

Intraocular and Intracranial Pressures During Head-Down Tilt with Lower Body Negative Pressure

Brandon R. Macias; John H. K. Liu; Noelia Grande-Gutierrez; Alan R. Hargens

- BACKGROUND:** Seven astronauts after 6-mo missions to the International Space Station showed unexpected vision problems. Lumbar punctures performed in the four astronauts with optic disc edema showed moderate elevations of cerebral spinal fluid pressure after returning to Earth. We hypothesized that lower body negative pressure (LBNP) imposed during head-down tilt (HDT) would reduce intraocular pressure (IOP) and transcranial ultrasound pulse amplitude, a noninvasive intracranial pressure (ICP) surrogate.
- METHODS:** Participating in this study were 25 normal healthy nonsmoking volunteers (mean age: 36 yr). Subjects were positioned supine (5 min), sitting (5 min), 15° whole body HDT (5 min), and 10 min of HDT with LBNP (25 mmHg). The order of HDT and HDT+LBNP tests was balanced. Right and left IOP, transcranial ultrasound pulse amplitude, arm blood pressure, and heart rate were measured during the last minute (steady state) of each testing condition.
- RESULTS:** IOP significantly decreased from supine to sitting posture by 3.2 ± 1.4 mmHg (mean \pm SD; $N = 25$), and increased by 0.9 ± 1.3 mmHg from supine to the HDT position. LBNP during HDT significantly lowered IOP to supine levels. In addition, LBNP significantly reduced transcranial ultrasound pulse amplitudes by 38% as compared to the HDT condition ($N = 9$). Sitting mean blood pressure (BP) was significantly higher (+5 mmHg) than BP values after 10 min of LBNP during HDT. However, heart rate was not significantly different across all conditions.
- DISCUSSION:** These data suggest that short duration exposures to LBNP attenuate HDT-induced increases in IOP and ICP.
- KEYWORDS:** lower body negative pressure, intraocular pressure, intracranial pressure, vision impairment, spaceflight.

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Ophthalmic evaluations of seven astronauts after their 6-mo missions to the International Space Station (ISS) reveal unexpected vision problems.¹⁶ These astronauts presented anomalies, including decreased near vision, globe flattening, optic disc edema, choroidal folds, nerve fiber layer thickening, and cotton wool spots within the retinal nerve fiber layer. Five ISS astronauts with postflight near vision changes had a hyperopic shift of 0.50 diopters in one or both eyes. While it is unknown if microgravity elevates intracranial pressure (ICP), lumbar punctures performed on four astronauts with optic disc edema exhibited moderate elevations of lumbar puncture opening pressure after the 6-mo ISS missions.¹⁶ The exact mechanisms and risk factors that cause vision impairment during spaceflight are unknown. However, the headward fluid shift that occurs when entering microgravity is hypothesized to be an initiating factor.²⁹

Hydrostatic pressure gradients significantly alter intraocular pressure (IOP) and ICP. Whole-body 10° head-down tilt

(HDT) significantly increases IOP by 4.7 mmHg as compared to the sitting posture.¹⁷ Following 48 h of 10° HDT, sitting IOP was reduced by 3 mmHg as compared to baseline sitting IOP values before tilt. This reduction in IOP following 48-h 10° HDT may suggest an adaptive decrease in aqueous volume from tilt-induced choroidal volume expansion. Recent data demonstrate that 10° HDT (for 30 min) increases subfoveal choroidal thickness from 300 μ m in the sitting posture to 333 μ m in the 10° HDT position.²⁴ Therefore, headward fluid shifts increase choroidal volume and affect IOP.

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Whole body tilt experiments enable precise and reproducible methods to alter gravitational hydrostatic pressure gradients. In addition, lower body negative pressure (LBNP) is a technique that shifts fluid away from the central circulation.⁴ Traditionally, whole body head-up tilt LBNP has been used to evaluate cardiovascular function and simulate gravitational hydrostatic pressures.²⁸ Hinghofer-Szalkay and coworkers report that HDT (-6° to -24°) counters hemodynamic, endocrine, and fluid volume changes induced by LBNP (-15 to -35 mmHg).¹¹ The purpose of the present study was to determine if LBNP normalizes the translaminar pressure difference during simulated microgravity. We hypothesized that LBNP imposed during HDT would reduce IOP and transcranial ultrasound pulse amplitude, a noninvasive ICP surrogate.

METHODS

This study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of California, San Diego. Healthy nonsmoking adults were recruited, informed of the study protocol, possible risks, and written informed consent was obtained. Participating in the IOP study were 14 male and 11 female paid volunteers (ages 18-60 yr). Among them, nine subjects participated in the transcranial ultrasound (ICP) study. Volunteers were instructed to refrain from contact lens use at least 4 h prior to participation the study.

Procedure

Proparacaine 0.5% was applied to the eye as a local anesthetic. The same technician performed all IOP measurements in this study. Both real-time and hard-copy IOP data outputs were visually inspected following each IOP measurement to ensure that the deviation index was below 0.5 mmHg. Subjects were positioned on a whole-body tilt table with the lower body inside the LBNP chamber. This custom tilting LBNP apparatus has been described previously.²⁸ In this study, the whole-body tilt table angles were supine (0°) and 15° head-down tilt (15HDT). To maintain stable negative pressures during the experiment, the lower body was sealed at the waist with a neoprene skirt. Subjects were instructed to maintain a relaxed body posture and minimize conversation, but remain alert to experiment instructions. The volunteers were positioned on the tilt-LBNP table for 5 min prior to the first supine data measurement. During the last minute of each experimental condition (e.g., minute 4) data were recorded. The order of 15HDT and 15HDT with LBNP stages were randomized to minimize confounding effects of order. The volunteer was tilted to the 15HDT position for 5 min. Next, with the volunteer in 15HDT, the LBNP was lowered to -25 mmHg for 5 min. The tilt and LBNP levels were maintained for another 5 min. In total, the volunteer was exposed to 10 min of 15HDT with LBNP. The volunteer was returned to the supine position and LBNP terminated for 5 min supine measurement. Following this second supine measurement, the subject was removed

from the tilt-LBNP chamber and seated in a chair for data collection in the sitting posture.

Equipment

IOP was measured using a pneumatometer (Reichert, Inc., Depew, NY). The pulsed phase lock loop (PPLL) measured ICP-associated skull expansions continuously and in real-time during the entire experimental protocol. The PPLL ultrasound probe was placed on the forehead and secured with surgical tape.¹⁴ Measurement of transcranial oscillations using the PPLL technique has been described in detail.^{14,26,27} Briefly, the ultrasound signal was focused to reflect against the posterior inner surface of the skull. Once a maximal ultrasound signal was achieved, the PPLL is locked, allowing the device to track the cardiac-cycle associated transcranial oscillations. Arm blood pressure and heart rate were measured using an automated arm blood pressure device (Omron Healthcare, Lake Forest, IL).

Statistical Analysis

IOP, blood pressure, and heart rate data were analyzed using repeated measures ANOVA (SPSS, version 21). Right and left IOP values were not statically different under all testing conditions. Therefore, right and left IOPs were averaged and used for statistical analysis. In addition, the supine IOP measurements were not statistically different. Therefore, supine IOP measurements were averaged for statistical analysis. Transcranial ultrasound pulse amplitudes during the last minute of each test condition were used for data analysis. Transcranial pulse waveforms over the 1-min data set were averaged to determine the mean pulse amplitude over one cardiac cycle. The peak-to-peak transcranial pulse amplitude was determined for each test condition and used for statistical analysis.²⁶ A paired *t*-test was used to determine significant differences between transcranial pulse amplitudes in the 15HDT and 15HDT with LBNP conditions. Mean arterial blood pressure was calculated as the diastolic blood pressure plus one-third of the difference between the systolic and diastolic blood pressures. Data are presented as mean \pm SD. Significance was accepted when $p < 0.05$.

RESULTS

The novel finding of the present study was the reduction of IOP and transcranial ultrasound pulse amplitudes using LBNP (25 mmHg) during 15° HDT. The repeated measures ANOVA revealed a main effect of test condition [$F(4,96) = 41.012$, $MS_{\text{error}} = 1.635$, $p < 0.001$]. IOP significantly decreased from supine to sitting posture by 3.2 ± 1.4 mmHg ($p < 0.001$), and significantly increased by 0.9 ± 1.3 mmHg from supine to the HDT position ($p = 0.013$) (Fig. 1).

During HDT, 10 min of LBNP significantly lowered IOP to supine levels (difference from supine, 0.3 ± 1.1 mmHg). Moreover, added LBNP during HDT significantly decreased transcranial ultrasound pulse amplitudes (noninvasive surrogate of ICP) by 2.1 ± 3.4 microns [$t(8) = 3.913$, $p = 0.004$, $N = 9$]

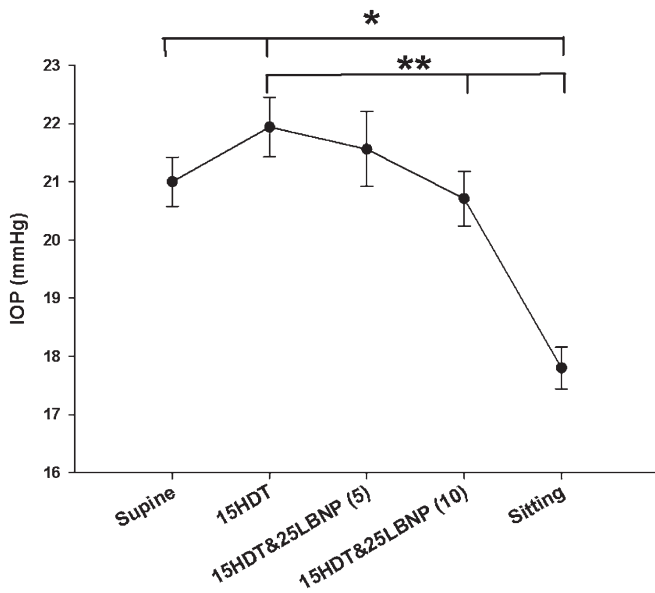


Fig. 1. Intraocular pressures (IOP) for the supine, whole-body 15° head-down tilt (15 HDT), 15 HDT and 25 mmHg lower-body negative pressure (25LBNP), 15HDT and 25LBNP (10 min), and sitting conditions. * $p < 0.001$ for IOP during supine, 15HDT, and sitting positions. ** $p < 0.001$ for IOP during 15HDT vs. 15HDT and 25LBNP (10 min) and sitting positions.

(Figs. 2 and 3). This represents a 38% reduction in ICP by LBNP relative to the HDT ICP pulse amplitude.

Sitting mean blood pressure was significantly higher (5 mmHg) than blood pressure during 10 min of 15HDT and 25 mmHg LBNP ($p = 0.012$; Table I). However, heart rate was not significantly different across all conditions.

DISCUSSION

The present data support our hypothesis that LBNP blunts HDT-induced elevations in IOP and transcranial pulse amplitude. During HDT, 10 min of LBNP normalized IOP to supine

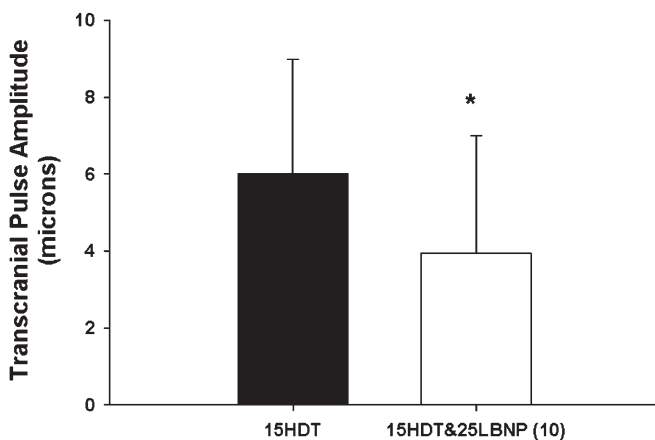


Fig. 2. Noninvasive ICP as assessed by transcranial pulse amplitudes. * $p = 0.004$ for 10 min of 25 mmHg lower body negative pressure (25LBNP) during 15° head-down tilt (15HDT).

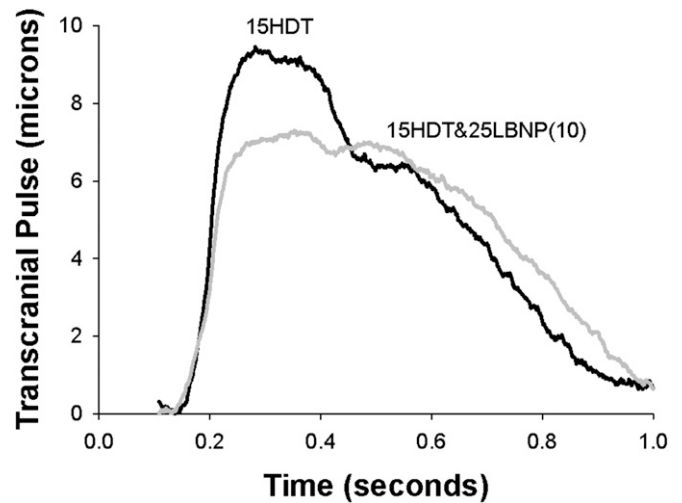


Fig. 3. Noninvasive ICP as assessed by transcranial pulse amplitude (1-min average) from one subject during 15° head-down tilt (15HDT) and with 10-min application of 25 mmHg lower body negative pressure [25LBNP (10)].

posture values. In addition, 10 min of LBNP lowered transcranial pulse amplitude, a noninvasive test of ICP, during HDT. HDT-induced elevations of ICP²² and IOP¹⁷ have been described previously. However, this is the first study to demonstrate that LBNP reduces IOP and ICP-associated transcranial pulse amplitude. Evidence suggests that translaminar pressure (IOP-ICP) across the optic disc may be critical to the maintenance of visual function.^{18,19}

IOP provides the necessary biomechanical force to the eye to maintain visual acuity. When the vertical distance between the eye and heart shortens, IOP elevates due to an increase of episcleral venous pressure and redistribution of blood to the choroid.¹⁰ Short-duration simulated microgravity during parabolic flight increased IOP by 58% (19 mmHg) as compared to normal gravity (12 mmHg).¹⁵ Those measurements that have been conducted during spaceflight demonstrate an immediate increase in IOP upon entering microgravity.^{6-9,23} However, evidence suggests that after the first week of spaceflight, IOP gradually returns to preflight values.^{7-9,23} During the German-Russian Mir mission and later the German Spacelab-D2 mission, measurements of IOP using the self-tonometer in one astronaut and later in three astronauts showed that IOP readings gradually return to the preflight values within 5 d.^{7-9,23} However, recent data from one Korean astronaut using the phosphene tonometer indicate that elevated IOP on the fourth day of spaceflight persists to the eighth day.⁶

IOP responds to hydrostatic pressure gradients. Linder and coworkers report a 23.6-mmHg increase in IOP when subjects were transitioned from the upright posture to a 90° inverted position after 1.5 min.¹³ In addition, following 2 h in the 6° HDT position, IOP increased 3 mmHg as compared to the upright posture.¹³ Prior to the start of a 48-h 10° HDT bed rest protocol, sitting IOP was 14.2 mmHg and increased by 4.7 mmHg after 30 min in the 10° HDT position.¹⁷ After 48 h of bed rest, IOP was 17.9 mmHg and decreased by 6.7 mmHg when subjects were positioned in sitting posture.¹⁷ This higher

Table 1. Blood Pressure and Heart Rate During Supine, HDT, LBNP, and Sitting Conditions.

| | SUPINE | 15HDT | 15HDT&25LBNP (5) | 15HDT&25LBNP (10) | SITTING |
|----------------|---------|---------|------------------|-------------------|----------|
| Blood pressure | 86 ± 9 | 87 ± 11 | 86 ± 11 | 85 ± 11 | *90 ± 14 |
| Heart rate | 69 ± 14 | 68 ± 13 | 69 ± 12 | 69 ± 13 | 72 ± 11 |

Mean ± SD; 15HDT: 15° head-down tilt; 15HDT&25LBNP (5): 15HDT with -25 mmHg LBNP for 5 min; 15HDT&25LBNP (10): 15HDT with -25 mmHg LBNP for 10 min.

* Blood pressure was significantly higher than the 15HDT&25LBNP (10) condition ($p = 0.012$).

magnitude IOP change after bed rest lead Mader and associates to hypothesize that HDT induced greater choroidal reservoir capacity.¹⁷ In another bed rest study, IOP decreased 1.56 mmHg after 7 d of 6° HDT as compared to IOP in the supine posture.⁵ During the recovery phase, 2 d after the bed rest protocol, supine IOP returned to pre-bed-rest values (14.1 mmHg).⁵ In the present study, IOP significantly increased by 0.9 mmHg after 4-5 min of 15° HDT exposure. In addition, the application of 10 min of LBNP during 15° HDT reduced IOP to supine levels. The increase in IOP by HDT and reduction of IOP by LBNP may be explained by changes in choroidal volume.

Choroidal engorgement is observed when positioned in the 10° HDT position.²⁴ Optical coherence tomography (OCT) measurements of choroid thickness are being conducted by the National Aeronautics and Space Administration (NASA) on some ISS crewmembers. Periodic OCT choroid thickness measurements during actual spaceflight will help determine the time course of choroidal expansion. However, the long-term implication of suspected choroidal expansion during spaceflight on ocular function is unknown.

Persistent elevation of ICP can affect eye structure and function. For example, papilledema is disc swelling associated with increased ICP. Retrospective investigations of 62,468 neurological patients show that disrupted translaminar pressures are significantly correlated with the development of optic disc cupping.^{1,2} Cerebrospinal fluid pressure, measured by lumbar puncture, suggests that ICP is lower in patients with glaucoma as compared to normal healthy controls.^{12,21} Therefore, these data suggest that the translaminar pressure difference (IOP-ICP) across the lamina cribrosa may be an important factor to maintain eye structure and function. ICP responds within seconds to changes of posture.^{14,22,26} Thus, both ICP and IOP respond to posture-induced hydrostatic pressure gradients. Therefore, the loss of hydrostatic pressure and resultant impact on translaminar pressure dynamics during long-duration spaceflight may alter eye function.²⁹

Lumbar puncture opening pressure is elevated in some astronauts postflight. Lumbar punctures performed in the four astronauts with optic disc edema showed moderately elevated cerebrospinal fluid (CSF) pressure (16-21 mmHg, measurements taken 12-66 d postlanding). However, the magnitude of the CSF pressure elevation is unclear because preflight pressures were not conducted. For comparison, the average opening CSF pressure in healthy individuals is approximately 12 mmHg. This suggests that the translaminar pressure difference may be higher during spaceflight than that observed on Earth.

The gold standard ICP measurement technique requires insertion of a catheter into the cranial vault. Therefore, few invasive ICP measurements have been conducted on healthy patients or during HDT. Those invasive measurements that have been conducted are typically of patients undergoing treatment for elevated ICP. Therefore, noninvasive measurement modalities to estimate ICP, such as the PPLL device, enable routine measurements of hydrostatic pressure induced alterations of ICP. The PPLL measures transcranial pulsations on the order of micrometers using bone-penetrating ultrasound. Ueno and coworkers demonstrated that PPLL pulse amplitude was linearly associated with invasively measured ICP in patients.²⁷ In addition, calibrated ultrasound pulse amplitudes increased by approximately 3 microns from the supine to the 15°HDT position.²⁶ This previous report of HDT-induced elevation of transcranial pulse amplitude is similar to the 2.4-micron reduction in transcranial pulse amplitude during 10 min of LBNP in the present study.²⁶ Therefore, the present data suggest that LBNP alters ICP-induced transcranial pulse amplitude.

Gravity causes blood to pool in the lower limbs when standing upright, therefore lowering ventricular preload. Similarly, LBNP (-50 mmHg) acutely decreases circulating blood volume by 500-1000 ml due to venous pooling in the legs.^{20,25} Interpreting change in the ICP pulse wave is complex and variable. However, three components of the ICP pulse waveform tend to be consistent: the arterial pulse wave, the tidal wave, and the dicrotic wave.³ It is noteworthy that only the arterial pulse wave appears to be reduced with LBNP exposure during tilt (Fig. 3). Future studies of invasively measured ICP may help elucidate the mechanism of LBNP on ICP waveforms.

Noninvasive PPLL measures of ICP-associated cranial pulsations provide real-time, high-frequency, and long-duration measurements. However, due to the noninvasive nature of the PPLL technology, the transducer requires placement on the skin surface. Therefore, cutaneous arterial pulses may have contributed to probe movement. To minimize the contribution of skin pulsation and movement, the transducer was secured with surgical tape. In addition, ultrasound targets that are near the inner surface of the skull were selected to prevent confounding effects of soft tissue pulsations.

In conclusion, 10 min of LBNP restored 15° HDT-induced increases of IOP. In addition, LBNP lowers ICP-associated transcranial pulsations during 15° HDT. The HDT-induced increase in IOP was reduced to IOP values observed in the supine posture. In addition, LBNP reduced a noninvasive ICP surrogate

by 38% during HDT. Therefore, our results support the hypothesis that LBNP imposed during simulated microgravity conditions reduces IOP and transcranial ultrasound pulse amplitude (the noninvasive ICP surrogate). The use of two different fluid shift modalities, HDT and LBNP, further support the growing evidence that choroidal expansion alters IOP. The use of HDT and LBNP may provide a useful ground-based model to investigate the impact of fluid shifts on ocular and cerebral structure and function.

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