ARTICLE

Effectiveness of Preacclimatization Strategies for High-Altitude Exposure

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FULCO, C.S., B.A. BEIDLEMAN, and S.R. MUZA. Effectiveness of preacclimatization strategies for high-altitude exposure. *Exerc. Sport Sci. Rev.*, Vol. 41, No. 1, pp. 55–63, 2013. *Acute mountain sickness (AMS) and large decrements in endurance exercise performance occur when unacclimatized individuals rapidly ascend to high altitudes. Six altitude and hypoxia preacclimatization strategies were evaluated to determine their effectiveness for minimizing AMS and improving performance during altitude exposures. Strategies using hypobaric chambers or true altitude were much more effective overall than those using normobaric hypoxia (breathing, <20.9% oxygen).*
Key Words: hypobaric hypoxia, normobaric hypoxia, staging, acute mountain sickness, moderate altitude residence, altitude acclimatization, endurance exercise performance

INTRODUCTION

Numerous physiological adaptations are initiated almost immediately with altitude exposure to compensate for the lower partial pressure of oxygen (PO_2). Nevertheless, the first few days of exposure of unacclimatized sea level residents to altitudes greater than 2500 m are often associated with acute mountain sickness (AMS) and a large decrement in endurance exercise performance (11,16). Symptoms of AMS include headache, nausea, lethargy, dizziness, lightheadedness, tiredness, weakness, and insomnia of varying severities and are affected by factors such as ascent rate, elevation obtained, intensity of physical exertion, hydration level, and individual variability (7,16,23,29). For unacclimatized individuals rapidly ascending to a target altitude of 4300 m, for example, 80% or more will develop AMS within a few hours and will have symptoms that will reach peak severity in 24 to 48 h (15). In addition, even without the presence of AMS, there can be a 60% or greater impairment in time-trial endurance exercise performance compared with sea level (2,8).

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Continuous altitude residence induces progressive ventilatory, hemodynamic, hematological, neural, hormonal, metabolic, intracellular, molecular, and body water compensatory adaptations that are generally proportional to the elevation (11,22,29). The orchestrated development of these compensatory adaptations over time is referred to as altitude acclimatization. In this review, the term "acclimatization" is used to indicate both acclimatization (natural environment) and acclimation (artificial environment). With altitude acclimatization, AMS is ameliorated or eliminated, and endurance exercise performance improves relative to that during the initial exposure at the same altitude. A key early component of altitude acclimatization is ventilatory acclimatization, which is characterized by a progressive increase in the hypoxic ventilatory response that results in a decrease in end-tidal CO_2 ($PetCO_2$) and an increase in arterial oxygen saturation (SaO_2) while at altitude (29).

There is a wide range in the rate of change among compensatory adaptations and in the time required for each to stabilize at a given altitude. For example, at high altitudes (defined here as 4300 m), ventilation, SaO_2, and exercise performance are altered almost immediately on arrival. However, the rates of adaptation in ventilation and SaO_2 are most rapid within the first few days and become relatively stable in about a week to 10 d, whereas the improvement in endurance exercise performance usually occurs more gradually over weeks or longer (11). For such reasons, acclimatization status should be monitored often, preferably using multiple indices of acclimatization that include physiological adaptations such as higher SaO_2 levels and functional

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14. ABSTRACT

Acute mountain sickness (AMS) and large decrements in endurance exercise performance occur when unacclimatized individuals rapidly ascend to high altitudes. Six altitude and hypoxia preacclimatization strategies were evaluated to determine their effectiveness for minimizing AMS and improving performance during altitude exposures. Strategies using hypobaric chambers or true altitude were much more effective overall than those using normobaric hypoxia (breathing, <20.9% oxygen).

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outcomes such as improved endurance exercise performance and AMS status.

"Staging" or living for a few or more days at moderate altitudes (defined here as 2000–3100 m) and slow gradual ascent (considered here as a type of staging) before arriving at high altitude also have been used traditionally and successfully to induce acclimatization and to reduce both AMS and the decrement in endurance exercise performance during subsequent exposures to higher elevations. A major advantage of using staging as a preacclimatization strategy before ascent to high altitudes, in contrast to direct and rapid exposure to the same elevation, is that staging induces at least partial acclimatization such that individuals typically will not experience severe AMS or as large of a decrement in exercise performance soon after they arrive at high altitudes (1,10). The term "preacclimatization strategy" will refer to approaches reviewed in this article that had the potential to attenuate AMS and the decrement in endurance exercise performance for the ensuing exposure to a target altitude of 4300 m.

Although continuous living at high altitudes and staging at moderate altitudes induce sufficient acclimatization that will effectively reduce or eliminate AMS and limit the decrement in endurance exercise performance at high altitudes, they are obviously dependent on a continuous presence at altitude. This "altitude residency" requirement imposes a time-consuming burden for the many unacclimatized individuals who may not have adequate time or opportunity to use these well-accepted and time-honored acclimatization strategies. Therefore, another strategy to reduce the altitude residency requirement has been to use medications that effectively reduce susceptibility to AMS and other altitude illnesses such as high-altitude cerebral edema and high-altitude pulmonary edema (15,22). However, all such medications have potential adverse effects that limit their use in many situations (28). For example, the recommended dosages of the U.S. Food and Drug Administration–approved acetazolamide (or Diamox(R)) taken just before, during, and for a couple of days after altitude ascent attenuates AMS (28) but may exacerbate the already significant altitude-induced endurance exercise performance impairment (27). Unfortunately, there currently are no medications that concomitantly reduce AMS and improve exercise performance at high altitudes. Thus, the use of medications before, during, and after altitude ascent has not been nearly as safe or effective overall as naturally induced altitude acclimatization.

Other more recent preacclimatization strategies have used discontinuous, repeated daily treatment exposures either to *hypobaric hypoxia* ((HH) *i.e.*, reduced P_B with maintained O_2 of 20.9%) using hypobaric chambers or terrestrial altitude or to *normobaric hypoxia* ((NH) *i.e.*, maintained P_B with O_2 <20.9%) using commercially available low O_2 rooms, tents, or breathing masks. The use of either HH or NH treatment involves four related "hypoxia dose" factors: 1. Hypoxia intensity of each daily session as defined by the partial pressure of inspired oxygen (PIO_2); 2. Duration of each daily session(s); 3. Total number of daily sessions; and 4. Overall length of time from the first to the last session. Whereas there appear to be many hypoxia dose combinations using either HH or NH treatment that result in some physiological response and outcomes suggestive of acclimatization, the most beneficial combination for subsequent exposure to high altitude is yet to be determined (17,18).

The Question

A question of particular relevance to athletes, mountaineers, high-altitude vacationers, skiers, workers, first response rescue personnel, and soldiers who may be required to ascend rapidly to high altitudes and then perform effectively is: What specifically can be done to minimize the possibilities of suffering from AMS and experiencing a large reduction in physical capabilities at high altitudes? A quick and general reply might be to use preacclimatization strategies like staging or HH or NH treatment before the high-altitude ascent. Such a response implies that all preacclimatization strategies are equally effective and therefore could be used interchangeably, with the only major considerations being convenience and availability of the chosen strategy. However, if the preacclimatization strategies are not equally effective (or some not at all effective!), choosing an incorrect strategy would waste much time and effort and may result in unnecessary risks at high altitude because of insufficient acclimatization.

The Problems

Despite the large volume of scientific literature devoted to the description of various preacclimatization strategies, there exists little information of their effectiveness at a target altitude. A simple literature search using keywords that include altitude or hypoxia preacclimatization provides well more than 20,000 responses. Nevertheless, attempting to use the available information collected from independent and vastly different studies and laboratories to determine the effectiveness of a particular preacclimatization strategy *per se* or each strategy relative to others yields results and conclusions that are often inconsistent and contradictory (17,18). There simply has not been an objective systematic approach to determine if one preacclimatization strategy is more beneficial than another for preparing previously unacclimatized individuals for subsequent exposure to high altitudes. Closer inspection of the literature indicates that a major problem can be traced to numerous uncontrolled experimental issues among studies that relate to differences in study design, procedures, and methods as well as multiple differing ascent profiles to differing target altitudes. Many studies also 1. do not objectively confirm that at least partial acclimatization was successfully induced before ascending to high altitudes; 2. assume that the degree of acclimatization induced during the conduct of the preacclimatization strategy was still evident on subsequent exposure to high altitude; and 3. do not include multiple physiological indices, acclimatization markers, or functional outcome assessments such as AMS or exercise performance to determine the success of a preacclimatization strategy at high altitudes.

For any preacclimatization strategy reported in the literature, there can be an endless combination of "hypoxia dose" variables (18). For example, staging strategies will differ by the elevation of, and duration at, the staging site(s), whereas

HH or NH treatment strategies will differ by PIO_2 levels and the number, frequency, and duration of daily sessions. Some of these hypoxia dose combinations may provide a meaningful degree of acclimatization at the target altitude whereas others may not, for reasons that are not always apparent (17,18,26). Part of this lack of consistency is that many studies do not monitor or report any physiological or functional outcome variables during the conduct of the preacclimatization strategy that would provide objective evidence that the strategy used actually induced acclimatization before the high-altitude ascent (18). Without this information, it is difficult to determine if the lack of effect at the target altitude was caused by a less than optimal selection of hypoxia dose variables or some other reason (17,18). Even if the preacclimatization strategy subsequently proved successful at the target altitude, it could be that the same benefit could have been obtained more efficiently using less or shorter preacclimatization sessions or a different acclimatization strategy.

A Practical Solution

For the previously noted reasons, it long has been our contention that during the conduct of any preacclimatization strategy, there should be objective evidence that physiological changes are being induced that could be of benefit during the ensuing target altitude exposure (18). Furthermore, the criteria of an appropriate measure(s) should include being independent of volunteer motivation or strategy studied and should be easily and quickly obtained as frequently as needed without concern of measurement carryover from a previous assessment. It also must be widely accepted as reflective of the strength of the overall acclimatization process regardless of the acclimatization strategy chosen. Such measures might include a reduction in exercise heart rate, an increase in blood norepinephrine, or a decrease in plasma volume. Our laboratory has chosen to use progressive adaptations in effective ventilation (*i.e.*, $PetCO_2$) or in SaO_2 during the conduct of each preacclimatization strategy as well as during the subsequent exposures to high altitudes (20,21,29). Adaptations in $PetCO_2$ and SaO_2 at altitude also may be used interchangeably for monitoring purposes when the use of one rather than the other is more convenient (*e.g.*, SaO_2 collection via finger pulse oximetry during exercise or sleep). Thus, by repeatedly assessing $PetCO_2$ or SaO_2 or both, we have been able to monitor the progress of each preacclimatization strategy, verify that the strategy induced acclimatization before ascending high altitudes, and confirm whether the strategy-induced acclimatization remained during subsequent exposure to high altitudes.

Review Purpose and Overview

The purpose of this review is to compare the findings of several major altitude and hypoxia preacclimatization strategy studies conducted by our research group and collaborators during the last two decades. Similar among these studies were the investigative team, volunteer characteristics, assessment times and procedures, and the target altitude of 4300 m. Deliberately different, however, were the strategies used to induce acclimatization. By maintaining consistency among studies, except for the preacclimatization strategy used, we were able to uniquely evaluate the benefits, effectiveness, and limitations of each strategy during rapid exposure to the target altitude.

Our first objective was to establish acclimatization "benchmarks" that would provide a means to judge the success or failure of each preacclimatization strategy. The benchmarks consisted of data collected from a total of 88 previously unacclimatized and nonmedically treated sea level residents who rapidly ascended and then lived at 4300 m for up to three consecutive weeks. The progressive change in their overall acclimatization status was closely and repeatedly monitored using $PetCO_2$, SaO_2, AMS, or endurance exercise performance while living at 4300 m (8,12,13,20,21,24). The benchmarks, therefore, encompassed time periods that included rapid ascent, the progressive development of ventilatory acclimatization, initial onset and then resolution of AMS, and the large decrement and subsequent improvement in exercise performance during continuous exposure to 4300 m.

Then for our preacclimatization strategy studies, similar well-defined and objective physiological or functional outcome measures were again assessed during continuous, albeit shorter, exposures at the same target altitude of 4300 m. However, the critical difference from the benchmarks was that the unacclimatized individuals first underwent preacclimatization strategies before rapid ascent to 4300 m that included 1. living at 2200 m for approximately 2 yr; 2. being "staged" at 2200 m for a week; 3. spending 4 h each day for 7 or 15 d under hypobaric hypoxia conditions (460 mm Hg, 20.9% O_2); or 4. spending 6 d or seven nights under differing normobaric hypoxia conditions (756 mm Hg, <20.9% O_2). Brief descriptions of the benchmark and preacclimatization strategy studies are presented in Table 1.

Thus, by maintaining consistency among similar studies, except for the preacclimatization strategy used, we systematically evaluated for the first time the relative effectiveness of different preacclimatization strategies on physiological responses (*e.g.*, SaO_2) and functional outcomes (*e.g.*, endurance performance) of previously unacclimatized individuals. Moreover, strategy effectiveness was also assessed by equating the strategy-induced change in $PetCO_2$ or SaO_2 to the number of days of continuous exposure at the target altitude that would be required to obtain a similar change in $PetCO_2$ or SaO_2.

For all studies by our group described in this review, regardless of the strategy used, 4300 m was used as the target altitude. The relative success or failure of a preacclimatization strategy was primarily determined during the first 24 h after rapid ascent to the target altitude, a period of time that is often vitally important for many individuals. It also should be noted that, with continued stay at the target altitude, all individuals continue to acclimatize and that the relative order among strategies that was established during the first 24 h typically remains during the subsequent 1 to 3 d.

In some studies, target altitude assessments were conducted at the Pikes Peak Laboratory Facility (P_B, ~459 mm Hg) on the summit of Pikes Peak, CO, whereas others were conducted in the USARIEM Hypobaric Chamber Facility (P_B, ~459 mm Hg) located in Natick, MA (P_B, ~756 mm Hg).

TABLE 1. Overview of featured studies.

Experimental Description and Design[a]	Short Title	Represented in Figures	Reference
6 studies, 66 M and 22 W, 23 yr, 73 kg, and 48 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$). All were transported to Pikes Peak (4300 m) to live for 12 to 21 d. $PetCO_2$, SaO_2, AMS, and exercise performance were assessed repeatedly.	Benchmark	.....	(8,12,13,20,21,24)
5 M and 1 W, 23 yr, 77 kg, and 45 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$). Hypobaric chamber study. Rapidly exposed to 4300 m (446 mm Hg) before and after 15 of 19 d of intermittent altitude exposure (IAE). Each IAE lasted 4 h·d^{-1} at 4300 m. $PetCO_2$, SaO_2, AMS, and exercise performance were compared Pre-IAE with those during Post-IAE.	IAE 15	•	(2,3)
8 M and 2 W, 26 yr, 78 kg, and 44 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$). Hypobaric chamber study. Rapidly exposed to 4300 m (446 mm Hg) before and after 7 of 9 d of IAE consisting of 4 h·d^{-1} at 4300 m. SaO_2 and exercise performance were compared Pre-IAE with those during Post-IAE.	IAE 7	○	(4)
11 M, 21 yr, 78 kg, and 47 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$). Prestaging in hypobaric chamber (4300 m, 446 mm Hg; 8 h); Staging: 6 d at 2200 m (AFA); Poststaging: Pikes Peak (4300 m, 8 h). $PetCO_2$, SaO_2, AMS and exercise performance were compared Prestaging with those during Poststaging.	Staging	▲	(1,10)
9 M and 6 W, 30 yr, 70 kg, and 42 mL·kg^{-1}.min^{-1} (2200 m $\dot{V}O_{2peak}$). Moderate altitude residents (MAR) lived at 2200 m for 21 months. $PetCO_2$, SaO_2, AMS, and exercise intensity were assessed before (2200 m, at AFA) and after rapid ascent to Pikes Peak (4300 m).	MAR	▼	(14)
Normobaric hypoxia (NH) rooms and Pikes Peak (4300 m). NH group: 12 M and 2 W, 24 yr, 76 kg, and 46 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$) and sham group: 8 M and 1 W, 25 yr, 75 kg, and 48 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$), Matched groups and blinded to treatment. NH slept for 7 consecutive nights as O_2% decreased from 16% O_2 (2200 m equivalent) on the first night to 14% O_2 (3100 m eq.) on the seventh night. Sham slept only under SL conditions. After the seventh night, both groups were transported to Pikes Peak, where $PetCO_2$, SaO_2, AMS, and exercise performance were assessed.	NH (Sleep)	■	(9)
Normobaric hypoxia (NH) rooms and hypobaric chamber (4300 m). NH group: 9 M and 2 W, 22 yr, 79 kg, and 47 mL·kg^{-1}·min^{-1} (SL $\dot{V}O_{2peak}$) and sham, 5 M and 1 W, 20 yr, 77 kg, and 50 mL·kg^{-1} min^{-1} (SL $\dot{V}O_{2peak}$). Blinded to treatment. NH were rapidly exposed to 4300 m (446 mm Hg) for 30 h before and after 6 or 7 consecutive daily NH sessions that consisted of 2 hr of rest at a PO_2 of 90 mm Hg and 50 min of moderate exercise at a PO_2 of 110 mm Hg. Daily sham sessions were identical except maintained near SL. $PetCO_2$, SaO_2, AMS and exercise performance were assessed before and after treatment.	NH (Awake)	□	(5,19)

[a]Volunteers for all studies (except those used in the MAR study) resided permanently at sea level (SL). AFA, Air Force Academy; M, Men; W, Women.

For all studies, during both the acclimatization strategy and target altitude assessment phases, volunteers lived and were tested under similar and comfortable ambient conditions. From a practical point of view, our goal was to study outcomes using preacclimatization periods that were long enough to acquire a sufficient degree of acclimatization to reduce the severity of AMS and the initial decrement in exercise performance at the target altitude yet short enough to minimize the inconvenience and sacrifices that potential users (*e.g.*, military, vacationers) would otherwise experience. To that end, except for the benchmark and moderate-altitude resident studies, the strategies outlined in this review were deliberately limited from 6 to 15 HH or NH exposures.

ASSESSMENTS

The original publications of the benchmark and preacclimatization studies provide specific experimental descriptions of the assessments and their number and times of day performed, as well as in-depth rationales for conducting each of the studies (1–5,8–10,12–14,19,20). Provided here is only a brief overview of some of the major assessments that were common to all studies.

Ventilatory Measures

The ventilatory response to altitude was assessed using breath-by-breath end-tidal gases (*e.g.*, $PetCO_2$) and noninvasive pulse oximetry (*i.e.*, SaO_2) after the volunteers had been awake, fasting, and rested for at least 2 h. During the ventilatory assessments, volunteers remained in a semirecumbent position while connected to a breathing circuit by a rubber mouthpiece and nose clip (Vmax 229 SensorMedics Inc., Yorba Linda, CA) and to a finger pulse oximeter (Model 8600, Nonin Medical, Inc., Plymouth, MN). Ventilatory assessments were conducted repeatedly during all phases of each study.

Acute Mountain Sickness

AMS was assessed frequently using information gathered from the Environmental Symptoms Questionnaire (ESQ-III). The ESQ-III is a self-reported questionnaire (68-item version (25) or truncated 20-item version (6)) used to document symptoms induced by altitude or hypoxia exposure. A weighted average of scores from 11 symptoms (headache, lightheaded, dizzy, etc.) designated "AMS-C" was calculated up to several times daily in each study. AMS-C scores equal to or greater than 0.70 indicated the presence of AMS. The

ESQ was administered using paper/pencil or a personal digital assistant ((PDA) HP model iPAQ). At the completion of each ESQ, SaO_2 was obtained.

Endurance Exercise Performance

Endurance exercise performance among studies was assessed using either a motor-driven treadmill or an electromagnetically braked cycle ergometer. Multiple practice and baseline assessments were conducted at the resident altitude (*i.e.*, SL or 2200 m). After warm-up, volunteers were asked to complete a prolonged time trial (TT) of either 7 miles (if a treadmill was used) or 720 kJ of total work (if a cycle ergometer was used) as fast as possible. The volunteers could increase or decrease the power output at any time. Volunteers were continuously informed of the distance or kilojoules elapsed, but not the time. The TT targets of 7 miles and 720 kJ were chosen for each study such that they would be completed in approximately 60 to 80 min at sea level, 80 to 90 min at 2200 m, and 100 to 130 min during initial exposure to 4300 m. The only exception to these cycle TT targets was in the IAE 15 (2) and IAE 7 (4) studies, which used 216 kJ for men and 156 kJ for women.

STUDY SUMMARIES

Table 1 provides overviews of the studies that were conducted by our group and collaborators and highlighted in this review. In column one is a summary of each study and includes the number and physical characteristics of the volunteers and the major physiological and outcome measures collected during the study. All studies used a longitudinal design that began data collection at their resident altitude (SL or 2200 m) and ended at 4300 m. Two of the studies ("NH Sleep" and "NH Awake") also used sham control volunteers, who underwent the same experimental procedures as the NH groups, except that they breathed only ambient air having approximately 20.9% O_2. All volunteers in both NH studies were blinded to treatment. In columns two and three are a short title and a symbol, respectively, to represent the benchmark or a specific study throughout the text, tables and figures. In the last column are the references where the original data and results were published. In most cases, only the mean values and error bars previously published for each study were used throughout this review.

The studies being reviewed represent three very distinct categories of acclimatization strategies: those that involve continuous altitude exposure (Benchmark, MAR, staging), those that involve short daily exposures to hypobaric hypoxia (IAE 15 and IAE 7), and those that involve short daily exposures to normobaric hypoxia while awake (NH Awake) or sleeping (NH Sleep). The studies within each category were chosen so that we also could determine if there is benefit to, for example, prolonging a continuous altitude exposure, increasing the number of repeated hypobaric exposures, or increasing the exposure time under normobaric hypoxia conditions.

RESULTS

Table 2 shows the degree of acclimatization that was induced during the benchmark studies and for each of the preacclimatization strategies. For each study listed, $PetCO_2$ or SaO_2 was measured in the same environment that was used to induce acclimatization. The change in $PetCO_2$ or SaO_2 reflects the difference between the first and last preacclimatization exposures. As shown, each study provided objective evidence that the strategy used was "Effective" to "Highly Effective" for inducing acclimatization during the conduct of the strategy (see Table 2 legend). For the benchmark and for the IAE 15, MAR, and NH (Awake) preacclimatization strategies, there were large adaptations in either $PetCO_2$ or SaO_2. An "Effective" degree of acclimatization was induced during the IAE 7, staging, and NH (Sleep) studies. As expected, the sham groups in the NH (Sleep) and NH (Awake) studies showed no evidence of acclimatization. It should be strongly emphasized that whereas living continuously at high altitude becomes a "Highly Effective" acclimatization strategy,

TABLE 2. Evidence and strength of induced acclimatization.

Compared from the Beginning to the End of the Acclimatization Strategy				
Reference	Short Title	Acclimatization Strategy	$PetCO_2$, mm Hg	SaO_2, %
(20,21)	Benchmark (After prolonged exposure)	Highly effective	Decreased +++++	Increased +++++
(2,3)	IAE 15	Highly effective	n/a	Increased +++++
(4)	IAE 7	Effective	n/a	Increased +++
(1,10)	Staging	Effective	Decreased +	Increased +++
(14)	MAR	Highly effective	Lower[a] +++++	Higher[a] +++++
(9)	NH (Sleep)	Effective (NH Treatment)	Decreased +++	n/a
		None (Sham)	No change	n/a
(5,19)	NH (Awake)	Highly effective (NH Treatment)	Decreased[a] +	Increased[b] +++++
		None (Sham)	No change	No change

[a]Measured at 2200 m and compared with SLR values at 2200 m; [b]Measured at 4500 m equivalent (90 mm Hg); +++++, ≥4 mm Hg reduction in $PetCO_2$ or an increase of ≥5% in SaO_2; +++, 3 or 4 mm Hg reduction in $PetCO_2$ and a 3% to 5% increase in SaO_2; +, 1 to 2 mm Hg reduction in $PetCO_2$ and a 1% to 2% increase in SaO_2; Highly Effective, +++++ for either $PetCO_2$ or SaO_2; Effective, +++ for either $PetCO_2$ or SaO_2; n/a, not assessed.

TABLE 3. Strategy effectiveness when assessed at the target altitude of 4300 m.

Reference	Short Title	$PetCO_2$	SaO_2	AMS Prevalence	Exercise Performance
(8,12,13,20,21,24)	Benchmark (24 h)	35 mm Hg	80%–81%	80%–100%	−60% to −70%
	Benchmark (After prolonged exposure)	Lower +++++	Higher +++++	Zero	Improved +++
(2,3)	IAE 15	Lower +++++	Higher +++	Zero	Improved +++++
(4)	IAE 7	n/a	Higher +++	n/a	Improved +++
(1,10)	Staging	Lower +++	Higher +++	45%	Improved +++
(14)	MAR	Lower +++++	Higher +++++	Zero	No reduction in exercise intensity from 2200 m +++++
(9)	NH (Sleep)	No effect	No effect	64%	No effect
(5,19)	NH (Awake)	Lower +	No effect	50%	No effect

+++++, ≥4 mm Hg reduction in $PetCO_2$, an increase of ≥5% in SaO_2, or >20% endurance exercise performance improvement; +++, 3 or 4 mm Hg reduction in $PetCO_2$, a 3% to 5% increase in SaO_2, or a 10% to 20% Endurance exercise performance improvement; +, 1 or 2 mm Hg reduction in $PetCO_2$, or a 1% or 2% increase in SaO_2. No effect, no difference from Sham.

it is not without severe penalty. That is, during the first few days of high-altitude exposure, AMS prevalence can be 80% or more and there is a large reduction in endurance exercise performance. In contrast, during the conduct of the other preacclimatization strategies reviewed here, issues associated with AMS and exercise performance were of minor consequence.

Presented in the first row of Table 3 are reference values reported during the first 24 h of exposure at 4300 m for $PetCO_2$, SaO_2, AMS prevalence, and exercise performance. The second row (Benchmark, After prolonged exposure) shows the result of living for 2 to 3 wk at 4300 m compared with the first 24 h of exposure to the same elevation. Starting in the third row, for the IAE 15, IAE 7, staging, and the two NH strategies, changes in $PetCO_2$, SaO_2, and endurance exercise performance were compared from before to after completion of each strategy during the first 24 h of exposure to 4300 m. For the MAR strategy, $PetCO_2$, SaO_2, AMS, and endurance exercise performance results were compared with those obtained from unacclimatized sea level residents (8,12,13,20,21,24).

As expected, living for up to 3 wk at 4300 m resulted in large and highly beneficial changes for $PetCO_2$, SaO_2, AMS, and endurance exercise performance. That is, relative to initial exposure, $PetCO_2$ was reduced by approximately 7 mm Hg; SaO_2 was raised by approximately 7%; AMS was eliminated; and endurance exercise performance improved by approximately 20%. Similar adaptations in $PetCO_2$ and AMS were observed for the IAE 15 strategy, although the improvement in SaO_2 was smaller than the benchmark (see table legend). It is noteworthy that the IAE 15 strategy caused a larger improvement in endurance exercise performance than the benchmark at 4300 m, which was possibly related to preservation of cardiac output, as discussed in the original paper (2).

The MAR preacclimatization strategy also was highly effective at 4300 m. With initial exposure of the MAR to 4300 m, $PetCO_2$ was greatly reduced, SaO_2 was greatly increased, and AMS was absent. With regard to exercise performance, the MAR did not suffer any reduction in exercise intensity (*i.e.*, % Peak power output) during endurance exercise assessments at 4300 m when compared with those at 2200 m. This finding is in stark contrast to the large initial reduction in exercise intensity typically experienced for at least 3 d by previously unacclimatized volunteers when living continuously at high altitudes (8,14). The MAR strategy therefore provided a high degree of ventilatory acclimatization, eliminated AMS, and preserved and benefited endurance exercise performance immediately after ascent to 4300 m.

The benefits of the IAE 7 and staging preacclimatization strategies were similar to each other and also resulted in similar degrees of improvement for SaO_2 and exercise performance at 4300 m. The prevalence of AMS after the staging strategy was 45% (1). AMS and $PetCO_2$ were not assessed during IAE 7. Overall, the IAE 7 and staging preacclimatization strategies were effective at the target altitude but not as effective as the IAE 15 and MAR strategies. Interestingly, the degree of acclimatization induced (Highly Effective or Effective) during the conduct of the IAE 15, MAR, IAE 7, and staging preacclimatization strategies was quite consistent with the magnitude of the benefits subsequently observed at 4300 m.

An entirely different relationship was observed for the normobaric hypoxia (NH) preacclimatization strategies during the NH treatment phases and their subsequent effectiveness at the target altitude. First, each NH preacclimatization strategy provided either a "Highly Effective" (NH Awake) or "Effective" (NH Sleep) degree of acclimatization when assessed during the conduct of the strategy under NH ambient treatment conditions. As shown previously in Table 2, the NH (Awake) strategy caused a large increase in SaO_2 that was equivalent to that observed for the benchmark and for the IAE 15 and MAR preacclimatization strategies, whereas the NH (Sleep) strategy resulted in a reduction in $PetCO_2$ that was greater than that induced for the staging strategy. However, when both NH strategies were subsequently assessed under the hypobaric hypoxia (HH) conditions at the target altitude, values for $PetCO_2$ and SaO_2 differed little from before undergoing the NH strategies. In other words, very little of the ventilatory benefit induced by either NH strategy carried over to the HH conditions of the target altitude. In addition, there was no benefit of either NH strategy

for endurance exercise performance at 4300 m. The prevalence of AMS was 50% after the NH (Awake) strategy and 64% after the NH (Sleep) strategy. Overall, when ventilatory acclimatization, AMS, and exercise performance are considered collectively, the IAE 15 and MAR strategies provided the most benefits whereas both NH strategies provided the least benefits at the target altitude.

Another way to express strategy effectiveness is to equate the number of days of continuous exposure at the target altitude required to attain the degree of acclimatization induced by the preacclimatization strategy. In Figure 1 the benchmark curves for $PetCO_2$ were drawn to show the normal rate of $PetCO_2$ decline for men (n = 37, 19 d) and women (n = 22, 12 d) during exposure to 4300 m. Also shown are mean values for $PetCO_2$ for each of the preacclimatization strategies on the first day of exposure to the target altitude. On the first day, the IAE 15 strategy resulted in a mean $PetCO_2$ of approximately 28 mm Hg whereas unacclimatized individuals of the benchmark had a $PetCO_2$ of approximately 35 mm Hg. A reduction in $PetCO_2$ of this magnitude typically does not occur in previously unacclimatized sea level residents until they lived for approximately two consecutive weeks at 4300 m, as illustrated in Figure 1. The MAR preacclimatization strategy also was very effective during the first day at 4300 m. The decrease in $PetCO_2$ was equivalent to approximately 7 d of continuous

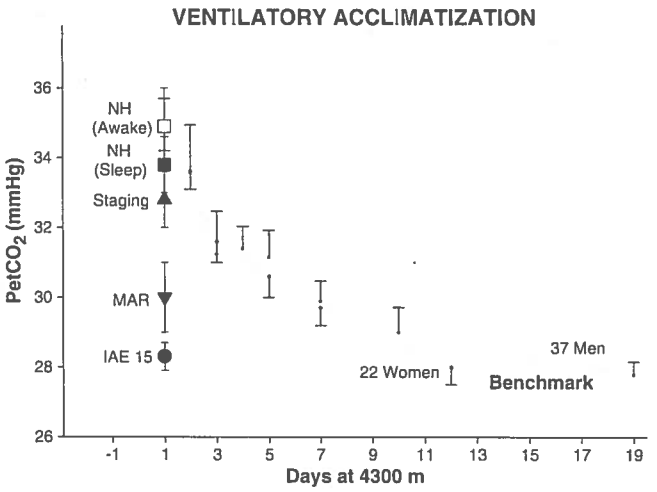

Figure 1. Ventilatory acclimatization as described by the progressive fall in partial pressure of end-tidal carbon dioxide ($PetCO_2$, mean ± SE) for 37 men (21) and 22 women (20) while living on the summit of Pikes Peak (4300 m). Men were assessed on days 1 to 5, 7, 10, and 19, whereas women were assessed on days 1 to 3, 5, 7, and 12. Collectively, the curves represent a ventilatory acclimatization benchmark to allow determination of the effectiveness of each preacclimatization strategy. Also shown are the $PetCO_2$ values (mean ± SE) obtained on the first day at 4300 m for each preacclimatization strategy reviewed. The most effective strategies had the lowest $PetCO_2$ values. Thus, the IAE 15 and MAR strategies are more effective than the NH (Awake) and NH (Sleep) strategies. Moreover, the IAE 15 and MAR strategies on the first day at 4300 m provided the ventilatory acclimatization equivalent of having lived at 4300 m for a week or more. In contrast, the NH (Awake) and NH (Sleep) strategies do not provide much benefit relative to that afforded to unacclimatized individuals rapidly exposed to 4300 m. IAE 15, 15 d of Intermittent altitude exposure; MAR, Moderate altitude residents; NH (Sleep), Ambient normobaric hypoxia conditions while sleeping; NH (Awake), Ambient normobaric hypoxia conditions while awake. [Adapted from (20). Copyright © 2001 The American Physiological Society. Used with permission.]

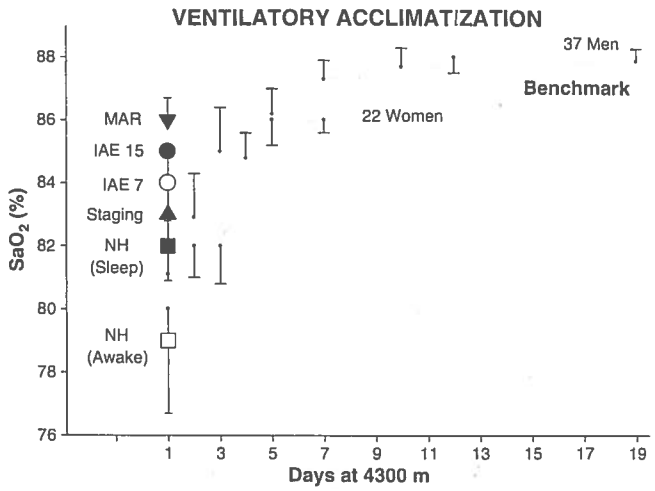

Figure 2. Ventilatory acclimatization as described by the progressive rise in arterial oxygen saturation (SaO_2, mean ± SE) for 37 men (21) and 22 women (20) while living on the summit of Pikes Peak (4300 m). Men were assessed on days 1 to 5, 7, 10, and 19, whereas women were assessed on days 1 to 3, 5, 7, and 12. Collectively, the curves represent a ventilatory acclimatization benchmark to allow determination of the effectiveness of each preacclimatization strategy. Also shown are the SaO_2 values (mean ± SE) obtained on the first day at 4300 m for each preacclimatization strategy reviewed. The most effective strategies had the highest SaO_2 values. As shown, there was a range of effectiveness among the preacclimatization strategies. Whereas the MAR and IAE 15 preacclimatization strategies resulted in increases in SaO_2 (to 85%–86%) that were equivalent to sea level residents living for three to five continuous days at 4300 m, the NH strategies had minimal, if any effect, on SaO_2. IAE 15, 15 d of intermittent altitude exposure; IAE 7, 7 d of intermittent altitude exposure; MAR, Moderate altitude residents; NH (Sleep), Ambient normobaric hypoxia conditions while sleeping; NH (Awake), Ambient normobaric hypoxia conditions while awake. [Adapted from Muza SR, Rock PB, Zupan MF, Miller JC, Thomas WR, Cymerman A. Residence at moderate altitude improves ventilatory response to high altitude. *Aviat. Space Environ. Med.* 2004; 75:1042–1048. Copyright © 2004 Aerospace Medical Association. Used with permission.]

living at 4300 m. The other strategies were not as effective. That is, staging provided an equivalent $PetCO_2$ decrease of 2 to 3 d of continuous living at 4300 m whereas NH (Sleep) and NH (Awake) provided, at most, approximately 1 d. A similar analysis was performed using SaO_2 and is illustrated in Figure 2. The MAR preacclimatization strategy resulted in an increase in SaO_2 that was equivalent to that acquired by sea level residents who lived for five continuous days at 4300 m; IAE 15, 3 to 4 d of continuous living at 4300 m; and IAE 7 and staging, 2 to 4 d of continuous living at 4300 m. The NH strategies had little impact on increasing SaO_2 at the target altitude. Thus, using $PetCO_2$ or SaO_2 as an index of acclimatization at 4300 m, the preacclimatization strategies of IAE 15 and MAR were the most beneficial, followed by staging and IAE 7. In contrast, the preacclimatization strategies using NH provided relatively minimal benefit at 4300 m.

Figure 3 shows the effect of the strategies on TT performance at 4300 m. The data are presented as %TT performance improvement from before (no acclimatization) to after 2 to 3 wk of continuous living at 4300 m (benchmark) and after each of the preacclimatization strategies. The only exception is for the NH (Sleep) study in which the volunteers who had undergone the NH strategy were compared with the matched

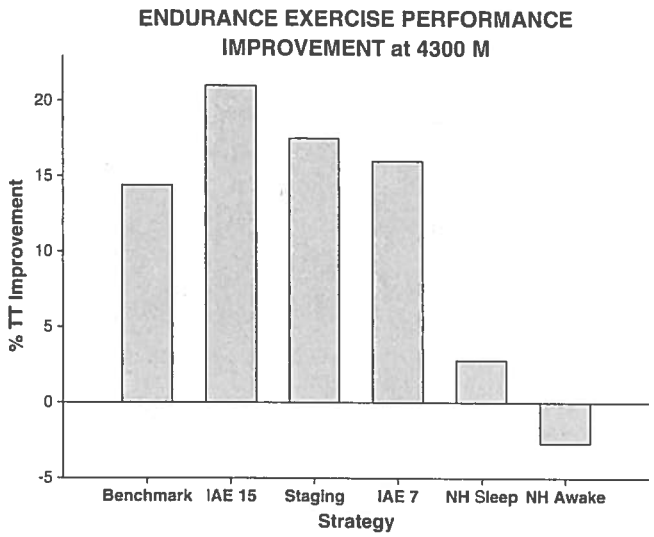

Figure 3. All of the strategies that used hypobaric hypoxia (*i.e.*, either altitude chamber or true altitude) improved time trial (TT) performance by at least 14% when assessed at 4300 m under hypobaric conditions. In contrast, for strategies that used normobaric hypoxia, TT performance was little changed when tested under the identical hypobaric conditions. IAE 15, 15 d of intermittent altitude exposure; IAE 7, 7 d of intermittent altitude exposure; NH (Sleep), Ambient normobaric hypoxia conditions while sleeping; NH (Awake), Ambient normobaric hypoxia conditions while awake.

sham group at 4300 m because there was no prestrategy measure. For the benchmark, TT performance at the target altitude improved by 14% while living continuously at 4300 m. At least as good as the benchmark was the TT performance improvement induced by IAE 15 (21%), staging (18%), and IAE 7 (16%). In contrast, there was no statistically significant TT performance improvement for either the NH (Sleep) or NH (Awake) strategy. Endurance exercise performance results for the MAR strategy could not be directly compared with the other strategies because we were unable to assess the volunteers at sea level before they had acclimatized to moderate altitude. However, in the original publication (14), we estimated that the initial endurance exercise performance impairment from 2200 m to 4300 m would be 50% less than that expected for sea level residents.

SUMMARY AND CONCLUSIONS

We evaluated the relative effectiveness of different preacclimatization strategies for reducing both AMS and the large decrement in endurance exercise performance during early exposure to 4300 m. We acknowledge possible limitations of this review in that there were a small number of studies examined; most of the preacclimatization strategies were of relatively short duration; and that the volunteers in all studies were mainly young, fit, nonsmoking, moderately active, and not on medication. Nevertheless, by maintaining similarity of important experimental factors such as assessment procedures, volunteer characteristics, random recruitment of similar volunteers into each study, target altitude, comfortable living conditions, confirmed acclimatization, and the use of a systematic and consistent approach among similar studies except for the preacclimatization strategy used, we feel very confident stating that:

1. The degree of ventilatory acclimatization induced by the MAR and IAE 15 strategies was the equivalent of 4 d or more of continuous living at 4300 m; that of staging and IAE 7, 2 to 4 d of continuous living; and that of NH (Sleep) and NH (Awake), 0 to 1 d. It is important to emphasize the efficiency and benefits of the IAE 15 and IAE 7 strategies. Both the IAE strategies required less than 20% of the respective continuous altitude time to result in similar AMS and endurance exercise performance benefits at 4300 m. Moreover, whereas many volunteers undergoing continuous exposure to 4300 m suffered severe AMS for the first 1 to 3 d of exposure, those undergoing the IAE 15 strategy reported minimal AMS.
2. A longer (MAR ~2 yr) compared with shorter (staging, 6 d) residence at moderate altitudes resulted in a more developed ventilatory acclimatization, less AMS, and likely better exercise performance at 4300 m.
3. IAE 7 was effective, but not as effective as IAE 15, for inducing ventilatory acclimatization and for subsequently reducing the decrement in endurance exercise performance at 4300 m.
4. Overall, preacclimatization strategies using HH (altitude chamber or terrestrial) were much more effective than those using NH. All HH strategies compared with the two NH strategies resulted in a much more developed ventilatory acclimatization when assessed at 4300 m. This result occurred despite evidence of a similar degree of ventilatory acclimatization having been induced by HH and NH strategies before ascent to 4300 m. The HH strategies, when assessed at 4300 m, also were in general much better than the NH strategies for attenuating the decrement in endurance exercise performance and for reducing the prevalence of AMS.
5. Our finding that a difference in effectiveness exists between HH and NH strategies when assessed under the HH conditions of the target altitude is consistent with some, although not all, observations (17). However, our results clearly indicated that this difference was not caused by the NH strategies causing less ventilatory adaptation than the HH strategies before ascending 4300 m. What the sum of these results does indicate is that NH and HH treatments cannot be used interchangeably to reduce AMS and improve exercise performance during subsequent target altitude exposures for reasons that remain elusive (17).
6. The degree of ventilatory acclimatization induced during each of the strategies requiring HH, but not NH, was reflective of the degree of ventilatory acclimatization observed on the first day of exposure to the target altitude of 4300 m. This, in turn, was linked to the effectiveness of the preacclimatization strategy for reducing AMS and improving exercise performance at 4300 m (1–3,9,10,14). Thus, the degree of ventilatory acclimatization induced using HH strategies but not NH strategies may be a good predictor of subsequent physiological and functional outcomes at high altitudes.

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