THE RELATIONSHIP BETWEEN ACUTE MOUNTAIN SICKNESS, PATENT FORAMEN OVALE, AND SYSTEMIC INFLAMMATION

Karina A. Shah[1], K. DiMarco[1], K.M. Beasley[1], J.P. Speros[1], J.E. Elliott[2, 3], S.S. Laurie[4], R.D. Goodman[5], E. Futral[5], & A.T. Lovering[1]

[1]University of Oregon, Eugene, OR; [2]VA Portland Health Care System, Portland, OR; [3]Oregon Health and Science University, Portland, OR; [4]NASA Johnson Space Center, Houston, TX, [5]Oregon Heart and Vascular Institute, Springfield, OR

Introduction

The low oxygen levels that exist at high altitudes are often a difficulty for those that live, work, and travel to these extreme environments. Most people successfully adjust to the low partial pressure of oxygen, while those who do not use proper acclimatization or ascent profiles can develop acute mountain sickness (AMS). AMS occurs when individuals go too high in altitude too quickly. The pathophysiology behind AMS remains unknown, however, AMS is associated with hypoxemia (low blood oxygen) which everyone gets when going to high altitude (Loeppky et. al., 2008). A patent foramen ovale (PFO) is a passage for blood between the left and right atria. It allows deoxygenated blood to pass from the right atrium to the left atrium directly without going through pulmonary circulation to be oxygenated. Overall, this decreases the amount of oxygen in the blood. Therefore, it contributes to hypoxemia which can lead to increased incidence of AMS. Previous studies have found that the prevalence of AMS in subjects with PFO is much greater than the prevalence in those without a PFO (Elliott, 2015; West, 2019). AMS is reported to be associated with systemic inflammation as measured by elevated cytokines such as interleukins (Wang, 2018). Preliminary data from our lab suggests that subjects with PFO (PFO+) have elevated levels of systemic inflammation which decreases after PFO closure. It was hypothesized that PFO+ subjects would have a higher level of systemic inflammation at baseline compared to subjects without PFO (PFO-). Upon exposure to a simulated altitude of 15600 feet, inflammation will increase in both groups but will be highest in the PFO+ group which will explain the increased susceptibility to AMS.

Methodology

- 34 subjects (17 female)
- Saline contrast echocardiography to determine PFO presence
- UO Evonuk environmental chamber with 11.5% oxygen simulated ~15,600 ft
- AMS scores & plasma samples collected before & at 10 hours in the chamber
- AMS scores assessed using the Lake Louise Questionnaire (LLQ)
- A subject with an LLQ score ≥ 3 plus a headache was characterized as AMS+
- Plasma samples were stored at -80°C in a freezer
- Plasma samples were assayed using a 13-Plex Bead Based Assay Kit
- Inflammatory markers include: IL-1β, INF-α2, IFN-γ, TNF-α, MCP-1, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33
- Beads were divided by size & internal fluorescence intensity to determine the quantity the cytokine concentration in each sample using flow cytometry.

Results

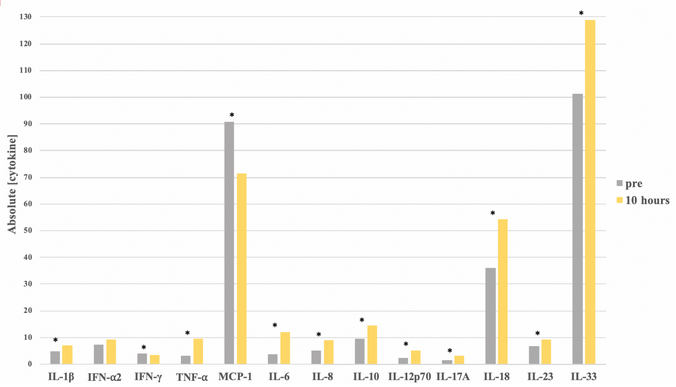


Figure 1. **Inflammatory cytokines increase after 10 hours of hypoxia compared to baseline.** Paired t-test. *p<0.05

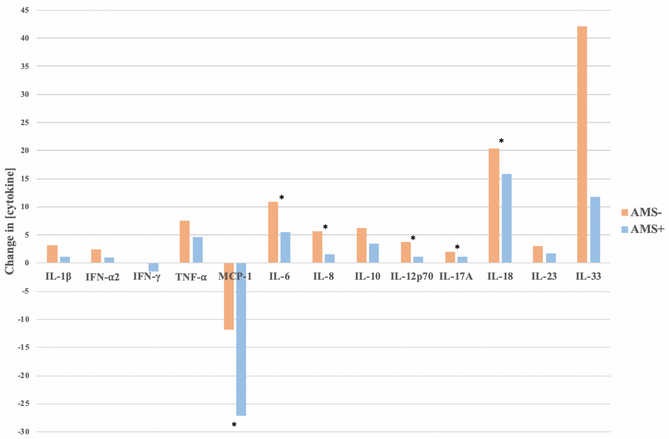


Figure 2. **AMS+ subjects have a smaller increase in inflammation upon exposure to hypoxia than AMS- subjects.** Two-way repeated measures ANOVA with Sidak post-hoc correction comparing the pre and 10-hour time points in AMS- and AMS+ participants. *p<0.05

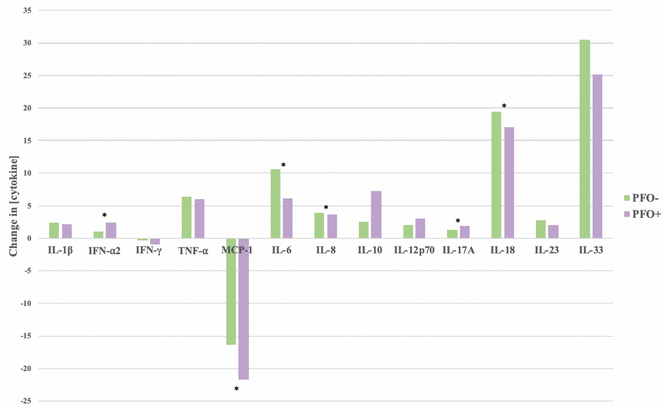
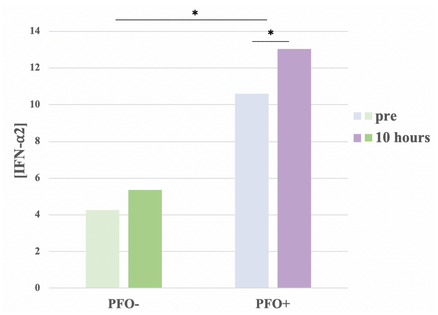


Figure 3. **PFO+ subjects had a lower change in IL-1β, TNF-α, IL-6, IL-8, IL-18, IL-23, IL-33 compared to PFO- subjects.** Two-way repeated measures ANOVA with Sidak post-hoc correction comparing the pre and 10-hour time points in AMS- and AMS+ participants. *p<0.05

Results



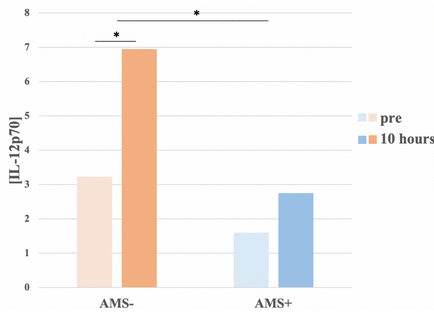


Figure 4. **IFN-α2 levels before and after hypoxia between PFO- and PFO+ subjects and IL-12p70 levels before and after hypoxia between AMS- and AMS+ subjects.** PFO+ subjects had significantly higher IFN-α2 levels than PFO- subjects and IFN-α2 was significantly increased after 10 hours of hypoxia in PFO+ subjects. AMS- subjects have significantly higher IL-12p70 levels than AMS+ subjects and IL-12p70 was significantly increased after 10 hours of hypoxia in AMS- subjects. Two-way repeated measures ANOVA with Sidak post-hoc correction comparing the pre and 10-hour time points in AMS- and AMS+ participants. *p<0.05

Summary & Conclusions

- Inflammation increased with exposure to hypoxia
- PFO+ group had the smallest increases in inflammation
- AMS+ group had the smallest increases in inflammation
- IFN-α2 was significantly greater in the PFO+ group and may provide biomarkers for determining AMS susceptibility
- IL-12p70 was significantly greater in the AMS- group and may prevent AMS
- We conclude that inflammation induced by hypoxia may be beneficial and protective in those with low baseline levels of inflammation, thereby reducing AMS susceptibility
- We conclude that those individuals with chronically elevated baseline levels of inflammation have a blunted change in hypoxia-induced inflammation and therefore increased AMS susceptibility

References

Elliott, J. E., et al., *Journal of Applied Physiology* (2015).

Wang, C., et al., *High Altitude Medicine and Biology* (2018).

West, B. H., et al., *Am Journal of Cardiology* (2019).

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