Two patterns of daily hypoxic exposure and their effects on measures of chemosensitivity in humans

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Koehle MS, Sheel AW, Milsom WK, McKenzie DC. Two patterns of daily hypoxic exposure and their effects on measures of chemosensitivity in humans. J Appl Physiol 103: 1973–1978, 2007. First published October 18, 2007; doi:10.1152/japplphysiol.00545.2007.—The purpose of this study was to compare chemoresponses following two different intermittent hypoxia (IH) protocols in humans. Ten men underwent two 7-day courses of poikilocapnic IH. The long-duration IH (LDIH) protocol consisted of daily 60-min exposures to normobaric 12% O2. The short-duration IH (SDIH) protocol comprised twelve 5-min bouts of 12% O2, separated by 5-min bouts of room air, daily. Isocapnic hypoxic ventilatory response (HVR) was measured daily during the protocol and 1 and 7 days following. Hypercapnic ventilatory response (HCVR) and CO2 threshold and sensitivity (by the modified Read rebreathing technique) were measured on days 1, 8, and 14. Following 7 days of IH, the mean HVR was significantly increased from 0.47 ± 0.07 and 0.47 ± 0.08 to 0.70 ± 0.06 and 0.79 ± 0.06 l·min⁻¹·%SaO2⁻¹ (LDIH and SDIH, respectively), where %SaO2 is percent arterial oxygen saturation. The increase in HVR reached a plateau after the third day. One week post-IH, HVR values were unchanged from baseline. HCVR increased from 3.0 ± 0.4 to 4.0 ± 0.5 l·min⁻¹·mmHg⁻¹. In both the hypoxic and hypoxic modified Read rebreathing tests, the slope of the CO2/ventilation plot was unchanged by either intervention, but the CO2/ventilation curve shifted to the left following IH. There were no correlations between the changes in response to hypoxia and hypercapnia. There were no significant differences between the two IH protocols for any measures, indicating that comparable changes in chemoreflex control occur with either protocol. These results also suggest that the two methods of measuring CO2 response are not completely concordant and that the changes in CO2 control do not correlate with the increase in the HVR.

Furthermore, there are multiple methods by which CO2 response is measured. With differences in both protocol and measurement between studies, it is impossible to determine whether differences are due to the protocol or the measurement method. To understand the differences between the various means of determining CO2 response, a study looking at response to intermittent hypoxia using more than one measurement of CO2 response is necessary.

The CO2 threshold is the partial pressure of CO2 below which there is no ventilatory response to an increase in CO2 (8). Some investigators have posited that a lowering of this threshold causes an increase in ventilation for a constant level of hypoxia, thus explaining the enhanced ventilation in hypoxia following IH (23). To test this hypothesis it is necessary to measure HVR and CO2 threshold in the same study.

In animals there is some evidence that multiple brief bouts of hypoxia per day may be more efficacious than a single continuous daily bout. Animals exposed to episodic hypoxia exhibit a sustained increase in respiratory motor output that is not evident following sustained hypoxia (26). Peng and Prabhakar (28) demonstrated in rodents following IH that multiple shorter durations of IH (SDIH) caused larger increases in chemoreceptor output than longer durations of IH (LDIH). They concluded that the transients from hypoxia to normoxia and back appear to be the stimulus for the upregulation in response to hypoxia through an increase in oxidative stress (28). It is unclear whether SDIH is more efficacious than LDIH in humans. Because of the amount of interindividual variability in these measures in humans, a randomized crossover design is necessary, with each subject undergoing both protocols. To assess the time course of the change in HVR, and thus determine the optimal duration of a given protocol for augmenting ventilation, daily measurements of HVR are required.

On the basis of the above brief summary, the purpose of this study was to examine the effect and time course of two different protocols of IH in the same individual on the resting response to both hypoxia and CO2 by a variety of methods. Our second purpose was to assess the contribution of alterations in CO2 chemosensitivity on the augmentation of ventilation following IH. We also hypothesized that SDIH would increase HVR more than LDIH. We hypothesized that IH would cause similar changes in CO2 sensitivity as measured by the HCVR and modified Read rebreathing methods and that there would be a close interaction between the changes in CO2 response and hypoxic ventilatory response.

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METHODS

The study was approved by the University Ethics Board and conformed to the Declaration of Helsinki. A nonblinded randomized crossover study design was used. Subjects were evaluated before, during, and following two intermittent hypoxia protocols: a SDIH and a LDIH protocol. Ten male subjects were recruited from the University population and the local mountaineering and endurance sports community. None of the subjects had been to significant altitude (>2,500 m) in the preceding year. All subjects were asked to come to the laboratory 19 times, totaling ~40 h each. These visits included one orientation visit, seven visits for SDIH exposure, seven visits for LDIH exposure, and four follow-up measurement sessions. On the initial visit, informed consent was obtained, followed by baseline spirometry and familiarization with the equipment. At least one HVR test and two modified Read rebreathing tests were performed to acquaint the subjects with the testing protocol and equipment.

Chemosensitivity testing procedures. Resting ventilatory tests were performed in a quiet environment with distractions minimized. Inspiratory flow was measured using a heated pneumotachometer (Hans-Rudolph, Kansas City, MO). Minute ventilation was calculated using the integrated flow signal and the frequency of breathing. Arterial O₂ saturation was measured using pulse oximetry at the finger (Criticare Systems model 504, Waukesha, WI). End-tidal CO₂ (PETO₂) and inspired O₂ concentrations were measured on a breath-by-breath basis using a CO₂ and an O₂ sensor (Applied Electrochemistry, Pittsburgh, PA).

HVR. The HVR testing protocol followed that used in previous studies in our laboratory (14, 21) and was based on an earlier method used in other facilities (3). Briefly, subjects breathed through a respiratory mask attached to a one-way nonrebreathing valve (Hans-Rudolph). Ventilatory and gas values were displayed in real time during testing (PowerLab, ADInstruments, Colorado Springs, CO). During the entire HVR test, subjects listened to quiet, ambient music through headphones. The subjects rested in a supine position while breathing room air for 5 min. The resting PETCO₂ was determined from the last minute of this rest period. The test started when 100% N2 was introduced into the inspired gas mixture. The flow of N2 increased at a rate of 1 l/min every 30 s. This protocol gradually lowered inspired O₂ concentration from 21% to ~5% over a period of 5 min. To maintain isocapnia, CO₂ was added to the inspired mixture using a manually controlled valve. The test ended once the arterial saturation reached 80%. Ventilation was then plotted against saturation, with the absolute value of the magnitude of the slope representing the HVR. Using a linear model, a best-fit slope was plotted by computer (Microsoft Excel 2000, Redmond, WA).

Rebreathing tests. Both the hypercapnic ventilatory response (HCVR) and modified Read rebreathing tests used a similar setup. Wearing nose clips, subjects breathed room air ad libitum through a three-way rebreathing valve (Hans-Rudolph) connected to a rebreathing bag. Ventilatory and gas values were displayed in real time during testing (LabVIEW 7.0, National Instruments, Austin, TX). Testing was terminated once PETCO₂ reached 60 mmHg, minute ventilation reached 100 l/min, or in the instance of subject discomfort.

The HCVR testing protocol was based on the protocol of Katayama et al. (16). The test involved no prior hyperventilation. Subjects rested in a seated position before their HCVR test for ~5 min. The rebreathing bag was filled with 7% CO₂, balance O₂. After reaching steady-state resting ventilation, subjects exhaled completely before they were switched over to the rebreathing bag. They took three large breaths to equilibrate the gas in their lungs with that in the bag. Subjects were then asked to breathe ad libitum. HCVR sensitivity was determined as the slope of minute ventilation (l/min) plotted against PETCO₂ (mmHg). The modified Read rebreathing testing protocol was based on the protocol of Read (29) as modified by Duffin (7, 27). At the start of each test, subjects hyperventilated for 5 min to reduce their PETCO₂ to between 19 and 25 mmHg. They were coached during this rebreathing period to maintain this desired PETCO₂. Subjects were then switched to the rebreathing bag that was filled with a mixture of 42 mmHg CO₂ and either 50 or 200 mmHg of oxygen (for the hypoxic and hyperoxic tests, respectively). The rebreathing bag was maintained iso-oxic using a computer-controlled valve (LabVIEW 7.0, National Instruments, Austin, TX) while PETCO₂ was allowed to progressively rise. The test was performed twice, with end-inspiratory O₂ pressures maintained at either 50 mmHg (hypoxic condition) or 150 mmHg (hyperoxic condition). Using specifically designed software, the data from each test were used to calculate CO₂ threshold and sensitivity.

This software fits a straight line to the CO₂/time relationship and derives a predicted CO₂ for each breath on the basis of this model. Ventilation is then plotted against this predicted CO₂, and a threshold and sensitivity are determined from this plot. Using the technique, one will often find that above the threshold, the CO₂/ventilation relationship can appear to consist of two segments (Fig. 1): the first one is more gradual and is mainly mediated through increases in tidal volume, whereas the second slope seems to be more frequency mediated (8). The sensitivity calculated using this software is for the first (lower) slope, while the second slope (if present) is not assessed.

IH exposures. The first task for the subjects on their second visit day was their IH exposure. Normobaric hypoxic gas (12% O₂, balance N₂) was provided by mask. End-tidal CO₂ was not controlled. For the LDIH protocol, subjects breathed the hypoxic gas for 60 min daily for 7 days. This protocol was chosen because it was the normobaric equivalent of that used in the study of Katayama et al. (17) that showed the increases in exercise ventilation during hypoxia. For the SDIH protocol, the subjects spent 115 min breathing from the mask each day. They alternated through 12 cycles of 5 min of hypoxia (simulated 4,400 m) followed by 5 min of normoxia. Subjects were then required to return to the lab for six additional IH sessions. These were identical to the session on the first day. Each IH exposure was preceded by measurement of isocapnic HVR.

Follow-up. The first day following the final IH protocol, the subjects returned for post-IH testing. This testing was exactly the same as the pretesting. It consisted of an isocapnic HVR test, an HCVR test, and two modified Read rebreathing tests (hypoxic and hyperoxic). One week following the completion of the first round of IH, subjects returned to the laboratory for 7-day post-IH testing. This session included HVR testing, an HCVR test, and two modified Read rebreathing tests. Subjects were given at least a 2-wk reprise between each arm of the study (range 14–96 days). Two weeks was chosen.
because previous studies had shown that the HVR remained somewhat elevated at 1 wk after IH (17), but not 2 wk post-IH (18). Pre- and posttesting was the same in both arms of the study; the only difference was the nature of the IH training (SDIH or LDIH).

Statistics. Each chemosensitivity test (HVR, HCVR, modified Read rebreathing) was performed at three time points (pre-, post-, and 7 days post-IH) using ANOVA with repeated measures over time and the IH protocol as an independent factor. Where the null hypothesis was rejected, Tukey’s honestly significant difference was calculated to determine the significant differences. Data are presented as means ± SE. Linear correlations were also performed between HVR and CO2 sensitivity by the HCVR and modified Read rebreathing methods. To calculate the time constant for the increase in HVR over time the following exponential model was used: $\text{HVR}(t) = \Delta\text{HVR}_{SS}(1 - e^{-\tau t})$, where $t$ is time in days, $\tau$ is the time constant, and $\Delta\text{HVR}_{SS}$ represents the difference between the HVR at baseline and the HVR at steady state. Statistical analysis was performed using computer software (SPSS, Chicago, IL); an $\alpha$ of 0.05 was used to determine statistical significance.

RESULTS

All 10 subjects completed all parts of the study. Anthropometric and spirometric data are presented in Table 1.

HVR. HVR results are presented in Fig. 2. The mean baseline HVR for both protocols was $0.47 ± 0.07$ and $0.47 ± 0.08 1\text{ min}^{-1} \cdot \%\text{SaO}_2^{-1}$ for LDIH and SDIH, respectively. After the 7-day IH protocols, the mean HVR was increased to $0.70 ± 0.06$ and $0.79 ± 0.06 1\text{ min}^{-1} \cdot \%\text{SaO}_2^{-1}$ (for LDIH and SDIH, respectively). These data represent significant increases of 67 and 49% ($P < 0.01$ and $P < 0.05$, for LDIH and SDIH, respectively). There was no difference between the two protocols ($P = 0.44$). After the third day, the mean HVR was significantly increased from the baseline and not significantly different from the final day of the protocol. Curve fitting derived time constants of 1.41 and 0.60 for LDIH and SDIH, respectively. When protocol order was examined (to assess for protocol order), the derived time constants of 1.41 and 0.60 for LDIH and SDIH, respectively. After the third day, the mean HVR was increased 0.70 ± 0.06 and 0.79 ± 0.06 for LDIH and SDIH, respectively.

HCVR. The HCVR was significantly increased by IH from $3.0 ± 0.4$ to $4.0 ± 0.5 1\text{ min}^{-1} \cdot \text{mmHg}^{-1}$ ($P < 0.01$). This value remained elevated at $3.8 ± 0.5 1\text{ min}^{-1} \cdot \text{mmHg}^{-1}$ at 7 days following IH ($P < 0.01$). When analyzed by protocol, the mean HCVR was increased significantly by the LDIH protocol by 44% ($P < 0.01$) and remained elevated by 42% at 7 days post-IH ($P < 0.01$). The changes following the SDIH protocol were smaller at 21% and 13% at 1 and 7 days post-IH, respectively. The increases following SDIH were not significant, nor were the differences between the two protocols. These data are presented in Fig. 3.

Modified Read rebreathing technique. In both the hypoxic and hypoxic modified Read rebreathing tests, the CO2-sensitivity was unchanged by both SDIH and LDIH. In hypoxia, the mean sensitivity was $5.2 ± 0.6 1\text{ min}^{-1} \cdot \text{mmHg}^{-1}$ pre-IH and $5.1 ± 0.4 1\text{ min}^{-1} \cdot \text{mmHg}^{-1}$ post-IH, while in hypoxia, the mean sensitivities were $3.4 ± 0.3 1\text{ min}^{-1} \cdot \text{mmHg}^{-1}$ pre-IH and $3.1 ± 0.3 1\text{ min}^{-1} \cdot \text{mmHg}^{-1}$ post-IH, respectively. In hypoxia, the CO2 threshold was significantly reduced following both protocols. There were no significant differences between the two protocols. These results are displayed in Figs. 4 and 5.

Table 1. Anthropometric and spirometric data (n = 10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>26.0±2.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177±3</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>72.8±4.4</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>5.8±0.22</td>
</tr>
<tr>
<td>%Predicted FVC</td>
<td>112.9±3.1</td>
</tr>
<tr>
<td>FEV1.0, liters</td>
<td>5.0±0.19</td>
</tr>
<tr>
<td>%Predicted FEV1.0</td>
<td>114±3</td>
</tr>
<tr>
<td>FEV/FVC, %</td>
<td>85.9±1.2</td>
</tr>
<tr>
<td>%Predicted FEV/FVC, %</td>
<td>101±1</td>
</tr>
</tbody>
</table>

Values are means ± SE. FVC, forced vital capacity; FEV1.0, forced expired volume in 1 s.

Fig. 2. Mean (±SE) hypoxic ventilatory response (HVR) vs. time. LDIH, long-duration intermittent hypoxia; SDIH, short-duration intermittent hypoxia; %SaO2, %arterial oxygen saturation. *Significantly different from pre-IH value ($P < 0.05$).

Fig. 3. Mean (±SE) hypercapnic ventilatory response vs. time. Pre-, pre-IH, Post-, post-IH. 7 Days Post-, 7 days post-IH. *Significantly different from Pre-value ($P < 0.05$).
and hyperoxic conditions, respectively). Second, when the change in HVR was compared with the change in CO2 threshold by the modified Read rebreathing technique, no significant correlations were found ($r = -0.058$ and 0.091). HCVR was significantly correlated with CO2 sensitivity by the hyperoxic modified Read rebreathing method ($r = 0.422; P = 0.03$).

**DISCUSSION**

There are three main findings of this study. First, we observed significant increases in HVR following 7 consecutive days of hypoxia in humans. The increase in HVR was similar between SDIH and LDIH and reached a plateau following the third day of the protocol. Second, significant decreases in the CO2 threshold in both hyperoxia and hypoxia were observed following both protocols. Finally, following IH we observed a transient increase in HCVR. Collectively, our findings point to a consistent change in human chemoreflex ventilatory control following intermittent hypoxia. Unique to our study was the use of the same subjects in a crossover design for the LDIH and SDIH protocols with daily measurement of HVR, as well as the measurement of CO2 sensitivity using both the HCVR and modified Read rebreathing method. As such, our experimental design provides novel insight into the potential causes of altered ventilatory control following IH in humans.

**HVR.** The observed increases in HVR are consistent with previous work that showed comparable changes in HVR with similar IH protocols (10, 19). This is the first study, however, to measure the HVR daily over 7 consecutive days of IH. From these measurements the majority of the augmentation of resting HVR following these protocols occurs in the first 3 days. The HVR measurements from the 4th to the 8th days were not different. This finding may indicate that shorter IH protocols may be adequate if the goal of IH is augmentation of the HVR.

There was no difference between SDIH and LDIH for any of the measured variables. As with the other studies of IH in healthy humans, there was a large amount of inter- and intra-individual variation in the chemosensitivity measures (21). This variability would make it more difficult to notice subtle differences between protocols. From the present study, it may be impossible to rule out a very small difference in efficacy between SDIH and LDIH, but a large (and arguably physiologically significant) difference between them is unlikely. Foster et al. (10) obtained similar findings when comparing SDIH and LDIH, but there were a number of limitations to that study. Namely, the subjects did not act as their own controls, increasing the potential for variation. Furthermore, the IH protocol consisted of 5 days on, two days off, 5 days on. This somewhat irregular protocol would be expected to cause a more uneven profile of HVR augmentation. The doses of IH in the current study were also double that of Foster et al. (2005), and more typical of the previous studies of IH (17, 19, 20). Thus, for the above reasons the current study provides more convincing evidence of a lack of benefit of SDIH over LDIH.

**HCVR.** Reports of the relationship between IH and augmentation of the HCVR have been much less consistent than for the HVR. In earlier work, Katayama et al. (17) showed no change in HCVR after 7 days of poikilocapnic IH (60 min per day), but more recently demonstrated an increase after a 14-day protocol (3 h per day)(15). Ainslie et al. (1) were also able to demonstrate an increase in the slope of the HCVR following 5 nights of 8–9 h of poikilocapnic IH. Using isocapnic IH (with only 30 min per day of hypoxia), Foster et al. (10) showed no difference in HCVR. It appears that the studies that incorporate longer durations of poikilocapnic hypoxia tend to affect HCVR, whereas those that maintain isocapnia or employ shorter bouts of hypoxia do not augment HCVR. Longer and poikilocapnic exposures may cause a more profound, prolonged hypocapnic stimulus, which in turn may increase the sensitivity to CO2.

**Modified Read rebreathing tests.** Using the modified Read rebreathing tests, we were able to examine both the CO2 threshold and the CO2 sensitivity. The test was performed under both hypoxic and hyperoxic conditions. The purpose of the hyperoxic trial was to attenuate the contribution from the peripheral chemoreceptors, thus preferentially targeting the central chemoreceptors, while the hypoxic trial potentiates the contribution of the peripheral chemoreceptors. We found that CO2 threshold was reduced following both IH protocols in hypoxia and hyperoxia, indicating central chemoreceptor mechanism. In the only other study to examine IH and CO2 threshold (23), subjects were exposed to 14 consecutive daily exposures to 20 min of isocapnic hypoxia. Mahamed and Duffin (23) found a decrease in threshold only under the hypoxic condition and not the hyperoxic condition, attributing this alteration to the effects of intermittent hypoxia on the peripheral chemoreceptor in the absence of any change in CO2.
The present study differs in that the exposures were longer and were poikilocapnic; no study had previously looked at the effects of poikilocapnic IH on CO₂ response by the modified Read rebreathing technique. Mahamed et al. (24) showed that the repeated hypoxic hypercapnic exposures of obstructive sleep apnea caused an overnight increase in sensitivity to CO₂ (in the hyperoxic test) but no change in threshold. They found no changes in the hypoxic rebreath test. In summary, it appears that intermittent hypoxia has variable effects on the CO₂ sensitivity and threshold in hypoxia and hyperoxia that depend on the level of CO₂ (poikilo-, iso-, or hypercapnic) and the duration and severity of the hypoxia. A study that compares the CO₂ responses to intermittent hypoxia under poikilocapnic, isocapnic, and hypercapnic conditions is required to clarify the role of CO₂ level on the effect of IH.

This study is the first to directly compare CO₂ sensitivity by the HCVR and the modified Read rebreathing techniques following the same intervention. Although there was a modest ($r = 0.422$) but significant correlation between the two measurements, the sensitivity to hypercapnia was increased following IH in the HCVR test, but not the hyperoxic modified Read rebreathing test. A similar discrepancy occurred when two separate but similar previous studies are compared. Fuse et al. (11) and Mahamed et al. (24) both looked at overnight changes in response to hypoxic hypercapnia in patients with obstructive sleep apnea using the HCVR and the modified Read rebreathing method, respectively. Fuse and coauthors found no change in CO₂ sensitivity. They attributed this discrepancy to the fact that the modified Read rebreathing method measures CO₂ sensitivity over a different range of end-tidal CO₂ than the HCVR method. Because the hyperventilation reduces end-tidal CO₂ to a subthreshold level, the slope of the CO₂ sensitivity is measured from a lower point (by about 4 to 8 mmHg) than in the HCVR. This lower starting point is even lower following IH. Such a difference becomes important if the CO₂/ventilation relationship is not truly linear. As HCVR slope assessment occurs at higher CO₂ levels, these two assessments may not overlap as much as one would initially expect. Thus the HCVR may be assessing response at higher partial pressures of CO₂ than the modified Read rebreathing technique, leading to the differing outcomes.

Another explanation for the differences between the two measures relates to the 5 min of hyperventilation in the modified Read rebreathing technique. Hyperventilation may cause other inputs to the control of breathing, which are not present in HCVR measurement. For example, in some individuals, it can induce a short-term potentiation (STP) of ventilation (2). Furthermore, there may be behavioral inputs to ventilation following hyperventilation that may affect the result. The threshold occurs at the intersection of the basal (subthreshold) ventilation and the suprathreshold ventilation. If this basal ventilation is increased or decreased, there will be a resultant effect on the CO₂ threshold. Datta et al. (4) showed that ventilation following a period of hyperventilation to induce hypocapnia is affected by wakefulness. When asleep, subjects showed a longer, more consistent apnea following hyperventilation than while awake, demonstrating that behavioral drives contribute to ventilation during this period, and may add error to the determination of the CO₂ threshold. Thus either STP or behavioral drives to breathing (or both) may act as further inputs to ventilation, increasing the error and diluting the effect of an alteration in CO₂ sensitivity from IH. As the HCVR technique does not involve hyperventilation, it would not be subject to these other influences.

In summary, this is the first study to compare the traditional method of assessing HCVR to the modified Read rebreathing protocol. Possible reasons for the discordance include variations in the $\text{PetCO}_2$, at which the sensitivity was assessed (higher with HCVR) and altered ventilation brought about by the 5 min of prior hyperventilation. The modified Read rebreathing method has the advantage of being able to assess response to CO₂ in a hypoxic environment, and the ability to determine CO₂ threshold, but may introduce other confounders into this assessment that should be taken into consideration.

Study limitations. One potential criticism of the methods used in the present study is that the interval between each arm of the protocol may have been inadequate. Recent work from Katayama (15) suggests that if two IH protocols are done consecutively, the HVR might increase sooner in the second than in the first protocol (indicating a form of metaplasticity). To assess whether the length of the washout period was adequate, we compared the daily HVRs from the first and second protocols (chronologically) and found no significant differences. Second, there was no difference in the increase in HVR between the protocol performed chronologically first and that performed second. Finally, there was no significant correlation between interval time and augmentation of HVR.

To measure chemosensitivity by a variety of methods, each subject underwent a series of measurements on days 1, 8, and 14. As these measurements involve altering inspired gases, there is the potential for interference between the different measurements. To mitigate such a possibility, measurements were performed in a standardized order with an interval between measurements to minimize interaction. Hypoxic ventilatory response testing was always performed first, followed by the HCVR (after a 20-min rest). As the HVR was isocapnic, there should not have been large changes in CO₂ stores as a result of the HVR. Modified Read rebreathing was always performed after the HCVR, as any increases in body CO₂ stores from the HCVR were reversed by the hyperventilation protocol.

For logistical reasons, there was no sham trial in this study. To ensure that repeated consecutive daily measurements of HVR would not increase the HVR, a preliminary study was performed (21). In this study, we studied daily measurements of HVR with no other intervention and found that there was no change in the HVR over time. Furthermore, this study demonstrated the coefficient of variation of this method of HVR measurement was 27%, which was comparable to other methods (9, 30, 31).

Conclusions. Both protocols caused increases in HVR and HCVR, along with a left shift in the CO₂ threshold in both hypoxia and hyperoxia. The majority of the augmentation in HVR occurred after the 3rd day of IH. The poikilocapnic IH protocol appeared to cause more potentiation of the central chemoreceptors (as measured by HCVR and hyperoxic rebreathing methods) than in previous studies using shorter doses of isocapnic IH. Although CO₂ sensitivity by HCVR and the modified rebreath techniques are correlated, they do not demonstrate an equivalent response to IH. The duty cycle of SDIH
used in this study does not provide a more profound augmentation of resting chemoresponsiveness to IH than LDIH.

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