Informational Briefing:

Risk of Microgravity-Induced Visual Impairment and Elevated Intracranial Pressure (VIIP)

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Outline

- Background
- Ocular Findings
- Cephalad Fluid Shift
- Current Assessment Methodologies
- Cases
- Contributing Structures of the Eye
- CSF Production
- CSF Resorption
- Exacerbating Factors
- Current Measures
- Draft Research Plan
- Opportunities for Partnership
Eight cases identified, represent 23.5% of the 34 crewmembers flown on the ISS, with inflight visual changes and pre-to-postflight refractive changes. In some cases, the changes were transient while in others they are persistent with varying degrees of visual impairment.

- Decreased intraocular pressure (IOP) postflight was observed in 3 cases.
- Fundoscopic exams revealed postflight findings of choroidal folds in 4 cases, optic disc edema in 5 cases and presence of cotton wool spots in 3 cases.
- Optical coherence tomography (OCT) confirmed findings of choroidal folds and disc edema and documented retinal nerve fiber layer thickening (4 cases).
- Findings from MRI examinations showed posterior globe flattening (5 cases) and optic nerve sheath distension (6 cases).
- Opening cerebrospinal fluid (CSF) pressure was elevated in 4 cases postflight reflecting raised intracranial pressure.

While the etiology remains unknown, hypotheses speculate that venous insufficiency or hypertension in the brain caused by cephalad fluid shifts during spaceflight are possible mechanisms for ocular changes in astronauts.
Risk Background - Ocular Symptoms

• 8 cases identified (23.5% of 34 long duration crew) with inflight visual changes and pre-to-postflight refractive changes.
  • Elevated Intracranial Pressure measured postflight

Hyperopic Shifts
Up to +1.75 diopters

Globe Flattening
MRI Orbital Image showing globe flattening

Optic Disc Edema (swelling)

Choroidal Folds
parallel grooves in the posterior pole

Vision distortion
Cotton “wool” spots
Cephalad Fluid Shift

On ground 1G

Initial stage in space

Initial stage in space
Hydrostatic Pressure Changes

Venous Pressure & ICP Increases in Microgravity-Supine Model

ICP=3.9 mmHg

ICP=11.9 mmHg

Standing

Supine

Internal Jugular Vein Caliber
Increased Volume = Increased Pressure
Risk Background - Intracranial Pressure

MRI Brain Venogram
• Choroidal folds are parallel grooves or striae that involve the choroid in the posterior pole.
• They are usually horizontal but may be vertical, oblique, or irregular and are usually situated temporally, rarely extending beyond the equator.
• Their characteristic appearance on funduscopic examination, with the crests appearing yellow and less pigmented, is caused by the stretching and thinning of the retinal pigment epithelium, and the troughs appearing darker are caused by retinal pigment epithelium compression.
• Known causes of choroidal folds include orbital diseases or tumors, choroidal tumors, posterior scleritis, hypotony, chronic papilledema or optic nerve tumor, choroidal neovascular membrane, scleral buckle, and central serous
The choroid contains a dense vascular network terminating with the fenestrated choriocapillaris.
Case Report 1: Pre & Post Flight Fundoscopy

[Top Pre Flight]
Fundoscopic images of the right and left posterior pole.

[Bottom Post Flight]
Fundoscopic images of the right and left posterior pole showing choroidal folds below the optic disc (top arrow) and a “cotton-wool” spot (bottom arrow) in the inferior arcade in the right eye.
Optic disc imaging did not show presence of observable disc edema.
Case Report 3: Pre & Post Flight Fundoscopy

[Top Pre Flight] Fundoscopic images of the right and left optic disc.

[Bottom Post Flight] Fundoscopic images of the right and left optic disc showing Grade 3 edema at the right optic disc and Grade 1 edema at the left optic disc. Fig.
Pre flight Zeiss Cirrus OCT showing right and left NFL ‘TSNIT’ (temporal, superior, nasal, inferior and temporal curve).

Post flight Zeiss Cirrus OCT showing increased thickness of the nasal (red arrow) NFL. Greater increase is noted in the right eye in the nasal quadrant NFL thickness; 42μ pre flight to 70μ post flight. Fundus and optic disc imaging did not show presence of observable disc edema-choroidal folds may be an early sign of elevated ICP which precedes papilledema (important to obtain accurate in flight measurement of choroidal fold development-OCT)
PanOptic Ophthalmoscope

![PanOptic Ophthalmoscope Image]

- Eye Cup
- Focusing Wheel
- Aperture Dial
- Light Rheostat Dial
- Panoptic Handle
- Otoscope USB Cable
- Battery Cap

![User Using PanOptic Ophthalmoscope Image]

- Distance: 18-20"

![PanOptic Ophthalmoscope Software Image]

- Gallery showing multiple photos
Raised Intracranial Pressure-Qualitative Measurement?

Elevated ICP transmitted to optic nerve
Optic nerve x-section (post-mortem) from patient with papilledema.

- Large space, filled with web-like strands of arachnoid between nerve & nerve sheath.
Ocular Sonography

- Image optic nerve and nerve sheath with ultrasound
- Optic nerve sheath diameter (ONSD) → ICP
- Gives broad sense of increased ICP versus normal
- No reliable linear relationship

In Flight B-scan Ultrasound
Optic Nerve Sheath Diameter

- Generally accepted that ONSD > 5 mm ≈ ICP > 20 cm H₂O

Case Report 4 - Increased Optic Nerve Sheath Diameter On-Orbit

12 mm
Case Report 5: MRI Globe Imaging

T1 MRI orbital imaging of the right eye. Pre flight (left) and Post flight (right) showing flattening of the posterior globe.
CASE Report 4 - Flattening of Posterior Wall - and Raised Optic Disk

Elevation of optic disc
Ocular Venous Hypertension via Optic Nerve Compression

- Increasing ICP transmitted to optic nerve via CSF space causes compression of central retinal vein
- Arterial blood continues to flow into eye but venous drainage impaired
- Result= venous hypertension, optic disc edema, disc protrusion, globe flattening & retinal engorgement, hemorrhage etc.

A. Normal distal optic nerve/sheath complex & head in longitudinal cross section

B. Papilledema showing enlargement of subarachnoid space & compression central retinal vein (CV)

- V-vitreous
- D-Disc
- Sc-sclera
- C-Choroid
- A-Arachnoid space
- S-Optic nerve sheath
- N-Optic Nerve
- CV-Central retinal vein
Measurement of Intraocular Pressure with Applanation Tonometry

Dr. Story Musgrave conducting tonometry on STS 44
Elevated ICP - Is it Transmitted to the Eye?

MRI Brain Venogram

Also transmitted to eye via ophthalmic veins
<table>
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<tr>
<th>ISS Crew Member</th>
<th>Mission Duration</th>
<th>Refractive Change</th>
<th>Intraocular Pressure (mmHg)</th>
<th>Fundoscopic Exam Postflight</th>
<th>Disc Edema (Frisen)</th>
<th>OCT Postflight</th>
<th>Eye MRI Postflight</th>
<th>CSF Pressure Postflight (cmH2O)</th>
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</thead>
<tbody>
<tr>
<td>CASE 1</td>
<td>6 months</td>
<td>Preflight: OD: -1.50 sph OS: -2.25 -0.25x135</td>
<td>Preflight: 15 OU</td>
<td>Choroidal folds OD Cotton wool spot OD</td>
<td>Edema: No disc edema</td>
<td>Choroidal folds still visible inferior to the OD disc (R+ &gt;5yrs)</td>
<td>MRI not performed</td>
<td>Not measured</td>
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<td>Postflight: OD: -1.25 - 0.25x005 OS: -2.50 -0.25x160</td>
<td>Postflight: 10 OU</td>
<td>Bilateral disc edema OD&gt;OS Choroidal folds OD &gt; OS Cotton wool spot OS</td>
<td>Edema: Grade 1 OD and OS</td>
<td>NFL thickening c/w disc edema</td>
<td>Elevated • 22 at R+66 days; • 26 at R+17 months; • 22 at R+19 months; • 23 at R+ &gt;5yrs</td>
<td>Globe Flattening: OD and OS</td>
</tr>
<tr>
<td>CASE 2</td>
<td>6 months</td>
<td>Preflight: OD: 0.75 OS: 0.75 -0.25x165</td>
<td>Preflight: 14 OU</td>
<td>Bilateral disc edema OD&gt;OS Choroidal folds OD &gt; OS Cotton wool spot OS</td>
<td>Edema: Grade 1 OD and OS</td>
<td>NFL thickening c/w disc edema</td>
<td>Elevated • 22 at R+66 days; • 26 at R+17 months; • 22 at R+19 months; • 23 at R+ &gt;5yrs</td>
<td>Globe Flattening: OD and OS</td>
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<tr>
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<td>Postflight: OD: 1.00 OS: 0.50-0.50x140</td>
<td>Postflight: 14 OU</td>
<td>Bilateral disc edema OD&gt;OS Small hemorrhage OD</td>
<td>Edema: Grade 3 OD and OS</td>
<td>NFL thickening c/w Disc edema</td>
<td>Elevated • 21 at R+19 days</td>
<td>Globe Flattening: None observed</td>
</tr>
<tr>
<td>CASE 3</td>
<td>6 months</td>
<td>Preflight: OD: 0.50 sph OS: 0.25 sph</td>
<td>Preflight: 10 OU</td>
<td>Bilateral disc edema OD&gt;OS</td>
<td>Edema: Grade 1 OD</td>
<td>NFL thickening OD&gt;OS c/w Disc edema</td>
<td>Elevated • 28.5 at R+57 days</td>
<td>Globe Flattening: OD &gt; OS</td>
</tr>
<tr>
<td></td>
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<td>Postflight: plano Plano</td>
<td>Postflight: 10 OU</td>
<td>Small hemorrhage OD</td>
<td>Edema: Grade 1 OD</td>
<td>NFL thickening OD&gt;OS c/w disc edema</td>
<td>Elevated • 28.5 at R+57 days</td>
<td>Globe Flattening: OD &gt; OS</td>
</tr>
<tr>
<td>CASE 4</td>
<td>6 months</td>
<td>Preflight: OD: 0.75 -0.50x100 OS: plano-0.50x090</td>
<td>Preflight: 15/13</td>
<td>Disc edema OD Choroidal folds OD</td>
<td>Edema: Grade 1 OD</td>
<td>Mild NFL thickening OD&gt;OS c/w disc edema</td>
<td>Elevated • 28.5 at R+57 days</td>
<td>Globe Flattening: OD &gt; OS</td>
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<tr>
<td></td>
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<td>Postflight: OD: 0.75 -0.50x105 OS: 0.75 -0.75x090</td>
<td>Postflight: 11/10</td>
<td>Normal</td>
<td>Edema: No disc edema</td>
<td>Subclinical disc edema Mild/moderate NFL thickening OD</td>
<td>Elevated • 28.5 at R+57 days</td>
<td>Globe Flattening: OD and OS</td>
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<tr>
<td>CASE 5</td>
<td>6 months</td>
<td>Preflight: OD: 0.50 -1.25x010 OS: 5.00 -1.50x180</td>
<td>Preflight: 14/12</td>
<td>Normal</td>
<td>Edema: No disc edema</td>
<td>Subclinical disc edema Mild/moderate NFL thickening OD</td>
<td>Elevated • 28.5 at R+57 days</td>
<td>Globe Flattening: OD and OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postflight: OD: 5.00 -1.50x015 OS: 4.75 -1.75x170</td>
<td>Postflight: 14/12</td>
<td>Normal</td>
<td>Edema: No disc edema</td>
<td>NFL thickening OD&gt;OS c/w disc edema</td>
<td>Elevated • 28.5 at R+57 days</td>
<td>Globe Flattening: OD &gt; OS</td>
</tr>
<tr>
<td>CASE 6</td>
<td>6 months</td>
<td>Preflight: OD: 0.25 OS: 0.25 -0.50x152</td>
<td>Preflight: 14 OU</td>
<td>Disc edema OD Cotton wool spot OS</td>
<td>Edema: Grade 1 OD</td>
<td>NFL thickening c/w disc edema Choroidal folds OD</td>
<td>Elevated • 28 at R+12 days (with +SVP) • 19 at R+ days</td>
<td>Globe Flattening: OD and OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postflight: OD: 2.00 -0.50x028 OS: 1.00 sph</td>
<td>Postflight: 14 OU</td>
<td>Disc edema OD Cotton wool spot OS</td>
<td>Edema: Grade 1 OD</td>
<td>NFL thickening c/w disc edema Choroidal folds OD</td>
<td>Elevated • 28 at R+12 days (with +SVP) • 19 at R+ days</td>
<td>Globe Flattening: OD and OS</td>
</tr>
<tr>
<td>CASE 7</td>
<td>6 months</td>
<td>Preflight: OD: 1.25 sph OS: 1.25 sph</td>
<td>Preflight: 16 OU</td>
<td>Disc edema OU Choroidal folds OD &gt; OS</td>
<td>Edema: Grade 1 OD and OS</td>
<td>Moderate NFL thickening c/w disc edema OD and OS Choroidal folds OD and OS</td>
<td>Elevated • 28 at R+12 days (with +SVP) • 19 at R+ days</td>
<td>Globe Flattening: OD and OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postflight: OD: 2.75 sph OS: 2.50 sph</td>
<td>Postflight: 12/14</td>
<td>Disc edema OU Choroidal folds OD &gt; OS</td>
<td>Edema: Grade 1 OD and OS</td>
<td>NFL thickening c/w disc edema OD and OS Choroidal folds OD and OS</td>
<td>Elevated • 28 at R+12 days (with +SVP) • 19 at R+ days</td>
<td>Globe Flattening: OD and OS</td>
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</table>
Impacts

- Elevated intracranial pressure and vision disturbance in spaceflight are serious health risks to the astronaut population.
  - Much longer missions are being planned that will subject personnel to even greater periods of microgravity and hence prolonged exposure to elevated IOP and/or ICP.
- VIIP Risk team formed with membership from Med Ops and HRP.
  - Current plan for HRP content is to work via project team within HHC.
- High-level research plan in development
- What are the physiological causes?
Summit held February 8-10 with national and international experts in ophthalmology, neuro-ophthalmology, neurosurgery, neurophysiology, and cardiology.

- Obtained suggestions for current pre, in, and post-flight operations as well as research areas with respect to detection, monitoring, treatment, imaging, susceptibility, computer modeling, and/or use of analogs.

Results from the summit further reinforced the existence of multiple contributing factors with no clear cause identified. While Medical Operations approaches from a clinical perspective, research is needed to further quantify and mitigate the risk.

The NASA HRP has added this risk to its portfolio and established the VIIP Project within the Human Health Countermeasures Element.
Glaucoma

Tissues Involved in Glaucoma

- TM = trabecular meshwork
- SC = Schlemm’s canal
- JCT = juxtacanalicular tissue
- IW = inner wall
- OW = outer wall
- LC = lamina cribrosa

Lamina cribrosa, en face view

Iris

Cornea

Lens

Retina

Optic nerve head

Sclera

Optic Nerve
Posterior Eye & Optic Nerve Anatomy
The Lamina Cribosa: Barrier Between the Intraocular Space and SAS

The LC serves as a barrier to separate the intraorbital space, with typically higher pressure, from the subarachnoid space, with typically lower pressure. The LC therefore prevents orbital contents from leaking into the subarachnoid space.
Lamina Cribosa Structure

- LC is a series of cribiform plates, with pores that line up to permit nerve axons to pass through.
- LC cores are filled with fibrillar collagen and elastic fibres, during aging constituents are altered.
- LC becomes stiffer and thinner, thus ability to support nerve axons passing though is compromised especially around the ages of 40-50 years.
Myopes put Greater Shear Stress on LC
Higher Risk for Glaucomatous Changes

Stress on any part of ocular shell related to IOP and radius of structure: $\sigma = \frac{PR}{2t}$
$\sigma$=circumferential stress
P=IOP
R=radius of curvature at that part of the globe
T=thickness
Thus, in myopic eyes when LC is cupped, radius is larger, and stress is greater.
Lamina Cribosa: Normal vs Myopic

- Shear stresses are dominant, and maximal at the periphery owing to the greater curvature in myopic eye.
- LC increases in stiffness with age = decreased compliance’ means higher likelihood of permanent deformation and at lower pressures.
- Change in mechanical compliance most marked after 40-50 years of age, same age incidence of glaucoma increases.
- Any elevation in deformation pressure, even transient, may result in permanent shape.
Key Brain Areas

- CSF Production
- CSF Resorption
- Venous Congestion
CSF Production: Choroid Plexus

Choroid plexus in lateral, third & fourth ventricle produces 70-90% of CSF in brain

Increased filtration?
Choroidal Cell Responses in Microgravity-Atrial Naturiestic Peptide

- ANP neurohormone
- In CNS when ANP activated, decreases CSF by inhibiting Na-K-ATPase proteins in cerebral capillaries
- Increased ANP binding sites 1.5-2.5x in HLU rat studies

Immunodetection of (red) Na-K-ATPase at the apical pole of choroid plexus (B) in a control rat (D) in a ground-based model simulating cephalad fluid shift

Choroidal Cell Responses in Microgravity - Aquaporin-1 Expression

Immunodetection of aquaporin 1 (in green) at the apical pole of choroid plexus,
(A) in a control rat (homogeneously covered with long bulbous apical microvilli, and tufts of kinocillia)

(C) in a model simulating cephalad fluid shift. AQP1 was reduced 64% after 14d spaceflight (STS-58), by 44%
after 14 days HLU, and by 68% after 28d HLU.
A net decrease was noted at the epithelial cells, suggesting that CSF production was decreased.
Loss of microvilli, failure of exocytosis, loss of kinocillia

Suggests brain adaptation in microgravity with a reduction in CSF secretory activity.
Overshoot of AQP-1: A Mechanism for Elevated ICP Post Flight?

- Once rats returned to 1G, at 2 days readaptation, AQP1 expression was 48% greater than control rats.
- In the 14d HLU rats there was a 57% increased expression in AQP-1 after 6 hours readaptation, compared to controls.
- Could over-expression of AQP-1 upon return to 1G be a mechanism for the persistently elevated ICP seen in some crew members?
Flow analysis of CSF through the aqueduct

- The flow analysis of CSF through the aqueduct (axial oblique section noted as dashed line --Bottom).
- A CINE phase contrast sequence obtained perpendicular to the mid cerebral aqueduct showing velocity versus time after the QRS wave (graph --- top left) Case #5:
  - R+30: CSF production rate=305 ul/min
    - CSF peak velocity=3.65 cm/s
  - R+57: LP opening pressure=28.5
  - R+180: CSF production rate=682 ul/min
    - CSF peak velocity=7.80 cm/s
  - Normal CSF production 150-270 ul/min
- Cross sectional image through the mid cerebral aqueduct (Middle) showing the area of flow analysis
- T1 weighted mid sagittal image (Bottom) showing plane of section through the mid cerebral aqueduct
- There is no obvious narrowing of the cerebral aqueduct. CSF production rate is approximately one standard deviation above average in several cases
Normal CSF Diffusion Gradient

Normal SSVP:CSFP = 0.60
Therefore delta driving pressure only ~3-5 mmHg

Venous Sinus Pressure = 5-7 mmHg

ICP = 10 mmHg
Risk Background - Intracranial Pressure

As SSVP:CSFP increases, approaches 1.0
Driving pressure falls < 3-5mmHg and decreased CSF absorption
CSF Resorption: Arachnoid Granulations

Electron micrograph of outer arachnoid granulation-apical region- showing collagen fibers surrounding the pores and linking the granulations

Electron Micrograph of clustered arachnoid granulations from the floor of the superior sagittal sinus. Arrows pointing to lobules

Inflammation of the arachnoid villi as one mechanism inhibiting resorption?

Electron micrograph of outer arachnoid granulation-apical region- showing collagen fibers surrounding the pores and linking the granulations
Blocked Lymphatic Drainage of CSF

Perineural pathways along cranial nerves for subarachnoid CSF-lymphatic connections may become congested decreasing absorption (thin curved arrows)

Low pressure system
Exacerbating Factors?

Strength training may cause potentially damaging transient spikes in ICP
Carbon Dioxide

Normal Sea Level CO2=0.0314%

Main symptoms of Carbon dioxide toxicity

- Visual: Dimmed sight
- Auditory: Reduced hearing
- Central: Drowsiness, Mild narcosis, Dizziness, Confusion, Headache, Unconsciousness
- Respiratory: Shortness of breath
- Muscular: Tremor
- Skin: Sweating
- Heart: Increased heart rate and blood pressure
CO2 on ISS

- CO2 level mission average=3.56mmHg (0.33%)
  - Ten times normal atmospheric
  - (Normal sea level atmospheric CO2=0.0314%)
- No mission under 2.0mmHg
- Average Peak CO2=8.32mmHg (0.7%)
- CO$_2$ potent vasodilator
- Cerebral CO$_2$ autoregulation not changed in microgravity.$^{1}$
- Causes increased blood flow
  - Every 1mmHg increase PaCO2=4% increase in cerebrovascular dilation
  - Problem-cerebral blood vessels are already congested
  - Thought to be contributory to the symptoms occurring at lower levels.
  - Causes increased CSF production.
Compliance: Intracranial

INTRACRANIAL PRESSURE (mm Hg)

UNITS OF VOLUME

\( dP \)

\( dV \)
CO2 Symptoms in Space

- Symptom onset 1.3-1.6mmHg
- Primarily noted to be headache and visual changes.
- When CO2 level dropped headaches dissipate
- Noted onset at levels far lower than terrestrially i.e.
- Mission Control personnel noticed behavioral changes had occurred at lower levels in crewmembers. Procedural errors, unwarranted comments from crewmembers, and increased “aggravation”
- EVA crewmembers “felt better” post initiation of Oxygen pre-breath and donning the suit (100% O₂ and 4.3 psi environment).
Pre-Flight MRID 1.10 (L-180 - L-30)
All Long Duration crew members

Previous

- Refraction
- Near and far visual acuity
- Tonometry
- Automated visual fields
- Dilated Fundoscopy
- Contact lens/spectacle storage plan
- Amsler Grid
- Retinal photography
- Extraocular muscle examination
- Spectral domain optical coherence tomography (OCT)
- Pupil reflex
- Biomicroscopy
- A-Scan Ultrasound

Additional

- PanOptic video fundoscopy baseline and training
- 3T orbital MRI with contrast
- 2-D imaging ultrasound baseline and training

Red = currently performed as per existing MRID
Blue = currently performed, but are added to new MRID
## In-Flight MRID 1.10 (L+30, R-30, L+100)

### All Long Duration crew members

<table>
<thead>
<tr>
<th>Previous</th>
<th>Additional</th>
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<tbody>
<tr>
<td>Ø None previously required per MRID</td>
<td>L+30 and R-30, potentially at L+100</td>
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<tr>
<td></td>
<td>• Near and far visual acuity</td>
</tr>
<tr>
<td></td>
<td>• Amsler grid</td>
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<tr>
<td></td>
<td>• Questionnaire</td>
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<tr>
<td></td>
<td>• Tonometry</td>
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<tr>
<td></td>
<td>• Dilated PanOptic video</td>
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<td></td>
<td>fundoscopy exam</td>
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<td>• Remotely guided HRF eye ultrasound</td>
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</table>
Post-Flight MRID 1.10 (R+ 0- R+3 or ASAP)
All Long Duration crew members

Previous

- Near and far visual acuity
- Tonometry
- Pupil reflex
- Extraocular muscle examination
- Biomicroscopy
- Questionnaire
- Amsler Grid
- Dilated Fundoscopic exam
- Automated visual fields
- Refraction
- Retinal photography
- Spectral domain optical coherence tomography (OCT)
- A-Scan Ultrasound

Additional

- 3T orbital MRI with contrast
- 2-D imaging ultrasound

Red = currently performed as per existing MRID
Blue = currently performed, but are added to new MRID
Visual Impairment and Intracranial Pressure Flow Chart

1) Predisposing Factors
   1.a) Age
   1.b) ↓ ICC
   1.c) ↑ R_{out}
   1.d) Crowded Disc

2) Environmental Factors
   2.a) Microgravity
   2.b) ↑ CO₂
   2.c) Nutrition (↑ Na)
   2.d) Resistive Exercise
   2.e) Hypobaria
   2.f) Hypoxia
   2.g) Toxins
   2.h) Radiation

3) Systemic Physiologic Changes
   3.a) ↑ CVP
   3.b) Cephalad Fluid Shift
   3.c) ↓ Lymphatic Drainage
   3.d) ↑ Interstitial Fluid
   3.e) Spinal Lengthening

4) Eye Physiologic Changes
   4.a) ↑ IOP
   4.b) Posterior Orbit Flattening
   4.c) ↑ ICP
   4.d) Arachnoid Villi
   4.e) CSF Outflow
   4.f) CSF Production
   4.g) Choroid Plexus

5) CNS Physiologic Changes
   5.a) ICC
   5.b) ↑ ICP
   5.c) ↑ ICV
   5.d) Arachnoid Villi
   5.e) CSF Outflow
   5.f) CSF Production
   5.g) Choroid Plexus

6) Eye Anatomic Changes
   6.a) Choroidal Folds
   6.b) Posterior Orbit Flattening
   7.a) Papilledema
   7.b) Optic Nerve Sheath Edema
   8.a) Visual Impairment (Decreased Acuity/Visual Field Deficit)
   8.b) Cognitive Impairment

Acronyms & Key
- IOP = Intraocular Pressure
- ICV = Intracranial Volume
- ICP = Intracranial Pressure
- ICC = Intracranial Compliance
- R_{out} = Resistance to CSF Outflow
- CSF = Cerebrospinal Fluid
- CVP = Central Venous Pressure
- Documented/Measured
- Insufficiently Documented / Insufficiently Measured
- Well Documented Relationship
- Documented Relationship
- Hypothetical Relationship
Hypothesized Mechanisms of Cerebral Blood Flow Autoregulation Inflight and Postflight for Asymptomatic and Symptomatic Crewmembers

**Microgravity**
- **Asymptomatic Crewmember**
  - ↓ CSF Production
  - ↑ CSF Outflow
  - Normal ICC
  - Normal $R_{csf}$
  - ↑ ICV
  - No ΔICP
  - No ΔCPP
  - No ΔCBF
  - No Papilledema or Visual Impairment

**Symptomatic Crewmember**
- ↑ ICV
  - Low ICC
  - High $R_{csf}$
  - ↑ ICP
  - ↓ CPP
  - ↓ CBF
  - Cerebral Arteriole Vasodilation (Possibly Due To ANS Control And Hormonal Response)
  - Normalization of CBF
  - ↑ ICP Persists

**Inflight**
- Return to 1G
- ↓ ICV
- ↑ CSF Production
- ↓ CSF Outflow
- No ΔICP
- No ΔCPP
- No ΔCBF
- No Papilledema or Visual Impairment

**Postflight**
- Return to 1G
- ↓ ICV
- ↑ CSF Production
- ↓ CSF Outflow
- No ΔICP
- No ΔCPP
- No ΔCBF
- No Papilledema and/or Visual Impairment
- ↑ ICP Persists
VIIP Knowledge Gaps

- Gaps (VIIP1) What is the etiology of visual acuity and ocular structural and functional changes seen in-flight and post-flight?
- Gap (VIIP2) Does exposure to microgravity cause changes in visual acuity, intraocular pressure and/or intracranial pressure? Are the effects related to mission duration?
- Gap (VIIP3) What in-flight diagnostic tools are needed to measure changes in intraocular pressure and intracranial pressure?
- Gap (VIIP4) Are changes in visual acuity related to changes in chronic choroidal engorgement, elevated intraocular pressure and/or intracranial pressure? Gap
- (VIIP5) Do multiple or cumulative exposures to spaceflight increase the risk of changes in visual acuity, intraocular pressure or intracranial pressure?
- Gap (VIIP6) How do changes in vascular compliance/pressures influence intraocular pressure or intracranial pressure?
- Gap (VIIP7) Is intracranial hypertension and visual impairment an all or nothing phenomenon or a continuum of severity that occurs in all individuals during spaceflight?
VIIP Knowledge Gaps

- Gap (VIIP8) What is the role of the ISS environment (e.g. high salt diet, CO$_2$ pockets, pharmaceutical use, exercise countermeasures) on ocular structure and function and intracranial pressure?
- Gap (VIIP9) What is the time course for recovery of intracranial hypertension and visual impairment and do anatomical structures of the eye recover? What factors determine the rate of recovery?
- Gap (VIIP10) Are asymptomatic crewmembers with anatomic eye changes or low grade intracranial hypertension at risk for future visual impairments?
- Gap (VIIP11) Does long-term, low grade intracranial hypertension predispose individuals to disease processes other than what manifests in the eye?
- Gap (VIIP12) Are there suitable ground-based analogs to study this spaceflight-associated phenomenon?
- Gap (VIIP13) Can safe and effective countermeasures be designed (in-flight and post-flight) to mitigate changes in visual acuity, intraocular pressure and intracranial hypertension if a problem it exists?
Braslet (left): 1 - belt; 2 - pull-up strap; 3 - compression cuff; 4 - tightening strap; 5 - compression scale
Braslet-M (right): 1 - compression cuff; 2 - tightening strap; 3 - compression scale

Рис. 3.12 Браслет-М
Russian-US ISS Braslet Study
Femoral Vein Images with and without Braslet Applied
Internal jugular vein cross sections with and without Braslet applied, with breathing maneuvers:

With Braslet application, the internal jugular vein responds to Valsalva with smaller changes, and with Mueller maneuver, the vein almost completely collapses.
Combining Countermeasures?

Aerobic exercise may be protective as it draws cephalad fluid caudally into lower limbs
Countermeasures for Arterial and Venous Circuits?

Rat Basilar Artery:
A. Control
B. 14d Hindlimb Unloaded
Cerebral artery hypertrophies with cephalad fluid shift

Rat Hindlimb Skeletal Artery:
A. Control
B. 14d Hindlimb Unloaded
Hindlimb skeletal artery artrophies with cephalad fluid shift

Braslet does not prevent upper body arterial circuit from seeing elevated pressures, nor lower body arteries from seeing decreased pressures.

Is there an additional technology that could assist?

Braslet good for sequestering venous volume on lower limb venous capacitance vessels
Chibis LBNP Device
Chibis LBNP Device

Components:

- Chibis suit (ПВК-1)
- Chibis suit pressure control unit (ПВК-Д)
- Hose harness in kit
- ПВК-Д unit control handle
- Removable waist seal curtain
- Corrugated sheath
- Belt
- Shoulder straps with clasps
- Hose harness
- Rigid boots

Chibis Suit (ПВК-1)
VIIP Project Structure

- **Research/Clinical Advisory Panel**
- **iVIIP**
  - **oVIIP**
  - **rVIIP**

**Clinical**
- **Epidemiology/Data Mining**
- **Risk Identification**
- **Diagnostic Monitoring Technology**
- **Analog Development**
- **Countermeasure (CM) Development**

**Clinical Practice Guidelines (CPGs)**

Data we have – but requires analysis
- Data we need to acquire - clinical/research
- Development of additional hardware required to obtain new data
- Analogs required to enable understanding of VIIP and testing of CMs

Risk Mitigation
Preliminary review of data for affected crew members reveals that blood pressure, serum lipids and homocysteine may be elevated compared to those non-affected. Also, maximal aerobic oxygen uptake may be lower in those affected.
Exercise Protective?

Physiological ageing

Mechanisms → Effects → Consequences

**Structural**
- Elastin:
  - ↑ Fragmentation
  - ↑ Density
- Collagen:
  - ↑ Concentration
  - Δ Phenotype
  - ↑ Cross-linking
  - ↑ AGEs
  - ↑ VSM cells
  - ↑ Growth factors

**Functional**
- ↑ VSM cell tone
- Subclinical atherosclerosis
- Age-gene interactions

- Large elastic artery remodelling
- ↑ Internal diameter
- ↑ IMT
- ↓ Aortic and carotid arterial compliance
  (↑ stiffness)
- ↓ Aortic PWV
- ↑ Systolic pulse augmentation
  (↑ carotid AI)

- ↑ SBP and PP
- Systolic hypertension
- ↑ Aneurysms, stroke
- Endothelial damage
- ↑ Atherosclerosis
- ↑ MI, thrombosis
- ↑ CAD, PAD, etc.
- ↑ Aortic impedance
- ↑ LV wall tension
- ↑ LV hypertrophy
  (↑ CHF)
- ↑ LV work, VO₂
  prolonged contraction
- ↑ Early diastolic filling
- ↓ LV systolic reserve
- ↑ Peak LV ESV
- ↑ Peak LV EF
- ↓ Arterial BRS
- ↑ BP variability
- ↑ V Fib, SCD

Regular aerobic/combined aerobic and resistance exercise
**Proposed Pre/In/Post-Flight VIIP Research Testing**

**Preflight Exams**
- L-365
- L-90/45

**In-flight Exams**
- L+10
- L+30
- L+60
- L+100

**Post flight Exams**
- R-30
- R+1 to R+3
- R+30
- R+90
- R+180
- R+365

**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.

**L-90/45 days**
- Ultrasound Eye/Orbit
- Fundoscopy - PanOptic Ophthalmoscope
- Tonometry
- Visual Acuity Including Amsler Grid Testing

**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

**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 Tests for consideration**
- Vascular Compliance
- Other Tests - biomicroscopy (slit lamp), high resolution retinal photography, OCT (high resolution), and A-Scan.
### Proposed In-Flight VIIP Data Collection Sequence Per Increment Time Point

#### Data Collection Per Increment Time Point (L+10, L+30, L+60, L+100, L-30)

<table>
<thead>
<tr>
<th>Data Collection Measures</th>
<th>Day 1</th>
<th>Time</th>
<th>Day 2 or 3</th>
<th>Time</th>
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<tbody>
<tr>
<td>Manual Cuff BP</td>
<td>7 min</td>
<td></td>
<td>Manual Cuff BP</td>
<td>7 min</td>
</tr>
<tr>
<td>Visual Acuity</td>
<td>5 min</td>
<td></td>
<td>Visual Acuity</td>
<td>5 min</td>
</tr>
<tr>
<td>Amsler Grid</td>
<td>5 min</td>
<td></td>
<td>Amsler Grid</td>
<td>5 min</td>
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<tr>
<td>PanOptic Retinal Imaging</td>
<td>45 min</td>
<td></td>
<td>IOP Tonometry</td>
<td>20 min</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Manual Cuff BP</td>
<td>7 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiac Echo measures</td>
<td>5 min</td>
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<td></td>
<td></td>
<td></td>
<td>Ocular Ultrasound</td>
<td>35 min</td>
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<tr>
<td><strong>Total Time:</strong></td>
<td><strong>1:02 Hours</strong></td>
<td></td>
<td><strong>Total Time:</strong></td>
<td><strong>1:24</strong></td>
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</table>

**Real-time Guidance**
## VIIP Schedule Summary

### Fiscal Year Schedule

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<tbody>
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<td>Shuttle &amp; ISS</td>
<td>Retire Shuttle</td>
<td>ISS End of US Commitment</td>
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</table>

### Project Formulation
- **Research Content of Evidence Book and RMAT**
- Data Mining
- Inputs to Project-Level Plan/Dev of Sub-Project Plan
- Research Content of TBD Plan

### Technology Development
- Develop Standard Measures
- Feasibility Assessments
- TBD Hardware Developments

### Ground Analog
- Animal Studies/Model Validation
- Validate HDT Bed Rest Model
- TBD Countermeasure Development

### ISS Research
- Pre-, In-, Post-flight Monitoring of Visual Health
- In-Flight Measures (Risk Characterization)
- Fluid Loading and Distribution Studies
- TBD Countermeasure Dev/Validation

---

**NOTE:** Products iterative over time pending Research/Med Ops results. Schedule indicates planned completion of first drafts and some key dependencies.
VIIP Risk - Research Approach

Conduct data mining; Compile evidence base

Develop research plan

Identify and obtain additional measures

Complete technology development

Identify and validate analogs

Conduct research to characterize risk

Data sharing

Inflight monitoring of visual health

Med Ops

HRP

Develop and validate countermeasures

Utilize internal and external experts to:
- Develop plan
- Complete tasks
- Review and assess progress

Research/Clinical Advisory Panel

Monitor visual health via crewmember annual physical
Summary

- Background
- Ocular Findings
- Cephalad Fluid Shift
- Current Methodologies
- Cases
- Contributing Structures of the Eye
- CSF Production
- CSF Resorption
- Exacerbating Factors
- Current Measures
- Draft Research Plan
- Opportunities for Partnership
Risk of Microgravity-Induced Visual Impairment and Elevated Intracranial Pressure (VIIP)

Wednesday May 25, 2011.

Christian Otto, M.D., VIIP Project Scientist