The Visual Impairment Intracranial Pressure Syndrome in Long Duration NASA Astronauts: An Integrated Approach

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Background
VIIP Clinical Findings

- To date 22/31 U.S. astronauts have developed some or all of the following findings either during or following a six-month spaceflight:
  - Hyperopic shift
  - Choroidal folds
  - Optic Nerve Sheath Distention
  - Optic nerve kinking
  - Globe flattening
  - Optic disc edema (papilledema) N=7
  - Cotton wool spots N=3
  - ↑ CSF pressure postflight 5/6 subjects: 21.0-28.5 cmH₂O

- Kramer et al. (2012)
Pre to Postflight Disc Edema (First case 2005)

**Pre Flight**
Fundoscopic images of the right and left optic discs.

**Post Flight**
Fundoscopic images of the right and left optic discs showing Grade 3 edema (right) and Grade 1 edema (left).
1. Normal Visual Field with normal blind spot (in black)

2. Early Defect, Enlarged Blind Spot and Inferior Nasal Loss

3. Severe Visual Constriction

Prolonged Disc Edema May Lead to Peripheral Visual Field Loss
Main Hypothesis
Head-ward fluid shift due to microgravity

Increased intracranial pressure (ICP)

Elevated ICP transmitted to the eye and optic nerve
Evidence
NASA Crewmember LPs to Date

- LPs are done in crewmembers only if clinically indicated
- 6 LPs conducted postflight in crewmembers with optic disc edema, no preflight LP as baseline
- Postflight measurements of ICP via LP have demonstrated elevated ICP in 5/6, ranging 15.4-21mmHg. Clinical intervention recommended when ICP>20.0mmHg
  - Does not reflect in-flight ICP (fluid shift + CO₂), suspected to be higher

<table>
<thead>
<tr>
<th>Case</th>
<th>Opening pressure (cm H₂O) Normal range 10-20 cm H₂O</th>
<th>Opening pressure (mmHg) Normal range 5-15 mm H₂O</th>
<th>Time after flight (days)</th>
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<tr>
<td>D</td>
<td>28.5</td>
<td>21.0</td>
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<td>C</td>
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<td>E</td>
<td>18</td>
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</table>
Alternative Hypotheses:

1. Genetic VIIP predisposition to the spaceflight environment

Probably a combination or other causes as well!
One-Carbon Metabolism

Smith & Zwart et al. 2015
Alternative Hypotheses:

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2. CO₂ induced VIIP

Probably a combination or other causes as well!
A Possible Role for CO₂ in VIIP?

- CO₂ is an extremely potent vasodilator, and its levels on ISS are x10 of Earth levels.

- A study by a joint NASA team (medical operations, LSAH, toxicology) evaluated in-flight data from expeditions 2-31, looking for a relationship between levels of CO₂ and symptoms.

- A statistically significant association was found between the probability of headaches and average CO₂, for both 24-hour and 7-day averages.

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2. CO₂ induced VIIP

3. Ocular structural changes
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4. Brain structural changes
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Research Approach
The VIIP Research Plan

Zero VIIP Incidence

Current Incidence of VIIP Findings = 66.7%
The VIIP Research Plan

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The VIIP Research Plan

- VIIP 1 - Knowledge Acquisition
- VIIP 3 - Technology Development
- VIIP 12 - Analogs

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VIIP 1 - Knowledge Acquisition

VIIP 3 - Technology Development

VIIP 12 - Analogs

VIIP 13 – Countermeasures

Human Research Program

NSBRI

Medical Operations

LSAH
The VIIP Research Plan

Zero VIIP Incidence

VIIP 13 – Countermeasures

VIIP 12 - Analogs

VIIP 3 - Technology Development

VIIP 1 - Knowledge Acquisition

Current Incidence of VIIP Findings = 66.7%
VIIP 1: Etiology and Risk Factors

- VIIP Data Mining
  - Venous/Arterial Compliance

- CSF Dynamics pre/postflight (MRI)
- Venous Sinus Evaluation
- Diffusion Tensor Imaging (MRI)
- Brain Gene Expression Signatures
- CSF Production & Outflow (rodents)
- Cephalad Fluid Redistribution (MRI)
- VIIP Biomarker

- CO₂ Data Mining Vision
- CO₂ Data Mining headaches

- Mapping by VEGEN
  - Data Mining – Ocular Structure
  - Ocular Structure & Biomechanics
  - Compartment Syndrome
  - SD-OCT Analysis
  - Effects of Gamma Radiation

- 1-Carbon Polymorphism
- Retinal Gene Expression during μG
- Retinal Gene Changes in HLS

- ICP in Short & Simulated Microgravity
  - Direct ICP in Microgravity

- Ocular Health Study
- Fluid Shifts
- Occ. Surveillance Data Mining
- SD/Visual Health (MRID)
- Digital Astronaut Modeling

- Eye & Cranio-Venous Modeling
- Contribution of Medications
- Influence of Exercise Modality
- Acute CO₂ & HDT (1 hr)
- Pilot CO₂ & HDT (1 day)
- Short-Term CO₂ & HDT (1 wk)
- Chronic CO₂ & HDT (1 month)
- Long-Term Impacts of VIIP
- Evidence Report
  - Med Ops In-Flight Monitoring

- HHC
  - Completed
- NSBRI
  - Ongoing
- SD
  - Planned
Example:

The Ocular Health Study on ISS

(PI: Christian Otto)
Comprehensive Examinations in Ocular Health

B-scan Ocular Ultrasound

Intraocular Pressure

Optical Coherence Tomography (OCT)

Fundoscopy

Computer-based vision testing

Cardiac and transcranial Doppler for vascular compliance
Example:

The Fluid Shifts Study on ISS

(PI’s: Michael Stenger, Alan Hargens & Scott Dulchavsky)
In-Flight Sessions (FD 45, R-45)

Test Day 1

Fluid compartmentalization measures:
- Total Body Water (D₂O)
- Extracellular (NaBr)
- Intracellular (Calculated)

Test Day 2

Ultrasound measures of fluid shifts:
- Vascular measures of head/neck (i.e., carotid, jugular, vertebral, cerebral)
- Cardiovascular, ophthalmic, and portal vein measures
- Tissue thickness forehead and eyelid

Other physiological measures:
- Intracranial Pressure (CCFP/DPOAE)
- Intraocular Pressure (Tonopen/iCare and Ultrasound)
- Ocular Structure (OCT)
- Blood Pressure / Heart Rate / Vascular Resistance

Test Days 3 & 4
- Similar to Day 2 w/ addition of Chibis LBNP
Reversal of Fluid Shift by LBNP (Chibis)
Fluid Shifts Timeline

- **L-21/18 months**: MRI concurrent with Med Ops schedule
- **L-90**: Day 1 supine, upright sitting, 15° HDT baseline
- **FD45**: Day 1 dilution measures
- **R-45**: Day 2 supine, 15° HDT with LBNP
- **R+1/3**: Day 2 all other baseline measures
- **R+10**: Day 3 Chibis LBNP - part 1
- **R+30**: Day 4 Chibis LBNP - part 2
- **R+180**: Single Day Sessions supine, upright sitting, 15° HDT measures No LBNP
Preliminary Results:

Intracranial pressure during parabolic flight induced zero G
**Ommaya Reservoir** - Commonly used intraventricular chemotherapeutic delivery device. Allows access to brain’s ventricular system through overlying skin allowing pressure measurement.
Preliminary Results:

Cardiovascular predisposition
Correlation of Preflight Cardiovascular Score and Postflight Eye Outcomes

Best correlation = 0.91, Max = .96, Min .86, P<0.001

Crew Average Best VIIP Health Score

Crew Average Best Cardio Health Score

Averaged across 200 imputed datasets

Correlation of Preflight Cardiovascular Score and Postflight Eye Outcomes

N=31

Best correlation = 0.91, Max = .96, Min .86, P<0.001

Crew Average VIIP Eye Score

Crew Average Cardio Score

N=31
### VIIP 3: Diagnostic Tools

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<tr>
<th>Status</th>
<th>Project</th>
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**In-Flight Technologies**

- HHC
- NSBRI
- SD

- ✓ Completed
- ❑ Planned
- ❑ Ongoing
VIIP 12: Ground-based Analogs & Models

- Ophthalmic and Optic nerve Sheath Modeling
- HLS Rodent Model for VIIP
- Digital Astronaut: VIIP Modeling
- Cranial Venous Circulation Modeling
- Acute CO₂ & HDT (1 hr)
- Pilot CO₂ & HDT (1 day)
- Short-Term CO₂ & HDT (1 week)
- Chronic CO₂ & HDT (1 month)
- Rodent Retinal Changes with HLS
- Rodent Retinal Changes with Spaceflight
- Rodent Retinal Changes with Radiation

HHC
- Completed

NSBRI
- Ongoing

SD
- Planned
VIIP 13: Countermeasures

- In-Flight CO₂ Reduction
- Fluid Shifts Flight Study (LBNP)
- Influence of Exercise Modality
- Evaluation of an Impedance Threshold Device
- Mechanical Countermeasures - Evaluation of Marketed Devices
- Thigh Cuffs Ground Evaluation
- Pharmacological Countermeasures
- Countermeasure Optimization Ground Study
- Countermeasure Optimization In-Flight

- HHC
- NSBRI
- SD
- Completed
- Ongoing
- Planned
Thank you!