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INCREASED NOS ACTIVITY CONTRIBUTES TO VASCULAR CONTRACTILE HYPORESPONSIVENESS IN A TERRESTRIAL MODEL SIMULATING MICROGRAVITY

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Introduction: Cardiovascular remodeling in response to microgravity predisposes astronauts to orthostatic intolerance and decreased exercise tolerance on return to a 1G environment. It is now becoming appreciated that altered loading of heart and blood vessels, as well as neuro-hormonal signals, drive these changes. While these conditions are adaptive in space, they leave the system unable to adequately compensate on return to gravity. Central autonomic processing and efferent sympathetic and para-sympathetic responses have been shown to contribute to orthostatic intolerance. However, end organ hyporesponsiveness has recently been appreciated to be of critical importance in the deconditioning/hyporesponsive phenotype. We tested the hypothesis that the endothelium and specifically upregulation of the NO/cGMP pathway contributes to vasculature contractile hyporesponsiveness,

Methods: We used the hind limb unweighted (HLU) rat, a well recognized terrestrial model simulating microgravity. Wistar rats were HLU for 3, 14, or 21 days. Vascular contractile responses to NE and phenylephrine (PE) were tested in aortic rings. In order to determine the influence of the endothelium on contractile function, responses were tested in both endothelial intact (E+) and endothelial denuded (E-) rings.

Results: Contractile responses in E+ rings were attenuated to all agonists at 3 days. However, removal of the endothelium abolished the significant contractile hyporesponsiveness to all agonists observed in the aortic rings from HLU rats. At 7 days contractile responses were attenuated in both E+ and E- rings, suggesting the development of an endothelial-independent component at this time. The effect of basal NOS activity on vessel tone was determined by examining the effect of the specific NOS inhibitor L-NAME on vascular tension in precontracted rat aortic rings. In C rats, L-NAME resulted in an increase in tension in E+ rings, while there was no significant change in E- rings. L-NAME resulted in a much greater increase in tension in E+ rings from HLU rats supporting an increase in basal NOS activity in HLU rings. To further elucidate the mechanisms, we determined whether the observed responses were cGMP dependent. The specific GC inhibitor ODQ (1 μ M) was added to precontracted vessels and the alteration in tension measured. As with L-NAME, the addition of ODQ resulted in a significant increase in tension in E+ rings (21 \pm 6%) This response was markedly enhanced in rings from HLU rats (59 \pm 6%, vs C, p<0.05) supporting the role of cGMP and sGC as signaling pathways involved in HLU-dependent vascular hypo-responsiveness. To further examine mechanisms underlying enhanced NOS activity (increased enzyme expression or enzyme phosphorylation), we used Western blot analysis with phosphospecific antibodies to eNOS. We demonstrated a significant increase in PieNOS (1177) without a significant increase in total eNOS protein.

Conclusion: Upregulation of eNOS activity secondary to eNOS phosphorylation may contribute to vascular hyporesponsiveness and orthostatic intolerance following exposure to microgravity.