ventilatory response. *Respiratory Physiology Neurobiology* **133**, 259-270.

FERRETTI G. (2001). Extreme human breath-hold diving. *European Journal of Applied Physiology* **84**, 254-271.

FLETCHER EC. (2001). Invited review: Physiological consequences of intermittent hypoxia: systemic blood pressure. *Journal of Applied Physiology* **90**, 1600-1605.

FLETCHER EC, LESSKE J, BEHM R, MILLER CC, 3RD, STAUSS H & UNGER T. (1992). Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. *Journal of Applied Physiology* **72**, 1978-1984.

TASK FORCE OF THE EUROPEAN SOCIETY OF CARDIOLOGY AND THE NORTH AMERICAN SOCIETY OF PACING AND ELECTROPHYSIOLOGY. (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* **93**, 1043-1065.

GARCIA-RIO F, PINO J, RAMIREZ T, ALVARO D, ALONSO A, VILLASANTE C & VILLAMOR J. (2002). Inspiratory neural drive response to hypoxia adequately estimates peripheral chemosensitivity in OSAHS patients. *European Respiratory Journal* **20**, 724-732.

GARCIA N, HOPKINS SR, ELLIOTT AR, AARON EA, WEIGNER MB & POWELL FL. (2000). Ventilatory response to 2-h sustained hypoxia in humans. *Respiration Physiology* **124**, 11-22.

GARCIA N, HOPKINS SR & POWELL FL. (2000). Effects of intermittent hypoxia on the isocapnic hypoxic ventilatory response and erythropoiesis in humans. *Respiration Physiology* **123**, 39-49.

GARCIA N, HOPKINS SR & POWELL FL. (2000). Intermittent vs continuous hypoxia: effects on ventilation and erythropoiesis in humans. *Wilderness and Environmental Medicine* **11**, 172-179.

GONZALES RJ & WALKER BR. (2002). Role of CO in attenuated vasoconstrictor reactivity of mesenteric resistance arteries after chronic hypoxia. *American Journal of Physiology* **282**, H30-37.

GOZAL E & GOZAL D. (2001). Respiratory plasticity following intermittent hypoxia: developmental interactions. *Journal of Applied Physiology* **90**, 1995-1999.

GRASSI B, FERRETTI G, COSTA M, FERRIGNO M, PANZACCHI A, LUNDGREN CE, MARCONI C & CERRETELLI P. (1994). Ventilatory responses to hypercapnia and hypoxia in elite breath-hold divers. *Respiration Physiology* **97**, 323-332.

GREENBERG HE, SICA A, BATSON D & SCHARF SM. (1999). Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. *Journal of Applied Physiology* **86**, 298-305.

GROSS PM, WHIPP BJ, DAVIDSON JT, KOYAL SN & WASSERMAN K. (1976). Role of the carotid bodies in the heart rate response to breath holding in man. *Journal of Applied Physiology* **41**, 336-340.

GUENETTE JA, DIEP TT, KOEHLE MS, FOSTER GE, RICHARDS JC & SHEEL AW. (2004). Acute hypoxic ventilatory response and exercise-induced arterial hypoxemia in men and women. *Respiratory Physiology and Neurobiology* **143**, 37-48.

HARMS CA & STAGER JM. (1995). Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. *Journal of Applied Physiology* **79**, 575-580.

HARMS MP, VAN LIESHOUT JJ, JENSTRUP M, POTT F & SECHER NH. (2003). Postural effects on cardiac output and mixed venous oxygen saturation in humans. *Experimental Physiology* **88**, 611-616.

HARMS MP, WESSELING KH, POTT F, JENSTRUP M, VAN GOUDOEVER J, SECHER NH & VAN LIESHOUT JJ. (1999). Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clinical Science (London)* **97**, 291-301.

HIRSCHL MM, BINDER M, GWECHENBERGER M, HERKNER H, BUR A, KITTLER H & LAGGNER AN. (1997). Non-invasive assessment of cardiac output in critically ill patients by analysis of the finger blood pressure waveform. *Critical Care Medicine* **25**, 1909-1914.

HONDA Y, HASHIZUME I, KIMURA H & SEVERINGHUAS JW. (1988). Bilateral carotid body resection in man enhances hypoxic tachycardia. *Japanese Journal of Physiology* **38**, 917-928.

HOUTMAN S, OESEBURG B & HOPMAN MT. (1999). Non-invasive cardiac output assessment during moderate exercise: pulse contour compared with CO2 rebreathing. *Clinical Physiology* **19**, 230-237.

INSALACO G, ROMANO S, SALVAGGIO A, BRAGHIROLI A, LANFRANCHI P, PATRUNO V, DONNER CF & BONSIGNORE G. (1996). Cardiovascular and ventilatory response to isocapnic hypoxia at sea level and at 5,050 m. *Journal of Applied Physiology* **80**, 1724-1730.

JANSEN JR, SCHREUDER JJ, MULIER JP, SMITH NT, SETTELS JJ & WESSELING KH. (2001). A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *British Journal of Anesthesiology* **87**, 212-222.

JELLEMA WT, WESSELING KH, GROENEVELD AB, STOUTENBEEK CP, THIJS LG & VAN LIESHOUT JJ. (1999). Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* **90**, 1317-1328.

JENSEN JB, SPERLING B, SEVERINGHAUS JW & LASSEN NA. (1996). Augmented hypoxic cerebral vasodilation in men during 5 days at 3,810 m altitude. *Journal of Applied Physiology* **80**, 1214-1218.

JERNIGAN NL & RESTA TC. (2002). Chronic hypoxia attenuates cGMP-dependent pulmonary vasodilation. *American Journal of Physiology* **282**, L1366-1375.

JORDAN AS, CATCHESIDE PG, O'DONOGHUE FJ & MCEVOY RD. (2002). Long-term facilitation of ventilation is not present during wakefulness in healthy men or women. *Journal of Applied Physiology* **93**, 2129-2136.

KATAYAMA K, MATSUO H, ISHIDA K, MORI S & MIYAMURA M. (2003). Intermittent hypoxia improves endurance performance and submaximal exercise efficiency. *High Altitude Medicine and Biology* **4**, 291-304.

KATAYAMA K, SATO K, MATSUO H, ISHIDA K, IWASAKI K & MIYAMURA M. (2004). Effect of intermittent hypoxia on oxygen uptake during submaximal exercise in endurance athletes. *European Journal of Applied Physiology* **92**, 75-83.

KATAYAMA K, SATO Y, ISHIDA K, MORI S & MIYAMURA M. (1998). The effects of intermittent exposure to hypoxia during endurance exercise training on the ventilatory responses to hypoxia and hypercapnia in humans. *European Journal of Applied Physiology* **78**, 189-194.

KATAYAMA K, SATO Y, MOROTOME Y, SHIMA N, ISHIDA K, MORI S & MIYAMURA M. (1999). Ventilatory chemosensitive adaptations to intermittent hypoxic exposure with endurance training and detraining. *Journal of Applied Physiology* **86**, 1805-1811.

KATAYAMA K, SATO Y, MOROTOME Y, SHIMA N, ISHIDA K, MORI S & MIYAMURA M. (2001). Intermittent hypoxia increases ventilation and SaO_2 during hypoxic exercise and hypoxic chemosensitivity. *Journal of Applied Physiology* **90**, 1431-1440.

KATAYAMA K, SATO Y, SHIMA N, QIU JC, ISHIDA K, MORI S & MIYAMURA M. (2002). Enhanced chemosensitivity after intermittent hypoxic exposure does not affect exercise ventilation at sea level. *European Journal of Applied Physiology* **87**, 187-191.

KATAYAMA K, SHIMA N, SATO Y, QIU JC, ISHIDA K, MORI S & MIYAMURA M. (2001). Effect of intermittent hypoxia on cardiovascular adaptations and response to progressive hypoxia in humans. *High Altitude Medicine and Biology* **2**, 501-508.

KOEHLE MS, FOSTER GE, MCKENZIE DC & SHEEL AW. (In Press). Repeated measurement of hypoxic ventilatory response as an intermittent hypoxic stimulus. *Respiratory Physiology and Neurobiology*.

KOLB JC, AINSLIE PN, IDE K & POULIN MJ. (2004). Effects of five consecutive nocturnal hypoxic exposures on the cerebrovascular responses to acute hypoxia and hypercapnia in humans. *Journal of Applied Physiology* **96**, 1745-1754.

LEVINE BD, FRIEDMAN DB, ENGFRED K, HANEL B, KJAER M, CLIFFORD PS & SECHER NH. (1992). The effect of normoxic or hypobaric hypoxic endurance training on the hypoxic ventilatory response. *Medicine and Science in Sports and Exercise* **24**, 769-775.

LINDHOLM P, SUNDBLAD P & LINNARSSON D. (1999). Oxygen-conserving effects of apnea in exercising men. *Journal of Applied Physiology* **87**, 2122-2127.

LONG W, LOBCHUK D & ANTHONISEN NR. (1994). Ventilatory responses to CO2 and hypoxia after sustained hypoxia in awake cats. *Journal of Applied Physiology* **76**, 2262-2266.

MACDONALD ML, KIRBY RL, NUGENT ST & MACLEOD DA. (1992). Locomotor-respiratory coupling during wheelchair propulsion. *Journal of Applied Physiology* **72**, 1375-1379.

MADSEN PL & SECHER NH. (1999). Near-infrared oximetry of the brain. *Progress in Neurobiology* **58**, 541-560.

MAHAMED S & DUFFIN J. (2001). Repeated hypoxic exposures change respiratory chemoreflex control in humans. *Journal of Physiology (London)* **534**, 595-603.

MAHLER DA, MORITZ ED & LOKE J. (1982). Ventilatory responses at rest and during exercise in marathon runners. *Journal of Applied Physiology* **52**, 388-392.

MARTIN BJ, SPARKS KE, ZWILLICH CW & WEIL JV. (1979). Low exercise ventilation in endurance athletes. *Medicine and Science in Sports* **11**, 181-185.

MASUDA Y, YOSHIDA A, HAYASHI F, SASAKI K & HONDA Y. (1981). The ventilatory responses to hypoxia and hypercapnia in the Ama. *Japanese Journal of Physiology* **31**, 187-197.

MATEIKA JH, MENDELLO C, OBEID D & BADR MS. (2004). Peripheral chemoreflex responsiveness is increased at elevated levels of carbon dioxide after episodic hypoxia in awake humans. *Journal of Applied Physiology* **96**, 1197-1205.

McCLEAN PA, PHILLIPSON EA, MARTINEZ D & ZAMEL N. (1988). Single breath of CO_2 as a clinical test of the peripheral chemoreflex. *Journal of Applied Physiology* **64**, 84-89.

McEVOY RD, POPOVIC RM, SAUNDERS NA & WHITE DP. (1996). Effects of sustained and repetitive isocapnic hypoxia on ventilation and genioglossal and diaphragmatic EMGs. *Journal of Applied Physiology* **81**, 866-875.

MITCHELL GS, BAKER TL, NANDA SA, FULLER DD, ZABKA AG, HODGEMAN BA, BAVIS RW, MACK KJ & OLSON EB, JR. (2001). Invited review: Intermittent hypoxia and respiratory plasticity. *Journal of Applied Physiology* **90**, 2466-2475.

MITCHELL GS & JOHNSON SM. (2003). Neuroplasticity in respiratory motor control. *Journal of Applied Physiology* **94**, 358-374.

MIYAMURA M & ISHIDA K. (1990). Adaptive changes in hypercapnic ventilatory response during training and detraining. *European Journal of Applied Physiology* **60**, 353-359.

MOHAN R & DUFFIN J. (1997). The effect of hypoxia on the ventilatory response to carbon dioxide in man. *Respiration Physiology* **108**, 101-115.

MOHAN RM, AMARA CE, CUNNINGHAM DA & DUFFIN J. (1999). Measuring central-chemoreflex sensitivity in man: rebreathing and steady-state methods compared. *Respiration Physiology* **115**, 23-33.

MORGAN BJ, CRABTREE DC, PALTA M & SKATRUD JB. (1995). Combined hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. *Journal of Applied Physiology* **79**, 205-213.

MORGAN BJ & JOYNER MJ. (2002). Sleep apnea: a new 'risk factor' for cardiovascular disease? *Exercise and Sport Science Reviews* **30**, 145-146.

MORRIS KF, BAEKEY DM, NUDING SC, DICK TE, SHANNON R & LINDSEY BG. (2003). Invited review: Neural network plasticity in respiratory control. *Journal of Applied Physiology* **94**, 1242-1252.

NEUBAUER JA. (2001). Physiological and pathophysiological responses to intermittent hypoxia. *Journal of Applied Physiology* **90**, 1593-1599.

NIEMINEN T, KOOBI T & TURJANMAA V. (2000). Can stroke volume and cardiac output be determined reliably in a tilt-table test using the pulse contour method? *Clinical Physiology* **20**, 488-495.

PENG Y-J & PRABHAKAR NR. (2004). Effect of two paradigms of chronic intermittent hypoxia on carotid body sensory activity. *Journal of Applied Physiology* **96**, 1236-1242.

PENG Y, KLINE DD, DICK TE & PRABHAKAR NR. (2001). Chronic intermittent hypoxia enhances carotid body chemoreceptor response to low oxygen. *Advances in Experimental Medicine and Biology* **499**, 33-38.

PHILLIPS SA, OLSON EB, MORGAN BJ & LOMBARD JH. (2004). Chronic intermittent hypoxia impairs endothelium-dependent dilation in rat cerebral and skeletal muscle resistance arteries. *American Journal of Physiology* **286**, H388-H393.

POWELL FL & GARCIA N. (2000). Physiological Effects of Intermittent Hypoxia. *High Altitude Medicine and Biology* **1**, 125-135.

POWELL FL, MILSOM WK & MITCHELL GS. (1998). Time domains of the hypoxic ventilatory response. *Respiration Physiology* **112**, 123-134.

PRABHAKAR NR. (2001). Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. *Journal of Applied Physiology* **90**, 1986-1994.

PRABHAKAR NR, FIELDS RD, BAKER T & FLETCHER EC. (2001). Intermittent hypoxia: cell to system. *American Journal of Physiology* **281**, L524-528.

PRABHAKAR NR & KLINE DD. (2002). Ventilatory changes during intermittent hypoxia: importance of pattern and duration. *High Altitude Medicine and Biology* **3**, 195-204.

QUANJER PH, TAMMELING GJ, COTES JE, PEDERSEN OF, PESLIN R & YERNAULT JC. (1993). Lung volumes and forced ventilatory flows. Official statement of the European Respiratory Society. *European Respiratory Journal* **6**, 5-40.

READ DJ. (1967). A clinical method for assessing the ventilatory response to carbon dioxide. *Australian Annals of Medicine* **16**, 20-32.

REBUCK AS. (1976). Measurement of ventilatory response to CO2 by rebreathing. *Chest* **70**, 118-121.

REMMEN JJ, AENGEVAEREN WR, VERHEUGT FW, VAN VER WERF T, LUIJTEN HE, BOS A & JANSEN RW. (2002). Finapres arterial pulse wave analysis with Modelflow is not a reliable non-invasive method for assessment of cardiac output. *Clinical Science (London)* **103**, 143-149.

REY S, DEL RIO R, ALCAYAGA J & ITURRIAGA R. (2004). Chronic intermittent hypoxia enhances cat chemosensory and ventilatory responses to hypoxia. *Journal of Physiology (London)* **560**, 583-592.

SAHN SA, ZWILLICH CW, DICK N, MCCULLOUGH RE, LAKSHMINARAYAN S & WEIL JV. (1977). Variability of ventilatory responses to hypoxia and hypercapnia. *Journal of Applied Physiology* **43**, 1019-1025.

SATO M, SEVERINGHAUS JW & BICKLER P. (1994). Time course of augmentation and depression of hypoxic ventilatory responses at altitude. *Journal of Applied Physiology* **77**, 313-316.

SATO M, SEVERINGHAUS JW, POWELL FL, XU FD & SPELLMAN MJ, JR. (1992). Augmented hypoxic ventilatory response in men at altitude. *Journal of Applied Physiology* **73**, 101-107.

SEMENZA GL. (1999). Perspectives on oxygen sensing. *Cell* **98**, 281-284.

SEREBROVSKAYA TV, KARABAN IN, KOLESNIKOVA EE, MISHUNINA TM, KUZMINSKAYA LA, SERBROVSKY AN & SWANSON RJ. (1999). Human hypoxic ventilatory response with blood dopamine content under intermittent hypoxic training. *Canadian Journal of Physiology and Pharmacology* **77**, 967-973.

SMITH ML & MUENTER NK. (2000). Effects of hypoxia on sympathetic neural control in humans. *Respiration Physiology* **121**, 163-171.

TANSLEY JG, FATEMIAN M, HOWARD LS, POULIN MJ & ROBBINS PA. (1998). Changes in respiratory control during and after 48 h of isocapnic and poikilocapnic hypoxia in humans. *Journal of Applied Physiology* **85**, 2125-2134.

TIMMERS HJ, KAREMAKER JM, WIELING W, MARRES HA, FOLGERING HT & LENDERS JW. (2003). Baroreflex and chemoreflex function after bilateral carotid body tumor resection. *Journal of Hypertension* **21**, 591-599.

VAN DER ZEE P, COPE M, ARRIDGE SR, ESSENPREIS M, POTTER LA, EDWARDS AD, WYATT JS, MCCORMICK DC, ROTH SC, REYNOLDS EO & ET AL. (1992). Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of inter optode spacing. *Advances in Experimental Medicine and Biology* **316**, 143-153.

VAN LIESHOUT JJ, TOSKA K, VAN LIESHOUT EJ, ERIKSEN M, WALLOE L & WESSELING KH. (2003). Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *European Journal of Applied Physiology* **90**, 131-137.

VAN LIESHOUT JJ & WESSELING KH. (2001). Continuous cardiac output by pulse contour analysis? *British Journal of Anesthesiology* **86**, 467-469.

VOVK A, CUNNINGHAM DA, KOWALCHUK JM, PATERSON DH & DUFFIN J. (2002). Cerebral blood flow responses to changes in oxygen and carbon dioxide in humans. *Canadian Journal of Physiology and Pharmacology* **80**, 819-827.

WEIL JV, BYRNE-QUINN E, SODAL IE, FRIESEN WO, UNDERHILL B, FILLEY GF & GROVER RF. (1970). Hypoxic ventilatory drive in normal man. *Journal of Clinical Investigations* **49**, 1061-1072.

WESSELING KH, JANSEN JR, SETTELS JJ & SCHREUDER JJ. (1993). Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *Journal of Applied Physiology* **74**, 2566-2573.

XIE A, SKATRUD JB, CRABTREE DC, PULEO DS, GOODMAN BM & MORGAN BJ. (2000). Neurocirculatory consequences of intermittent asphyxia in humans. *Journal of Applied Physiology* **89**, 1333-1339.

XIE A, SKATRUD JB, PULEO DS & MORGAN BJ. (2001). Exposure to hypoxia produces long-lasting sympathetic activation in humans. *Journal of Applied Physiology* **91**, 1555-1562.

YASUMA F & HAYANO JI. (2000). Impact of acute hypoxia on heart rate and blood pressure variability in conscious dogs. *American Journal of Physiology* **279**, H2344-2349.

ZHANG S & ROBBINS PA. (2000). Methodological and physiological variability within the ventilatory response to hypoxia in humans. *Journal of Applied Physiology* **88**, 1924-1932.