The Effects of Propranolol on Acute Mountain Sickness (AMS) and Well-Being at 4300 Meters Altitude.

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ABSTRACT

A number of physiological responses and adjustments occur at high altitude to compensate for the hypoxia. We hypothesized that interference with one component of the normal compensatory process, the sympathetic nervous system, would hinder altitude acclimatization and thereby exacerbate acute mountain sickness (AMS) and compromise well-being. Twelve young males (21 $\pm$ 2 yr) received either 80 mg propranolol (PRO;n=6) or placebo (PLA;n=6), t.i.d. at sea level (SL) and during the first 15 days of a 19-day residence at 4300 m (HA). Individuals were randomly assigned to each group. The Environmental Symptoms Questionnaire (ESQ) was administered at SL and twice daily (AM and PM) during the entire altitude exposure to assess AMS symptoms and subjective feelings of well-being. Supine heart rate (HR) was determined at rest twice at SL and four times at HA. HR in the PLA group increased 40% over SL values (57 $\pm$ 3 to 80 $\pm$ 4 beats/min) by day 7 at HA ($p<.01$). HR in the PRO group did not increase above SL values during medication at HA. Four days after the medication administration was terminated, HR in the PRO group increased and did not differ from the PLA group. Throughout the entire altitude exposure, ESQ scores for the PRO group were lower than or similar to the PLA group. Furthermore, cessation of PRO treatment did not result in a change in well-being. These findings suggested that interference with the normal acclimatization process by beta-adrenergic blockade did not exacerbate AMS or reduce feelings of well-being.

Key words:acute mountain sickness, AMS, Beta-blockade, high altitude, sympathetic nervous system

INTRODUCTION

A number of well-documented ventilatory, cardiovascular and hematological compensatory responses are initiated within the first few days of exposure to altitude and are continually undergoing some degree of change for the entire sojourn (1,3,5,6,7,9). Many of these changes are thought to be directly or indirectly mediated by an increase in sympathetic activity (3,5,6,7,9). If the ascent to altitude is both rapid and greater than 3000 meters, most unacclimatized individuals will also experience some degree of a symptom complex termed acute mountain sickness (AMS). The symptoms, which include headache, nausea, dizziness, insomnia, tiredness, and weakness, typically become evident within several hours of exposure, reach their peak severity within 24-48 hours and then gradually recede over the ensuing two to four days (8). It is not known if the symptoms associated with AMS, or subjective feelings of well-being in general, are related to the concomitant physiological adjustments.

The opportunity to study the possible interrelationships between the physiological adjustments, AMS, and subjective well-being was made possible during recent investigations in which propranolol, a non-selective beta-adrenergic blocking agent (4,10), was administered during the first 15 days of a 19-day exposure to 4300 meters (3,9). During the period of propranolol administration, some of the physiological adjustments associated with a normal altitude acclimatization process such as increases in heart rate and blood pressure, did not occur (3).

This paper reports the effect of beta-adrenergic blockade on AMS symptomatology and subjective feelings of well-being. Also reported will be the effect of abruptly terminating 15 days of propranolol treatment at altitude on well-being.

METHODS

The subjects were 12 healthy males with an average age, height and weight of 21 years, 174.9 cm and 73.7 kg, respectively. None had been exposed to high altitude for at least six months prior to initiation of this study, and none had any contraindication to altitude exposure or to administration of propranolol. All gave their informed consent prior to participation. The subjects were randomly assigned to either an experimental (n=6) or control (n=6) group. The experimental group was given 80 mg propranolol (Inderal; Ayerst Labs) and the control group an identically-appearing placebo, orally t.i.d. (4,10) during a seven-day period at sea level (Natick, MA; 50 m). The subjects were then taken off the medication for thirteen days. Medication was resumed at sea level beginning three days immediately prior to and continuing through to 11 p.m. on day 15 of 19 days of residence at Pikes Peak, CO. (4300 m). Subjects were flown from Boston, MA to Denver, CO and were driven directly to the summit of Pikes Peak in a total time of less then six hours, arriving at 2 p.m. (day 0). Although the subjects were blind as to which treatment they were receiving, the investigators were not because of an obvious attenuation of heart rate responses observed during concomitant studies (3,9).

Symptoms of acute mountain sickness (AMS) and well-being at altitude were evaluated using the Environmental Symptoms Questionnaire (ESQ), a 67-item symptoms inventory (12). The justification and validity of using the ESQ to determine symptom severity at altitude and during other stressful environmental conditions is presented elsewhere (11). In this study, the self-administered, interactive computer version of the ESQ was utilized (2). At the completion of each questionnaire, the numerical values for each of the

responses were added together and the total score was printed out. Also printed out were nine statistically-weighted factor groups: AMS-C ("cerebral"), AMS-R ("respiratory"), ENT (ear, nose and throat discomfort), cold distress, distress, alertness, exertion stress, muscular discomfort and fatigue. The factor groups were previously derived using image factcring and oblique rotation on 650 ESQs completed at altitude (11). Seven to twelve symptoms defined each of the factor groups. For example, the leading symptoms under AMS-C included "feeling sick," "feeling hungover," and "headache," while the symptoms such as "hard to breathe," "short of breath" and "hurts to breathe" defined AMS-R. Subjects with weighted-average scores greater than 0.7 for AMS-C and 0.6 for AMS-R were considered to be "sick". Although only AMS-C and AMS-R have been shown to be reliable indicators of altitude sickness (11), the other seven factor groups were included because the effects of chronic propranolol administration on well-being during a long-term exposure to high altitude were unknown. For each of the factor groups except "alertness", the higher the reported score the less was the individual's feeling of well-being for the particular grouping. A complete listing of the symptoms under each of the factor groups can be found elsewhere (11).

The ESQ was administered in the mornings of three separate days at sea level and twice daily throughout the entire altitude exposure (beginning on day 1). Each questionnaire took 5-10 minutes to complete. Subjects were not allowed to participate in any activity more strenuous than walking for at least one hour prior to taking the ESQs. The first ESQ was administered to familiarize the subjects with the task, and the results were not included in any of the analyses. The second ESQ was completed prior to the selection of treatment groups and thus provided a non-treatment, sea-level baseline value for each of the test subjects (OFF TREATMENT). The third sea-level ESQ was

completed after the test subjects had been on placebo or propranolol treatment for six days (ON TREATMENT). The three sea-level ESQs and all morning ESQs administered at altitude were completed daily between 7 a.m. and 9 a.m. The afternoon ESQs at altitude were completed daily between 5 p.m. and 7 p.m.

The heart rate data used in this study to monitor effectiveness of beta-blockade were collected in the supine position during tilt-tests performed at sea level and during days 2, 7, 15 and 19 of the exposure (3). All of the data were analyzed using a repeated measures ANOVA and, where appropriate, the Neuman-Keuls post-hoc test. Statistical significance was chosen at $p<.05$.

RESULTS

At sea level, there were no significant differences in the total score or in the nine factor scores between the two groups during either the OFF-TREATMENT or ON-TREATMENT days. There were also no significant differences between the OFF-TREATMENT and ON-TREATMENT days for either of the groups. (Table I).

*** TABLE I HERE ***

During altitude exposure, the total and factor scores for the afternoon ESQs were, in general, slightly less than the morning scores for each day. However, very few statistically significant differences between morning and evening ESQs were found. Therefore, only the morning scores at altitude are presented in Tables II and III. On day 1, both groups reported being "sick" as indicated by significant increases over sea-level values for the total, AMS-C, AMS-R, and muscular discomfort scores. Furthermore, the AMS-C scores for both groups surpassed the criterion score for altitude sickness (>0.7) as previously established (11). However, only the placebo group surpassed the criterion score for AMS-R (>0.06). The placebo group, but not the propranolol group, had scores for cold stress, distress, alert, exertion, and fatigue that were statistically different from sea level. The total, cold stress, and distress scores for the propranolol group were significantly lower than the respective placebo group scores.

*** TABLE II HERE ***

By the second day at altitude, both groups improved. The total and factor scores for each of the groups were lower than the values from the

previous day with the improvement in the propranolol group being complete; that is, all of the scores did not differ statistically from the sea-level values. However, the placebo group was still "sick" as reflected by an AMS-C > 0.7 and by values for the total and other factor scores which were significantly different from sea level. Furthermore, the total, AMS-C, AMS-R, and cold stress scores for the placebo group were significantly higher than the propranolol group scores.

On day 3 of the altitude exposure, the placebo group also fully recovered from AMS as reflected by all of the scores being similar to the sea-level values. During days 4 through 15 while ON TREATMENT, all of the scores of both groups did not differ from sea level or between groups.

Table III shows the last day the subjects were ON TREATMENT (day 15) and the subsequent two days when the subjects were OFF TREATMENT (days 16 and 17). As indicated, all of the scores of the placebo and propranolol groups were not altered from day 15 to days 16 and 17.

*** TABLE III HERE ***

Figure I shows the heart rates at sea level and at altitude, ON and OFF TREATMENT. There were no statistical differences at sea level between the groups, ON or OFF TREATMENT. At altitude, heart rates differed between the groups only during the ON-TREATMENT phase (days 2 through 15). On day 19, the mean heart rate of the propranolol group increased to a value (74 beats/min) which was not statistically different from the mean heart rate value of the placebo group (78 beats/min).

DISCUSSION

It was previously observed that during an acute ascent to, and descent from 6000 m (<4 hours) in a hypobaric chamber, subjects' subjective feelings of well-being were not diminished following 14 hours of treatment with propranolol (1). However, there were at least two major reasons why results from that study (1) were thought not to be applicable to a longer study. One reason was related to the time course of AMS symptomatology. The symptoms of AMS usually become evident four to six hours after rapid exposure to high altitude and reach their peak severity in 24 to 48 hours (8). Therefore, it could not be determined if interfering with the early, rapid physiological adjustments to altitude would affect the period of peak symptomatology of AMS.

Another reason concerns beta-adrenergic blockade and the direct and indirect consequences of preventing a number of significant physiological alterations from occurring between the acute and chronic stages of an exposure to altitude (3,5,6,7,9). For example, during the first two to three days of continued exposure, resting cardiac output is increased due to an increase in heart rate (5). After this time and up to two weeks, there is a progressive reduction in cardiac output primarily due to a reduction in stroke volume (5). The fall in cardiac output is limited somewhat by a gradual increase in heart rate occurring concomitantly. It seemed reasonable, therefore, that an increase in heart rate was essential to defend cardiac output. Furthermore, it seemed possible that by blocking the normal increase in heart rate and thereby interfering with what was assumed to be a major portion of the normal, compensatory physiological process, altitude acclimatization would be hindered and well-being would be compromised.

Results from the present study indicate that propranolol administration did not exacerbate or prolong symptoms of AMS, and did not diminish feelings of well-being. On the contrary, the group receiving propranolol had a lesser incidence and less severe symptoms of AMS, and recovered from AMS more quickly than the placebo group. These results suggest that the increase in beta-adrenergic tone that occurs with altitude exposure exacerbates AMS symptomatology. There was also no indication from the ESQ scores that either beta-blockade due to propranolol administration or propranolol per se adversely affected well-being after the symptoms of AMS subsided. Furthermore, cessation of propranolol treatment while at altitude did not result in a change in well-being.

In conclusion, under the constraints of this investigation, beta-adrenergic blockade has been found not to adversely affect symptoms of AMS during the first couple of days of altitude exposure, or well-being in general during the first 15-days of altitude acclimatization even though a major component of the normal compensatory process (an increase in heart rate) was blocked. There was also no suggestion of a rebound effect on well-being upon abrupt cessation of propranolol administration at altitude. However, as previously mentioned by Moore et al. (9), the results from this study were obtained from healthy, young individuals and should not be extrapolated to people who would be taking propranolol for heart or blood pressure disorders. In those individuals the altitude-induced tachycardia may be an essential compensatory mechanism and its' elimination may adversely affect well-being.

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Subjects participated in this study after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC regulation 70-25 in use of volunteers in research. The views, opinions, and findings in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other official documentation.

FIGURE LEGEND

Figure 1. The effect of propranolol on supine heart rate at sea level and altitude. *Indicates a statistically significant difference ($p<.05$) between the placebo and propranolol groups. #Indicates a statistically significant difference ($p<.05$) from the corresponding sea level, OFF TREATMENT value.

TABLE I

Mean Values for the Total and 9 Factor Scores of the ESQ for the Placebo and Propranolol Groups at Sea Level (morning).

	OFF TREATMENT		ON TREATMENT	
	Placebo	Propranolol	Placebo	Propranolol
Total	10 ± 1	7 ± 4	9 ± 4	7 ± 2
AMS-C	0.06 ± 0.05	0.04 ± 0.04	0.19 ± 0.10	0.07 ± 0.03
AMS-R	0.09 ± 0.07	0.06 ± 0.06	0.06 ± 0.12	0.04 ± 0.02
ENT	0.10 ± 0.07	0.08 ± 0.03	0.08 ± 0.05	0.03 ± 0.03
COLD STRESS	0.07 ± 0.06	0.05 ± 0.03	0.10 ± 0.07	0.04 ± 0.03
DISTRESS	0.21 ± 0.06	0.12 ± 0.09	0.15 ± 0.11	0.16 ± 0.07
ALERT	4.04 ± 0.36	3.37 ± 0.76	4.17 ± 0.49	3.36 ± 0.40
EXERTION	0.02 ± 0.02	0.23 ± 0.16	0.06 ± 0.04	0.18 ± 0.12
FATIGUE	0.30 ± 0.11	0.16 ± 0.10	0.22 ± 0.11	0.27 ± 0.11
MUSCULAR DISCOMFORT	0.30 ± 0.16	0.05 ± 0.03	0.30 ± 0.14	0.12 ± 0.08

n=8: Values are means ± S.E.

TABLE II

Mean Values for the Total and 9 Factor Scores of the ESQ for the Placebo and Propranolol Groups During the Mornings of Days 2,3, and 4 at Altitude.

	DAY 1 ON TREATMENT		DAY 2 ON TREATMENT		DAY 3 ON TREATMENT	
	Placebo	Propranolol	Placebo	Propranolol	Placebo	Propranolol
TOTAL	46 ± 12$^{\#}$	24 ± 8$^{*\#}$	31 ± 7$^{\#}$	14 ± 4*	17 ± 4	13 ± 4
AMS-C	1.11 ± 0.40$^{\#}$	0.77 ± 0.31$^{\#}$	0.84 ± 0.30$^{\#}$	0.22 ± 0.09*	0.15 ± 0.04	0.09 ± 0.09
AMS-R	0.71 ± 0.23$^{\#}$	0.52 ± 0.25$^{\#}$	0.56 ± 0.15$^{\#}$	0.16 ± 0.06	0.34 ± 0.12	0.19 ± 0.06
ENT	0.48 ± 0.46	0.17 ± 0.05$_{*}$	0.29 ± 0.14	0.23 ± 0.08$_{*}$	0.27 ± 0.13	0.16 ± 0.04
COLD STRESS	0.80 ± 0.22$^{\#}$	0.21 ± 0.09$_{*}$	0.50 ± 0.10$^{\#}$	0.07 ± 0.04	0.25 ± 0.10	0.07 ± 0.04
[illegible]TRESS	0.80 ± 0.28$^{\#}$	0.27 ± 0.12	0.46 ± 0.10$^{\#}$	0.19 ± 0.09	0.31 ± 0.11	0.28 ± 0.13
	1.79 ± 0.56$^{\#}$	2.49 ± 0.47	1.78 ± 0.57$^{\#}$	3.73 ± 0.48	3.75 ± 0.36	3.24 ± 0.51
[illegible]ON	0.79 ± 0.23$^{\#}$	0.55 ± 0.19	0.38 ± 0.15$^{\#}$	0.27 ± 0.16	0.31 ± 0.15	0.35 ± 0.18
FATIGUE	1.19 ± 0.37$^{\#}$	0.60 ± 0.19	0.81 ± 0.27$^{\#}$	0.31 ± 0.11	0.32 ± 0.11	0.24 ± 0.15
MUSCULAR DISCOMFORT	0.76 ± 0.21$^{\#}$	0.26 ± 0.07$^{*\#}$	0.49 ± 0.13	0.22 ± 0.08	0.35 ± 0.17	0.20 ± 0.09

n=8; Values are means ± S.E.

*Significantly different from placebo ($p<.05$)

#Significantly different from the corresponding. ON TREATMENT. sea-level trial ($p<.05$).

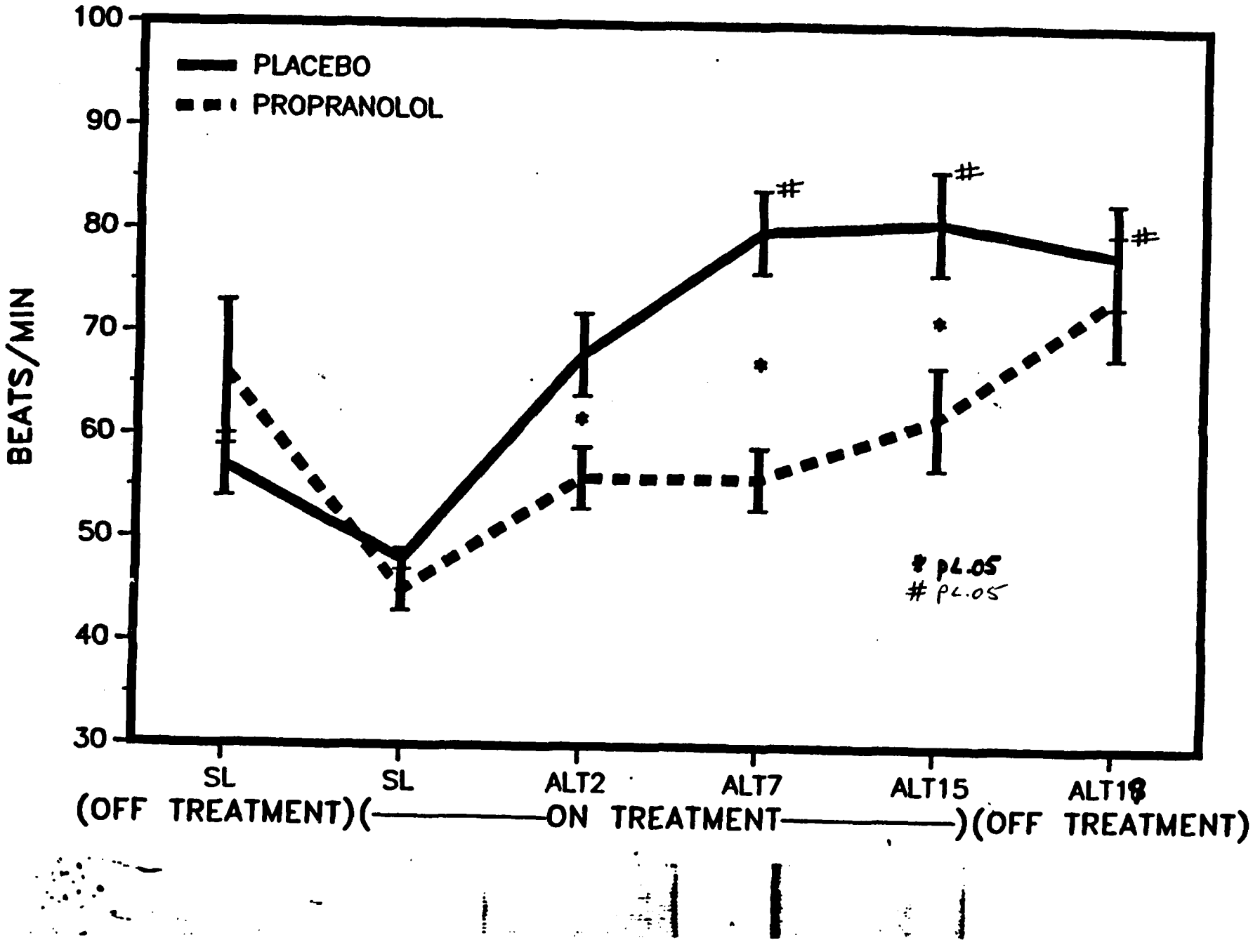
TABLE III

Mean Values for the Total and 9 Factor Scores of the ESQ for the Placebo and Propranolol Groups During the Mornings of Days 14,15, and 16 at Altitude.

	DAY 15 ON TREATMENT		DAY 16 OFF TREATMENT		DAY 17 OFF TREATMENT	
	Placebo	Propranolol	Placebo	Propranolol	Placebo	Propranolol
TOTAL	16 ± 6	11 ± 3	14 ± 5	12 ± 3	17 ± 7	11 ± 3
AMS-C	0.17 ± 0.13	0.02 ± 0.01	0.03 ± 0.03	0.02 ± 0.02	0.14 ± 0.13	0.03 ± 0.02
AMS-R	0.24 ± 0.13	0.09 ± 0.03	0.24 ± 0.10	0.08 ± 0.04	0.22 ± 0.07	0.10 ± 0.05
ENT	0.20 ± 0.10	0.13 ± 0.04	0.16 ± 0.08	0.21 ± 0.04	0.26 ± 0.11	0.17 ± 0.06
COLD STRESS	0.24 ± 0.15	0.06 ± 0.04	0.31 ± 0.14	0.08 ± 0.08	0.18 ± 0.12	0.11 ± 0.11
DISTRESS	0.46 ± 0.13	0.53 ± 0.47	0.66 ± 0.45	0.45 ± 0.18	0.49 ± 0.17	0.49 ± 0.16
ALERT	4.37 ± 0.22	3.30 ± 0.36	3.44 ± 0.86	3.79 ± 0.52	4.10 ± 0.37	3.80 ± 0.46
EXERTION	0.05 ± 0.05	0.21 ± 0.10	0.14 ± 0.08	0.21 ± 0.12	0.12 ± 0.08	0.16 ± 0.10
FATIGUE	0.17 ± 0.06	0.11 ± 0.04	0.43 ± 0.28	0.20 ± 0.07	0.21 ± 0.11	0.12 ± 0.05
MUSCULAR DISCOMFORT	0.15 ± 0.07	0.21 ± 0.00	0.27 ± 0.15	0.11 ± 0.03	0.25 ± 0.13	0.27 ± 0.07

Values are means ± S.E.

HEART RATE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