Hypoxia, Hypobaria, and Exercise Duration Affect Acute Mountain Sickness

Dana M. DiPasquale; Gary E. Strangman; N. Stuart Harris; Stephen R. Muza

INTRODUCTION: This study simultaneously quantified the effects of normobaric hypoxia (NH), hypobaric hypoxia (HH), exercise duration, and exposure time on acute mountain sickness severity (AMS-C).

METHODS: Thirty-six subjects (27.7 ± 7.8 yr) participated in a partial repeated measures study, completing two of six conditions: normobaric normoxia (NN: 300 m/984 ft equivalent), NH or HH (Po_2 = 91 mmHg; 4400 m/14,436 ft equivalent), combined with moderate intensity cycling for 10 or 60 min. Subjects completed the Environmental Symptoms Questionnaire and oxygen saturation (S_po_2) was measured before, 1.5 h, 4 h, and 6.5 h into an 8-h exposure, and 1.5 h post-exposure. We fit multiple linear regression models with cluster adjusted standard errors on the exposure times using NH, HH, and long exercise as indicator variables, and AMS-C as the outcome variable. The S_po_2 and pre-exposure AMS-C score were used as covariates.

RESULTS: NH and HH led to substantial and progressively increasing AMS-C, but NN did not. The effect of HH on AMS-C was significantly different from NH, with AMS-C in HH being 1.6 times higher than in NH. HH led to significantly increasing AMS-C, regardless of the exercise duration, while NH only did so in combination with longer exercise.

DISCUSSION: Increases in AMS-C were each independently related to NH, HH, and long duration exercise, with HH affecting AMS-C more severely. This suggests that hypobaria may affect AMS development above the level induced by hypoxia alone. This further suggests that NH and HH may not be interchangeable for studying AMS and that exercise duration may impact physiological responses.

KEYWORDS: normobaric, hypobaric, altitude, physical activity, severity, acute mountain sickness.

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Acute mountain sickness (AMS), the most common form of altitude sickness, is a symptom complex with headache, anorexia, nausea, vomiting, insomnia, lassitude, and/or malaise.[12] While AMS is usually self-limiting, symptoms can progress to life-threatening high altitude cerebral or pulmonary edema. Currently, primary treatment is rest and return to low altitude. Peak symptoms of AMS occur between 18-24 h, exacerbated by dysfunctional sleep,[7] and usually resolve in 2-3 d if no additional gain in altitude takes place.

AMS can occur in both hypobaric hypoxia (HH) and normobaric hypoxia (NH).[13] AMS is generally thought to be primarily the result of hypoxia. Emerging data, however, suggests that not only hypoxia, but also the hypobaria of high altitude contributes to the development of AMS. For example, Roach et al.[15] found a higher incidence of AMS in HH than in NH. Conversely, Richard et al.[13] found no difference in AMS severity between HH and NH. However, both of these studies measured AMS symptoms after 6 or more hours of exposure, making the roles of NH and HH in the initials hours (< 6 h) of acute hypoxia unclear.

Previous research also suggests that the incidence and severity of AMS is greater in unacclimatized individuals performing sustained physical work. For example, lower AMS incidence was observed during passive ascent (e.g., by helicopter) to high altitude than when actively climbing.[5] However, passive transport is often much more rapid than active transport and, as

From the Psychiatry Department and the Division of Wilderness Medicine, Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA; Harvard Medical School, Boston, MA; and the Environmental Medicine and Military Performance Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA.

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Address correspondence to: Dana M. DiPasquale, dipasquale.dana@gmail.com.

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such, the rate of ascent may affect results. Some studies controlling for rate of ascent found that exercise did not exacerbate AMS,[17,20] while others found that exercise during early exposure did influence AMS.[1,9,16] A search of the literature did not reveal any studies that directly examined the influence of exercise duration at a fixed workload on AMS severity, nor compared these results in NH and HH. The main objectives of this study were to directly compare AMS severity in the very early hours of exposure to NH and HH and to quantify the modulating role of exercise duration in that comparison.

METHODS

Subjects

There were 36 healthy, nonsmoking subjects (**Table I**) who participated in this study, which was approved by the Institutional Review Boards of the Massachusetts General Hospital and U.S. Army Research Institute of Environmental Medicine. Subjects were regular exercisers who were born at < 2134 m (7001 ft), living in areas that were < 1220 m (4003 ft), and had not traveled to areas that were > 1220 m (4003 ft) for more than 2 d in the last 2 mo. All subjects met Army height:weight standards. After providing written consent, subjects were medically cleared following a clinical exam and routine blood and urine testing.

Each subject was randomly assigned to two of six groups, defined by three environments crossed with two exercise durations: normobaric normoxia (NN), NH, and HH crossed with short exercise (10 min) and long exercise (60 min). This was a partial repeated-measures design; having subjects participate in all six conditions maximizes power, but was deemed impractical from both retention and potential condition carry-over effects perspectives. Having each subject participate in only one condition (fully between-subjects design) greatly reduces power due to between-subject variability. Intermediate cases (participating in two-five conditions) represent compromises between power and subject retention. Statistical power was further optimized—and bias minimized—by having fully counterbalanced condition-pairs and orders, resulting in 12 exposures per condition. None of the subject characteristics were different among groups ($P > 0.05$).

Subjects performed sea-level testing, underwent ascent (~15 min), exercised, spent 8 h in the environmental condition with periodic testing, and were tested again at sea level after descent (**Fig. 1**). Subjects were advised not to consume alcohol or exercise for more than 30 min for at least 24 h prior to testing. Regular coffee drinkers were permitted their usual morning beverage prior to testing. Subjects were provided food and caffeine-free drinks ad libitum throughout the remainder of the day. Testing days were separated by 2 wk.

Subjects were naïve to the conditions they were assigned. They were not provided any information on which room was for NN, NH, or HH, and all research personnel used supplemental oxygen regardless of the condition. NN was performed in the hypobaric chamber at P_B = 752 mmHg, which enabled secure sealing of the chamber door, further ensuring subject naivety (P_IO_2 = 147.3 mmHg; 300 m/984 ft equivalent altitude). HH was also performed in the hypobaric chamber (P_B = 439 mmHg; P_IO_2 = 81.9 mmHg; 4400 m/14,436 ft equivalent altitude). NH was performed at ambient pressure in a clear, hard, vinyl-sided hypoxia room (Colorado Altitude Training, Boulder, CO) with ambient oxygen partial pressure (PO_2) matched to the HH condition at 91.7 mmHg (P_B = 760 mmHg; P_IO_2 = 86.1 mmHg; 4400 m/14,436 ft equivalent altitude). Following all testing, subjects were asked if they knew which conditions they participated in and > 90% could not or incorrectly guessed their experimental condition.

Following ascent, subjects performed moderate exercise as a stimulus to accelerate AMS. Those assigned to 60 min of exercise began cycling immediately, while subjects assigned to 10 min began 50 min later, such that both exercise sessions ended at the same time of exposure. Cycling exercise was performed at 52.1 ± 4.4% of heart rate reserve (HR_{rsv}) (Excalibur Lode, Groningen, The Netherlands). HR_{rsv} was calculated using age-predicted maximum HR and HR at rest was measured on a day prior to the environmental exposures to minimize anticipatory effects. Target HR was stabilized within 5-8 min. Absolute exercising workload was adjusted to maintain target HR. Exercising HR was measured via 3-lead ECG (Physioflow, Poissy, France).

Questionnaire

The Environmental Symptoms Questionnaire was administered at each time point (Fig. 1) to assess AMS. Having AMS (AMS+) was defined, per Sampson,[18] as an AMS-C score greater than or equal to 0.7. Seated HR at rest and S_pO_2 were measured by fingertip pulse oximetry for 2 min at each time point shown in Fig. 1. In addition, S_pO_2 was measured immediately before exercise (after ascent) and during the last 2 min of the exercise bout.

Table I. Subject Characteristics.

ENVIRONMENT	NN		NH		HH	
EXERCISE	10 MIN	60 MIN	10 MIN	60 MIN	10 MIN	60 MIN
Sex (*N*)	M = 6, *F* = 6	M = 6, *F* = 6	M = 6, *F* = 6	M = 6, *F* = 6	M = 5, *F* = 6	M = 7, *F* = 6
Age (yr)	24.4 ± 4.2	30.6 ± 8.4	28.5 ± 10.0	25.1 ± 4.9	30.5 ± 8.3	26.9 ± 7.1
Height (cm)	172.0 ± 6.9	172.0 ± 6.4	171.5 ± 8.6	167.9 ± 10.4	170.9 ± 9.7	174.0 ± 6.6
Weight (kg)	68.7 ± 8.7	66.8 ± 8.2	68.3 ± 12.1	67.5 ± 12.0	71.3 ± 9.8	70.7 ± 10.3
HR at rest (bpm)	65.6 ± 7.1	62.2 ± 11.0	62.3 ± 12.6	61.3 ± 10.6	60.0 ± 9.1	62.0 ± 9.2

None of the subject characteristics were different among groups ($P > 0.05$). Data are expressed as means ± SD.

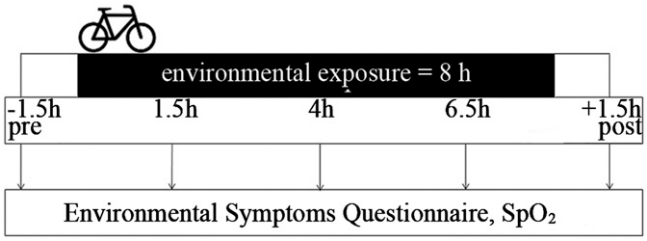

Fig. 1. Schematic of experimental design. Subjects cycled at the beginning of the exposure period. Arrows indicate the testing times. Periodic testing included a ~75-min battery of measurements (i.e., in addition to those measurements presented in this paper, cerebral hemodynamics, cognition, mood, optic nerve sheath ultrasound, metabolism, and ventilation). In between testing bouts, subjects were permitted to rest, read, listen to music or watch movies for ~75 min.

Statistical Analysis

We fit multiple linear regression models with cluster adjusted standard errors (to account for the partial repeated measures) on the three exposure times, using NH, HH, and long exercise as indicator variables, and acute mountain sickness severity (AMS-C) as the outcome variable. This tested the hypotheses that NH, HH, and longer exercise significantly influence AMS-C. Chi-square analysis was then performed to test the hypothesis that AMS-C differs in NH vs. HH. In all models, the pre-exposure AMS-C score was used as a covariate to account for any baseline variation in how subjects felt the day of testing. Further recognizing that this model may overestimate effects because of the slightly mismatched partial pressure of inspired oxygen between NH and HH, we first performed a mixed effects linear regression to test whether S_pO_2 was different in NH and HH. We then added S_pO_2 as a covariate to our AMS severity model, since it represents the overall functional output of ventilation and pulmonary gas exchange.[14] This tests the same hypotheses after adjusting for each individual's S_pO_2. Additionally, sex was added to the model to verify that it did not significantly predict AMS-C during the first 7 h at altitude.[3]

Since exercise in hypoxia is known to further reduce S_pO_2,[10] it is possible that longer exercise could exert its effects by reducing SpO_2 during the exercise bout even more than short exercise. We thus used a separate mixed effects regression to test the hypothesis that long exercise reduced exercising S_pO_2 more than short exercise. For this, we examined only the NH and HH data, using HH and long exercise as indicator variables and exercising S_pO_2 at the end of the exercise period as the outcome variable.

We finally quantified the extent to which AMS-C evolves over the exposure period in all of our environment and exercise combinations. Using the following mixed-effects analysis model:

$$\begin{aligned} AMS\text{-}C \approx\ & NH + HH + long\,exercise + time \\ & + NH * time + HH * time + exercise * time \\ & + NH * exercise * time + HH * exercise * time \\ & + resting\,Spo_2 \end{aligned}$$

After fitting the model, post hoc linear combination of coefficients tests were used to compare the effects of exposure time between each of our experimental conditions. For this analysis, subjects and exposure time were random variables, thus allowing for different slopes and intercepts for each subject and, therefore, individual differences. We again restricted this analysis to the three time points collected during exposure periods to accurately assess the change in AMS-C per hour of exposure (across the points of 1.5 to 6.5 h into the exposure period).

RESULTS

We first analyzed the AMS severity across conditions. The distribution of AMS severities is presented in **Fig. 2**. From this figure, one can see that in both the NH and HH groups the exposure periods led to substantial and progressively increasing AMS symptoms compared to NN. Long exercise increased overall AMS severity in both NH and HH. AMS-C returned to baseline 1.5 h after return to sea-level, albeit incompletely for the HH condition. HH led to average AMS-C scores that were above 0.7 with both exercise durations, but NH did so only when combined with long duration exercise. Sex was not a significant predictor of AMS-C ($P = 0.781$), nor did it alter the significance of the other predictors in the model. Consequently, sex was dropped from the model.

Next, we predicted AMS-C from NH, HH, and long exercise, taking pre-exposure AMS-C score into account. For the two hypoxia conditions, the exercising S_pO_2 at the end of long exercise was not different than in short exercise ($z = -0.27$, $P = 0.705$). Consequently, exercising S_pO_2 was not used as a covariate in any of our models. Mixed-effects (repeated measures) linear regression modeling (**Table II**) supported the above visual observations (Fig. 1). In particular, significant increases in AMS severity were related to NH, HH, and long duration exercise, with the effect of HH on AMS-C being 1.6 times the magnitude of NH [$\chi^2(1) = 8.53$, $P = 0.0035$].

To account for our finding that resting S_pO_2 was 5.2% lower in HH than in NH [$\chi^2(1) = 291.48$, $P = 0.0001$] and effectively account for the 4.2 Torr difference in P_IO_2 between hypoxic conditions, resting S_pO_2 was added as a covariate to this model. As shown in Table II, resting S_pO_2 was found not significant ($P > 0.8$). Compared to a model without resting S_pO_2 (data not shown), resting S_pO_2's inclusion as a covariate had negligible effects on the magnitude of other coefficients and produced no change in coefficient significance of other variables in the model.

We then analyzed the temporal evolution of AMS-C. The effect of exposure time for each experimental condition is listed in **Table III**. There was no significant change in AMS-C over time in NN, as would be expected. In HH, AMS-C increased significantly over time regardless of exercise condition, whereas in NH, it only increased significantly in combination with long exercise. Specifically, in HH, short exercise resulted in the AMS-C score increasing by 0.10 per hour of exposure, and long exercise increased it by 0.18/h, thus predicting increases in AMS-C of 0.65 or 1.2 points over 6.5 h, respectively. In NH, long exercise increased AMS-C score by 0.15 per hour of

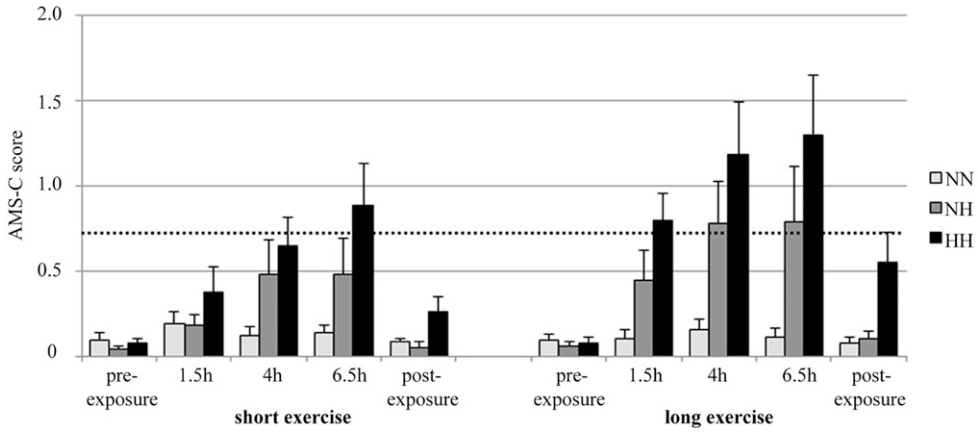

Fig. 2. Acute mountain sickness severity (AMS-C score) as a function of environmental condition, exercise condition, and time of exposure. The dotted line represents AMS-C = 0.7. Data are expressed as means ± SE (HH = hypobaric hypoxia, NH = normobaric hypoxia, and NN = normobaric normoxia).

exposure (0.98 points over 6.5 h). Note that these effects were significant even though our model adjusted for resting S_pO_2 and pre-exposure AMS-C score.

DISCUSSION

We compared the effects of hypoxia, hypobaria, exercise duration, and exposure time on AMS development and severity over an 8-h exposure period. In all analyses, there was a higher AMS-C score in both HH and NH compared to NN. Additionally, all of our models—including those adjusting for S_pO_2 and pre-exposure AMS-C score—found that AMS severity was significantly different in NH compared to HH, with AMS-C in HH being ~1.6-fold higher than in NH. This suggests there was an independent effect of hypobaria on AMS development, which presumably interacts with hypoxia.

NH and HH have often been used interchangeably to study the effects of altitude and, indeed, Richard et al.[13] found no difference in Lake Louise score following exposure to NH and HH. However, recent evidence suggests the two environments may not produce the same physiological or performance outcomes.[11] Our observations suggest that the response to hypoxia is modified by the presence of hypobaria, with AMS-C scores being 60% higher when exposed to HH compared to NH.

Table II. Regression Model Demonstrating That NH, HH, and Long Exercise All Affected AMS Severity Even When Accounting for Differences in Pre-Exposure AMS-C and S_pO_2.

AMS-C	COEF.	SE	Z	$P > \|Z\|$	95% CONF. INT.	
NH	0.53	0.17	3.1	0.002	0.10	0.87
HH	0.86	0.21	4.1	0.0001	0.45	1.27
Long exercise	0.19	0.09	2.2	0.030	0.02	0.36
Pre-exposure AMS-C	1.15	0.53	2.2	0.029	0.12	2.19
Resting S_pO_2	0.002	0.008	0.22	0.824	−0.01	0.02
Intercept	−0.30	0.85	−0.35	0.725	−1.97	1.37

The effect of HH on AMS-C was 1.62 times the magnitude of NH [$\chi^2(1) = 8.53$, $P = 0.0035$].

Our results agree with those of Roach et al.,[15] who found a higher AMS score after 9 h in HH compared to NH; however, we observed these differences as they evolved over time and at earlier time points (1.5–6.5 h). Previous work suggests that AMS development begins during the first 6-24 h after ascent,[22] but our results suggest that with physical activity both preclinical symptoms as well as AMS can begin much sooner than that, as early as 1.5 h into exposure (Fig. 2).

It is still debated whether or not performing exercise soon after ascent is associated with AMS. While it has been observed that exercise increases AMS severity in HH,[3,16] others found that exercise did not worsen AMS when performed in NH.[17,20] However, a search of the literature did not find prior studies examining the effects of exercise duration on AMS. Our models consistently found that long exercise was associated with increased AMS severity relative to short duration exercise. Specifically, the additional 50 min of moderate-intensity exercise increased the AMS-C score in NN by 0.19. Clearly, the AMS-C score in NN with long exercise is not representative of AMS, but the additional effect of long exercise on AMS can be observed when combining it with hypoxic conditions. This model allows the individual contributions of each factor to be quantitatively separated, thus seeing their respective influences.

We also found that in HH, regardless of the exercise duration, AMS severity significantly increased over the exposure period. However, in NH, AMS-C severity only significantly increased in combination with long exercise. Specifically, in NH, short exercise caused the AMS-C score to increase by 0.05 points per hour of exposure. On average, this would lead to an AMS-C score of 0.7 (AMS+) after 14 h in these conditions. In HH and short exercise, though, with a significant 0.10 increase in AMS-C per hour, one would, on average, be AMS+ after 7 h. In NH, long exercise caused the AMS-C score to significantly increase by 0.15 points per hour of exposure. So, on average, it would take 4.7 h for this person's AMS-C score to reach 0.7. Finally, HH with long exercise caused the AMS-C score to significantly increase by 0.18 points per hour of exposure. So after 3.9 h, on average, an individual's AMS-C score could go from 0 to 0.7. This pattern of results, along with Fig. 2, suggests that a more substantial time-evolution of AMS-C occurs with HH and even more so with longer exercise.

One potential difference between short and long exercise, besides the duration, could be that S_pO_2 was lower during the long exercise than during short exercise. However, our results did not support this hypothesis; the S_pO_2 during the end of the exercise bout was the same for both the short and long exercise

Table III. Linear Combination of Coefficients Testing the Effect of Exposure Time on AMS-C in Each of Our Six Experimental Conditions.

AMS-C	COEF.	SE	Z	P > |Z|	95% CONF. INT.	
NN, short exercise	0.02	0.04	0.56	0.575	−0.06	0.11
NH, short exercise	0.05	0.04	1.2	0.229	−0.03	0.14
HH, short exercise	0.10	0.04	2.3	0.023	0.01	0.18
NN, long exercise	−0.05	0.04	−1.1	0.294	−0.13	0.04
NH, long exercise	0.15	0.06	2.4	0.019	0.02	0.27
HH, long exercise	0.18	0.06	2.9	0.003	0.06	0.30

In HH, AMS-C increased over time no matter which exercise condition was performed, whereas in NH, it only increased in combination with short exercise. These effects were significant even after adjusting for S_pO_2 and pre-exposure AMS-C score.

groups. Thus, the observed effect of longer exercise on AMS-C would seem to be more directly related to the duration rather than the level of exercise-induced S_pO_2 depression. The extended stimulus of long exercise is presumed to have exacerbated the unknown but underlying pathophysiology and thereby contributed to more severe AMS symptoms. For example, Bartsch et al.[2] reported that exercise at high altitude significantly elevated aldosterone and ADH plasma levels in subjects who subsequently developed AMS. Thus, longer duration exercise likely exacerbates susceptibility to and severity of AMS through hormonal changes that favor enhanced renal sodium and water retention.

We recognize that this study has potential limitations. First, NH and HH were slightly mismatched in terms of P_IO_2 by 4.2 Torr, which caused a 5.2% difference in blood oxygenation. This was our rationale for adding resting S_pO_2 as a covariate. Interestingly, adding S_pO_2—over and above the environmental indicator variables NH and HH—did not affect the findings at all; we still found a significant difference between AMS severity in NH versus HH. This is particularly noteworthy because adding S_pO_2 as a covariate not only adjusts for the mismatched P_IO_2, but it also adjusts for the hypoxia-related decrease in oxygen availability. Still, observing a difference in NH and HH after statistically adjusting for the effects of a major driving force of AMS development suggests that this difference is substantial. Second, although great efforts were made, since the NH testing occurred in an acrylic chamber outside of the hypobaric chamber, this study was not entirely blinded, which may have our affected results. However, many other studies have used nonblinded methods.[4,19,21] Moreover, we note that the overwhelming majority of our subjects (> 90%) were unable to correctly identify which environmental condition they were experiencing and, hence, it appears subjects were effectively blinded. While it is also possible that there may have been effects due to repeated exposures to hypoxia, our 2-wk washout period was similar to or greater than others,[8,13,15] used only two exposures per person, and one-third of the exposures involved no hypoxia at all (i.e., NN). We also fully counterbalanced the order of conditions to mitigate these effects. Finally, it could be argued that concluding AMS severity is different in NH and HH after 8 h of exposure is premature since peak symptoms typically occur after 18-24 h at altitude. While this may be true, the purpose of this study was to observe differences during the early hours of AMS development. Moreover, by doing so, our results are not confounded by dysfunctional sleep that can exacerbate AMS symptoms.[6,7]

Our results show—in a single study—that hypoxia, hypobaria, and exercise duration each have independent effects on AMS severity. It is noteworthy that the magnitude of observed differences between NH and HH was quite large (1.6 times the overall effect of hypoxia alone). Moreover, physiological changes occurring during long duration exercise appear to exacerbate AMS progression even well after the cessation of the physical activity. While the mechanisms underlying such differences remain unclear, it supports the concept that NH and HH are not interchangeable environments with respect to AMS, and suggests that hypobaria by itself may exert an effect on AMS severity, at least when combined with hypoxia.

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Authors and affiliations: Dana M. DiPasquale, Ph.D., and Gary E. Strangman, Ph.D., Psychiatry Department, Massachusetts General Hospital, Boston, MA; Dana M. DiPasquale, Ph.D., Gary E. Strangman, Ph.D., and N. Stuart Harris, M.D., Harvard Medical School, Boston, MA; N. Stuart Harris, M.D., Division of Wilderness Medicine, Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA; and Stephen R. Muza, Ph.D., Environmental Medicine and Military Performance Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA.

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