

EXERCISE AT SIMULATED ALTITUDE INCREASES GASTROINTESTINAL BARRIER DAMAGE AND PROMOTES LEUKOCYTE ACTIVATION

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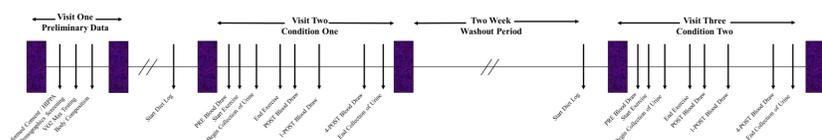
ABSTRACT

PURPOSE: This study tested whether altitude-associated ischemic stress damages the gastrointestinal barrier, activates leukocytes, and promotes inflammation. **METHODS:** Subjects (N = 5) completed two 60 min bouts of matched-workload treadmill exercise (65% $\dot{V}O_{2max}$). One under control conditions (Normoxia, $F_{I}O_2 = 20.9\%$) and the other at ~4000 m of simulated altitude (Hypoxia, $F_{I}O_2 = 13.5\%$). Pulse oximetry was used to measure peripheral oxygen saturation (SpO_2) and near-infrared spectroscopy was used to measure absolute tissue saturation (StO_2) at 5 min intervals throughout exercise. Fatty acid-binding protein (I-FABP), markers of leukocyte activation (CD14, ICAM-1, IL-8, MCP-1, MPO), and cytokines (TNF α , IL-1 β , IL-6, IL-10, IL-12) were measured in plasma samples that were collected Pre, Post, 1hr-Post, and 4hr-Post exercise. Data were analyzed with 2-Way (Condition x Time) RM ANOVAs with significance set at $p \leq 0.05$. *Post hoc*s (Newman-Keuls) were run where appropriate. **RESULTS:** Significant reductions in SpO_2 and StO_2 were shown during exercise at simulated altitude [SpO_2 : Hypoxia = $79 \pm 1\%$ vs Normoxia = $94 \pm 0.5\%$, $p = 0.03$ (StO_2 : Hypoxia = 61 ± 2 vs Normoxia = 69 ± 2 , $p < 0.01$)]. A significant interaction effect was shown for I-FABP ($p = 0.05$), with *post hoc* analysis indicating I-FABP increased more from Pre to Post in Hypoxia (112%) than in Normoxia (30%). IL-8 increased more from Pre to Post (60%) and 1hr-Post (83%) in Hypoxia than in Normoxia (33% & 57%, respectively). Significant main effects were also shown for IL-6, ICAM-1, CD14, and MCP-1. All were higher in Hypoxia ($p \leq 0.05$). MPO increased at Post in Normoxia (121%, $p = 0.05$) but did not increase until 1hr-Post in Hypoxia (129%, $p = 0.02$). **CONCLUSIONS:** Preliminary data suggest exercise at altitude may increase gastrointestinal barrier damage and leukocyte activation, as indicated by higher levels of I-FABP, IL-8, and MCP-1. Increased CD14 and ICAM-1 suggest TLR4-mediated inflammatory signaling may also be elevated, but the delayed increase in MPO following exercise at altitude warrants further investigation.

INTRODUCTION

- Intense exercise increases gastrointestinal barrier damage and endotoxemia risk [1]. It is unknown whether performing exercise at altitude, which reduces perfusion of the gastrointestinal (GI) tract, further increases these factors.
- Gastrointestinal (GI) barrier damage causes an increased concentration of I-FABP in circulation [2]. GI damage also stimulates macrophages to secrete IL-8, which activates neutrophils and causes them to home to sites of inflammation [3]. IL-8, along with CD14, ICAM-1, MCP-1, and MPO serve as markers of leukocyte activation in response to inflammation [4]. Both IL-1 β and TNF can cause ICAM-1 to be upregulated. IL-6 can be produced by both muscle contraction and secreted by macrophages and monocytes; it acts as an anti-inflammatory myokine when produced by muscle and as a pro-inflammatory myokine when secreted by macrophages/monocytes. As IL-6 increases, it can lead to a reciprocal increase in IL-10 and TNF α . Higher levels of these cytokines suggest increased inflammation and endotoxemia risk [5].
- This single-blind, normoxia-controlled research protocol investigated the effect of exercise in a hypoxic environment on human subjects' responses to exercise at 13,250 ft of simulated altitude. Systems-level physiological responses were assessed. Enzyme linked immunosorbent assays were used to assess circulating markers of gut permeability, leukocyte activation, and inflammation.

METHODS



RESULTS

Barrier Damage

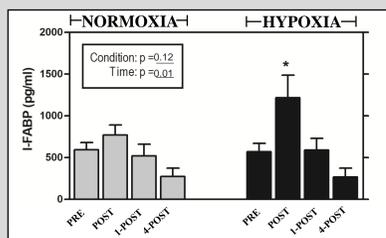


Figure 1. Exercise at simulated altitude increased gastrointestinal barrier damage. Intestinal Fatty Acid Binding Protein (I-FABP) response to 60 min exercise (60% $\dot{V}O_{2max}$) at simulated altitude of 13,250 ft. Data were analyzed by two way (Condition*Time) RM-ANOVAs with Newman-Keuls *post hoc*s. * indicates significant difference from PRE; $p \leq 0.05$.

Leukocyte Activation

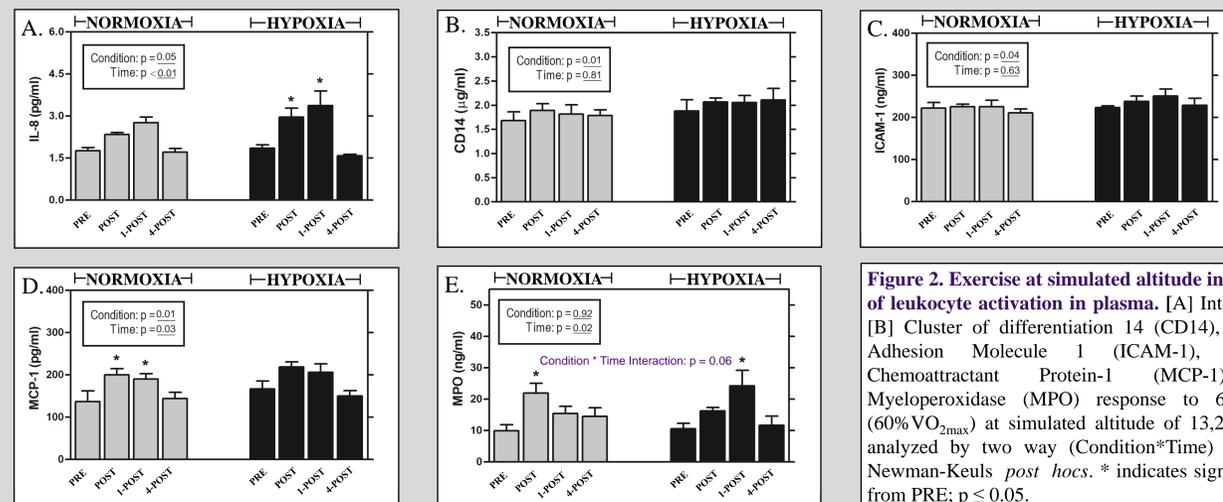


Figure 2. Exercise at simulated altitude increased markers of leukocyte activation in plasma. [A] Interleukin 8 (IL-8), [B] Cluster of differentiation 14 (CD14), [C] Intercellular Adhesion Molecule 1 (ICAM-1), [D] Monocyte Chemoattractant Protein-1 (MCP-1), and [E] Myeloperoxidase (MPO) response to 60 min exercise (60% $\dot{V}O_{2max}$) at simulated altitude of 13,250 ft. Data were analyzed by two way (Condition*Time) ANOVA with Newman-Keuls *post hoc*s. * indicates significant difference from PRE; $p \leq 0.05$.

Cytokine Responses

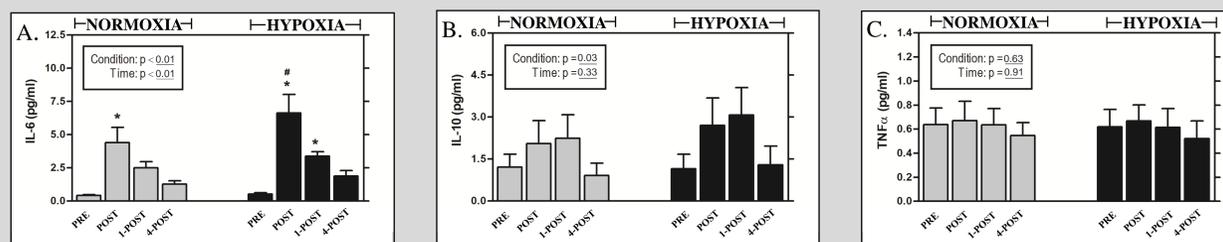


Figure 3. Exercise at simulated altitude increased the concentration of pro- and anti-inflammatory cytokines in circulation. [A] Interleukin 6 (IL-6), [B] Interleukin 10 (IL-10), and [C] Tumor Necrosis Factor Alpha (TNF α) response to 60 min exercise (60% $\dot{V}O_{2max}$) at simulated altitude of 13,250 ft. Data were analyzed by two way (Condition*Time) ANOVA and Newman-Keuls *post hoc*s. * indicates significant difference from PRE; $p \leq 0.05$. # indicates significant difference from the corresponding time point in the opposite study condition.

CONCLUSIONS

- Intestinal permeability (as shown by I-FABP) increased significantly from PRE to POST exercise in HYPOXIA, but not in NORMOXIA (Figure 1).
- Higher levels of IL-8, CD14, and ICAM-1 in HYPOXIA suggest increased leukocyte activation, which could contribute to an increase in TLR-4 mediated inflammatory signaling cascades (Figure 2).
- Increased IL-6 and IL-10 levels in HYPOXIA suggest that both inflammatory as well as anti-inflammatory cascades are increased during exercise at simulated altitude (Figure 3).
- Collectively, these data suggest that as compared to moderate intensity exercise at sea level, exercise at altitude may increase gut damage, leukocyte activation, and pro/anti-inflammatory cytokine secretion. It is possible that these factors could contribute to acute mountain-sickness associated symptomology.

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