Visual Impairment and Intracranial Pressure (VIIP):
What is it and what does it tell us about Spaceflight Physiology?

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Contributors

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- LSAH - epidemiology
- BDRA – increment roll up
- HRP HHC Element
- VIIP RCAP
- VIIP IWG
Agenda

- Duration of Spaceflight
- Historical Context
- Spaceflight Physiology
- Data Collected
- Countermeasures
- Transition to Operations

- Visual Impairment and Intracranial Pressure
  - Incidence
  - Vascular, Central Nervous, Ocular components
  - Cardiovascular Physiology Refresher
  - Fluid shift
  - Imaging of the Eye and Evidence
  - Theory - ICP
  - Clinical Practice Guideline
Human Spaceflight Experience: The Long and the Short of it...

- Characteristics of the Vehicle
- Habitat Environment
- Partial Gravity Exposure
- Countermeasure Availability
- Physiological, Medical, Environmental Data

**Graph:**
- **Y-axis:** Number of individual exposures
- **X-axis:** Flight Duration

- Data points for different flight durations ranging from 1 day or less to 14-15 months.
Historical Perspective

- Gemini 5 (8 day mission)
  - Visual Tester in-flight
  - Visual acuity measurement program
  - Large rectangles at ground sites in Texas and Australia.
  - No changes noted in astronaut visual acuity postflight.
  - Duntley et al, 1966

- Apollo
  - Retinal vascular photography reveals retinal vessels “decreased in size” at 3.5 hours into flight.
  - 100% oxygen atmosphere
  - No visual acuity changes
  - Hawkins and Zieglschmid, 1975
Shuttle

- 10-14 day missions
- Anecdotal reports of vision changes, but return to baseline.
- 1 astronaut with bilateral lens implants
- No optic disc edema cases, but an occasional choroidal fold.

- 122 crewmembers between 1995 and 1998, 15% indicated decrements in near vision on orbit. Returns to baseline.
- Paloski et al 2008
Differences Between Historical and Present

- Missions were 5 to 17 days generally (Skylab a notable exception)
- Astronaut age was mean of 38
- MRI and OCT not available
- Spacecraft ranged from 5.0 psi to 10.7 psi to 14.7 psi with varying oxygen concentrations

- Missions average 6 months on ISS
- Astronaut mean age 46.7
- MRI, OCT, Telemedicine fundoscopy
- 14.7 psi, 21% oxygen
- Robust exercise suite
Astronauts experience a spectrum of adaptations in flight and post flight.

- **Muscular**
- **Cardiovascular**
- **Neurovestibular**
- **Behavioral**
- **Immunological**
- **Skeletal**
- **Microvascular**
- **Nutritional**
- **Skeletal**
- **Muscular**
- **Immunological**
- **Nutritional**
- **Behavioral**

**Exposures:**
- Launch & Landing Loads
- Microgravity
- Closed Environment (air and water)
- Confined Habitat
- Radiation Exposure

**Balance disorders:**
- Cardiovascular deconditioning
- Decreased immune function
- Muscle atrophy
- Bone loss
Time Course of Physiological Changes During Weightlessness

- Neurovestibular System
- Fluids and Electrolytes
- Cardiovascular System
- Red Blood Cell Mass
- Bone and Calcium Metabolism
- Lean Body Mass
- Radiation Effects

Clinical Horizon

0-g Set Point

1-g Set Point

Time Scale (Months)

1 1/2

Point of Adaptation

NASA
Physiological & Psychosocial Manifestations Associated with Space Flight

**Bone**
- Bone mineral content
- Bone mineral density
- Urinary calcium
- Renal stone risk

**Skeletal Muscle**
- Skeletal muscle mass
- Skeletal muscle strength
- Skeletal muscle endurance
- Skeletal muscle capillary density

**Neurosensory**
- Vestibular disturbances
- Space motion sickness
- Sensorimotor function
- Postural & locomotor stability

**GI/Pharmacokinetics**
- GI motility and PK

**Cardiovascular**
- Fluid volume
- Orthostatic tolerance
- Aerobic capacity
- Arrhythmias

**Psychosocial**
- Team issues
- Confinement issues
- Fatigue
- Stress
- Errors
- Cognitive Function

**Environmental**
- CO2 (2-5 mmHg)*
- Hearing loss due to acoustics
- Radiation exposure
- Risk of cataracts/cancers
- Skin irritations due to microbial growths
• Data Collected via Medical Requirements
• Assessments of:
  – Bone
  – Cardiovascular
  – Aerobic Fitness
  – Sensory Motor
  – Functional Fitness
  – Nutritional Status
Pelvis Loss 7.7%     Recovery Half-life = 97 d

Percent Change in Estimated VO2 Index from Pre-Flight Expeditions 1-16 (n=20)

Postflight Functional Fitness Expeditions 1-16 (n=20)

Data can be used to assess the individual or the population.
Bone compartments or bone types

Cortical Bone/ “Compact Bone”

Cancellous “Spongy” Bone/Trabecular Bone

An example of a spaceflight adaptation that is well described but still lacks understanding of time course, recovery, and long term risk

Sources: L. Mosekilde; SL Bonnick; P Crompton
ISS Exercise Hardware Availability Timeline

<table>
<thead>
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<th>EXP</th>
<th>CEVIS Assembly</th>
<th>I-RED Assembly</th>
<th>TVIS Assembly</th>
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<tr>
<td>EXP1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXP2</td>
<td>restricted to arm ergometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXP3</td>
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<td>EXP4</td>
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<td></td>
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</tr>
<tr>
<td>EXP5</td>
<td>failing control panel</td>
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<tr>
<td>EXP16</td>
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- **CEVIS**
  - 10/00
  - 08/01
  - 12/01
  - 06/02
  - 11/02
  - 04/03
  - 10/03
  - 10/04
  - 04/05
  - 03/06
  - 09/06
  - 04/07
  - 10/07

- **I-RED**
  - 10/00
  - 09/05
  - 06/02
  - 10/03
  - 04/05
  - 10/04
  - 04/03
  - 03/01
  - 12/01
  - 08/01
  - 04/04

- **TVIS**
  - 10/00
  - 09/05
  - 06/02
  - 10/03
  - 04/05
  - 10/04
  - 04/03
  - 03/01
  - 12/01
  - 08/01
  - 04/04

**Legend**
- **Green** = Nominal availability
- **Yellow** = Restricted use
- **Red** = No availability
Countermeasures

Research

Operational

NASA
• **Visual Impairment and Intracranial Pressure (VIIP)**

  • **What is the problem?**
    - Optic Disc Edema, Globe Flattening, Choroidal Folds, Hyperopic Shifts and Raised Intracranial Pressure has occurred in Astronauts During and After Long Duration Space Flight

  • **What is the risk?**
    - Given that all astronauts experience a microgravity-induced cephalad fluid shift and that both symptomatic and asymptomatic individuals have exhibited optic nerve sheath edema on MRI, there is a high probability that all astronauts have some degree of idiopathic intracranial hypertension. Those that are susceptible (due to eye architecture, anatomy, narrow disc, etc.) have a high likelihood of developing either choroidal folds or papilledema, and the degree of edema will determine impairment and long-term or permanent vision loss.
A consequence of human spaceflight

- Visual Impairment and Intracranial Pressure (VIIP)
  - Operational processes (medical requirement) put in place to diagnose and manage 2008 (fundoscope and eye ultrasound)
  - Sentinel case found retrospectively (2005; Exp 11)
  - Integrated approach kicked off to address the issue: 2010
  - Research and Clinical Advisory Panel formulated in 2011
  - Occupational Health Research Protocol developed 2012
  - 9 Studies funded in 2012
Incidence rate of VIIP per the CPG classifications
36 long duration US astronauts
21 Evaluated as of 7/2012

<table>
<thead>
<tr>
<th>CPG Classification</th>
<th>Number of Cases</th>
<th>Number of Crewmembers</th>
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<tbody>
<tr>
<td>Not Evaluated</td>
<td>N=15</td>
<td>42%</td>
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<tr>
<td>Class 0</td>
<td>N=6</td>
<td>29%</td>
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<tr>
<td>Class 1</td>
<td>N=2</td>
<td>10%</td>
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<tr>
<td>Class 2</td>
<td>N=8</td>
<td>38%</td>
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<td>Class 3</td>
<td>N=1</td>
<td>5%</td>
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<td>Class 4</td>
<td>N=4</td>
<td>19%</td>
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These crewmembers did not have MRIs, OCTs or cycloplegic refraction – NASA is in the process of obtaining this information/evaluation.

21 crew members have been evaluated
15 have symptoms – 15/21 = 71%
Class 3 and 4 – 5/21 = 24%
**VIIP: A Three-Part Story**

1. **The Vascular System**
   - Demographic
     - Gender
     - Age
     - Race
   - Body Composition
     - Height
     - Weight
     - % Lean Body Mass
     - % Fat Body Mass
   - Cardiac
     - Resting Blood pressure
     - Resting Cardiac output
   - Biochemistry
     - Homocysteine
     - Lipids (LDL, HDL, TGs)
     - Serum Insulin
     - HbA1c
     - Fasting serum glucose
   - Fitness
     - MVO2 (max oxygen uptake)

2. **The Brain**
   - MRI Intracranial (Pre/Post)
     - Peak CSF flow
     - CSF Production
     - Glove Flattening
     - Globe Axial Length
     - Optic Nerve Tortuosity
   - Ultrasound (Pre/In/Post)
     - ONSD
     - Nerve/Sheath Ratio
   - Environmental
     - CO2 Levels
   - MRI Intracranial (Pre/Post)
     - Peak CSF flow
     - CSF Production
     - Glove Flattening
     - Globe Axial Length
     - Optic Nerve Tortuosity
   - Ultrasound (Pre/In/Post)
     - ONSD
     - Nerve/Sheath Ratio
   - Environmental
     - CO2 Levels

3. **The Eye**
   - Intraocular pressure
   - Corneal Thickness
   - Visual acuity (Pre/In/Post)
   - Refractive error (Pre/Post)
   - Optic Disc:Cup ratio (Pre/Post)
   - OCT (Pre/Post)
     - RNFL
     - RPE angle
     - Optic nerve head
     - Choroidal Folds
   - High Res Retinal Photography
     - Retinal hemorrhages
     - Cotton wool spots
   - Optical Biometry (Pre/Post)
     - Globe axial length
Blood Vessel Compliance \[ C = \frac{\Delta V}{\Delta P} \]

Venous compliance is approximately 30 times larger than arterial compliance.

**Starling Equation:**

*hydrostatic* and *oncotic* forces (the so-called *Starling forces*) in the movement of fluid across *capillary membranes*.

The Starling equation reads as follows:

\[ J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_i]) \]

http://en.wikipedia.org/wiki/Starling_equation#cite_note-1
Fluid Shifts during Space Flight

In space, the fluid tends to redistribute toward the chest and upper body. At this point, the body detects a “flood” in and around the heart.

On Earth, gravity exerts a downward force to keep fluids flowing to the lower body.

The body rids itself of this perceived “excess” fluid. The body functions with less fluid and the heart becomes smaller.

Upon return to Earth, gravity again pulls the fluid downward, but there is not enough fluid to function normally on Earth.

Lujan and White (1995)
Redistribution of Venous Pressures From 1G to 0G

Standing 1G

-20
0

venous pressure (mmHg)

0G

15–20
7–9

venous pressure (mmHg)

9.8m/s²

- Cranium is rigid
- Venous congestion
- Obligate arterial flow
- Transcapillary leak
- ++ICP~30-40

Integrated Vision Impairment & Intracranial Pressure Project
Risk Background - Symptoms

Background:
- 15 known “clinical cases” (of 36 long duration crew members)
  - Each with different degrees of symptoms
  - Does not currently include data from international partners
  - Current assessment of Russian participation underway

- **Hyperopic Shifts**
  - Up to +1.75 diopters

- **Globe Flattening**

- **Choroidal Folds**
  - Parallel grooves in the posterior pole

- **Optic Disc Edema (swelling)**

- **Scotoma**
  - Altered/Disrupted Visual Field

- **Altered Blood flow**
  - "cotton wool" spots

- **Increased Optic Nerve Sheath Diameter**

Normal Globe

Flattened Globe

MRI Orbital Image showing globe flattening
1. Fluid Shift due to Microgravity

- Hyperopic Shifts
  - Up to +1.75 diopters

- Optic Disc Edema (swelling)

- Choroidal Folds
  - Parallel grooves in the posterior pole

2. Fluid shift causes increased intracranial pressure (ICP) (?)

3. ICP transmitted to optic nerve and eye

- Globe Flattening

- Increased Optic Nerve Sheath Diameter
Hyperopia

Hyperopia, or farsightedness, is a condition of the eye where incoming rays of light impinge on the retina before converging into a focused image, resulting in difficulty seeing nearby objects clearly.

Image can be located at:
http://medical-dictionary.thefreedictionary.com/hyperopia

Scotoma

Changes in visual acuity are assessed with regular vision testing on orbit.
• Ultrasound is used to track optic nerve sheath diameter and globe flattening pre-, in-, and post flight

• Current fundoscope (PanOptic) can not detect choroidal folds

• New Hardware:
  • Fundoscope with better resolution (ISS CR Approved June 2012)
    • Will give qualitative data
  • Optical Coherence Tomography (OCT)
    • Will give quantitative data: progression of choroidal folds and nerve fiber layer changes

Optical Coherence Tomography (OCT) measures

Increased Optic Nerve Sheath Diameter

Choroidal Folds - parallel grooves in the back of the eye

Optic Disc Edema

Altered Blood flow “cotton wool” spots
Key Brain Areas Potentially Affected by Fluid Shift

- **Interstitial fluid**
- **CSF Production**
- **CSF Resorption (AG-Venous/Lymphatic)**
- **Venous Congestion**
The Brain is an Expansile Vascular Organ Within a Rigid Cranium: An swollen brain can impair blood flow to itself.
Expanding Brain Parenchyma & Cerebellum Compresses Transverse Sinus
Case Definition for Spaceflight-Induced Intracranial Hypertension

**Class 0**
- < .50 diopter cycloplegic refractive change
- No evidence of papilledema, nerve sheath distention, choroidal folds, globe flattening, scotoma or cotton wool spots compared to baseline.

**Class 1**
- Refractive changes ≥ .50 diopter cycloplegic refractive change and/or cotton wool spot
- No evidence of papilledema, nerve sheath distention, choroidal folds, globe flattening, scotoma compared to baseline.
- CSF opening pressure (if measured) ≤ 25 cmH2O

**Treatment:**
- Repeat OCT, cycloplegic refraction, fundus exam and threshold visual field every 4 -6 weeks x 6 months, repeat MRI in 6 months

**Class 2**
- Class 1 plus:
  - Choroidal folds and/or optic nerve sheath distension and/or globe flattening and/or scotoma
  - No evidence of papilledema
  - CSF opening pressure ≤ 25 cm H2O (if measured)

**Treatment:**
- Repeat OCT, cycloplegic refraction, fundus exam and threshold visual field every 4 -6 weeks x 6 months, repeat MRI in 6 months

**Class 3**
- Class 2 plus:
  - Papilledema of Grade 0-2.

**Treatment:**
- Repeat OCT, cycloplegic refraction, fundus exam and threshold visual field every 4 -6 weeks x 6 months, repeat MRI in 6 months

**Class 4**
- Class 3 plus:
  - Papilledema Grade 2 or above.
  - Presenting symptoms of new headache, pulsatile tinnitus and/or transient visual obscurations
  - CSF opening pressure >25 cm H2O

**Treatment:**
- Institute treatment protocol as per CPG – LP, repeat MRIs, pharmaceutical intervention

**Least Severe Symptoms**

**Most Severe Symptoms**
Integrated Pre/In/Post-Flight VIIP Medical and Research Testing

Preflight Exams
- L-90/45 days
- Acceptable up to L-365 days
- MRI of Brain and Orbits Without Contrast
- Ultrasound Eye/Orbit
- Fundoscopy - PanOptic Ophthalmoscope
- Tonometry
- Visual Acuity including Amsler Grid Testing
- Other Tests - biomicroscopy (slit lamp), high resolution retinal photography, OCT (high resolution), and A-Scan.

In-flight Exams
- L+30 & R-30, L+100 if requested (+/- 7 days) & as clinically indicated
- Ultrasound Eye/Orbit
- Fundoscopy - PanOptic Ophthalmoscope
- Tonometry
- Visual Acuity including Amsler Grid Testing

Post-flight Exams
- L+10, 30, 60, 100 & R-30, (+/- 7 days)
- Ultrasound Eye/Orbit
- Fundoscopy - PanOptic Ophthalmoscope
- Tonometry
- Visual Acuity including Amsler Grid Testing
- Blood Pressure
- Vascular Compliance
- New Research Protocol
  - Blood Pressure
  - Vascular Compliance
  - Research
  - Medical Ops

Pre-flight Exams
- L-365
- L-90/45
- L+10, L+30
- L+60
- L+100
- R-30
- R+1 to R+3
- R+30
- R+90
- R+180
- R+365

In-flight Exams
- L+30 & R-30, L+100 if requested (+/- 7 days) & as clinically indicated
- Ultrasound Eye/Orbit
- Fundoscopy - PanOptic Ophthalmoscope
- Tonometry
- Visual Acuity including Amsler Grid Testing

Post-flight Exams
- L+10, 30, 60, 100 & R-30, (+/- 7 days)
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- Fundoscopy - PanOptic Ophthalmoscope
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- Visual Acuity including Amsler Grid Testing
- Blood Pressure
- Vascular Compliance
- New Research Protocol
  - Blood Pressure
  - Vascular Compliance
  - Research
  - Medical Ops
Clinical Implications

- Potential disability secondary to vision loss in astronauts susceptible to optic disc edema or choroidal folds
- Potential for long-term sequelae due to optic nerve cells ischemia (visual field defect or loss)
- Potential effect on white matter (senility, dementia, etc.)
- Decreased functional ability due to IIH
- Unknown contribution to space motion sickness, asthenia, or functional impairments
- Potential to worsen with repetitive flights or long term space missions
Questions?