White blood cell and hormonal responses to 4300 m altitude before and after intermittent altitude exposure


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ABSTRACT

Recent studies have demonstrated that brief daily IAE (intermittent altitude exposure) was equally as effective as continuous altitude residence in inducing physiological adaptations consistent with altitude acclimatization. Although the positive benefits of IAE have been clearly defined, the potential negative consequences of IAE on health, specifically the immune system, remain undefined. The present study determined the effects of IAE on WBC (white blood cell) and hormonal responses during rest and exercise at 4300 m altitude. Six lowlanders (age, 23 ± 2 years; body weight, 77 ± 6 kg; values are means ± S.E.M.) completed a V̇O₂max (maximal O₂ uptake) and submaximal cycle ergometer test during a 30-h SL (sea level) exposure and during a 30 h exposure to 4300 m altitude-equivalent once before (PreIAE) and once after (PostIAE) a 3-week period of IAE (4 h · day⁻¹, 5 days · week⁻¹, 4300 m). The submaximal cycle ergometer test consisted of two consecutive 15-min work bouts at 40 % and 70 % of altitude-specific V̇O₂max. Blood samples were obtained at rest and during both exercise work bouts for measurements of WBC count, leucocyte subset counts, cortisol, adrenaline (epinephrine) and noradrenaline (norepinephrine). WBC, neutrophil and lymphocyte counts increased significantly (P < 0.05) during rest and exercise from SL to PreIAE and decreased (P < 0.05) during rest and exercise from PreIAE to PostIAE. Monocyte counts decreased (P < 0.05) during rest and exercise from PreIAE to PostIAE, but eosinophil and basophil counts did not change. Cortisol, adrenaline and noradrenaline did not change during rest or exercise from SL to PreIAE or PostIAE, but all increased significantly (P < 0.05) from rest during the two work bouts. In conclusion, this type of IAE stimulus did not induce a hormonal stress response and did no harm in terms of activation of the immune system at altitude, as measured by WBC and leucocyte subset counts. This method of pre-acclimatization can therefore be highly recommended for inducing altitude acclimatization without the ‘altitude residency’ requirement.

INTRODUCTION

Cortisol, adrenaline (epinephrine) and noradrenaline (norepinephrine) are released in response to the hypoxic stress of acute altitude exposure [1]. Altitude acclimatization, induced by 2–3 weeks of continuous altitude residence, results in a return of plasma cortisol and adrenaline towards baseline levels, but noradrenaline

Key words: adrenaline, cortisol, hypobaric hypoxia, intermittent altitude exposure, noradrenaline, submaximal exercise.

Abbreviations: [Hb], haemoglobin concentration; Hct, haematocrit; IAE, intermittent altitude exposure; Pₚ, barometric pressure; PreIAE, before a 3-week period of IAE; PostIAE, after a 3-week period of IAE; SL, sea level; V̇O₂max, maximal oxygen uptake; WBC, white blood cell.

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remains elevated [1]. These stress hormones, particularly cortisol and adrenaline, are well known for their ability to increase WBC (white blood cell) count and exert differential effects on leucocyte subset counts [2,3]. The leucocyte response at altitude is characterized by a rapid (<30 min) increase in lymphocytes, followed by neutrophilia and lymphopenia in the next 2–4 h of altitude exposure [4,5]. Previous findings have suggested that altitude acclimatization, induced by continuous altitude residence, results in a return of WBC and leucocyte subset numbers towards baseline SL (sea level) values [6,7]. These findings suggest that altitude acclimatization normalizes the state of activation of the stress hormones and the pattern of distribution of immune cells in the body.

Athletes, soldiers and mountaineers rapidly deployed to altitude to participate in an athletic feat, military mission or search and rescue operation, however, may not have sufficient time to reap the benefits of altitude acclimatization induced by 2–3 weeks of continuous altitude residence. Therefore attempts to pre-acclimatize individuals before ascent to high altitude using daily intermittent exposure to either hypoxia or hypobaric hypoxia have gained popular acceptance [8–11]. Recent studies [11,12] have demonstrated that brief daily IAE (intermittent altitude exposure; 4 h · day\(^{-1}\), 5 days · week\(^{-1}\), 3 weeks) to high altitude (4300 m) was equally as effective as continuous altitude residence in reducing the incidence and severity of acute mountain sickness, improving physical performance and inducing physiological adaptations consistent with altitude acclimatization. However, although the positive physiological and logistic benefits of IAE have been clearly defined, the potential negative consequences of IAE on health, specifically the immune system, remain undefined. Furthermore, whether or not a bout of submaximal exercise exacerbates the hormonal stress and leucocyte response at altitude above and beyond that which occurs at SL has not been answered.

Previous findings have suggested that acute activation of the stress hormones enhances immune function by directing leucocytes to exit the spleen and bone marrow and enter the blood stream [13,14]. By increasing the numbers of leucocytes in the peripheral blood, the number of cells that can migrate into potential damage sites is increased, which enhances the surveillance and effector functions of the immune system [15]. However, chronic activation of the stress hormones suppresses cell-mediated immunity by decreasing leucocyte deployment to the peripheral blood stream, which negatively impacts on the ability of the immune system to respond to an immunological challenge [13]. If IAE induces altitude acclimatization such that the stress hormones and leucocyte counts return towards baseline SL values, IAE may not affect the body’s ability to fight infection and disease at altitude. In contrast, if IAE chronically activates the stress hormones, the negative impact of IAE on immune function and health at altitude may outweigh the positive benefits described previously. Determining the direction of the immune system response to IAE will provide insight as to whether IAE represents a viable option (e.g. benefits without consequences) for pre-acclimatizing individuals for military missions, athletic feats and search and rescue operations.

The present study examined the effects of 3 weeks of IAE (4 h · day\(^{-1}\), 5 days · week\(^{-1}\), 4300 m) on WBC and hormonal responses during rest and exercise during an acute (i.e. 30 h) exposure to 4300 m altitude-equivalent. We hypothesized that WBC and hormonal responses at 4300 m altitude following 3 weeks of IAE would be similar to responses following altitude acclimatization. Specifically, we hypothesized that WBC counts, cortisol and adrenaline would increase during acute exposure to 4300 m altitude and return to baseline SL values during acute re-exposure to 4300 m altitude following 3 weeks of IAE, whereas noradrenaline would increase during acute exposure to 4300 m altitude and increase further during acute re-exposure to 4300 m altitude following 3 weeks of IAE.

**MATERIALS AND METHODS**

**Volunteer test subjects**

Six non-smoking volunteers (five men and one woman) with a mean (±S.E.M.) age, body weight and height of 23(±2) years, 77(±6) kg and 177(±3) cm respectively, participated. Mean body weight did not change during the 5-week course of the study. Each gave written and verbal acknowledgment of their informed consent and was made aware of their right to withdraw without prejudice at any time. The research was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Investigators have adhered to the policies for protection of human subjects as prescribed in US Army Regulation 70-25, and the research was conducted in adherence with the provisions of 45 CFR Part 46.

Each participant was a lifelong low-altitude resident and had no exposure to altitudes greater than 1000 m for at least 6 months preceding the study. All volunteers received medical examinations, and none had any condition warranting exclusion from the study. All tested within normal ranges for pulmonary function. All had normal [Hb] (haemoglobin concentrations) and serum ferritin levels. The woman had a normal menstrual cycle length (28 ±1 day) over the 2-month testing period, had not taken oral contraceptives or hormone therapy for the previous 6 months and had never been pregnant. Testing was not controlled for menstrual cycle phase, because of the reported lack of menstrual cycle effect on physical performance or hormonal response at altitude [16]. All participants performed regular SL aerobic training (1–2 h · week\(^{-1}\)) before and during the study, and were of average physical fitness.
Study design
The present study used an unblinded two-factor (test condition and blood sampling time) repeated-measures experimental design as reported previously [11]. The test conditions were defined as SL, PreIAE (before a 3-week period of IAE) and PostIAE (after a 3-week period of IAE). The blood sampling times were at rest, and 40% and 70% of altitude-specific VO_{2max} (maximal oxygen uptake) during the submaximal cycle ergometer test. Each volunteer completed a submaximal cycle ergometer test during a 30-h SL exposure and during a 30-h exposure to 4300 m altitude-equivalent [P_b (barometric pressure) = 446 mmHg] once before and once after a 3-week period of IAE (4 h · day^{-1}, 5 days · week^{-1}, 4300 m). VO_{2max} was measured at SL, PreIAE and PostIAE [11]. To minimize the impact of potential learning effects, all volunteers performed two preliminary VO_{2max} and submaximal cycle ergometer tests (both at SL) prior to definitive data collection. At SL, PreIAE and PostIAE, the submaximal cycle ergometer test was performed at approx. 20–24 h into the 30-h test condition at approximately the same time of day and same number of hours after the last meal.

IAE
In the morning before each IAE, volunteers were weighed (wearing T-shirts, shorts, and socks) and were encouraged to maintain constant body weight throughout the study. During each 4-h IAE, three volunteers rested for the entire 4 h, whereas the other three volunteers exercised for approx. 45–60 min at 70–85 % of pre-training altitude maximal heart rate on a cycle ergometer and then rested for the remainder of the 4 h altitude exposure. As exercise training progressed, power output was increased, if necessary, to ensure achievement of appropriate training heart rate during each training session. Volunteers were encouraged to drink water to replace any fluid loss during exercise and/or altitude exposure. All volunteers were required to maintain (i.e. not increase or decrease) their 1–2 h · week^{-1} aerobic training at SL to maintain their pre-study level of physical fitness. Physical activity monitor logs were kept throughout the 5-week study.

Environmental conditions
All testing and training were performed in a hypobaric chamber maintained at a temperature and relative humidity of 21 ± 2 °C and 45 ± 5 % respectively. SL testing was performed at ambient P_b (approx. 760 mm Hg), and all altitude exposures were conducted at an altitude-equivalent of 4300 m (P_b = 446 mmHg).

Submaximal cycle ergometer test
Volunteers were given meals of identical nutrient and caloric content during each 30-h test condition at SL, PreIAE and PostIAE. At no time during the entire study were volunteers allowed to consume caffeine. Volunteers were also required to abstain from alcohol for at least 24 h prior to all testing and not to exercise on the testing day. Prior to each test on the electromagnetically braked cycle ergometer (Model 800s; Sensormedics), the volunteer was weighed (wearing T-shirt, shorts and socks) to the nearest 0.1 kg. Following a 5-min warm-up at 100 W, the submaximal cycle ergometer test consisted of two consecutive 15-min work bouts at 40% and 70% of SL VO_{2max} at SL and 40% and 70% of PreIAE VO_{2max} at PreIAE and PostIAE.

Blood sampling and analyses
An indwelling catheter was placed in an arm vein at least 40 min before the submaximal cycle ergometer test. Following a 40-min sitting equilibration period, blood samples were drawn at rest and 10 min into each of the two consecutive 15-min work bouts for measurements of [Hb], Hct (haematocrit), WBC and leucocyte subset (neutrophil, lymphocyte, monocyte, eosinophil and basophil) counts, and plasma cortisol, adrenaline and noradrenaline. Arm position was controlled for all blood draws. Whole blood [Hb], and WBC and leucocyte subset counts were measured in duplicate (Cell Dyn 3500; Abbott Diagnostic). Hct was measured using aliquots of heparinized blood and the microcapillary method. [Hb] and Hct determinations were used to calculate changes in plasma volume during exercise [17]. Serum cortisol was measured using a commercial radioimmunoassay kit (Diagnostic Products). Catecholamines were extracted from plasma (Alko Diagnostics) and measured by HPLC (Model 2345; Waters). The percentage recovery for extraction of the catecholamines was 82 %. The intra-assay coefficients of variation for cortisol, adrenaline and noradrenaline were 5.2 %, 2.0 % and 2.0 % respectively. All samples for each volunteer were analysed in the same assay to avoid inter-assay variations.

Statistical analyses
A two-way repeated-measures ANOVA was used to analyse differences among the repeated measures test condition factor (SL, PreIAE and PostIAE) and repeated measures blood sampling time factor (rest, 40 % and 70 %) during the submaximal cycle ergometer test. Significant main effects and interactions were analysed using Tukey’s least significant difference test. Given that cycle training during IAE did not elevate any of the haematological or hormonal variables further, data from all six subjects were combined. All data are means ± S.E.M.

RESULTS
Haematological responses
Table 1 shows the WBC and leucocyte subset responses at rest and during exercise (40% and 70%) during the submaximal cycle ergometer test in each test condition
Table 1 Haematological responses at rest and during exercise at SL and during 30 h exposures to 4300 m altitude-equivalent (P\textsubscript{02} = 446 mmHg) before (PreIAE) and immediately after (PostIAE) a 3-week period of IAE

Values are means ± S.E.M. Haematocrit (Hct), WBC count and leucocyte (neutrophil, lymphocyte, monocyte, eosinophil and basophil) counts in six volunteers at rest and at 40 % and 70 % of SL \( V\textsubscript{02}\text{max} \) at SL, and 40 % and 70 % of PreIAE \( V\textsubscript{02}\text{max} \) at PreIAE and PostIAE during a submaximal cycle ergometer test. * \( P < 0.05 \) compared with SL. † \( P < 0.05 \) compared with PreIAE. ‡ \( P < 0.05 \) compared with Rest.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>40%</th>
<th>70%</th>
<th>Rest</th>
<th>40%</th>
<th>70%</th>
<th>Rest</th>
<th>40%</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Hb] (g/dl)</td>
<td>14.1 ± 0.3</td>
<td>14.8 ± 0.4‡</td>
<td>15.4 ± 0.4‡</td>
<td>15.0 ± 0.4*</td>
<td>15.7 ± 0.5‡</td>
<td>16.1 ± 0.4‡</td>
<td>14.9 ± 0.6*</td>
<td>15.4 ± 0.5‡</td>
<td>15.8 ± 0.4‡</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>45.5 ± 1.1</td>
<td>47.5 ± 1.1‡</td>
<td>48.5 ± 1.9‡</td>
<td>47.4 ± 1.2*</td>
<td>48.9 ± 1.1‡</td>
<td>49.6 ± 1.0‡</td>
<td>46.7 ± 1.5</td>
<td>48.3 ± 1.2</td>
<td>49.0 ± 1.2‡</td>
</tr>
<tr>
<td>WBC count (10(^9)/l)</td>
<td>6.2 ± 0.9</td>
<td>8.2 ± 1.3‡</td>
<td>10.7 ± 1.8‡</td>
<td>7.5 ± 1.1*</td>
<td>9.6 ± 1.3‡</td>
<td>11.4 ± 1.4‡</td>
<td>5.0 ± 0.7†</td>
<td>6.2 ± 0.8‡</td>
<td>7.9 ± 0.8‡</td>
</tr>
<tr>
<td>Leucocyte counts (10(^9)/l)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Neutrophil</td>
<td>3.8 ± 0.7</td>
<td>4.8 ± 1.2‡</td>
<td>6.1 ± 1.6</td>
<td>4.8 ± 0.9*</td>
<td>6.1 ± 1.1‡</td>
<td>6.9 ± 1.2‡</td>
<td>2.6 ± 0.5†</td>
<td>3.4 ± 0.7‡</td>
<td>4.1 ± 0.8‡</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1.5 ± 0.1</td>
<td>2.1 ± 0.2†</td>
<td>3.0 ± 0.2‡</td>
<td>1.8 ± 0.1*</td>
<td>2.4 ± 0.2‡</td>
<td>3.0 ± 0.2‡</td>
<td>1.6 ± 0.1†</td>
<td>1.9 ± 0.1‡</td>
<td>2.6 ± 0.1‡</td>
</tr>
<tr>
<td>Monocyte</td>
<td>0.6 ± 0.1</td>
<td>0.9 ± 0.1‡</td>
<td>1.1 ± 0.2‡</td>
<td>0.6 ± 0.1</td>
<td>0.9 ± 0.2‡</td>
<td>1.2 ± 0.2‡</td>
<td>0.5 ± 0.1†</td>
<td>0.7 ± 0.1‡</td>
<td>0.9 ± 0.1‡</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.24 ± 0.05</td>
<td>0.28 ± 0.06‡</td>
<td>0.33 ± 0.07‡</td>
<td>0.14 ± 0.04*</td>
<td>0.16 ± 0.04*</td>
<td>0.18 ± 0.05‡</td>
<td>0.15 ± 0.03*</td>
<td>0.17 ± 0.04*</td>
<td>0.20 ± 0.05‡</td>
</tr>
<tr>
<td>Basophil</td>
<td>0.07 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>0.11 ± 0.01‡</td>
<td>0.08 ± 0.01</td>
<td>0.09 ± 0.02</td>
<td>0.11 ± 0.02‡</td>
<td>0.08 ± 0.02</td>
<td>0.09 ± 0.02</td>
<td>0.11 ± 0.02‡</td>
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(SL, PreIAE and PostIAE). During rest and exercise, WBC counts increased significantly (\( P < 0.05 \)) by approx. 10–20 % from SL to PreIAE, and decreased significantly (\( P < 0.05 \)) by approx. 30–35 % from PreIAE to PostIAE. WBC count increased similarly from rest during exercise in each test condition. During rest and exercise, the neutrophil count increased significantly (\( P < 0.05 \)) by approx. 13–30 % from SL to PreIAE, and decreased significantly (\( P < 0.05 \)) by approx. 40–45 % from PreIAE to PostIAE. Neutrophil count increased similarly from rest during exercise in each test condition. During rest and exercise, the lymphocyte count increased significantly (\( P < 0.05 \)) by approx. 14–20 % from SL to PreIAE and decreased significantly (\( P < 0.05 \)) by approx. 11–20 % from PreIAE to PostIAE. The lymphocyte count increased similarly from rest during exercise in each test condition. During rest and exercise, the monocyte count did not change from SL to PreIAE, but decreased significantly (\( P < 0.05 \)) by approx. 26–29 % from PreIAE to PostIAE during rest and exercise. The monocyte count increased similarly from rest during exercise in each test condition. During rest and exercise, the eosinophil count decreased significantly (\( P < 0.05 \)) by approx. 41–47 % from SL to PreIAE and remained unchanged from PreIAE to PostIAE. The eosinophil count increased similarly from rest during exercise in each test condition. During rest and exercise, the basophil count did not change from SL to PreIAE to PostIAE. The basophil count increased similarly from rest during exercise in each test condition.

Hormonal responses

Table 2 shows the hormonal responses at rest and during exercise (40 % and 70 %) during the submaximal cycle ergometer test in each test condition (SL, PreIAE and PostIAE). Cortisol, adrenaline and noradrenaline did not change from SL to PreIAE to PostIAE during rest or exercise. Cortisol did not increase with exercise in any test condition, whereas adrenaline and noradrenaline increased similarly from rest during exercise in each test condition. There were no differences (\( P > 0.05 \)) in the percentage change in calculated plasma volume from rest to the end of the submaximal exercise bout at SL (\( −13 ± 2 % \)), PreIAE (\( −11 ± 1 % \)) and PostIAE (\( −10 ± 2 % \)).
DISCUSSION

The most important findings from the present study are: (i) WBC and several leucocyte subset counts were elevated during acute exposure to 4300 m altitude, but returned to baseline SL values during acute re-exposure to 4300 m altitude following 3 weeks of IAE (4 h·day⁻¹, 5 days·week⁻¹, 4300 m); (ii) cortisol, adrenaline and noradrenaline were not elevated during acute exposure to 4300 m altitude and did not change during acute re-exposure to 4300 m altitude following 3 weeks of IAE; and (iii) a bout of submaximal exercise stimulated WBC count and catecholamine release, but the response was not exaggerated at 4300 m altitude before or after 3 weeks of IAE compared with the response at SL.

Resting leucocyte and hormonal responses
Several studies have reported that WBC and leucocyte subset counts are elevated during acute exposure to altitude, and return to baseline SL values following continuous altitude residence [6,7]. Previous research examining the WBC response to IAE, however, is limited. One study [18] reported similar results to our present study in that WBC and neutrophil counts were increased on the first day of exposure to 4500 m altitude-equivalent and decreased upon re-exposure to 4500 m following IAE (2 h·day⁻¹, 7 day, 4500 m). Although it is not known what causes leucocyte levels to return to normal following altitude acclimatization, adrenaline and cortisol are probable candidates, because of their known effects on increasing leucocyte counts in the peripheral blood via demargination from the vascular endothelium and release from the spleen and bone marrow [2,3]. Given that both adrenaline and cortisol return to normal levels following altitude acclimatization [1,19], it follows that leucocyte counts should also return to normal levels following altitude acclimatization. In the present study, however, there was no decrease in adrenaline or cortisol following IAE, yet WBC and leucocyte subset counts decreased following IAE, which suggests that a different mechanism accounts for the decrease in WBC count following IAE than that responsible for decreases in adrenal-hormone-mediated stimulation. However, low subject numbers may have contributed to the lack of decrease in cortisol and adrenaline levels following IAE, such that this mechanism cannot be ruled out.

Similar to the present study, Savourey et al. [20] reported no change in resting cortisol or adrenaline before and after IAE (8 h·day⁻¹, 5 day, 4500–8500 m) in mountaineers, whereas both cortisol and adrenaline were decreased following continuous altitude residence [5]. Reasons for the differences in the cortisol and adrenaline response to IAE compared with continuous altitude residence remain to be elucidated, but may be related to the interruption of the hypoxic stimulus with normoxia during IAE. Savourey et al. [20], however, did report a significant increase (i.e. 150 %) in noradrenaline following IAE [20], whereas we found no increase in the present study. The reason for our lack of increase in noradrenaline following 3 weeks of brief daily IAE compared with relatively severe hypoxia is unknown given the dramatic increase in noradrenaline following continuous altitude residence [19].

Exercise leucocyte levels and hormonal responses
The WBC and hormonal responses to exercise at high altitude following IAE have not been reported previously. Only one study [21] has examined the haematological and hormonal responses to exercise before and after IAE (45 min·day⁻¹, 5 days·week⁻¹, 2500 m compared with 45 min·day⁻¹, 5 days·week⁻¹, 0 m), but that study made postIAE measurements at SL. Training-induced reductions in the hormonal response to a given work rate at SL following IAE were reported in that study [21], but the reductions were not potentiated by hypoxic training. In the present study, a bout of submaximal exercise stimulated adrenaline and noradrenaline release and increased WBC and leucocyte subset counts, which agrees with previous findings at both SL and altitude [3,22,23]. However, the catecholamine and leucocyte responses to exercise were not exaggerated at an altitude of 4300 m before or after 3 weeks of IAE compared with SL. Other research has suggested a synergistic effect of hypoxia and exercise on neutrophil and lymphocyte counts [24], but the exercise protocols between groups were not standardized in that study.

Exercise-induced haemoconcentration (approx. 10 %) probably contributed to the observed increases in WBC and leucocyte subset counts with exercise (approx. 50–100 %) in each test condition. However, the greater magnitude of increase in WBC count compared with exercise-induced haemoconcentration suggests demargination of WBCs from the endothelium or release from the spleen and/or bone marrow during both normoxic and hypoxic exercise [3]. The fact that cortisol did not increase from resting values during the 30-min bout of submaximal exercise, despite exercise-induced haemoconcentration, was surprising. This finding differs from previous observations demonstrating an increase in cortisol during 30–60 min of hypoxic exercise [25,26]. One reason for the lack of increase in cortisol during exercise in the present study may be related to the lower exercise intensity (40 % \(\dot{V}O_2\text{max}\)) utilized in the first 15-min work bout.

Practical clinical implications
Given the widely popular acceptance and known benefits of utilizing IAE to induce physiological adaptations consistent with altitude acclimatization, the main purpose of the present study was to determine whether IAE had
any negative consequences on the immune system at altitude that could potentially outweigh these positive benefits. This research demonstrates that IAE does not induce a hormonal stress response and does no harm in terms of activation of the immune system at an altitude of 4300 m. Although determining the number and proportion of leucocytes in the blood are only one measure of immune function, the blood is an important immune compartment that serves as a conduit by which immune cells travel between different tissues. As such, blood leucocyte counts provide an important representation of the state of activation of the immune system, and redistribution of immune cells has significant consequences on the ability of the immune system to perform its surveillance and effector function [13]. Also, the fact that exercise did not exacerbate the hormonal and leucocyte stress response at altitude compared with SL is important information, because the population subgroups deployed to altitude often perform strenuous physical work either to reach or upon reaching altitude.

Conclusions
In conclusion, WBC and several leucocyte subset counts were elevated during acute exposure to 4300 m altitude, but returned to baseline SL values during acute re-exposure to 4300 m altitude following 3 weeks of IAE (4 h·day−1, 5 days·week−1, 4300 m). The stress hormones were not affected by acute exposure to 4300 m altitude before or after 3 weeks of IAE. Although, a bout of submaximal exercise stimulated WBCs and catecholamine release, the response was not exaggerated at an altitude of 4300 m before or after 3 weeks of IAE compared with SL. These findings suggest that IAE does not induce a hormonal stress response and does no harm in terms of activation of the immune system at an altitude of 4300 m. This method of pre-acclimatization can therefore be highly recommended for inducing altitude acclimatization without the ‘altitude residency’ requirement.

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