# Acute gravitational dose-response curves in hemodynamic and ocular variables induced by tilt

**Richard S. Whittle[1]*, Nathan Keller[2], Lindsay M. Stapleton[1], Eric A. Hall[3], Bonnie J. Dunbar[1], Ana Diaz-Artiles[1,2]**

[1]*Department of Aerospace Engineering, Texas A&M University, College Station, TX, USA*
[2]*Department of Health and Kinesiology, Texas A&M University, College Station, TX, USA*
[3]*Department of Biomedical Engineering, Texas A&M University, College Station, TX, USA*
**rswhittle@tamu.edu*

## INTRODUCTION

Exposure to microgravity causes the removal of hydrostatic pressure gradients and a permanent cephalad fluid shift, leading to a redistribution of blood. This has been potentially linked to a collection of neuro-ocular and functional changes developed in some astronauts, collectively known as Spaceflight Associated Neuro-Ocular Syndrome (SANS) (Marshall-Goebel *et al.*, 2017). Chronic fluid redistribution affecting intravascular, interstitial, and cerebrospinal fluids and pressures is widely hypothesized to be a contributing factor to SANS; however, the exact mechanisms are currently unknown. Additionally, recently demonstrated stagnant and retrograde blood flow and venous thrombosis in the left internal jugular vein during spaceflight could also be associated with sustained headward blood and tissue fluid shift (Marshall-Goebel *et al.*, 2019).

The objective of this ground-based research effort is to generate acute gravitational dose-response curves of cardiovascular (CV) and ocular variables due to changes in the gravitational vector induced by tilt. These dose-response curves inform us of the specific physiological response to a particular gravity level (or "dose"), leading to a greater understanding of hemodynamics and fluid shifts in both the eye and systemic circulation, deepening understanding of the etiology of SANS.

## MATERIAL AND METHODS

Eight male subjects (from a total of 12 subjects to be included in the study) were rotated from 45° head up tilt (HUT) to 45° head down tilt (HDT) in 15° increments. Subjects were tested in both prone and supine postures on two different days, in a counterbalanced design. After a 5-min rest period in each position, a range of cardiovascular and ocular variables were collected including: CV hemodynamics (Finapres NOVA, Finapres Medical Systems), cardiac output (Innocor, Cosmed), heart rate variability and other various autonomic indices (Finapres NOVA), intraocular pressure (IOP, iCare), internal jugular vein (IJV) and common carotid artery cross-sectional areas (Vscan Extend Ultrasound, GE Healthcare), and IJV pressure (VeinPress, VeinPress GmbH).

## RESULTS

Preliminary results from eight subjects show cardiac output increasing from 4.2±0.3 l/min to 6.2±0.3 l/min, from 45° HUT to 45° HDT, mostly due to an increase in stroke volume from 49.2±3.3 ml/beat to 91.0±5.8 ml/beat, blunted by a decrease in heart rate from 85.4±2.6 bpm to 70.0±2.8 bpm (Figure 1). Cardiac output in prone position (e.g., 4.9±0.3 l/min at 0°) was lower than in supine position (5.6±0.4 l/min at 0°). With tilt, there was a marked increase in IJV pressure (11.7±1.5 mmHg in 45° HUT to 57.9±2.6 mmHg in

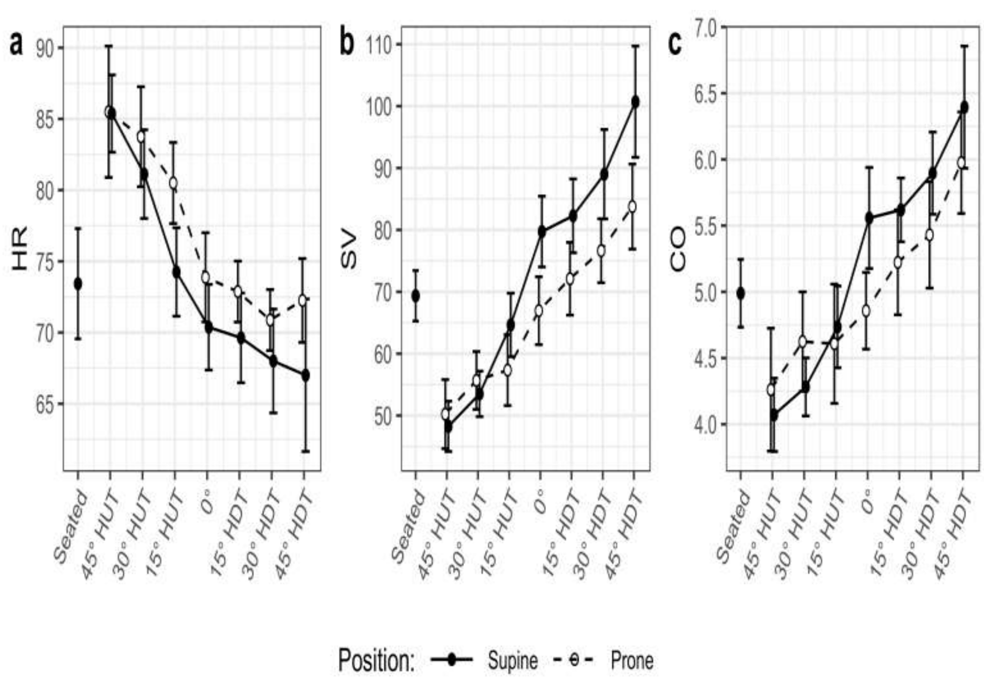


**FIGURE 1:** (**a**) Heart rate, (**b**) stroke volume, and (**c**) cardiac output of eight subjects tilted from 45° head up tilt (HUT) to 45° head down tilt (HDT). Solid line: supine (face up); dashed line: prone (face down). Data presented as mean and standard error.

45° HDT) (Figure 2). Heart rate variability also increased in multiple metrics with increasing HDT (Figure 3).

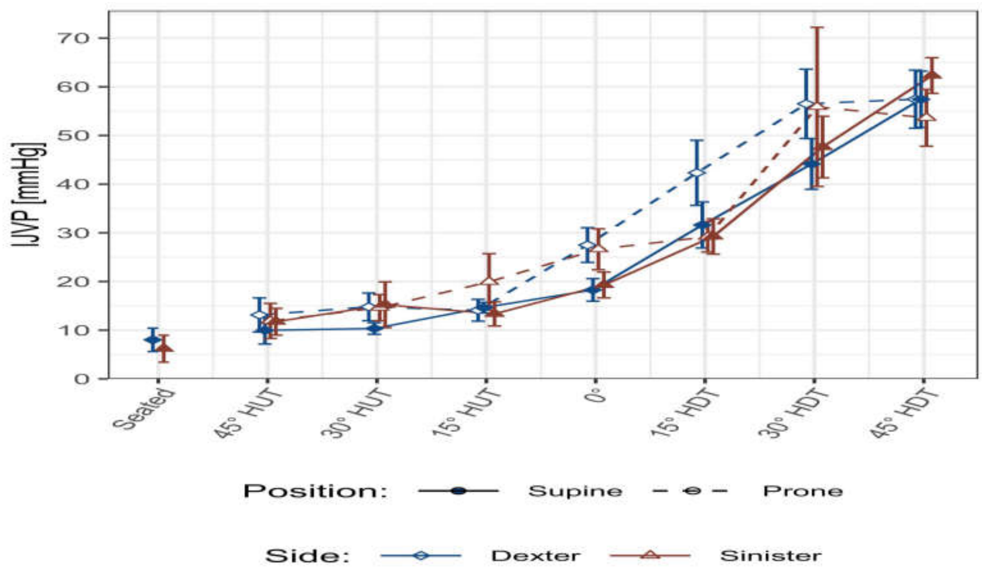


**FIGURE 2:** Internal jugular vein pressure (IJVP) of eight subjects tilted from 45° head up tilt (HUT) to 45° head down tilt (HUT). Solid line: supine (face up); dashed line: prone (face down); blue: dexter (right) side; red: sinister (left) side. Data presented as mean and standard error.

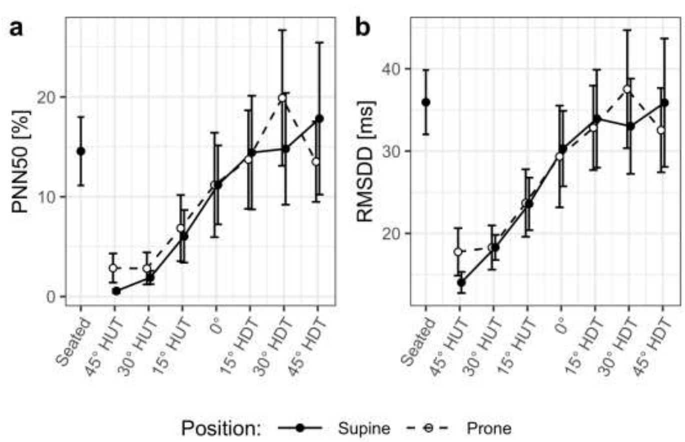


**FIGURE 3:** Heart rate variability of eight subjects tilted from 45° head up tilt (HUT) to 45° head down tilt (HDT). (**a**) PNN(50) represents the percentage of NN intervals that change by more than 50 ms between successive beats. (**b**) RMSDD is the root mean square of direct differences between successive NN intervals. Solid line: supine (face up); dashed line: prone (face down). Data presented as mean and standard error.

## DISCUSSION

Increasing head down tilt alters the effective gravitational vector in the head to foot direction (Diaz-Artiles *et al.*, 2019b). –6° HDT is often used as an analog for microgravity. The increase in cardiac output, together with increased stroke volume and reduced heart rate with increasing HDT agrees with both experimental studies and computational models of reduced gravity simulations (Diaz Artiles *et al.*, 2016; Whittle *et al.*, 2021) due to stimulation of the baroreceptors and enhanced venous return increasing preload. The finding that prone positioning reduces cardiac function has also been previously documented (Dharmavaram *et al.*, 2006) and is a result of reduced venous return and ventricular compliance compared with the supine position.

The cephalad fluid shift induced by HDT results in increasing IJV pressure. These findings match those found by multiple studies including Marshall-Goebel *et al.* (2017) up to –18° HDT and continue to increase all the way up to –45° HDT. We do not see any significant difference between left- and right-side pressures. However, it was noted that some subjects presented a clear asymmetry between their left and right IJV pressures (i.e., one side being significantly higher than the other side). Further investigation is required to examine the relationship between venous dominance, IJVP, and other measures of cephalad fluid shift (e.g., IJV cross-sectional area, IOP) in relation to outflow through different sides of the venous drainage pathways.

Finally, the two metrics of heart rate variability considered give some insight into the function of the autonomic nervous system during tilt. Both RMSDD (the root mean square of the direct differences in NN interval) and PNN(50) (the percentage of NN intervals that change by more than 50 ms between successive beats) are closely correlated with parasympathetic nervous system activity (Shaffer *et al.*, 2017). Hence, an increase matches the finding of a reduction in heart rate.

## CONCLUSION

The results of this study generate dose-response curves across a range of gravitational conditions in a number of different CV and ocular variables. Consideration of these curves leads to a greater understanding of the gravitational thresholds for different physiological parameters, e.g., where do the parameters depart from clinically permissible ranges. This is the first experiment of a larger study that will also consider the effect of countermeasures focused on producing hydrostatic gradients or reducing the microgravity-induced fluid shift, such as lower body negative pressure (LBNP) or centrifugation (Diaz *et al.*, 2015a; Diaz *et al.*, 2015b; Diaz Artiles *et al.*, 2018). Thus, in future experiments, we plan to test the same 12 subjects in a range of LBNP and artificial gravity conditions on the Texas A&M Aerospace Engineering Centrifuge. We are simultaneously developing a numerical framework to predict these CV and ocular responses to altered-gravity environments (Diaz-Artiles *et al.*, 2019a; Whittle *et al.*, 2020). Results from this investigation will inform current and future countermeasure development and in-flight prescriptions.

## ACKNOWLEDGMENTS

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**Keywords: Dose response, Tilt, Hemodynamics, Ocular, SANS**

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