GASTROINTESTINAL BARRIER PERMEABILITY AND ASSOCIATED INFLAMMATORY RESPONSE DURING EXERCISE AT SIMULATED ALTITUDE

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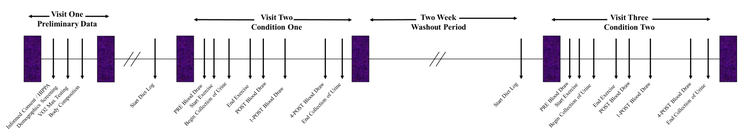
ABSTRACT

PURPOSE: Intense exercise at altitude can reduce blood flow to the gut by >70%. This study tested whether ischemic stress during exercise at altitude also promotes gastrointestinal barrier permeability and a pro-inflammatory response. **METHODS:** Subjects (N=5) completed two 60min treadmill runs at a workload equivalent to 60%VO_{2max}. One was performed at sea level (F_IO_2 = 21%) and the other at 13,250 ft of simulated altitude (F_IO2 = 14%). Blood samples were collected before (PRE), after(POST), 1hr (1-POST), and 4hrs after (4-POST) exercise. From these samples the circulating concentration of I-FABP (indicator of gut permeability/damage) and markers of leukocyte activation (CD14, GM-CSF, ICAM-1, IL-8, MCP-1) as well as inflammatory status (TNFα, IL-1β, IL-6, IL-10) were measured with ELISA. Data were analyzed with Two-Way RM-ANOVAs (Condition * Time) with statistical significance set at p≤0.05. Newman-Keuls *post hocs* were run where appropriate. **RESULTS:** I-FABP and IL-8 rose with exercise at simulated altitude but not when exercise was performed under normoxic conditions. IL-6 rose with exercise in both conditions but to a greater degree under simulated altitude. CD14, ICAM-1, and IL-10 were also significantly higher when exercise was performed at simulated altitude. **CONCLUSION:** Preliminary data suggest that exercise at altitude increases gastrointestinal barrier permeability. This may contribute to greater leukocyte activation, as indicated by the higher levels of IL-8 which is a known neutrophil chemotactic factor. Elevated circulating concentrations of CD14 and ICAM-1 suggest that TLR4-mediated inflammatory signaling cascades may also be increased. Collectively, these data suggest that gastrointestinal barrier permeability during exercise at altitude may be a previously unrecognized contributor to acute mountain sickness-associated symptomology.

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-1β 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 TNFα. 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

Gut Damage

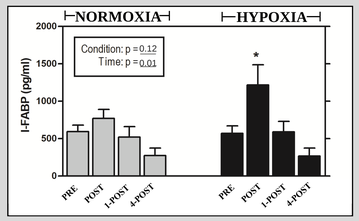


Figure 1. Exercise at simulated altitude alters gastrointestinal barrier permeability. Intestinal Fatty Acid Binding Protein (I-FABP) response to 60 min exercise (60%VO_{2max}) at simulated altitude of 13,250 ft. Data were analyzed by two way (Condition*Time) ANOVA and Newman-Keuls *post hoc*. * indicates significant difference from PRE; p ≤ 0.05.

Leukocyte Activation

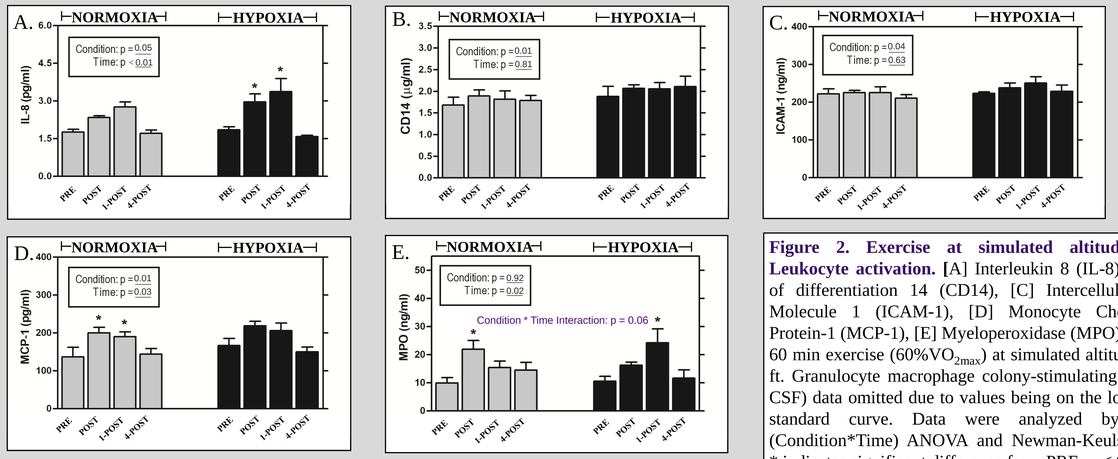


Figure 2. Exercise at simulated altitude increases Leukocyte activation. [A] Interleukin 8 (IL-8), [B] Cluster of differentiation 14 (CD14), [C] Intercellular Adhesion Molecule 1 (ICAM-1), [D] Monocyte Chemoattractant Protein-1 (MCP-1), [E] Myeloperoxidase (MPO) responses to 60 min exercise (60%VO_{2max}) at simulated altitude of 13,250 ft. Granulocyte macrophage colony-stimulating factor (GM-CSF) data omitted due to values being on the low end of the standard curve. Data were analyzed by two way (Condition*Time) ANOVA and Newman-Keuls *post hoc*. * indicates significant difference from PRE; p ≤ 0.05.

Cytokine Responses

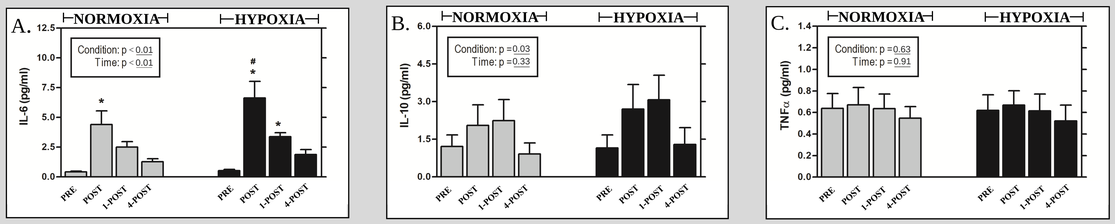


Figure 3. Exercise at simulated altitude increased pro- and anti-inflammatory cytokine secretion. [A] Interleukin 6 (IL-6), [B] Interleukin 10 (IL-10), [C] Tumor Necrosis Factor Alpha (TNFα) response to 60 min exercise (60%VO_{2max}) at simulated altitude of 13,250 ft. Interleukin 1 Beta (IL-1β) omitted due to values being on the low end of the standard curve. Data were analyzed by two way (Condition*Time) ANOVA and Newman-Keuls *post hoc*.*indicates significant difference from PRE; p ≤ 0.05. #indicates significant difference from the corresponding time point in opposite 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.

REFERENCES

[1] Pals, K. L., Chang, R. T., Ryan, A. J., & Gisolfi, C. V. (1997). Effect of running intensity on intestinal permeability. *J Appl Physiol*, *82*(2), 571-576.
[2] March, D. S., Marchbank, T., Playford, R. J., Jones, A. W., Thatcher, R., & Davison, G. (2017). Intestinal fatty acid-binding protein and gut permeability responses to exercise. *Eur J Appl Physiol*, *117*(5), 931-941.
[3] Harada, A., Sekido, N., Akahoshi, T., Wada, T., Mukaida, N., & Matsushima, K. (1994). Essential involvement of interleukin-8 (IL-8) in acute inflammation. *J Leuko Biol*, *56*(5), 559-564.
[4] Karakurum, M., Shreeniwas, R., Chen, J., Pinsky, D., Yan, S. D., Anderson, M., ... & Kuwabara, K. (1994). Hypoxic induction of interleukin-8 gene expression in human endothelial cells. *J Clin Invest*, *93*(4), 1564.
[5] Pedersen, B. K., & Steensberg, A. (2002). Exercise and hypoxia: effects on leukocytes and interleukin-6-shared mechanisms? *Med Sci Sports Exer*, *34*(12), 2004-2013.