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ORIGINAL RESEARCH

# The Effect of Dynamic Intermittent Hypoxic Conditioning on Arterial Oxygen Saturation

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**Background.**—Increases in arterial oxygen saturation ($SaO_2$) in response to intermittent hypoxic exposure (IHE) are well established. However, IHE protocols have historically involved static hypoxic environments. The effect of a dynamic hypoxic environment on $SaO_2$ is not known.

**Objective.**—The purpose of this study was to examine the effect of dynamic IHE conditioning on $SaO_2$ using the Cyclical Variable Altitude Conditioning Unit.

**Methods.**—Thirteen trained participants (9 males, age 30.1 ± 9.2 years; 4 females, age 30.3 ± 8.9 years) residing at or near sea level were exposed to a 7-week IHE conditioning protocol (mean total exposure time = 30.8 hours). Participants were exposed to a constantly varying series of hypobaric pressures simulating altitudes from sea level to 6858 m (22 500 feet) in progressive conditioning tiers, creating a dynamic hypoxic environment. $SaO_2$ was evaluated using pulse oximetry ($SpO_2$) 4 times: at 2740, 3360, and 4570 m, prior to and following the first 3 weeks of IHE, and at 4570, 5490, and 6400 m at the start and end of the final 4 weeks.

**Results.**—$SpO_2$ improved 3.5%, 3.8%, and 4.1% at 2470, 3360, and 4570 m, respectively ($P < .05$), and 3.3%, 3.4%, and 5.9% at 4570, 5490, and 6400 m, respectively ($P < .05$). At 4570 m, $SpO_2$ increased from 81.7% ± 6.5% to 89.1% ± 3.2% over the entire 7-week conditioning period.

**Discussion.**—The dynamic intermittent hypoxic conditioning protocol used in the present study resulted in an acclimation response, such that $SpO_2$ was significantly increased at all altitudes tested, with shorter exposure times than generally reported.

*Key words:* intermittent hypoxic exposure, $SaO_2$, $SpO_2$, high altitude, pulse oximetry, hypobaric hypoxia, acclimation, acclimitization

## Introduction

Acclimatization to altitude may be achieved through a variety of mechanisms, including respiratory responses leading to increased arterial oxygen saturation ($SaO_2$).[1–3] The idea that intermittent hypoxic exposure (IHE) can bring about changes in respiratory responses to increase $SaO_2$ at altitude is not new. As early as 1969, the initiation of ventilatory acclimation resulting from IHE had been reported.[4] A number of studies have reported $SaO_2$ improvements in response to both normobaric and hypobaric IHE conditioning.[1–3,5,6] Changes in $SaO_2$ have been attributed to increases in the magnitude of hyperventilation in response to hypoxia caused by increased hypoxic chemosensitivity.[1,3,7] Sato et al[8] reported that the resting hypoxic ventilatory response for participants living at 3810 m continued to rise over a 12-day period without reaching a plateau. However, Bender et al[9] stated that changes in ventilation in response to hypoxia plateaued after 1 week, while exercise $SaO_2$ continued to increase over a 3-week period. Therefore, the time course of ventilatory response adaptations due to hypoxia remains unclear. Additionally, previous studies have examined acclimatization (adaptations resulting from natural environmental exposure) and acclimation (adaptations resulting from simulated exposure) over relatively short periods of time (5–21 days).[1,5,6,9–14] While short-term time course changes (10–12 days) in ventilation and $SaO_2$ have been investigated,[1,3,7] changes in

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**Table 1.** Participant descriptive data*

| *Gender* | *Participants* (n) | *Age (y)* | *Height (cm)* | *Weight (kg)* | *$VO_{2\ max}$* ($mL \cdot kg^{-1} \cdot min^{-1}$) |
|---|---|---|---|---|---|
| Male | 9 | 30 ± 9 (20–44) | 177 ± 5 (171–187) | 73.9 ± 12.9 (58.0–98.2) | 58.3 ± 7.5 (43.1–69.0) |
| Female | 4 | 30 ± 8 (21–42) | 163 ± 7 (158–171) | 57.2 ± 2.9 (54.6–61.8) | 47.8 ± 4.7 (41.3–51.3) |

*Data are represented as mean ± SD (range).

$SaO_2$ occurring in response to minimal intermittent hypoxic exposure over longer periods of time and the magnitude of response at various altitudes have not been systematically investigated.

A number of devices have been used previously to induce hypoxic states at sea level; these devices range from normobaric tents to hypobaric chambers.[1,2,6] Changes similar to those associated with acclimatization to altitude have been reported in response to IHE using such devices.[1–3,6] However, these methods of inducing hypoxia involve static conditions in which simulated altitude levels remain constant throughout a single conditioning exposure. Recently, the effect of alternating exposure between normobaric ambient and hypoxic air within a single conditioning session has been explored.[3,7] However, the effect of a dynamic IHE conditioning protocol utilizing continuous changes in barometric pressure over a wide range of simulated altitudes within a single conditioning exposure has not been investigated previously. Katayama et al[14] reported that IHE representing rapid ascent-descent affects hypoxic ventilatory response. Thus, it is possible that dynamic IHE conditioning may affect hypoxic ventilatory response and $SaO_2$ differently than other IHE protocols in which participants maintain a constant simulated altitude.

The reduction in $SaO_2$ experienced by sea-level residents, military personnel, and athletic teams when traveling to altitude has been associated with the occurrence of acute mountain sickness (AMS) and decreased physical and mental performance.[5,15–20] Acute mountain sickness is associated with substantial discomfort and inconvenience, affecting activity levels in most symptomatic individuals.[21] Hypobaric hypoxia has also been shown to cause a reduction in $SaO_2$ during long- and short-haul commercial airline flights in individuals of all ages, possibly contributing to symptoms associated with AMS during and after air travel.[22–24] The etiology of AMS is complex and unclear,[25] and the role of $SaO_2$ in AMS has been questioned[26]; however, a number of studies have shown a relationship between the development of AMS and low levels of $SaO_2$.[5,15–20] This reduction in $SaO_2$ has been shown to attenuate in response to IHE prior to travel to altitude, possibly leading to decreased AMS effects.[5] The effect of exposure to a dynamic hypoxic environment on acclimation in $SaO_2$ responses at simulated altitudes is unknown. However, if $SaO_2$ responses to dynamic hypoxia are similar to previously reported protocols, then dynamic IHE prior to traveling to altitude may prove beneficial in attenuating the deleterious effects of AMS. Therefore, this study examined the effect of an intermittent hypoxic conditioning program involving exposure to continuous changes in barometric pressure over a wide range of simulated altitudes on $SaO_2$ using a hypobaric chamber. Specifically, this study investigated the time course changes in $SaO_2$, measured via pulse oximetry ($SpO_2$), in response to IHE at the following simulated altitudes: 2740, 3360, 4570, 5490, and 6400 m, over a 7-week conditioning period.

## Methods

### PARTICIPANTS

Thirteen aerobically conditioned men (9) and women (4) completed an IHE training protocol over a 7-week period during which they were progressively exposed to higher altitudes. Descriptive data for participants are presented in Table 1. The study protocol was approved in advance by the Institutional Review Board Committee on Human Subjects. Prior to participation, each participant provided written informed consent and completed a medical history form and preparticipation physical examination.

### INTERMITTENT HYPOXIC EXPOSURE

The dynamic IHE protocol was administered using a hypobaric chamber (CVAC Systems Inc, Poway, CA). The portable 1-person hypobaric chamber (shaped like a large egg) cycled pressure changes using a computerized program with a fail-safe, open-valve system that prevents carbon dioxide build-up. Participants were exposed to a constantly varying series of hypobaric pressures simulating altitudes from sea level to 6858 m (22 500 feet) in progressive conditioning tiers. Within a single training session, hypoxic stimulus was controlled by a computer interface to create a reproducible protocol of constantly increasing or decreasing pressures within the unit, creating a dynamic hypoxic environment.

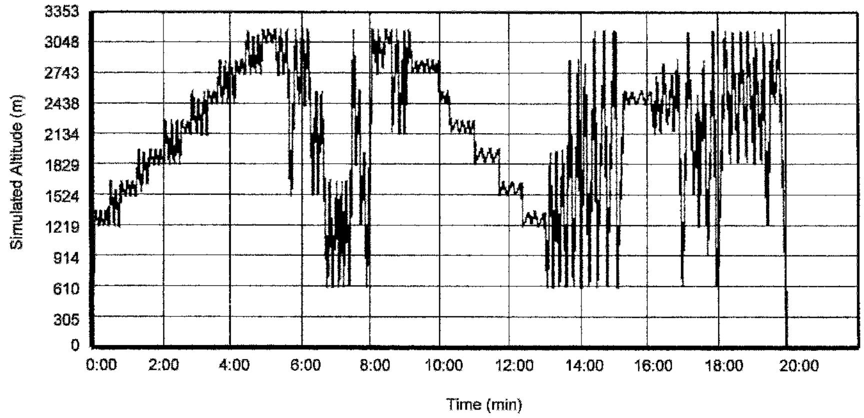


**Figure 1.** Sample altitude-time profile of dynamic intermittent hypoxic exposure (IHE) protocol: Tier 2; Altitude-time profiles were provided in 20-minute blocks and were repeated until completion of the given conditioning session.

The conditioning protocol was divided into 5 specific "tiers" designed to gradually increase altitude exposure over a 7-week period. Progression through the tiers resulted in a graded increase in mean altitude. Specific mean altitude exposure for each tier, as controlled by the computer interface, was considered proprietary information by the manufacturer. However, examples of the altitude-time plots used in the present study for Tiers 2 and 5 are presented in Figures 1 and 2, respectively. Altitude-time profiles were provided in 20-minute blocks and were repeated until completion of the given conditioning session. Maximal altitude attained in each tier increased approximately 1220 m after the completion of Tier 2 until the completion of Tier 5. Pressures within the chamber were monitored and adjusted by an integrated altimeter and displayed on a computer screen as a simulated altitude. Changes in altitude were confirmed using a Neptune Altimaster sky-diving altimeter (Alti-2 Inc, Deland, FL) and were found to be in good agreement with those reported by the computer interface (approximately ±20 m). The protocol employed in the present study used the manufacturer-designed "RGB" (Red, Green, Blue) coded tiers, randomly chosen from available manufacturer-provided protocols, to produce graded dynamic IHEs. In the interest of reproducibility, all participants completed the same computer-controlled coded tiers (RGB 1–5) during hypoxic conditioning.

## PROCEDURE

Participants were assigned to one of the following 3 groups: 1) IHE 60 minutes, 3 days a week (180 $min \cdot wk^{-1}$; $n = 3$); 2) IHE 80 minutes, 3 days a week (240 $min \cdot wk^{-1}$; $n = 2$); and 3) IHE 60 minutes, 5 days a week (300 $min \cdot wk^{-1}$; $n = 8$). Prior to beginning the IHE training protocol, participants completed 3 familiarization sessions in the chamber, consisting of 20-minute exposures over a 3-day period, to allow participants

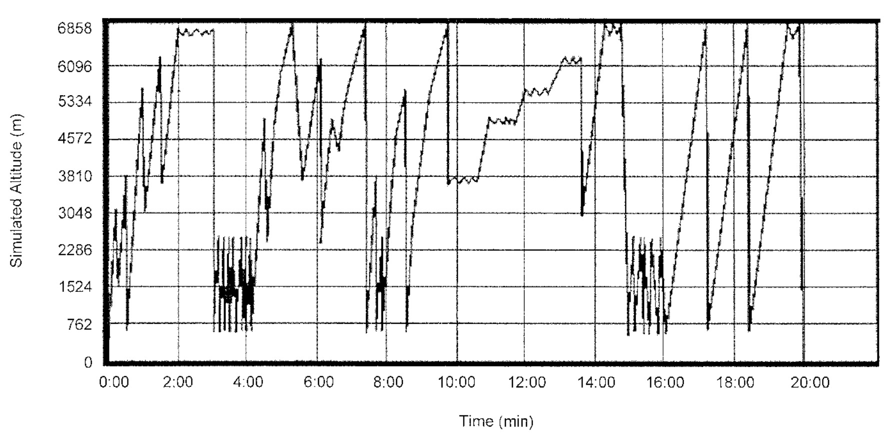


**Figure 2.** Sample altitude-time profile of dynamic intermittent hypoxic exposure (IHE) protocol: Tier 5; Altitude-time profiles were provided in 20-minute blocks and were repeated until completion of the given conditioning session.

to learn to equilibrate middle-ear pressure more quickly in response to the rapid changes in pressure experienced during the 7-week IHE conditioning. The first and second week (W1 and W2) of the study consisted of Tier 1 and Tier 2, respectively, with exposures equivalent to altitudes up to 3200 m (10 500 feet). The third week (W3) and fourth week (W4) consisted of Tiers 3 and 4, respectively, with exposure equivalent to altitudes up to 4420 m (14 500 feet) and 5639 m (18 500 feet), respectively. During the fifth week (W5) through the seventh week (W7), the participants were exposed to Tier 5, which variably cycled between 610 m (2000 feet) and 6858 m (22 500 feet). During IHE sessions, participants sat passively in the chamber. Participants were allowed to drink fluids, read, do computer work, listen to music, or sleep during the IHE sessions.

### PULSE OXIMETRY

Oxygen saturation changes in response to IHE exposure were assessed 4 times during the 7-week conditioning protocol: prior to IHE exposure, on the last day of Tier 3 exposure (Friday at the end of W3), at the start of Tier 4 exposure (Monday at the beginning of W4), and on the last day of Tier 5 exposure (end of W7). Tests prior to beginning Tier 1 and at the start of Tier 4 were completed immediately before exposure to the conditioning protocol for the first day of the tier. Similarly, tests at the end of Tier 3 and Tier 5 were completed immediately prior to the IHE protocol on the last day of exposure for the given tier.

All $SaO_2$ assessments were conducted using the following procedure. Oxygen saturation measurements were taken with an Avant 2120 pulse oximeter (Nonin Medical Inc, Plymouth, MN). While some studies have shown finger sensors to be more accurate than ear sensors in detecting $SaO_2$,[27,28] ear oximeters have been shown to effectively measure $SaO_2$[29–31] and were found to be more accurate than finger clips when evaluating oximetry in simulated altitude exposure.[32,33] Therefore, data in the present study were collected using the Nonin 8000Q ear sensor clip. Each participant vigorously massaged his or her ear lobe for 30 seconds to increase vascular flow prior to sensor placement. Participants were instructed to relax, sit passively, and breathe normally during the testing procedure. Testing consisted of 50-second measurement periods at each of 3 altitudes with a 20-second ramp time between altitudes. Altitudes measured prior to Tier 1 and at the completion of Tier 3 were 2740, 3360, and 4570 m. Altitudes measured at the start of Tier 4 and at the completion of Tier 5 were 4570, 5490, and 6400 m. Oxygen saturation was recorded as the lowest $SpO_2$ attained during each 50-second interval for each altitude based on the pulse oximeter's reading, representing $SpO_2$ sampled at 75 Hz and displayed as a 4-second average to the nearest percent.

### STATISTICS

Data were analyzed using SAS 9.1.3 (SAS Institute Inc, Cary, NC). Participants were grouped based on IHE time, and descriptive data were generated. Based on the limited number of female participants, gender differences were not examined. As a result of unequal group size, group differences in $SpO_2$ response were examined using the General Linear Model to analyze delta scores (pre vs post) with repeated-measures analysis of variance (ANOVA). No significant differences were found in $SpO_2$ response between groups ($P = .64$); therefore, group data were collapsed for subsequent evaluation. A repeated-measures ANOVA with contrast analysis was used to evaluate pretest vs posttest $SpO_2$ values for each altitude examined. The alpha level was set at $P < .05$. Data throughout the manuscript are presented as means ± SD.

## Results

The ANOVA for repeated measures revealed a significant main effect for differences in $SpO_2$ between W1 and W3 and between W4 and W7 ($P < .05$). Contrast comparisons included in the ANOVA revealed significant increases in $SpO_2$ at each altitude between W1 and W3 and between W4 and W7 ($P < .05$). The $SpO_2$ values prior to conditioning were 97.8% ± 0.4% at sea level. Table 2 presents the lowest $SpO_2$ values recorded prior to and after IHE conditioning. Mean percent changes between W1 and W3 were 3.5%, 3.8%, and 4.1% at 2740, 3360, and 4570 m, respectively. Mean percent changes between W4 and W7 were 2.3%, 3.4%, and 5.9% at 4570, 5490, and 6400 m, respectively. Mean percent change at 4570 m over the entire 7-week conditioning period was 7.4%.

## Discussion

The most important finding in this study was that the use of a novel IHE conditioning protocol, producing a dynamic hypoxic environment, resulted in significant mean increases in $SpO_2$ values across altitudes, similar to the result yielded by protocols utilizing traditional methods of inducing hypoxia. A strength of the present study was that changes in $SpO_2$ were examined over 5 simulated altitudes, compared to previous studies, which typically examined responses to a single simulated altitude. The $SpO_2$ significantly increased across altitudes between W1 and W3 (mean IHE conditioning time = 13.2 hours, range = 9–15 hours) and between W4 and

**Table 2.** $SpO_2$ values (%)*

| | *Simulated altitudes tested (m)* | | | | |
|---|---|---|---|---|---|
| | *2740* | *3360* | *4570* | *5490* | *6400* |
| Week 1 | 90.3 ± 3.4 | 86.4 ± 4.8 | 81.7 ± 6.5 | | |
| Week 3† | 93.8 ± 2.0 | 90.2 ± 2.7 | 85.8 ± 3.3 | | |
| Week 4 | | | 86.8 ± 3.8 | 81.5 ± 5.0 | 73.3 ± 5.6 |
| Week 7‡ | | | 89.1 ± 3.2 | 84.9 ± 4.1 | 79.2 ± 5.7 |

*Data are presented as mean ± SD.
†Week 3 values at all altitudes were significantly different from week 1 values ($P < .05$).
‡Week 7 values at all altitudes were significantly different from week 4 values ($P < .05$).

W7 ($P < .05$; mean IHE conditioning time = 17.6 hours, range = 12–20 hours; Table 2). Only 1 altitude (4570 m) was compared across the entire 7-week IHE conditioning program (mean IHE conditioning time = 30.8 hours, range = 21–35 hours). During the first 3 weeks, mean $SpO_2$ at 4570 m improved 4.1% and increased an additional 3.3% during the following 4 weeks, a total improvement of 7.4% for the 7-week program. The continued increase in $SpO_2$ at 4570 m, following the initial 3 weeks of exposure, indicates that percent change in $SpO_2$ occurring at the lower altitudes examined may have been greater if measured following the 7-week IHE program. An increase in $SpO_2$, such as that found in the present study, is a well-known effect of acclimation to altitude.[6] Therefore, the use of an IHE protocol creating a dynamic hypoxic environment resulted in positive changes in acclimation with minimal IHE conditioning for sea-level residents.

The lack of a ''wash-out'' period following completion of the familiarization trials may constitute a possible limitation of the present study. Although the familiarization trials were brief, these exposures to the dynamic hypoxic environment may have contributed to increasing $SpO_2$ at simulated altitude during the pretest, possibly decreasing the effect size. Finally, the short exposure times when collecting $SpO_2$ data (50 seconds) may constitute a limitation of the current study. Participants in the current study demonstrated $SpO_2$ values of 81.5% (pretest) and 84.9% (posttest) at approximately 5500 m. In contrast, Rodriguez et al[6] reported $SpO_2$ values of 60%, following 1 hour of exposure, at 4000 m prior to IHE conditioning and of 78% at 5500 m, following 13.5 total hours of IHE conditioning using hypobaric hypoxia. Based on design limitations of the hypobaric chamber used in the present study, maintaining a constant altitude for extended periods of time was impractical. Consequently, longer exposure times, such as those used in their study, may have elicited increased deficits in $SpO_2$. However, our findings are consistent with those of Beidleman et al,[5] who reported $SpO_2$ changes from 82.0% to 90.0% after 3 weeks of IHE conditioning (total IHE = 60 hours) using hypobaric hypoxia (446 mm Hg) during a 30-hour stay at 4300 m. This compares to a change in $SpO_2$ from 81.7% to 89.1% after a mean of 30.8 total hours of IHE conditioning at 4570 m in the present study. Additionally, decreases in $SpO_2$ at higher altitudes in the present study, as measured at the start of W4, may have been attenuated by the previous 3 weeks of conditioning at the lower altitude tiers prior to higher altitude exposures.

While a number of previous studies have reported increases in $SpO_2$ as a result of both hypobaric and normobaric intermittent hypoxic exposure,[1,2,5,6] these studies reported changes in response to a single altitude. To our knowledge, the protocol used in the present study is the only one to have examined changes in $SpO_2$ occurring over a range of simulated altitudes. The magnitude of change was similar across altitudes examined, ranging from a 3.4% to a 5.9% increase, in response to IHE conditioning, with a tendency toward larger changes at higher altitudes (Table 2).

The most time-efficient IHE schedule capable of bringing about optimal acclimation changes has yet to be determined. Garcia et al[12] and Fatemian et al[11] reported that minimal altitude exposures were capable of initiating ventilatory acclimatization and acclimation. Within IHE conditioning protocols, total IHE exposure time may be manipulated based on the exposure length of individual IHE sessions and the number of sessions. The present study was unique in that IHE was examined over a 7-week period. Previous studies only examined changes occurring over a period of 7 to 21 days of IHE, and it is unclear whether $SpO_2$ acclimation had reached a plateau. The extent to which continued conditioning is necessary when using IHE to elicit complete $SpO_2$ acclimation in unclear. Bender et al[9] reported that for participants living at 4300 m, resting $SpO_2$ rose from day 1 (78.4% ± 1.6%) to day 8 (87.5% ± 1.4%) and then did not increase further by day 20 (86.4% ± 0.06%). This was supported by the work of Sato et al,[8] who reported that $SpO_2$ rose from day 2 (86.2% ± 2.3%) to day 9 (91.9% ± 0.6%) for participants living at 3810 m and then did not increase further by day 12. Although $SpO_2$ acclimatization may be complete after 8 days of living at altitude, the amount of time required to elicit a similar magnitude of change in $SpO_2$ using IHE may be different. In the present study, similar changes in $SpO_2$ at a similar altitude were achieved using IHE after a mean of 30.8 total hours IHE conditioning time: a 4.1% increase over the first 13.2 hours and an additional 3.3% increase following an additional 17.6 hours of exposure. Therefore, time course changes may vary on a continuum depending on the IHE protocol employed. Further research is necessary to determine the most time-efficient combination of IHE type (static vs dynamic; normobaric vs hypobaric), individual session length, number of sessions, and program length capable of eliciting optimal acclimation. It is possible that a dynamic hypoxic conditioning program may be able to elicit beneficial acclimation changes in response to shorter IHE times. However, an exact determination of an optimal conditioning protocol may not be possible as a result of individual differences in response to IHE.

Based on the changes in $SpO_2$ demonstrated in the current study and the relationship between $SpO_2$ and AMS in unacclimatized individuals traveling to altitude,[5,15–20] dynamic IHE conditioning may be effective in preacclimation of low-altitude residents prior to traveling to high altitudes. Montgomery et al[34] found that 25% of 454 participants traveling from sea level to a Colorado ski resort at 2000 m (6561 feet) in elevation experienced AMS-like symptoms. Acute mountain sickness has been reported to commonly occur in travelers (~25%) to elevations exceeding 2500 m, especially in individuals normally residing at altitudes below 1000 m (3280 feet) and in those who are younger, less physically fit, or who have a history of AMS.[21] Additionally, Honigman et al[21] reported that 65% of those experiencing AMS developed symptoms within the first 12 hours of arrival at altitude; however, AMS usually resolves after acclimatization induced by a few days of chronic residence at the same increased altitude.[19] Roach et al[19] reported that a fair amount of individual variation exists in the relationship between $SpO_2$ and AMS symptoms ($r = .48$). However, these authors concluded that resting arterial hypoxemia is related to later development of clinical AMS. Therefore, preacclimation may result in increased $SpO_2$ at altitude, allowing for a more pleasurable response to altitude exposure by decreasing symptoms associated with AMS. The beneficial effects of preacclimation from IHE conditioning have been shown to last for at least a week at sea level, postconditioning, prior to traveling to altitude.[13,20]

Beidleman et al[5] demonstrated that 3 weeks of intermittent hypobaric hypoxia provided an effective alternative to chronic altitude residence for increasing resting minute ventilation and reducing the incidence and severity of AMS. The $SpO_2$ values at rest prior to IHE at 4300 m were reported to be 82.0% ± 2.0%, compared to 90.0% ± 1.0% following IHE. These changes were similar to those found in the present study, in which participants increased from 80.9% ± 2.0% to 89.1% ± 3.2% in response to IHE conditioning at 4570 m. However, participants in their study averaged 20 hours per week over a 3-week period (total exposure time of 60 hours). In the present study, participants averaged 4.4 hours per week over a 7-week period (a mean total exposure time of 30.8 hours). Sato et al[8] reported changes in $SpO_2$ for participants living at 3810 m of 86.2% ± 2.3% to 91.9% ± 0.6% over a 12-day period. These findings were also similar to those found in the present study at 3360 m, in which $SpO_2$ increased from 86.4% ± 4.8% to 90.2% ± 2.7% after the first 3 weeks of IHE conditioning (a mean total exposure time of 13.2 hours).

In conclusion, the dynamic IHE conditioning used in the present study resulted in an acclimation response, such that $SpO_2$ was significantly increased at all altitudes tested. These changes in $SpO_2$ were similar in magnitude to those reported previously. However, the exposure times required to elicit the response were minimal, and the dynamic nature of the IHE conditioning was different than that described in previous studies. The implication of these data is that IHE conditioning utilizing a dynamic hypoxic environment may allow individuals residing at sea level who intend to travel to altitude to improve $SpO_2$ responses at altitude by achieving some degree of altitude acclimation prior to traveling without requiring prohibitive exposure times. Though not examined in this study, this acclimation may allow for decreased symptoms associated with AMS when traveling from sea level to altitude.

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## References

1. Katayama K, Fujita H, Sato K, Ishida K, Iwasaki K, Miyamura M. Effect of a repeated series of intermittent hyp-

oxic exposures on ventilatory response in humans. *High Alt Med Biol.* 2005;6:50–59.

2. Ricart A, Casas H, Casas M, et al. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. *Wilderness Environ Med.* 2000;11:84–88.
3. Ainslie PN, Barach A, Cummings KJ, Murrell C, Hamlin M, Hellemans J. Cardiorespiratory and cerebrovascular responses to acute poikilocapnic hypoxia following intermittent and continuous exposure to hypoxia in humans. *J Appl Physiol.* 2007;102:1953.
4. Nagasaka T, Satake T. Changes of pulmonary and cardiovascular functions in subjects confined intermittently in a low-pressure chamber for 3 consecutive days. *Fed Proc.* 1969;28:1312–1315.
5. Beidleman BA, Muza SR, Fulco CS, et al. Intermittent altitude exposures reduce acute mountain sickness at 4300 m. *Clin Sci (Colch).* 2004;106:321–328.
6. Rodriguez FA, Ventura JL, Casas M, et al. Erythropoietin acute reaction and haematological adaptations to short, intermittent hypobaric hypoxia. *Eur J Appl Physiol.* 2000; 82:170–177.
7. Foster GE, McKenzie DC, Milsom WK, Sheel AW. Effects of two protocols of intermittent hypoxia on human ventilatory, cardiovascular and cerebral responses to hypoxia. *J Physiol.* 2005;567(Pt 2):689–699.
8. Sato M, Severinghaus JW, Bickler P. Time course of augmentation and depression of hypoxic ventilatory responses at altitude. *J Appl Physiol.* 1994;77:313–316.
9. Bender PR, McCullough RE, McCullough RG, et al. Increased exercise $SaO_2$ independent of ventilatory acclimatization at 4,300 m. *J Appl Physiol.* 1989;66:2733–2738.
10. Casas M, Casas H, Pages T, et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. *Aviat Space Environ Med.* 2000;71:125–130.
11. Fatemian M, Kim DY, Poulin MJ, Robbins PA. Very mild exposure to hypoxia for 8 h can induce ventilatory acclimatization in humans. *Pflugers Arch.* 2001;441:840–843.
12. Garcia N, Hopkins SR, Powell FL. Intermittent vs continuous hypoxia: effects on ventilation and erythropoiesis in humans. *Wilderness Environ Med.* 2000;11:172–179.
13. Katayama K, Sato Y, Morotome Y, et al. Intermittent hypoxia increases ventilation and Sa(O2) during hypoxic exercise and hypoxic chemosensitivity. *J Appl Physiol.* 2001; 90:1431–1440.
14. Katayama K, Shima N, Sato Y, et al. Effect of intermittent hypoxia on cardiovascular adaptations and response to progressive hypoxia in humans. *High Alt Med Biol.* 2001; 2:501–508.
15. Basnyat B, Lemaster J, Litch JA. Everest or bust: a cross sectional, epidemiological study of acute mountain sickness at 4243 meters in the Himalayas. *Aviat Space Environ Med.* 1999;70:867–873.
16. Burtscher M, Flatz M, Faulhaber M. Prediction of susceptibility to acute mountain sickness by $SaO_2$ values during short-term exposure to hypoxia. *High Alt Med Biol.* 2004; 5:335–340.
17. Ri-Li G, Chase PJ, Witkowski S, et al. Obesity: associations with acute mountain sickness. *Ann Intern Med.* 2003; 139:253–257.
18. Roeggla G, Roeggla M, Podolsky A, Wagner A, Laggner AN. How can acute mountain sickness be quantified at moderate altitude? *J R Soc Med.* 1996;89:141–143.
19. Roach RC, Greene ER, Schoene RB, Hackett PH. Arterial oxygen saturation for prediction of acute mountain sickness. *Aviat Space Environ Med.* 1998;69:1182–1185.
20. Lyons TP, Muza SR, Rock PB, Cymerman A. The effect of altitude pre-acclimatization on acute mountain sickness during reexposure. *Aviat Space Environ Med.* 1995;66: 957–962.
21. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med.* 1993;118:587–592.
22. Humphreys S, Deyermond R, Bali I, Stevenson M, Fee JP. The effect of high altitude commercial air travel on oxygen saturation. *Anaesthesia.* 2005;60:458–460.
23. Kelly PT, Swanney MP, Frampton C, Seccombe LM, Peters MJ, Beckert LE. Normobaric hypoxia inhalation test vs. response to airline flight in healthy passengers. *Aviat Space Environ Med.* 2006;77:1143–1147.
24. Lee AP, Yamamoto LG, Relles NL. Commercial airline travel decreases oxygen saturation in children. *Pediatr Emerg Care.* 2002;18:78–80.
25. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med.* 2001;345:107–114.
26. O'Connor T, Dubowitz G, Bickler PE. Pulse oximetry in the diagnosis of acute mountain sickness. *High Alt Med Biol.* 2004;5:341–348.
27. Jensen LA, Onyskiw JE, Prasad NG. Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. *Heart Lung.* 1998;27:387–408.
28. Martin D, Powers S, Cicale M, Collop N, Huang D, Criswell D. Validity of pulse oximetry during exercise in elite endurance athletes. *J Appl Physiol.* 1992;72:455–458.
29. Awad AA, Stout RG, Ghobashy MA, Rezkanna HA, Silverman DG, Shelley KH. Analysis of the ear pulse oximeter waveform. *J Clin Monit Comput.* 2006;20:175–184.
30. Hamber EA, Bailey PL, James SW, Wells DT, Lu JK, Pace NL. Delays in the detection of hypoxemia due to site of pulse oximetry probe placement. *J Clin Anesth.* 1999;11: 113–118.
31. Kocher S, Rohling R, Tschupp A. Performance of a digital PCO2/SPO2 ear sensor. *J Clin Monit Comput.* 2004;18: 75–79.
32. Mehm WJ, Dillard TA, Berg BW, Dooley JW, Rajagopal KR. Accuracy of oxyhemoglobin saturation monitors during simulated altitude exposure of men with chronic obstructive pulmonary disease. *Aviat Space Environ Med.* 1991;62:418–421.
33. Lindholm P, Blogg SL, Gennser M. Pulse oximetry to detect hypoxemia during apnea: comparison of finger and ear probes. *Aviat Space Environ Med.* 2007;78:770–773.
34. Montgomery AB, Mills J, Luce JM. Incidence of acute mountain sickness at intermediate altitude. *JAMA.* 1989; 261:732–734.