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## Cover Page

**Title:** Effect of gravity and microgravity on intracranial pressure

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**Running header:** Gravity on intracranial pressure

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## Key Points Summary

- Astronauts have recently been discovered to have impaired vision, with a presentation that resembles syndromes of elevated intracranial pressure on Earth.
- Gravity has a profound effect on fluid distribution and pressure within the human circulation. In contrast to prevailing theory, we observed that microgravity reduces central venous and intracranial pressure.
- This being said, intracranial pressure is not reduced to the levels observed in the 90° seated upright posture on earth. Thus, over twenty-four hours in zero gravity, pressure in the brain is slightly above that observed on earth, which may explain remodeling of the eye in astronauts.

## ABSTRACT

Astronauts have recently been discovered to have impaired vision, with a presentation that resembles syndromes of elevated intracranial pressure (ICP). This syndrome is considered the most mission critical medical problem identified in the past decade of manned spaceflight. We recruited five men and three women who had an Ommaya reservoir inserted for the delivery of prophylactic central nervous system chemotherapy, but were free of their malignant disease for at least 1 year. ICP was assessed by placing a fluid-filled 25 ga butterfly needle into the Ommaya reservoir. Subjects were studied in the upright and supine position, during acute zero gravity (parabolic flight) and prolonged simulated microgravity (6° head down tilt bedrest). ICP was lower when seated in the 90° upright posture compared to lying supine (Seated,  $4 \pm 1$  vs supine,  $15 \pm 2$  mmHg). Whilst lying in the supine posture, central venous pressure (supine,  $7 \pm 3$  vs microgravity,  $4 \pm 2$  mmHg) and ICP (supine,  $17 \pm 2$  vs microgravity,  $13 \pm 2$  mmHg) were reduced in acute zero gravity, although not to the levels observed in the 90° seated upright posture on earth. Prolonged periods of simulated microgravity did not cause progressive elevations in ICP (supine,  $15 \pm 2$  vs 24 hours head down tilt,  $15 \pm 4$  mmHg). Complete

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removal of gravity does not pathologically elevate ICP but does prevent the normal lowering of ICP when upright. These findings suggest the human brain is protected by the daily circadian cycles in regional ICPs, without which pathology may occur.

**Key words:** Space, Posture, bedrest, Ocular remodeling, Idiopathic intracranial hypertension.

## INTRODUCTION

When humans sit upright on Earth, the head-to-foot hydrostatic gradient (Gz) pulls fluid towards the feet. Conversely when lying in the supine posture, typically whilst asleep at night, fluid redistributes towards the head (Rowell, 1986). Thus, gravity profoundly affects pressure, volume and flow in the human circulation with habitual changes in posture causing diurnal fluctuations in the distribution of fluid and regional pressures.

On Earth, these pressure fluctuations are normal and generally do not cause pathology. However, there are specific human conditions that are exacerbated, or in some cases caused by these fluid shifts. For example, idiopathic intracranial hypertension and its symptoms are worse in the supine position, and in some cases may be detectable only at night (Torbey *et al.*, 2004). Intracranial hypotension occurs primarily in the upright position, and both of these conditions can cause severe and intractable headache (Ducros & Biousse, 2015).

In the absence of gravity, e.g., the microgravity environment encountered by astronauts on the International Space Station, this cephalad redistribution of body fluids, and in particular, the cephalad redistribution of cerebral spinal fluid (CSF), has been hypothesized to cause a newly-discovered syndrome of deterioration of visual acuity in astronauts (Mader *et al.*, 2011). In microgravity, redistribution of fluid towards the brain is hypothesized to elevate intracranial pressure (ICP) in a manner disproportionate to intraocular pressure (IOP), thus resulting in an reduced pressure gradient (IOP-ICP) across the lamina cribrosa at the posterior aspect of the eye. Indeed, in an acute model of

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simulated microgravity, head-down tilt (-9° and -10°) caused increased intracranial pressure (Petersen *et al.*, 2015; Eklund *et al.*, 2016) but not intraocular pressure (Eklund *et al.*, 2016). Astronauts with this syndrome develop physical findings suggestive of elevated ICP including papilledema, flattening of the globe of the eye, and dilation of the optic nerve sheath. This analogy and the theoretical link between cephalad fluid shift and intracranial hypertension has led NASA flight surgeons to refer to the syndrome as the Visual Impairment / Intracranial Pressure syndrome, or “VIIP” and it is considered to be NASA’s top health risk for long-duration spaceflight, including exploration missions to Mars (Mader *et al.*, 2011). In addition to the exposure to microgravity on the International Space Station, it has been hypothesized that other environmental conditions (i.e., elevated ambient CO<sub>2</sub> concentration) and rigorous strength based exercises regularly performed by astronauts to avoid musculoskeletal loss, create a “perfect storm” that causes raised ICP and visual impairments in astronauts (Nelson *et al.*, 2014; Michael & Marshall-Bowman, 2015).

Despite the attractiveness of this theory however, no direct ICP measurements in microgravity with or without elevated CO<sub>2</sub> or resistance exercise. Moreover, invasive studies of cardiovascular adjustments to microgravity have demonstrated that microgravity physiology is complex and at times counter-intuitive; for example, central venous pressure, (CVP) originally thought to be increased in astronauts, was decreased (Buckey *et al.*, 1993; Videbaek & Norsk, 1997). Despite our conceptual understanding of these fundamental relationships between gravity and human physiology, no investigation has documented the simultaneous adjustments in arterial, venous and cerebral spinal fluid pressures due to the influence of gravity.

## METHODS

## PARTICIPANTS.

Five men (age,  $35 \pm 13$  yrs; height,  $177 \pm 13$  cm; weight  $87 \pm 22$  lbs) and three women (age,  $36 \pm 4$  yrs; height,  $167 \pm 11$  cm; weight  $63 \pm 10$  lbs) who previously had an Ommaya reservoir (catheter placed from the lateral ventricle to a cerebral spinal fluid filled reservoir under the scalp) inserted for the delivery of prophylactic central nervous system chemotherapy as part of their treatment for hematologic malignancy were recruited to take part in this study. E-mails were sent to the medical directors of most major medical centers in the US managing adults with hematologic malignancies describing the inclusion/exclusion criteria and requesting referrals. A Facebook page was created, and patient support groups were messaged, though the physicians of all interested volunteers were also consulted. All participants had structurally normal brains documented with MRI, were free of their malignant disease for at least one year, had normal cardiovascular systolic and diastolic function documented by echocardiography, had normal complete blood counts including hematocrit, white blood cell count, and platelets, and were on no regular medications that affect cerebral hemodynamics. All participants were informed of the purpose and risks of each procedure and signed an informed consent form, which was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center and NASA Johnson Space Centre and followed guidelines set forth in the Declaration of Helsinki.

## DATA COLLECTION

Intracranial pressure: After a single intravenous dose of cefazolin, a fluid-filled 25 gauge butterfly needle was inserted in the Ommaya reservoir and connected to a pressure transducer (Transpac IV; Abbott, Fig. 1). The wings of the butterfly needle were sutured to the scalp surrounding the Ommaya reservoir and secured with a head dressing so participants could move freely without dislodging the butterfly needle. The presence of cardiac and respiratory oscillations concomitant with the appropriate response to cough, Valsalva maneuver, and head turning was used to confirm that the

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pressure waveform reflected intracranial pressure (ICP). The transducer was fixed at the level of the external acoustic meatus throughout all experimental conditions. As such, ICP was accurate through changes in posture and during microgravity. The pressure transducer was periodically zeroed to the atmospheric reference point.

Central venous pressure: A fluid-filled 4 French peripherally inserted central catheter was placed using ultrasound guidance into a brachial vein. Thereafter, the catheter was advanced to the level of right atrium under fluoroscopic guidance and the correct position was confirmed by fluoroscopy and the presence of characteristic central venous pressure (CVP) waveforms (Fig. 1). Position of the right atrium was marked on the body in the anteroposterior and lateral planes; the pressure transducer (Transpac IV; Abbott) was fixed to the body at level of the right atrium during parabolic flight (study 2). During changes in posture (study 1) and bedrest (study 3) the pressure transducer was fixed to a pole and leveled to the right atrium with each change in posture. The pressure transducer was periodically zeroed to the atmospheric reference point. Both ICP and CVP pressure transducers were connected to a patient monitor (Tram-rac, Marquette, USA) with analog signal digitized through an analog to digital converter (MP-150, Biopac Systems, USA).

Hemodynamics: With changes in posture (study 1) and throughout HDT (study 3), steady-state arterial blood pressure was measured by electrophygmomanometry (SunTechMedical Instruments Inc., USA, (Fig. 1)) with a microphone placed over the brachial artery to detect Korotkoff sounds. During parabolic flight (study 2), bedrest (Study 3) and throughout leg press exercise (study 4), beat-by-beat arterial blood pressure was also measured by photoplethysmography (Nexfin; BMEYE, Netherlands, (Fig. 1)), with changes in cardiac stroke volume calculated using the Modelflow method (Wesseling *et al.*, 1993; Shibata & Levine, 2011). Beat-by-beat blood pressure device was turned off during sleep (study 3). Prior to steady state data collection with changes in posture and during HDT,

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hemodynamic stability was confirmed by stable cardiac outputs [data not shown] via the acetylene rebreathing technique (model MGA1100, Marquette, USA) (Jarvis *et al.*, 2007).

Jugular venous diameter: As an indirect indicator of cephalad fluid volume (fluid shifts above the heart), the cross-sectional area of the right internal jugular vein was measured by cardiac gated B mode ultrasonography using a 7 - 12 MHz linear transducer (IE33, Phillips, USA, (Fig. 1)). The internal jugular vein was imaged 2 cm below the carotid bifurcation with care taken not to compress the vein. Identification of the Jugular vein was confirmed by color Doppler and by asking subjects to perform a small Valsalva maneuver. The maximum cross-sectional area was measured off-line at the ECG T-wave in triplicate for each condition (OsiriX, USA).

### Experimental Protocols

**Study one** assessed changes in ICP with change in posture from the 90° sitting upright to supine position. Moreover, whilst in the supine position, subjects placed their head on a pillow to assess the influence of this common procedure in patients obligated to long-term bed rest. Measurements were performed in a quiet, environmentally controlled laboratory with an ambient temperature of ~25°C. Five minutes of steady state hemodynamics were obtained in the 90° sitting and supine positions. **Study two** assessed changes in ICP during removal of all hydrostatic gradients with brief (~20 sec) exposure to microgravity during parabolic flight. Subjects received a single dose of weight adjusted intramuscular Scopolamine (<110 lbs, 0.1 mg; 111-160 lbs, 0.2 mg; 161-220 lbs, 0.3 mg; >220 lbs, 0.4 mg;) ~1 hour before flight to prevent nausea and vomiting, which would confound the data. Continuous data were averaged over at least one minute during 1G and over six sequential, 20-second periods of 0G. Gravity was measured continuously from the onboard accelerometer.

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Moreover, to document any effect of changes in cabin pressure during parabolic flight, separate pressure transducers were setup to measure cabin pressure directly and pressure within a closed, fluid-filled length of tubing positioned perpendicular to the direction of flight (i.e. the same direction as the subjects). No changes were observed in either pressure system during parabolic flight.

**Study three** assessed changes in ICP during prolonged exposure to simulated microgravity using a model of -6° HDT. During data analysis, careful attention was paid to identify pathological pressure waves as a sign of intracranial instability (Torbey *et al.*, 2004). Furthermore, the pulse amplitude of the ICP waveform was used to assess the compliance of the craniospinal system (Qvarlander *et al.*, 2013a). **Protocol four** assessed change in ICP associated with increased ambient Carbon Dioxide (CO<sub>2</sub>) equal to that measured on the International Space Station (F<sub>I</sub>O<sub>2</sub> of 0.7% (4 mmHg (Law *et al.*, 2014))), and with leg press exercise typically undertaken by astronauts to avoid musculoskeletal atrophy in space. Additional CO<sub>2</sub> was delivered by a tight fitting face mask. During parabolic flight, participants breathed this gas mixture for 3 to 5 minutes during the 1G turn around (supine condition) and throughout one set of 5 to 10 parabolas. During bedrest, subjects breathed this CO<sub>2</sub> mixture for 5 minutes in the supine position and after 5 minutes (acute) and 24 hours (prolonged) of -6° HDT. Onboard parabolic flight, data were averaged over the final minute of CO<sub>2</sub> breathing in 1G and averaged over the following 5 - 10 periods of 0G. In the supine and head down tilt conditions, data were averaged over the last minute of steady state.

To replicate the typical exercise regimes undertaken by astronauts to avoid musculoskeletal atrophy during spaceflight, leg press exercise was performed whilst breathing additional CO<sub>2</sub>. Therefore, during parabolic flight (5 -10 parabolas), the supine position and after 5 minutes and 24 hours head down tilt, participants continued to breathe additional CO<sub>2</sub> whilst performing moderate to heavy (7-8 on a 0-10 BORG rating of perceived exertion scale (Cooper *et al.*, 1979)) leg press



exercise with self-paced breathing. During head down tilt, participants also completed 5 repetitions whilst performing Valsalva maneuvers during the contraction phase and 5 repetitions whilst forcefully inhaling (Muller maneuver) during the contraction phase. Onboard parabolic flight, data were averaged over 1 minute in 1G and during the following 5 - 10 periods of 0G with leg press exercise. In the supine and head down tilt conditions, data were averaged over one minute prior to and throughout leg press exercise. Data are expressed as the average ICP at baseline and during each exercise condition.

## RESULTS

Study one: Changes in posture typically experienced during normal life on earth. Transitioning from the 90° sitting to the supine posture (Fig. 2A), which removes the Gz hydrostatic gradient, caused an immediate increase in ICP that peaked in ~13 seconds and then declined slightly to reach steady state by 3 minutes (Fig. 2B). At rest in the 90° sitting posture, the CVP was  $2 \pm 3$  mmHg and ICP was  $4 \pm 1$  mmHg (Fig 2C). Despite the large hydrostatic gradient from the brain to the heart, it is likely that the ICP was not lower than this value because the jugular veins are partially collapsed in the upright position (Fig 2D), functioning as Starling resistors that interrupt the venous fluid column between the dural venous sinuses and the right atrium, thus isolating the dural sinus pressure from the CVP (Qvarlander *et al.*, 2013b). The ICP was higher in the supine compared to the 90° sitting posture in every subject ( $\Delta 11 \pm 2.5$  mmHg, Fig. 2C). The immediate rise in ICP upon becoming supine was likely due to rapid redistribution of CSF and venous blood ( $\Delta$  CVP  $4.4 \pm 3.5$  mmHg, Fig. 2C) toward the head. Furthermore, in the supine posture, the jugular veins are widely patent (Fig. 2D), which permits the CVP to be transmitted directly to the dural venous sinuses, thereby influencing CSF resorption and ICP. This principle, that dural venous sinus pressure dictates ICP with changes in posture (Davson

equation; (Davson *et al.*, 1973; Qvarlander *et al.*, 2013b)), is supported by our data, which also found that the prediction of ICP based on a simple hydrostatic indifference point for the CSF system slightly underestimated the measured ICP (30°,  $-0.1 \pm 1.6$ ; 60°,  $-0.8 \pm 2.1$  mmHg, Fig. 2E), implying that another factor, such as collapsibility of the jugular veins, contributes to the absolute change in upright ICP.

The mean BP referenced at the heart, fell ( $\Delta 13 \pm 7.1$  mmHg, Fig. 2C) with the transition from the 90° sitting posture to the supine posture, predominantly because of a decrease in diastolic blood pressure from vasodilation. But when the BP was referenced to the external auditory meatus, to account for the heart-to-head hydrostatic fluid column to calculate cerebral perfusion pressure (CPP = mean BP – ICP), the BP was actually higher in the supine posture (90° sitting,  $74 \pm 18$  vs supine,  $84 \pm 16$  mmHg,  $P=0.01$ ). As a result of these balanced changes in BP and ICP at the level of the brain, CPP remained stable regardless of body posture (90° sitting,  $70 \pm 18$  vs supine,  $66 \pm 18$  mmHg,  $P=0.13$ ). While in the supine position, placing the head on a pillow consistently reduced ICP (supine  $14 \pm 2$  vs pillow,  $10 \pm 2$  mmHg,  $P=0.05$ ).

Study two: Acute Microgravity. To investigate the effect of acute microgravity on supine ICP, we examined subjects during parabolic flight (Fig. 3A), which creates periods of true 0G and its associated fluid shifts (Fig. 3B) (Petersen *et al.*, 2011). Throughout the parabolic flight, participants remained in the supine position with their spinal axis (z axis) perpendicular to the direction of flight to minimize any fluid shifts associated with change in the angle of the aircraft. As the aircraft flew level (1G) for baseline measurements, ICP was stable and comparable to supine measurements made in Study 1 ( $\sim 16$  mmHg, Fig. 3C). As the aircraft pulled-up to an angle of 45°, gravity almost

doubled in the Gx (front-to-back) direction, which increased the CVP and ICP (Fig. 3B), presumably due to an increase in intrathoracic pressure (Videbaek & Norsk, 1997). During descent of the aircraft, when gravity was reduced to zero, the ICP fell immediately (Fig. 3B) and was followed a further gradual decline to ~20% below the 1G supine value ( $\Delta -3.8 \pm 2.9$  mmHg, Fig. 3C). Importantly, although the ICP in OG decreased compared to the supine posture, it was not as low as the ICP in the 90° sitting posture on earth (1G) (Zero G,  $13 \pm 2.6$  mmHg, vs. 90° sitting,  $4.1 \pm 1.4$  mmHg,  $P < 0.0001$ , Fig. 4). As noted in previous parabolic flight experiments (Buckey *et al.*, 1993; Videbaek & Norsk, 1997), the CVP fell consistently upon entering OG ( $\Delta -2.8 \pm 2.5$  mmHg, Fig. 3C), which is likely due to the reduction of intrathoracic pressure in microgravity (Videbaek & Norsk, 1997). Ultrasound demonstrated that the cross-sectional area of the jugular veins increased during OG (Fig. 3D), which implies that a continuous venous fluid column between the dural venous sinuses and the right atrium exists in microgravity, which influences the ICP (Davson *et al.*, 1973). The location of the hydrostatic indifference point for the CSF was not related to the fall in ICP in OG (Fig. 3E); however there was a modest predictive trend between body weight (a surrogate measure of weight on the chest which is eliminated in OG) and the fall in ICP in OG (40% of the variance,  $P = 0.097$ , Fig. 3F). Arterial blood pressure was stable between the supine and OG conditions ( $\Delta -1.85 \pm 5.1$  mmHg, Fig. 3C).

Study three: Twenty-four hours simulated microgravity with -6° head down tilt. Although the reduction in ICP during acute microgravity (Study 2) was clear and unequivocal, the duration of microgravity with each parabolic arc lasted only ~20 – 30 seconds. Therefore the effect of longer periods of microgravity on ICP remained unknown. To address this question, we placed subjects in the -6° head down tilt position for 24 hours (Fig. 5A). This widely used earth-based model of prolonged microgravity has been shown to cause cephalad fluid shifts similar to those observed in space (Pavy-Le Traon *et al.*, 2007). Transition from supine to -6° head down tilt caused an

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immediate, albeit slight increase in ICP (Fig. 5B) in every subject ( $\Delta 1.8 \pm 0.5$  mmHg, Fig. 5C). In contrast, the CVP was unchanged ( $\Delta -0.49 \pm 0.5$  mmHg, Fig. 5C).

Because the head is below the heart in the  $-6^\circ$  head down tilt position, the pressure of the cerebral venous and CSF systems, when compared to their respective hydrostatic indifference points, is increased proportional to the length of the hydrostatic column which explains the increase in ICP (Fig 6). After 3 hours of head down tilt, the ICP returned to the supine value ( $\Delta 1.1 \pm 2.3$  mmHg, Fig. 5C) likely due to the reduction in CVP, which equates to sagittal sinus pressure in the head down tilt position. At night, during quiet rest and sleep, the ICP was slightly reduced compared to the supine posture ( $\Delta -3.1 \pm 1.4$  mmHg), also corresponding to a slight fall in CVP ( $\Delta -3.45 \pm 1.6$  mmHg, Fig. 5C). By the end of 24 hours head down tilt simulated microgravity, when subjects were awake, the ICP and CVP had returned to baseline supine values (ICP,  $14.8 \pm 3.7$ ; CVP,  $5.3 \pm 3.2$  mmHg, Fig. 5C). This normalization of ICP occurred despite a persistent hydrostatic gradient from the heart to the head over the previous 24 hours as evidenced by persistent jugular venous distension (Fig 5D).

During quiet rest and sleep in head down tilt, the ICP pulse amplitude was slightly reduced compared to the supine posture, implying that intracranial compliance was unchanged or slightly improved (Fig. 7). One subject was noted to have B-waves (normally associated with impaired intracranial compliance) sporadically during quiet rest and sleep during head down tilt; however, the same pattern was seen while this subject was awake in the supine posture; thus, the B-waves seen during sleep in the head down tilt posture were not necessarily due to simulated microgravity.

Study four: Elevated inspired carbon dioxide concentration and leg press resistance exercise. When compared to the resting condition while breathing ambient air, the addition of 0.7% CO<sub>2</sub> (which is

the maximum 24-hour peak concentration on the International Space Station (Alexander, 2012)) had no effect on ICP either in the supine posture, or at any time during the 24 hours of simulated microgravity with head down tilt bedrest (Fig. 8A). Furthermore, the addition of 0.7% CO<sub>2</sub> during parabolic flight slightly exaggerated the fall in ICP during acute zero gravity (normocapnia,  $-3.8 \pm 2.9$ ; 0.7% CO<sub>2</sub>,  $-5.4 \pm 2.6$  mmHg, Fig. 8B).

CVP and ICP generally increased during the contraction phase of leg press exercise (Fig. 9A). However, there were important differences observed based on the subject breathing pattern. For example, when participants performed a Valsalva maneuver during leg press thereby markedly increasing intrathoracic pressure, BP, CVP, and ICP rose (Fig. 9B), and during the relaxation phase, ABP, CVP, and ICP fell immediately (Fig. 9B). The synchronized rise and fall in all pressures resulted in an almost constant arterial-venous pressure gradient throughout the brain (Haykowsky *et al.*, 2003) and therefore cerebral perfusion was maintained throughout exercise. When participants performed a Muller maneuver, which reduces intrathoracic pressure and CVP, during the leg extension phase, the rise in ICP was attenuated (Fig. 9C). These observations were consistent in the supine, acute microgravity and prolonged microgravity conditions (Fig. 9D - G).

## DISCUSSION

This series of experiments, which are the first to make direct ICP measurements in humans during 0G and prolonged simulated microgravity, provide convincing evidence against the hypothesis that ICP is pathologically elevated in 0G. In fact, removing gravity *reduced* the ICP compared to the supine posture. Other key findings of this study that are relevant for the physiology of gravity and hydrostatic influences on the circulation of the brain include: a) in 1G conditions on earth, upright

ICP is always lower (and substantially so) than supine ICP; b) gravitational effects on fluid pressures in the head with postural adjustments occur rapidly, with no evidence for a slow progressive rise over time in the prolonged simulated microgravity condition; c) the reduction in ICP upon exposure to acute microgravity led to a microgravity ICP that was consistently above the upright values; and d) neither mildly elevated inspired CO<sub>2</sub> levels, nor resistance exercise are likely to contribute to, or exacerbate an elevation of ICP in space.

Humans typically spend 2/3 of their time in the upright position (lower ICP) while awake, and 1/3 of their time supine (higher ICP) while sleeping at night. Thus, due to the influence of gravity, ICP in humans is low for ~2/3 of each day. While ground based models of microgravity (Petersen *et al.*, 2015; Eklund *et al.*, 2016) suggests ICP may be elevated in space, in true OG, the influence of gravity is removed and ICP falls to an equilibrium point between the upright and supine postures. We here speculate that the absence of diurnal, postural reductions in ICP relative to intraocular pressure (Anderson *et al.*, 2015; Petersen *et al.*, 2015; Eklund *et al.*, 2016) in microgravity creates a persistently lower pressure gradient at the posterior aspect of the eye (i.e., a lower translaminar pressure gradient (IOP-ICP) that may result in optic remodeling (Zhao *et al.*, 2015). Interestingly, IOP is elevated in OG relative to the upright posture on earth; (Anderson *et al.*, 2015) thus the effect of microgravity on the pressure gradient at the posterior aspect of the eye (translaminar pressure) maybe smaller than expected, yet over prolonged periods of time, possibly sufficient to cause optic remodeling.

This proposed pathophysiology of visual impairment is in line with the observed time dependent, mild-moderate clinical pattern and persistent presence of optic remodeling seen in astronauts on their return to earth (Mader *et al.*, 2011). The fact that simply placing the head on a pillow lowers ICP, which would be greater with head of bed elevation (Qvarlander *et al.*, 2013b), explains why

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individuals clinically or experimentally confined to bed rest do not commonly present with visual abnormalities. The hypothesis of persistent “overloading” of the ICP in zero G is analogous to the pathological left ventricular remodeling due to regurgitant valvular heart disease, whereby volume loading of the left ventricle occurs with every heartbeat (Gaasch & Meyer, 2008). In contrast, the normal diurnal variation of ICP on earth may be considered analogous to the intermittent volume loading of the left cardiac ventricle, with endurance training, which causes beneficial remodeling. Thus the adaptive “stress-recovery” of exercise improves heart health, while unremitting stress causes cardiac dysfunction.

Clinically, female astronauts appear to have less severe visual impairment during long duration space missions than men (Platts *et al.*, 2014). Although the number of females we studied was small, some observations of apparent gender differences may be informative. Compared to males, hemodynamic changes were similar, yet females typically displayed an ICP in OG closer to their estimated 24 hour ICP on earth (calculated as 1/3<sup>rd</sup> supine; 2/3<sup>rd</sup> sitting; Fig 4B). Such a smaller dissociation between average earth and microgravity conditions would result in a lower relative pressure gradient behind the eye in females than males; possibly explaining the similar incidence but decreased severity of visual impairment in females astronauts (Platts *et al.*, 2014).

In conclusion, normal changes in posture cause very large changes in intracranial pressure in humans. Complete removal of gravitational gradients (zero gravity of space) does not pathologically elevate intracranial pressure but does prevent the normal lowering of ICP when standing. Importantly, despite the acute short duration of OG during parabolic flight, we saw no evidence of a progressive rise in ICP due to cephalad fluid shifts with prolonged simulated microgravity in the head down tilt position. Thus, at present, we have no physiological data to support the hypothesis that ICP should be greater than that observed in OG during parabolic flight. The clinical implication of these findings is that the

human brain and eye are protected by the daily circadian cycles in regional intracranial pressures, without which pathology occurs. Creative strategies to maintain relative circadian cycles in intracranial pressure should be employed in astronauts and clinical patients obligated to bed rest.

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#### ADDITIONAL INFORMATION SECTION

**Competing Interests:** The authors declare no conflicts of interest.

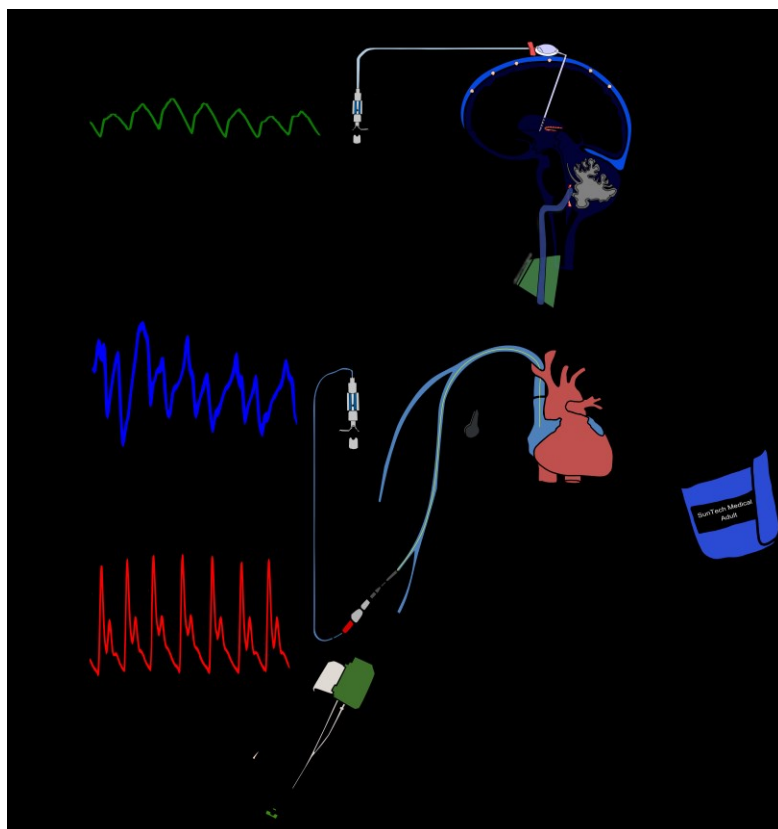
**Author Contributions:** R.Z., L.A.W., M.A.W., B.D.L conceived and designed the experiments J.S.L., L.G.P., E.J.H., S.S., W.K.C., R.Z., L.A.W., M.A.W., B.D.L. performed the experiments. All authors contributed to writing the paper.

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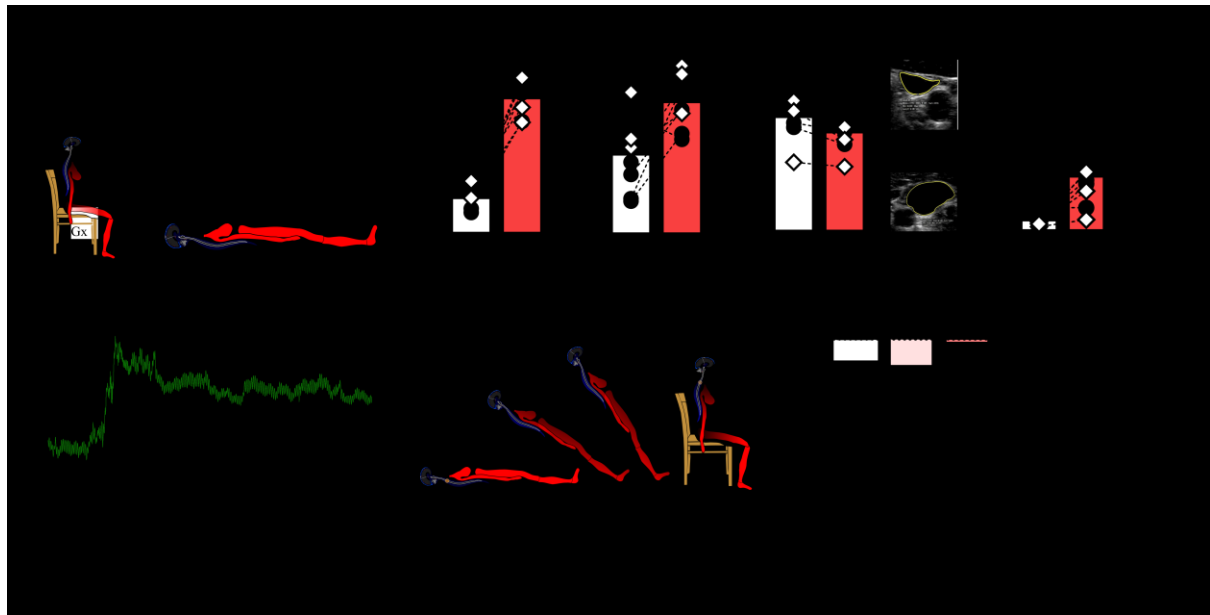


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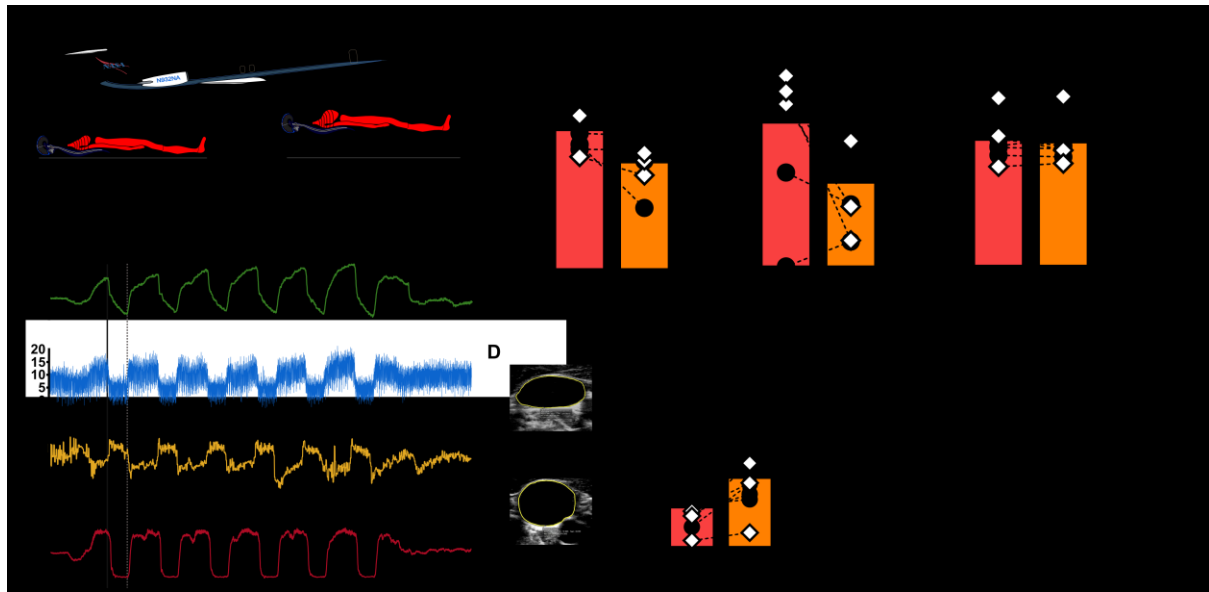
**Authors Translational perspective:** The human brain and eye are subject to large habitual variations in intracranial pressure simply by moving from the supine to the upright posture. Removal of gravity did not pathologically elevate pressure in the brain, but does prevent the normal lowering of ICP when standing. Thus, over twenty-four hours in zero gravity, pressure in the brain is slightly above that observed on earth, which may explain remodeling of the eye in astronauts. Clinically these data suggest that circadian cycles in intracranial pressure should be maintained in astronauts and in patients obligated to bed rest. Moreover, in contrast to contemporary thinking, these data imply that, if chronic, subtle deviations in pressure behind the eye may cause optic remodeling and visual impairment.



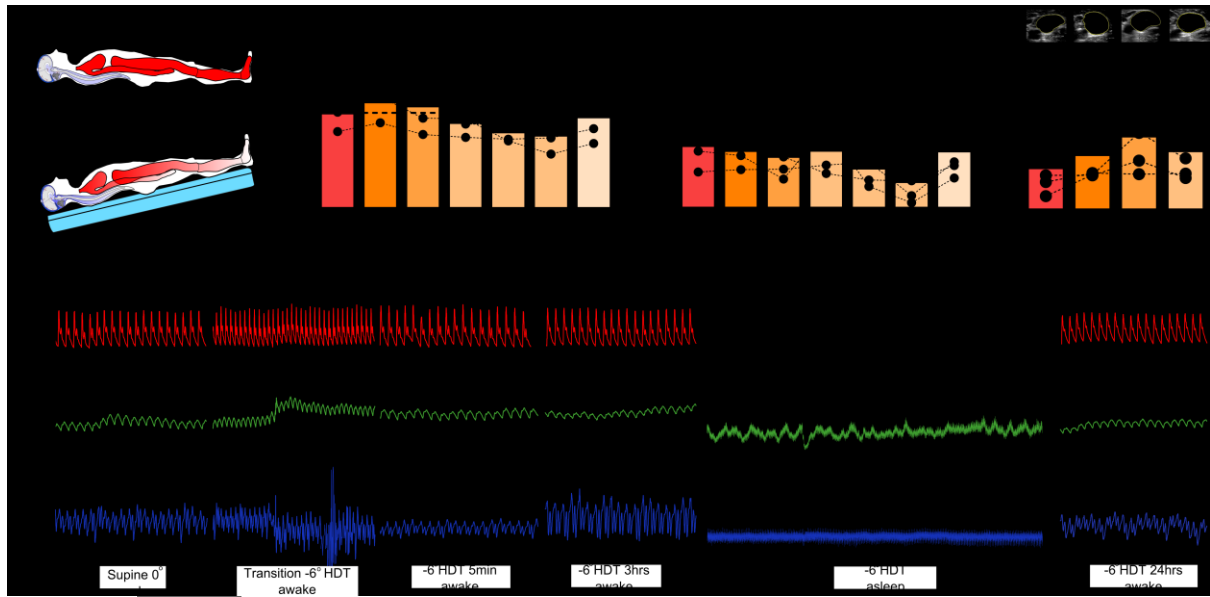
**Figure 1. Diagrammatic presentation of experimental setup** (a) Intracranial pressure and (b) central venous pressure were measured directly via fluid coupled pressure transducers. (c) Beat-by-beat arterial blood pressure, (d) arterial cuff pressure and (e) jugular venous cross-sectional area were measured non-invasively. Note that intracranial, central venous, and arterial pressure recordings were referenced to the external auditory meatus and right atrium respectively (dashed lines).



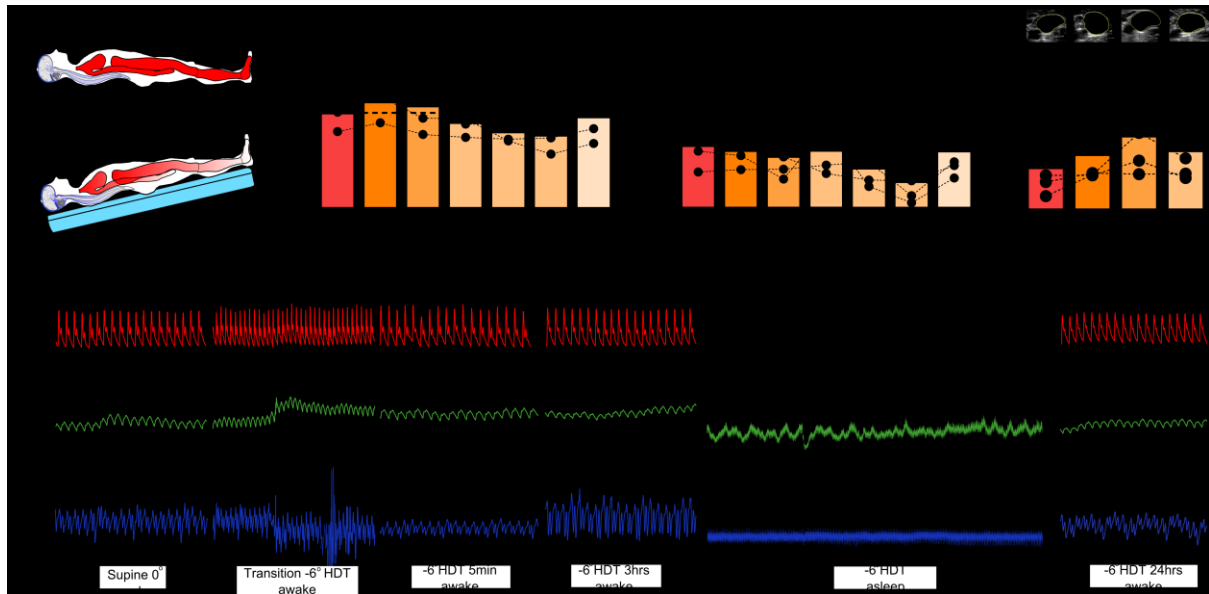
**Figure 2. Changing from the sitting to supine posture on Earth increases ICP.** **(A)** Experimental setup used to quantify pressures changes associated with change in posture on earth.  $G_z$ , head-to-foot hydrostatic gradient irrespective of position, which is eliminated in the supine posture.  $G_x$ , front-to-back hydrostatic gradient, which is present in the supine posture.  $G_y$ , side-to-side hydrostatic gradient. Needle access to an Ommaya reservoir and placement of a peripherally inserted central catheter permitted intracranial pressure (ICP) and central venous pressure (CVP) measurement by fluid-coupled pressure transducers, which were referenced to the external auditory meatus and right atrium, such that ICP and CVP were accurate throughout changes in posture. Arterial blood pressure (BP) was obtained by electrospigmomanometry. **(B)** Original recording of changes in ICP in 1 participant by changing from the 90° sitting upright posture to the supine posture. **(C)** Mean ICP and CVP are higher, whereas BP is slightly lower in the 90° sitting upright posture compared to supine;  $n = 8$ , paired  $t$ -tests. Black circles, males; white diamonds, females. **(D)** Original 2D images of jugular veins in the 90° sitting upright posture and supine posture from one participant. Jugular vein volume is smaller in the 90° sitting upright posture compared to supine;  $n = 8$ , paired  $t$ -test. **(E)** Participants ( $n = 4$ ) were passively placed in the 90°, 60°, 30° and 0° positions for two minutes (left). The  $HIP_{CSF}$ , where CSF pressure remains constant despite changes in posture, was calculated for each individual from the 90° seated upright and supine ICP. Prediction of ICP in the 30° and 60° position (right) by subtraction of the height of the fluid column superior to the  $HIP_{CSF}$  with tilt angle ( $\alpha$ ).



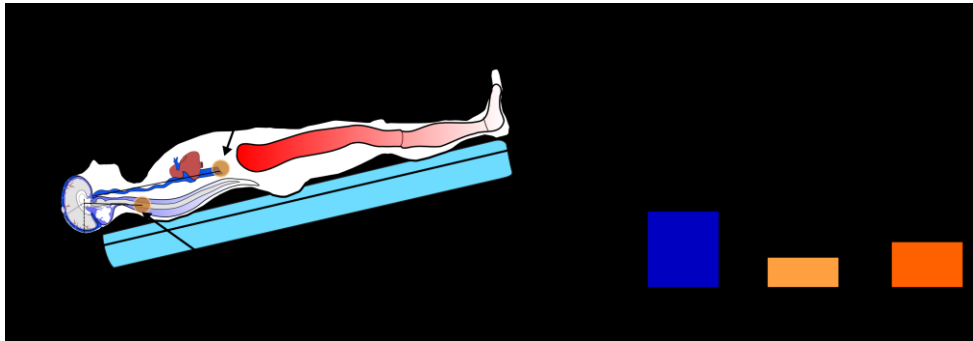
**Figure 3. Microgravity reduces ICP in the supine posture.** (A) Successive brief periods of microgravity (~20 sec) were generated during parabolic flight as participants lay in the supine posture, in which the  $G_z$  hydrostatic gradient is eliminated but the  $G_x$  gradient remains. In 0G all hydrostatic gradients are absent. (B) Original recordings in 1 participant of changes in intracranial pressure (ICP), central venous pressure (CVP), left ventricular stroke volume (SV), and gravity throughout 6 parabolas. Increased SV despite a fall in CVP during 0G confirms cardiac ventricular distension due to a fall in intrathoracic pressure and thus an increase in the transmural cardiac filling pressure. The solid line and the dashed line indicate the beginning and end of the first 0G period. ICP increases at the beginning of the parabola as gravity almost doubles in the  $G_x$  direction. However, immediately upon entering 0G, ICP falls rapidly to approximately the supine 1G value. ICP then continues to fall, and by the end of the 0G period, ICP is lower than the supine 1G value. (C) Mean ICP and CVP decrease, and BP remains stable in 0G compared to the supine 1G posture;  $n = 8$ , paired  $t$ -tests. (D) Original 2D images of jugular veins show further distension in 0G compared to the supine 1G posture. Relationships between the fall in ICP in 0G with (E) body weight and (F)  $HIP_{CSF}$ ;  $n = 8$ , linear regression. Black circles, males; white diamonds, females



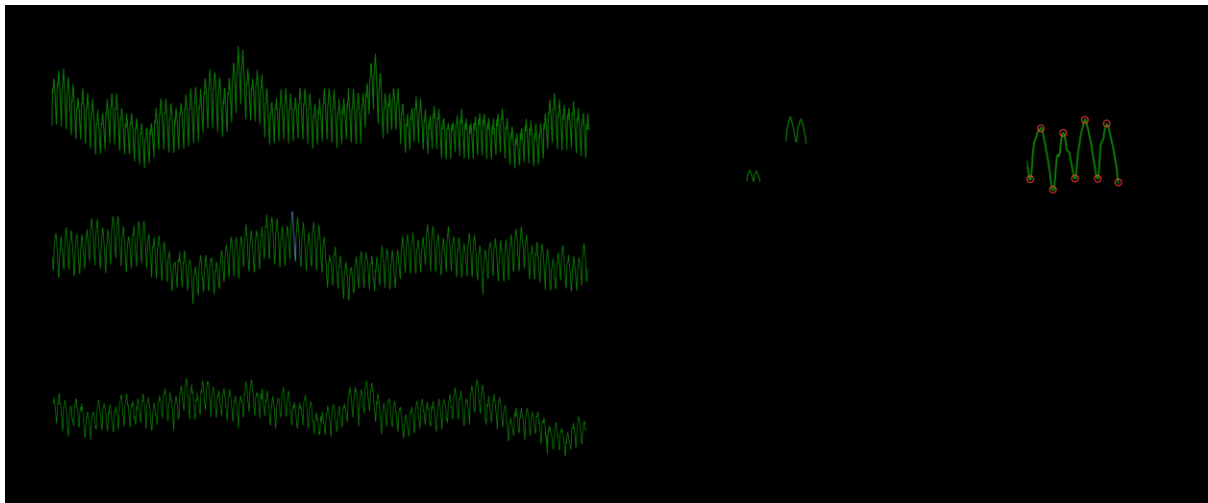
**Figure 4. Dissociation between 24 hour ICP on earth versus microgravity as a characteristic for optic remodeling during long duration space flight. (A)** Difference between 24 hours intracranial pressure (ICP) on earth (calculated as  $\frac{2}{3} \times 90^\circ$  sitting upright ICP +  $\frac{1}{3} \times$  supine ICP, where supine ICP is assumed to reflect sleep) and during 0G parabolic flight (assumed to reflect ICP throughout long duration space flight). **(B)** The same data split into males versus females. Although subject numbers are too low for conclusive between group statistical analysis, removal of a single suspected outlier ( $>2$  standard deviations from the mean) in the male cohort (dashed circle) suggests that females may have a smaller pressure differential between earth and microgravity  $n = 7$ , males; 3, females, unpaired  $t$ -test. Black circles, males; white diamonds, females. This calculation reflects the 24 hour difference in ICP between earth and microgravity environments, assuming short term measurements during parabolic flight reflect long-term measurements in space. Due to gravity, the brain and eye expect to “see” a low pressure environment throughout two thirds of the day, therefore in microgravity a greater relative posterior optic pressure would be “felt” throughout spaceflight, especially in males, which may explain the increased severity of optic remodeling observed in male versus female astronauts. The single male “outlier” may also explain the atypical male astronauts completely devoid of visual impairment in space.



**Figure 5. Twenty-four hours simulated microgravity does not elevate ICP. (A)** Diagram of the experimental setup used to simulate microgravity. Note that in  $-6^\circ$  head down tilt (HDT), the  $G_x$  hydrostatic gradient and a slight foot-to-head  $G_z$  hydrostatic gradient exist. **(B)** Original recordings in 1 participant of changes in arterial blood pressure (BP), intracranial pressure (ICP), and central venous pressure (CVP) throughout 24 hours simulated microgravity. The beat-to-beat blood pressure device was turned off during sleep. Arrow indicates onset of passive tilt to the  $-6^\circ$  HDT position. Note the compressed time scale in the 2<sup>nd</sup> graph to demonstrate the transition from supine to HDT. **(C)** In every subject, ICP was slightly higher in the  $-6^\circ$  HDT position compared to the supine posture, which is entirely explained by the increase in the  $G_z$  foot-to-head hydrostatic column within the CSF and venous compartments (Fig S4). During sleep, ICP falls below the supine value, and importantly, ICP returns to the supine baseline value after 24 hours of  $-6^\circ$  HDT;  $n = 4$ , one-way ANOVA,  $*P < 0.05$  vs  $0^\circ$ . **(D)** During sleep in  $-6^\circ$  HDT, CVP is lower than the supine value, and remains slightly lower than the supine value in 3 of the 4 subjects after 24 hours of  $-6^\circ$  HDT;  $n = 4$ , one-way ANOVA,  $*P < 0.05$  vs  $0^\circ$ . **(D)** Jugular vein distension persists throughout 24 hours of  $-6^\circ$  HDT, one-way ANOVA with follow up test, 5min ( $P = 0.0$ ), 3hrs ( $P = 0.09$ ) and 24hrs ( $P = 0.15$ ) vs  $0^\circ$ . Black circles, males.

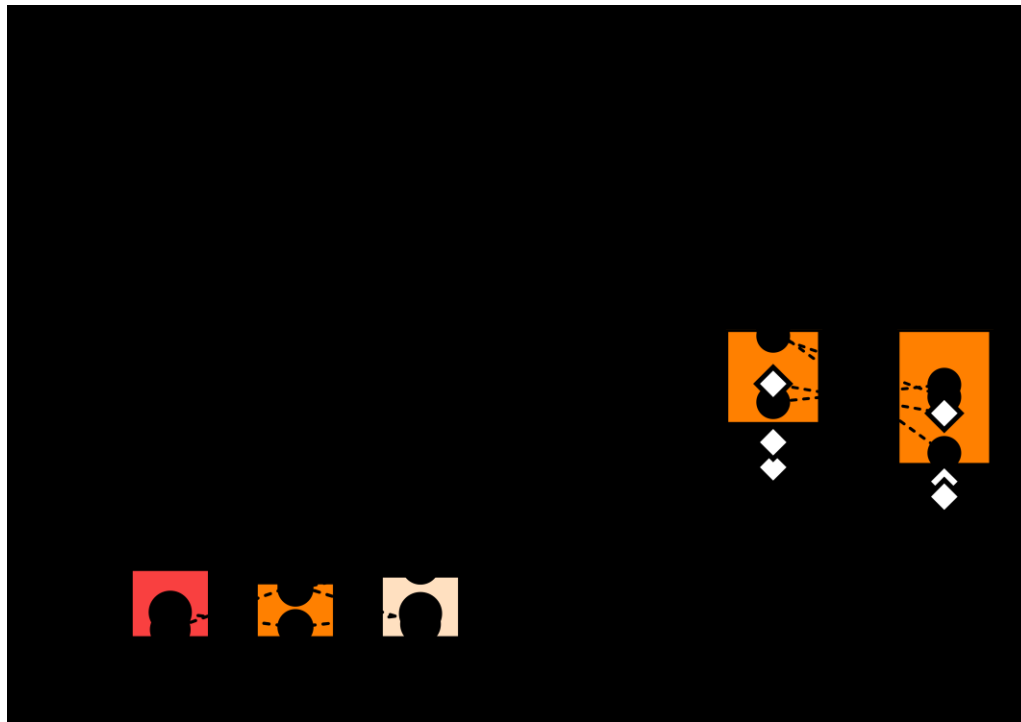


**Figure 6. Simple hydrostatics explain the increase in intracranial pressure with acute -6° head down tilt.** (A) In the -6° head down tilt model, the head is placed below the heart. Therefore, the slight foot-to-head (Gz) hydrostatic gradient causes pressure within both the venous and cerebral spinal fluid systems to increase proportional the length of the hydrostatic column superior to their respective hydrostatic indifference points. (B) From the supine measurement of central venous pressure and the L-HIP<sub>vein</sub>, dural sinus pressure ( $P_d$ ) was predicted to increase by  $2.9 \pm 0.2$  mmHg. Thus according to the Davson equation, intracranial pressure (ICP) must rise to exceed dural sinus pressure to maintain cerebral spinal fluid absorption into the sinus. Indeed, the predicted increase in ICP based on the L-HIP<sub>CSF</sub> model ( $1.2 \pm 0.6$  mmHg) and the measured increase in ICP were similar ( $1.8 \pm 0.5$  mmHg). Nevertheless, the important take home message, is that ICP did not increase substantially beyond that expected by simple hydrostatic gradients, thus cephalad fluid shifts do not cause disproportionate and pathological increases in ICP.

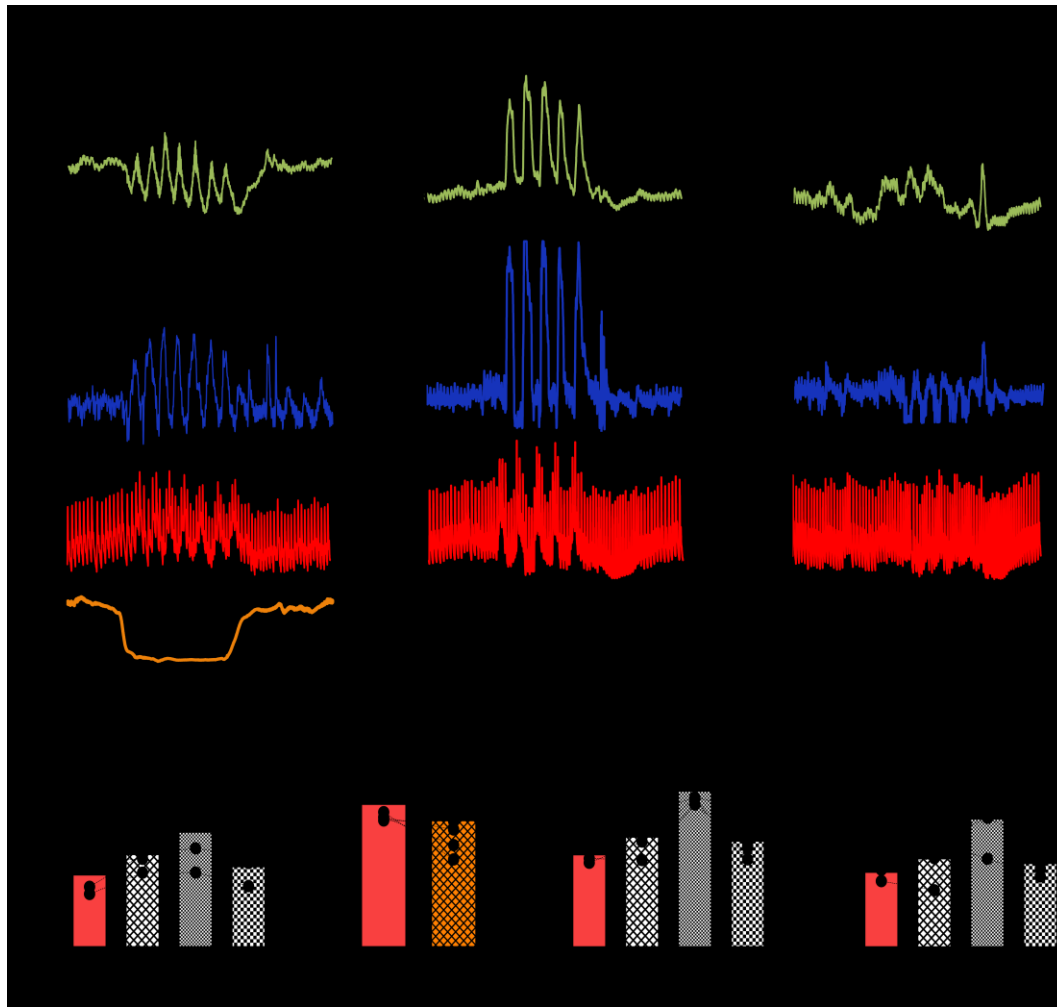


**Figure 7. Sleeping in simulated microgravity does not reduce intracranial compliance. (A)** Original recordings of pulsatile changes in intracranial pressure (ICP) in the awake supine position (top), in the  $-6^\circ$  head down tilt position (HDT) just prior to sleep (middle) and during quiet rest/sleeping as document by Registered Nurse in one human participant. **(B)** Pressure-volume intracranial compliance curve. In the steep part of the compliance curve, 1 ml change in volume (during each heart beat), causes a much larger increase in ICP pulsatility than in the flat portion of the curve; therein intracranial pulse amplitude ( $ICP_{AMP}$ ) reflects the compliance state of the intracranial compartment. **(C)** Successive diastolic and systolic peaks were detected from continuous ICP data by an automated ECG gated time-windowing algorithm.  $ICP_{AMP}$  was averaged over a two minutes of steady-state in each condition. **(D)** Compared to the supine position,  $ICP_{AMP}$  fell slightly in three of the four participants just prior to falling asleep and remained below the supine value while resting quietly/asleep.





**Figure 8. 0.7% carbon dioxide inhalation does not increase ICP during real or simulated microgravity.** Carbon dioxide ( $\text{CO}_2$ ) was administered via a tight fitting facemask for 3 – 5 minutes prior to a set of parabolas or steady-state data collection during bedrest. **(A)** The intracranial pressure (ICP) response to 0.7%  $\text{CO}_2$  is similar between the supine and acute (5min) and prolonged (24 hrs) simulated microgravity conditions. Note that 0.7%  $\text{CO}_2$  did not clinically increase ICP even after 5min of head down tilt despite mean ICP being slightly elevated;  $n = 4$ , one-way ANOVA. **(B)** Comparison of the decrease in ICP during microgravity whilst breathing normal air (normoapnia) versus 0.7%  $\text{CO}_2$ ;  $n = 8$ , paired  $t$ -test.



**Figure 9. Resistance exercise transiently increased ICP if combined with a Valsalva maneuver.**

Original recordings in one participant of changes in intracranial pressure (ICP), central venous pressure (CVP) and arterial blood pressure (BP) during repetitive leg press exercise while breathing 0.7% carbon dioxide. **(A)** During 0G, ICP rises during leg extension and falls with leg flexion (relaxation). The synchronized rise and fall in CVP and BP indicates that the participant performed a Valsalva during each leg extension. **(B)** In the head down tilt position, ICP, CVP and BP rise during leg extension and fall with leg flexion (relaxation) during 5 leg press exercises with a controlled Valsalva maneuver. **(C)** In the head down tilt position, ICP and BP remain mostly stable during 5 leg press exercises performed with a controlled Muller maneuver. Individual and mean intracranial pressure responses to the combination of 0.7% carbon dioxide and leg press exercise in the (D) supine posture, (E) during acute microgravity, and during (F) acute simulated microgravity and (G)

prolonged simulated microgravity. Microgravity, n = 8, paired *t*-tests; supine and head down tilt conditions, n = 4, one way ANOVA, \*  $P \leq 0.05$  vs baseline.

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