Assessment of Artificial Gravity as a Countermeasure to Cephalad Fluid Shifting

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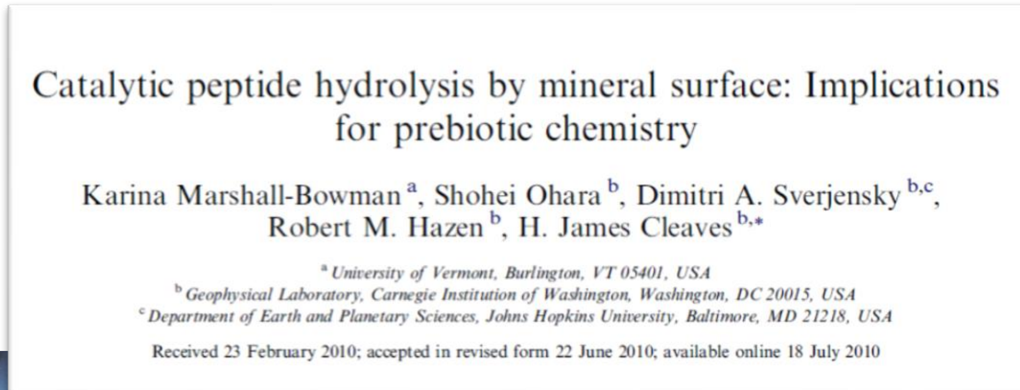
TRANSLATIONAL RESEARCH INSTITUTE FOR SPACE HEALTH

Overview

- **Background** (educational/professional)
- **Spaceflight Associated Neuro-Ocular Syndrome (SANS)**
  - Hypothesized pathophysiological mechanisms
  - Signs/Symptoms
  - Ground-based research studies
  - Countermeasures
- **Future Plans**

Educational/Professional Background

- **Bachelors in Biology and Chemistry** – University of Vermont
    - Summer Scholar – Carnegie Institution



Catalytic peptide hydrolysis by mineral surface: Implications for prebiotic chemistry

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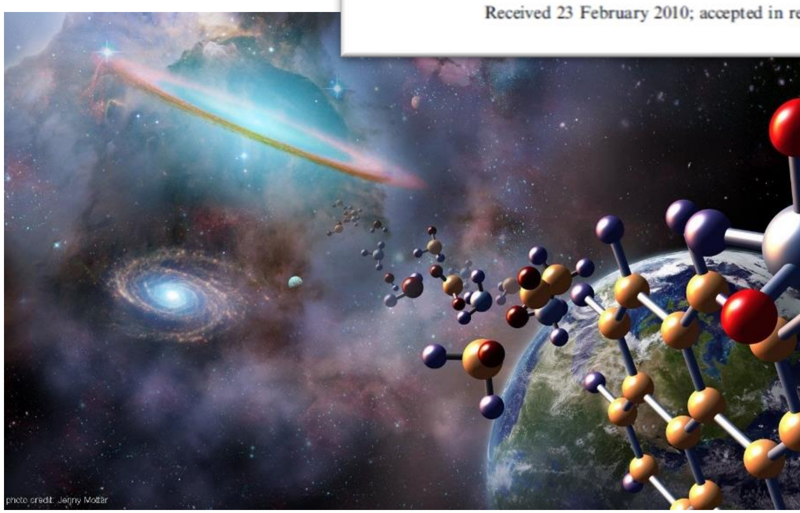
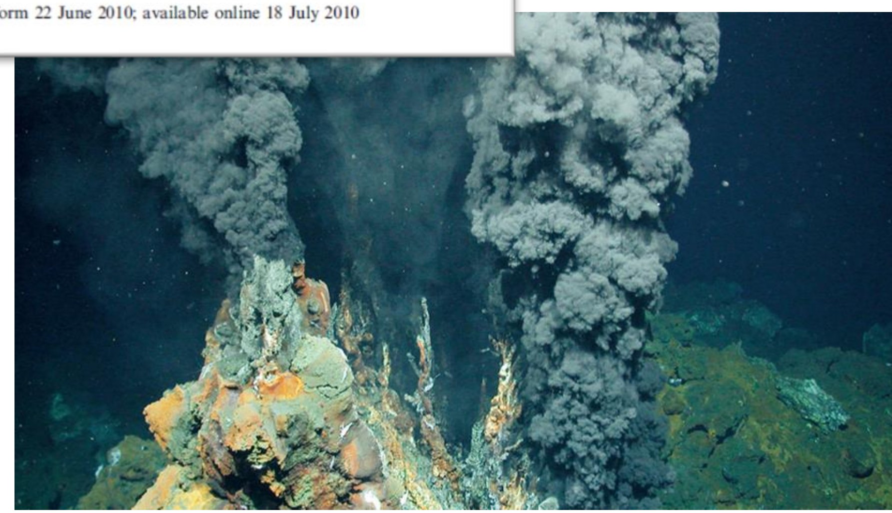


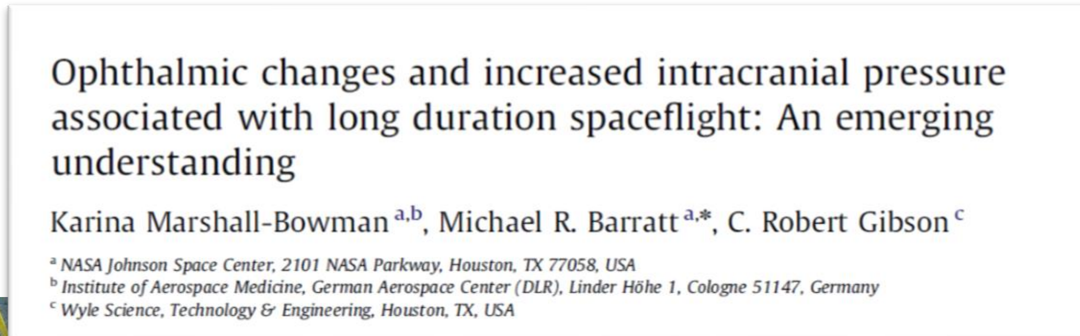
Source: Jenny Mottar



Source: NOAA

Educational/Professional Background

- **MSc in Space Studies** – International Space University
  - ➢ Intern – NASA Johnson Space Center



Ophthalmic changes and increased intracranial pressure associated with long duration spaceflight: An emerging understanding

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Educational/Professional Background

Junior Science Officer – European Science Foundation

- Development of the **THESEUS** (Towards Human Exploration of Space: a European Strategy) Roadmap (European Commission FP-7 Project) to identify the critical areas of research in human health in space

- Proposing new **Planetary Protection** guidelines to the European Space Agency (ESA) for a future Mars sample return mission

- Independent analysis and evaluation **of ESA's ELIPS program** (European program for life and physical sciences in space)

European Science Foundation

Educational/Professional Background

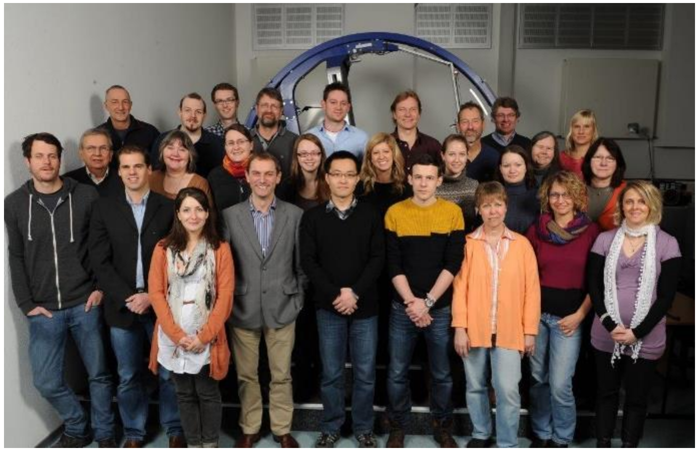
PhD in Health Science – University of Cologne

- ➢ SpaceLife PhD Program – DLR

DLR

HELMHOLTZ
ASSOCIATION

Medizinische Fakultät
der Universität zu Köln



Educational/Professional Background

PhD in Health Science – University of Cologne

- SpaceLife PhD Program – DLR

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Strangman GE, Zhang Q, **Marshall-Goebel K**, Mulder E, Stevens B, Clark JB, Bershad EM. Increased Cerebral Blood Volume Pulsatility during Head-Down Tilt with Elevated Carbon Dioxide: The SPACECOT Study. J Appl Physiol 123(1): 62-70, 2017.

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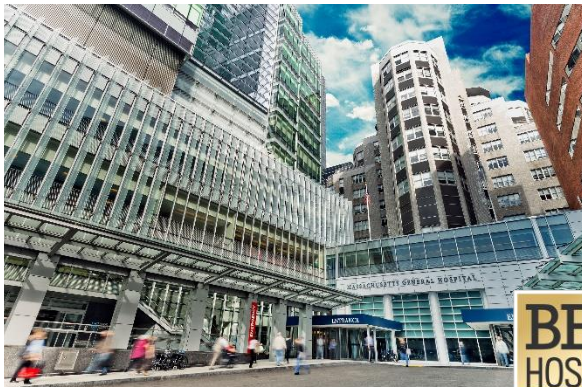
Michael, A.P, **Marshall-Bowman, K**. Spaceflight-induced Intracranial Hypertension. Aerosp Med Hum Perform 86(6), 557-562, 2015.

Educational/Professional Background

- Massachusetts General Hospital/Harvard Medical School



Source: Boston Magazine

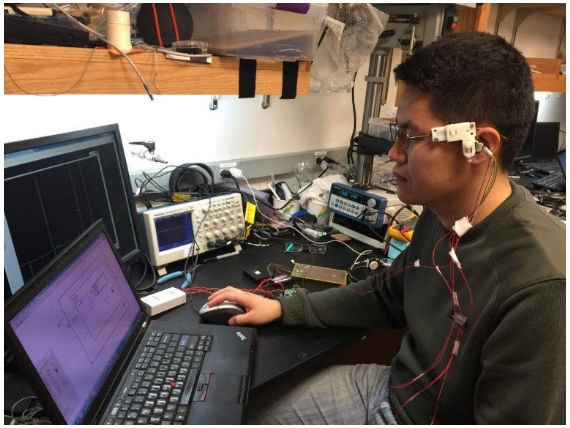
Source: MGH

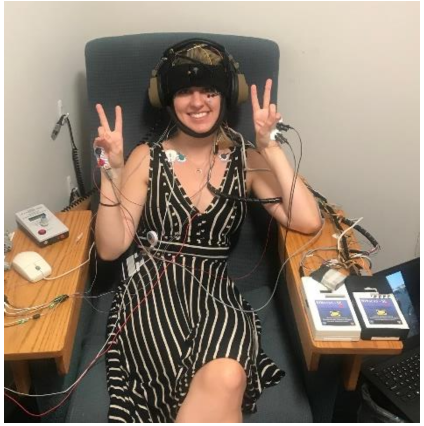
Source: HMPA

Educational/Professional Background

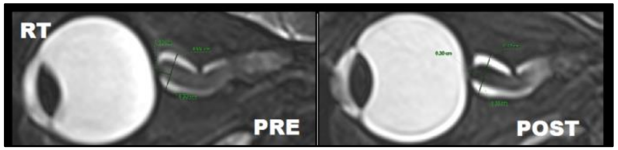
- Director: Dr. Quan Zhang

- The focus of the lab is to **develop novel wearable physiological monitoring and imaging technologies** for the prevention, diagnosis and management of cardiovascular diseases and psychiatric disorders (e.g. depression) and **physiological monitoring in extreme environments** including spaceflight, high altitude and high-impact sports

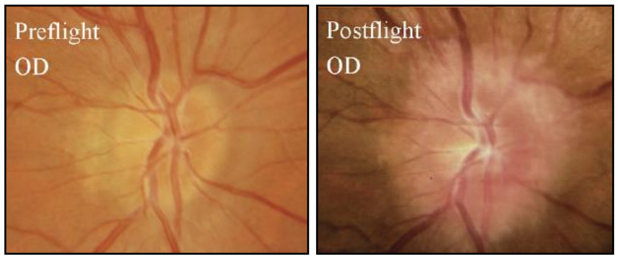




Spaceflight Associated Neuro-ocular Syndrome (SANS)



Source: Mader et al (2013)



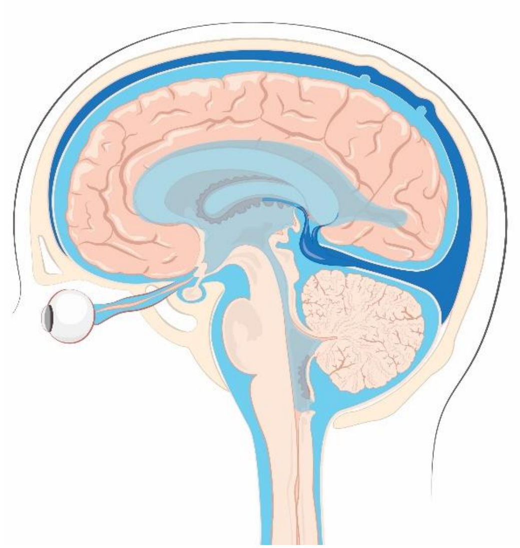
Source: Mader et al (2012)

Source: NASA

Symptoms and Signs in Astronauts:

- Hyperopic shifts (up to +3 Dtr)
- Optic disc edema
- Edema of optic nerve sheath
- Posterior globe flattening
- Choroidal folds
- Cotton wool spots
- Raised intracranial pressure post-flight
  - 21-29 cm H_2O

Spaceflight Associated Neuro-ocular Syndrome (SANS)



Functional and structural ophthalmic changes in astronauts may arise from:

Cephalad fluid shift

↓

Decreased cerebral venous outflow

↓

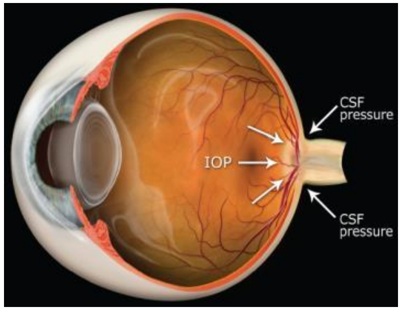
Increased intracranial pressure

↓

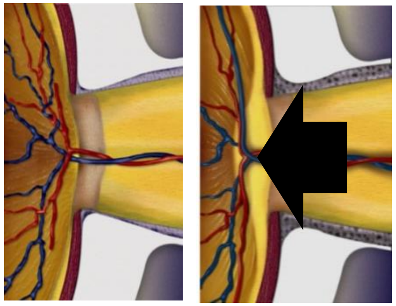
Decreased translaminar pressure difference

↓

Structural changes in the eye



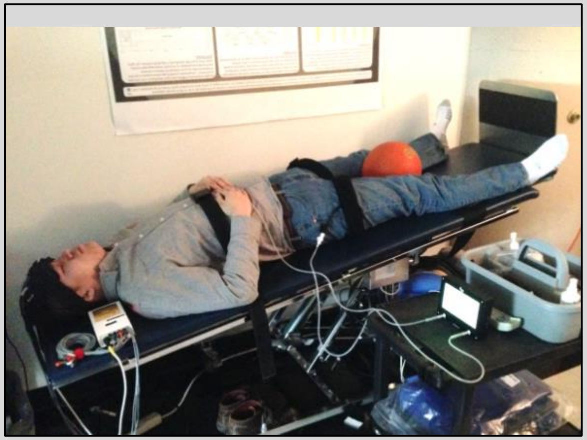
Source: Mark Erickson / jhrehdesign.com



Source: Berdahl et al. (2012)

A countermeasure that can successfully **redistribute body fluids** similar to the upright position on Earth is critical for the prevention of SANS

Potential SANS Countermeasures?



NASA HRP Risk: SANS

- NASA HRP Risk of **Spaceflight Associated Neuro-ocular Syndrome (SANS)**

- SANS Associated Gaps:
  - **SANS1**: We do not know the **etiological mechanisms and contributing risk factors** for ocular structural and functional changes seen in-flight and post-flight.

  - **SANS3**: We need a set of validated and minimally obtrusive **diagnostic tools** to measure and monitor changes in intracranial pressure, ocular structure, and ocular function.

  - **SANS12**: We do not know whether **ground-based analogs** and/or models can simulate Space Associated Neuro-ocular Syndrome.

  - **SANS13**: We need to identify preventative and treatment **countermeasures** (CMs) to mitigate changes in ocular structure and function and intracranial pressure during spaceflight. Relate my research to specific gaps needed by NASA

The enVIIP Study: Aims

- **Part I**: To study the effects of **headward fluid shifting** induced by various degrees of head-down tilt
- **Part II**: To determine the added effects of a hypercapnic environment (**1% CO_2**) during cephald fluid shifting
- **Part III**: To redistribute venous blood volume to the legs via lower body negative pressure (**LBNP**) as a potential countermeasure

-12° HDT + 1% CO_2

-6° HDT

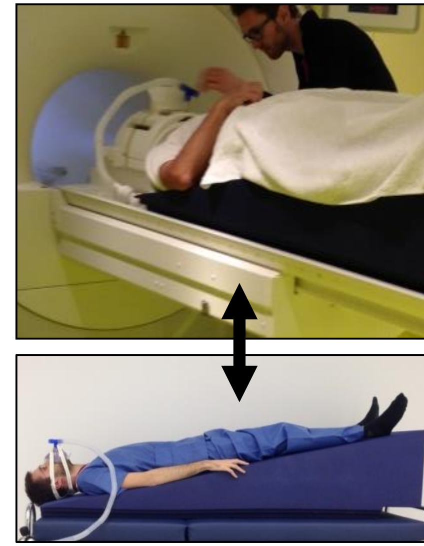
-12° HDT

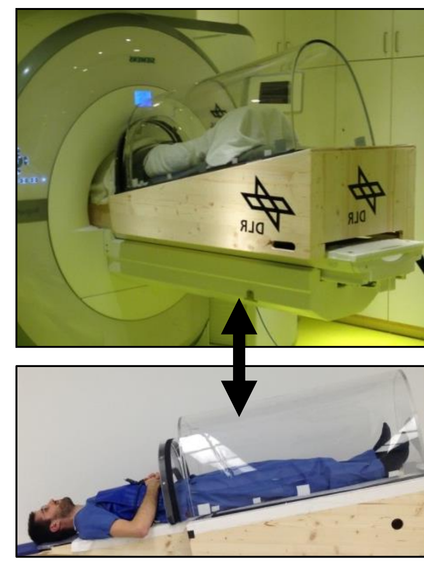
-18° HDT

-12° HDT + LBNP

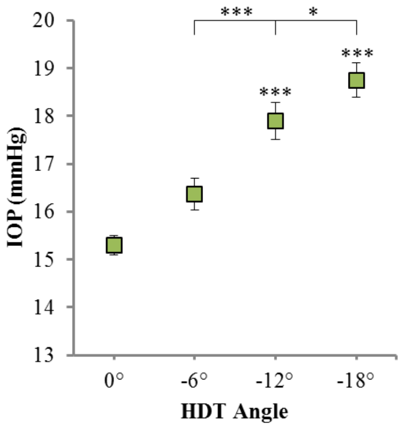
Measurements

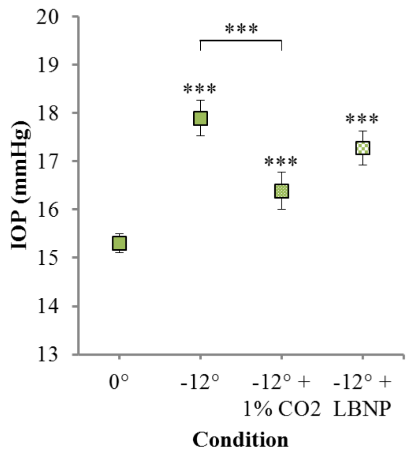
- **Ocular measures**
  - Intraocular pressure (iCare Pro Tonometer)
  - Retinal nerve fiber layer thickness and choroidal thickness (Spectralis SD-OCT, Heidelberg Engineering)
  - Optic nerve sheath diameter (MRI; Siemens Biograph mMR 3-T scanner)
- **Cerebral measures**
  - Non-invasive intracranial pressure (Vittamed 205 aICP meter)
  - Arterial and venous flow velocity and cross-sectional area (Phase contrast MRI; Siemens Biograph mMR 3-T scanner)
  - 3D volumetric scan of cranium to determine CSF, white matter and gray matter volumes (MRI; Siemens Biograph mMR 3-T scanner)
- **Cardiovascular and respiratory measures:**
  - End tidal CO_2 and minute ventilation (Innocor system, Innovision)
  - Mean arterial pressure, systolic blood pressure, diastolic blood pressure, heart rate (Finometer, Finapres Medical Systems; Biopac Systems)





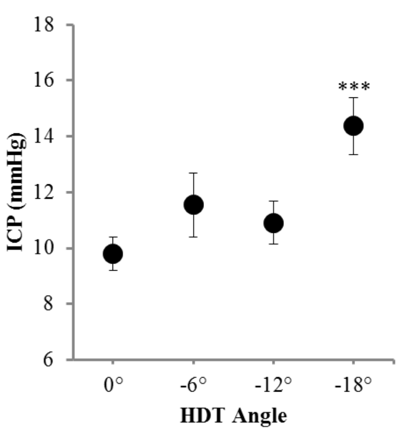
Intraocular and Intracranial Pressure (IOP, ICP)

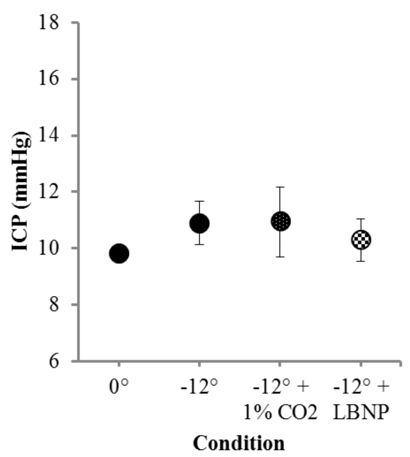




IOP

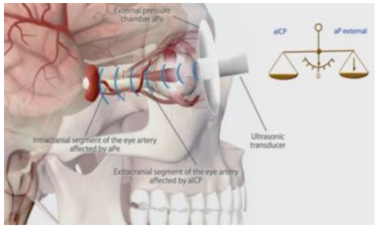
- ➢ HDT increases IOP with decreasing tilt angle
- ➢ IOP increased during all -12° conditions compared to 0° baseline





ICP

- ➢ HDT induces an increase in ICP only during steep HDT
- ➢ Neither LBNP nor 1% CO_2 had further effects on ICP



Source: Vittamed

Source: Marshall-Goebel et al (2017)

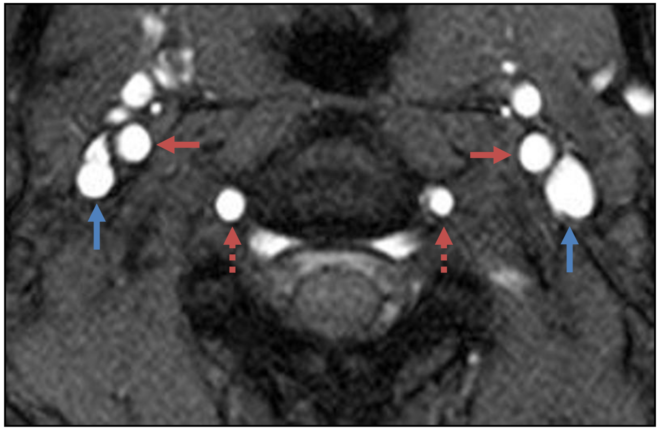
* *p<0.05, ***p<0.001*

Phase Contrast MRI (PC-MRI)

- PC-MRI allows for **quantification of flow velocity** (spins moving in the same direction as the gradient magnetic field develop a phase shift proportional to the velocity of the spins)

- Cross-sectional area, blood flow velocity and blood flow measurements were obtained for:
  - **Internal Carotid Artery (ICA)**
  - **Vertebral Artery (VA)**
  - **Internal Jugular Vein (IJV)**

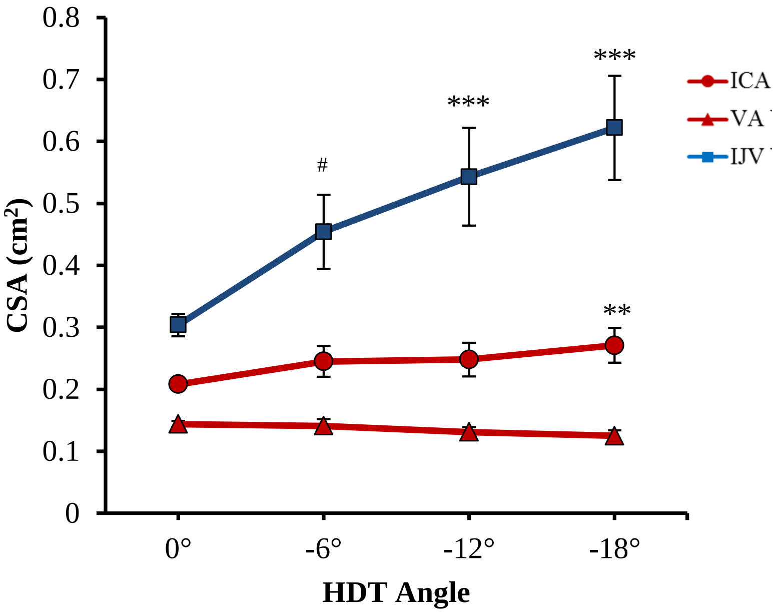
- Siemens Biograph mMR 3-T scanner

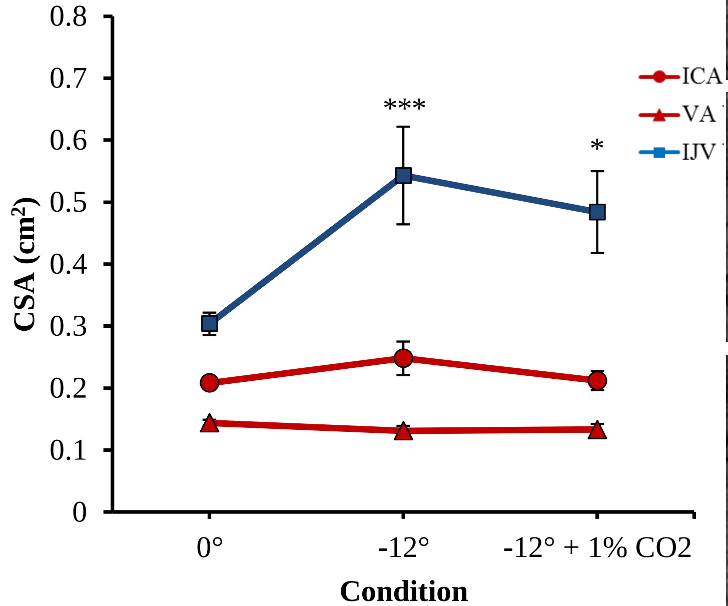


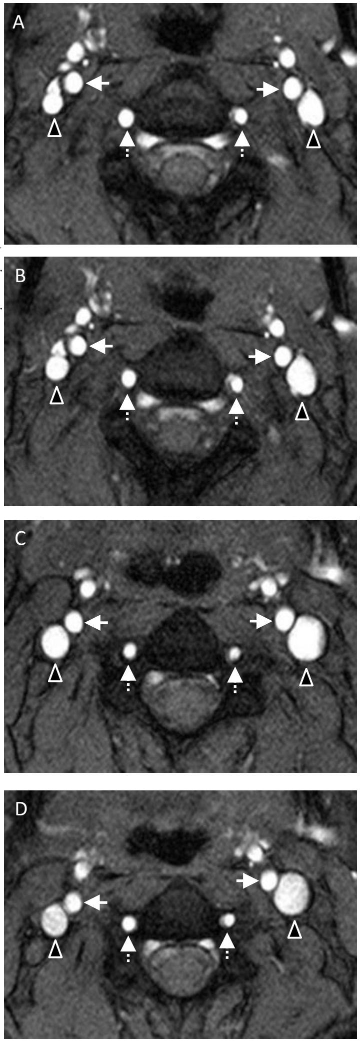
Total Arterial Inflow = Right and Left ICAs and VAs

Total Jugular Venous Outflow = Right and Left IJVs

PC-MRI Cross-Sectional Area







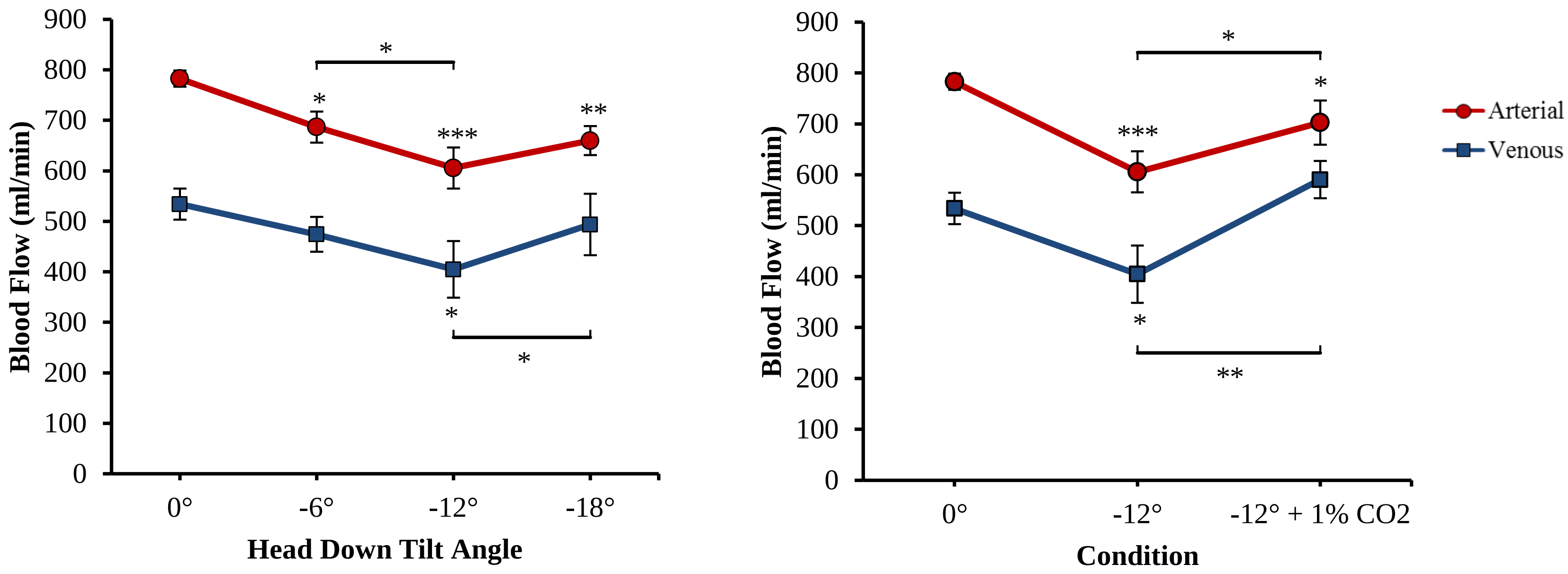
- Progressive increases in IJV CSA; demonstrates great compliance of the venous system

Source: Marshall-Goebel et al (2016)

Change from 0° baseline:

** p<0.05, ** p<0.01, ***p<0.001*

PC-MRI Derived Total Flow

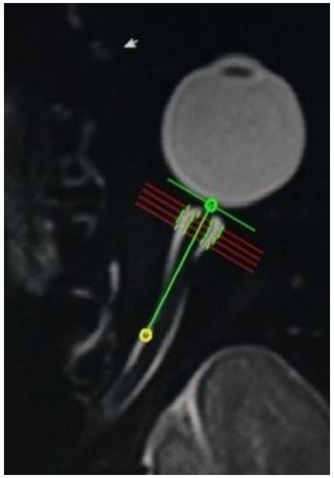


- HDT may increase post-capillary pressure, thus affecting the CPP gradient and blood flow in the cephalad regions leading to decreased cerebral arterial inflow and venous outflow

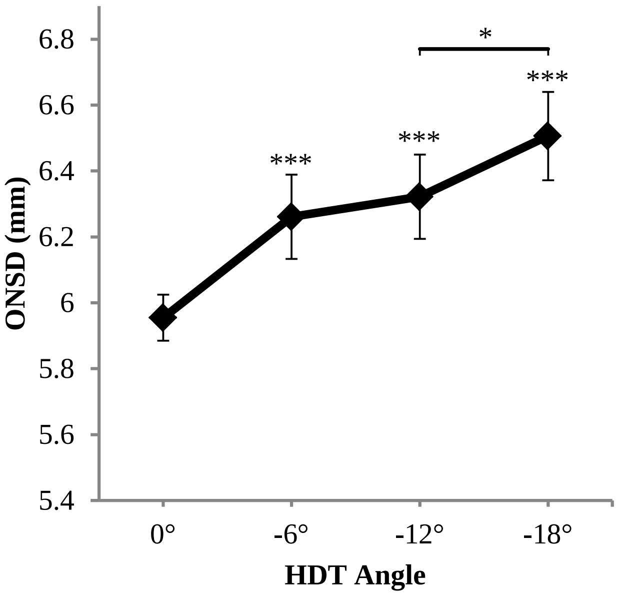
Source: Marshall-Goebel et al (2016)

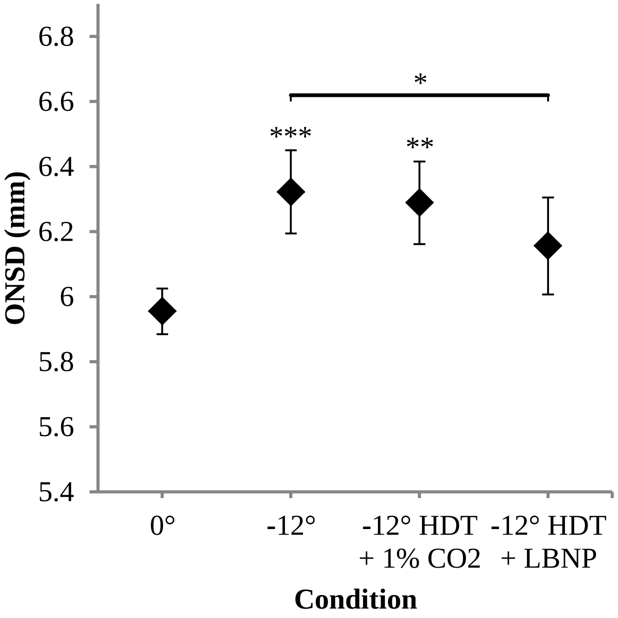
* *p<0.05*, ** *p<0.01*, ****p<0.001*

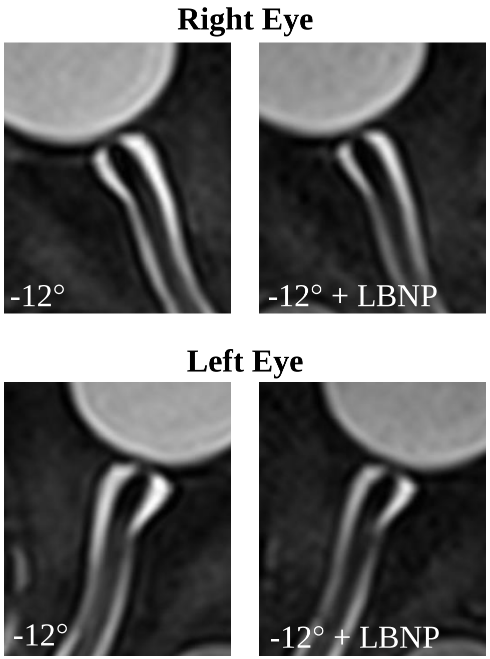
Optic Nerve Sheath Diameter



- T-2 weighted transverse slice of the orbita
- Optic nerve sheath diameter measured 3 mm behind globe







- ONSD increased with all HDT positions
- During -12° HDT, LBNP attenuated the HDT-induced increase in ONSD

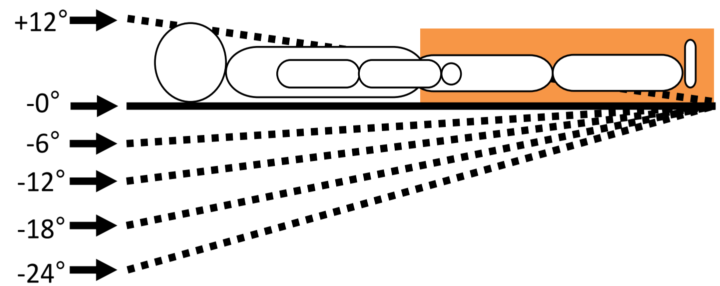
$***p<0.001$

The SETI Study:

Studying the Effects of Tilt and LBNP on Intraocular Pressure

Study Design

- 16 healthy subjects (8 male, 8 female)
  - Mean age: 27 ± 4.8 yrs
  - Mean BMI: 22.9 ± 1.9 kg/m^2
- **12 conditions**, randomized
  - 6 angles of whole body **tilt**, with and without **-40 mmHg LBNP**
  - 10 min supine baseline
  - 5 min tilt (with or without LBNP)



Start experiment	0°	12°	0°	0°+ LBNP	0°	-6°	0°	-12°+ LBNP	0°	-18°	0°	-24°+ LBNP	*Break*

Resume experiment	0°	12° + LBNP	0°	0°	0°	-6° + LBNP	0°	-12°	0°	-18° + LBNP	0°	-24°	*End*

The SETI Study

Aim:

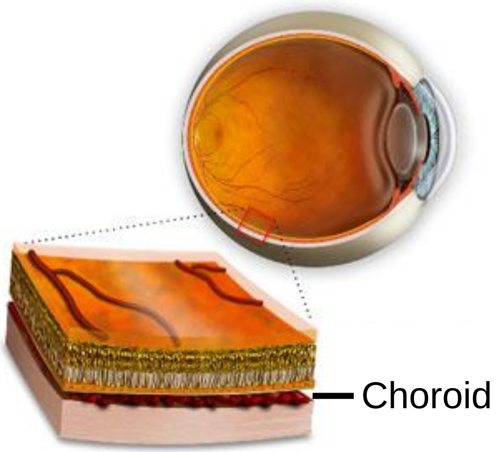
- To elucidate the effects of exposure to a **stronger level of LBNP** (-40 mmHg) for shorter durations of time with an extended range of tilt angles.

Hypothesis:

- Headward fluid shifts results in increased episcleral and vortex venous pressure and subsequent increase in IOP
- This increase in IOP can be attenuated with **lower body negative pressure** by redistributing venous blood to the lower limbs

Measurement/Method:

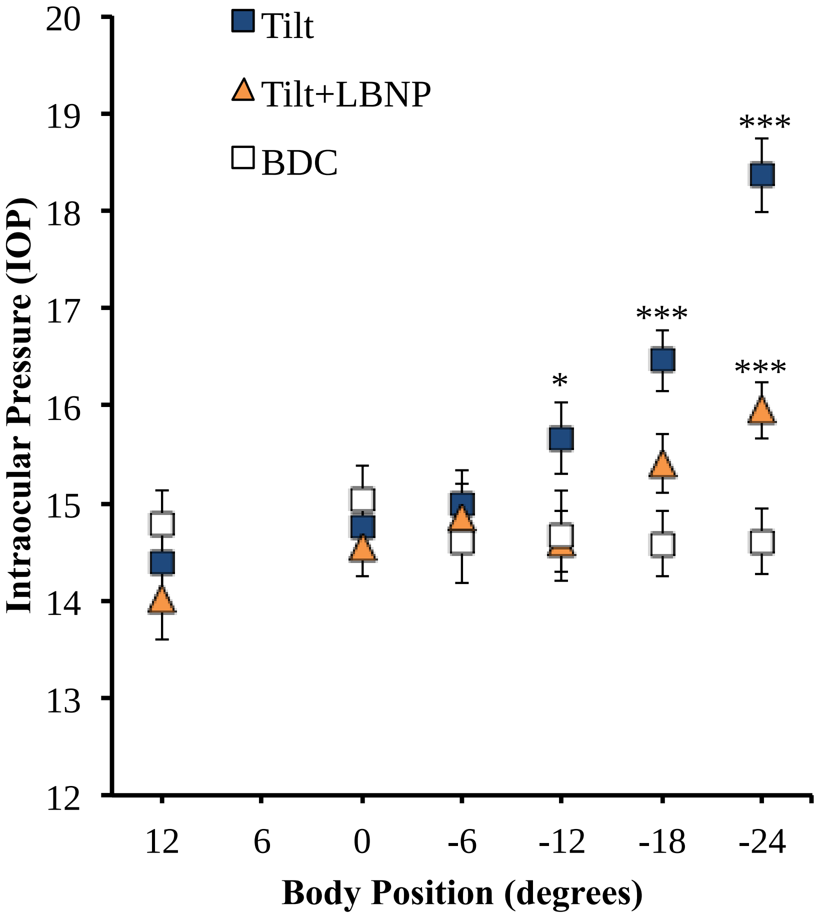
- Intraocular Pressure - Icare Tonometer Pro

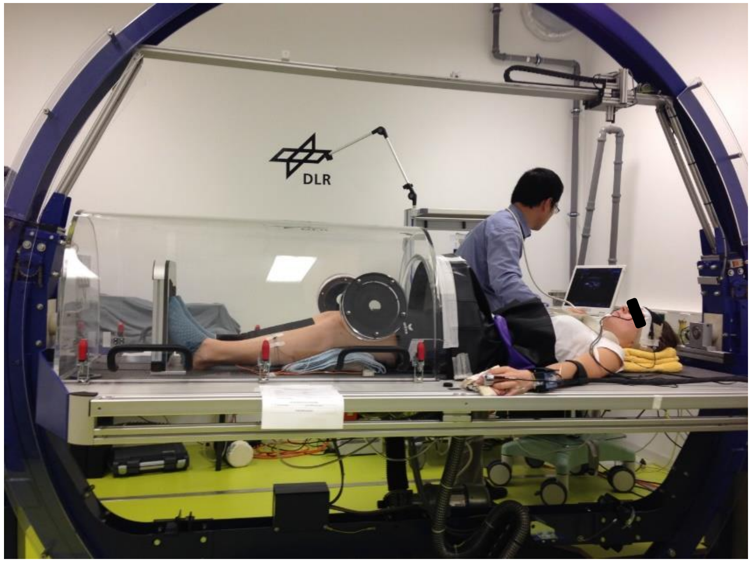


Source: jirehdesign.com

Source: iCare

Intraocular Pressure





- ➢ HDT induces an increase in IOP at steeper tilt angles
- ➢ LBNP at -40 mmHg is able to attenuate this increase until -18° HDT

Source: Marshall-Goebel al (2017)

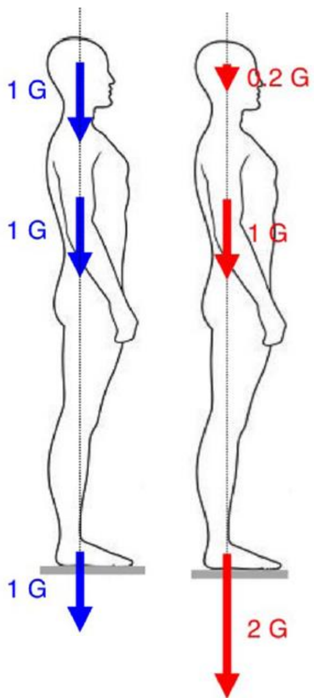
Change from 0° baseline:

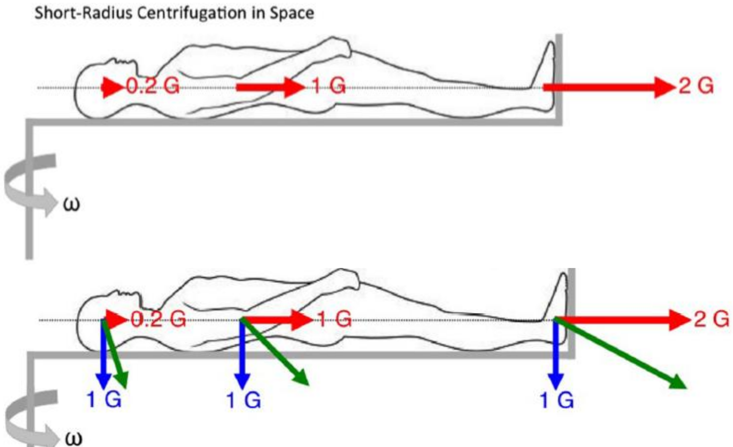
** p<0.05, ***p<0.001*

Artificial Gravity via Centrifugation

- AG may counteract headward fluid shifting through reinstating a Gz (head-to-foot) physiological hydrostatic gradient
- AG could represent an “all-inclusive” countermeasure for spaceflight

Standing on Earth **Centrifuge in Space**





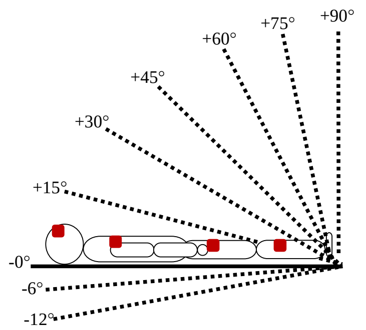
Source: Clement et al (2015)

Source: DLR

Source: DLR

Artificial Gravity via Centrifugation

- **Overarching Goal**
  - To quantify the ability of centrifugation to reinstate supine and upright fluid distribution as a countermeasure to cephalad fluid shifting
- **Experimental Plan**
  - **Study 1**: Tilt table – assessment of body fluid distribution
    - 4-body segment NIRS, ultrasound IJV/FV, cardiovascular parameters
  - **Study 2**: 60 day head-down tilt bed rest ± daily AG as a countermeasure
    - 4-body segment NIRS, ultrasound IJV/FV, cardiovascular parameters



Source: DLR

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DLR

The SpaceCENT Study:
Studying Physiological and Anatomical Cerebral Effects Of Centrifugation and Tilt

- 24 subjects (3 groups of 8):
    1. ***Control group***: 60 days of HDT bed rest (no AG)
    2. ***Intervention group 1***: 60 days of HDT bed rest + 30 min AG per day
    3. ***Intervention group 2****:* 60 days of HDT bed rest + 6x 5 min of AG per day

Specific Aims:

1. Determine the between-group effects of 60 day HDBR alone versus HDBR with AG (2 different regimens) on the cerebral, ocular, and sensorimotor systems
2. Determine the within-group effects of the experimental conditions (60 days HDBR +/- AG) on the cerebral, ocular and sensorimotor systems compared to pre HDBR baseline
3. Assess the transient (real-time) effects of AG (intervention groups only) on cerebral and ocular systems using non-invasive technologies

Source: DLR

Source: DLR

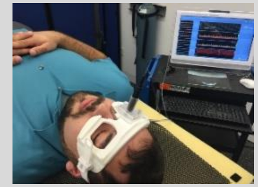
Source: DLR

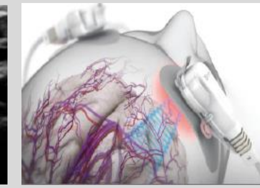
Measurements

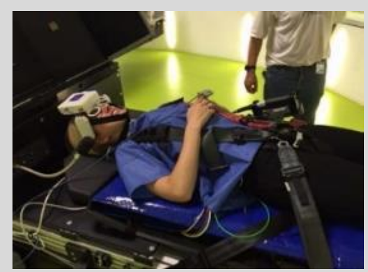
- **Cerebral/Vascular**
  - NIRS*
  - Transcranial Doppler*
  - Cerebral autoregulation*
  - Internal jugular vein dimensions*
  - Non-invasive intracranial pressure
  - cFLOW cerebral microvasculature assessment*
  - MRI (PCMRI, arterial spin labeling, DTI, optic nerve sheath diameter, 3d volumetric scan)

- **Ocular**
  - Intraocular pressure*
  - OCT (RNFL, choroidal thickness, Bruch's membrane opening)
  - Ophthalmic exam (visual acuity, cycloplegic refraction, slit lamp exam, fundoscopy, visual field testing, etc.)

- **Functional Balance and Vestibular Tests**







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