Long-Duration Space Flight and the Microgravity Ocular Syndrome (MOS)

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DoD Disclaimer

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Why We Do What We Do…
Recent Headlines:

- Too much space travel is hazardous for your eyeballs
- Possible Mars Mission 'Showstopper': Vision Risks for Astronauts
- The mysterious syndrome impairing astronauts’ sight
- Astronauts' eyes are at risk after too much time in space
- Astronauts Returning to Earth With Vision Problems
- Space travel is causing visual impairment for some astronauts. Will this prevent travel to Mars?
Background: *The Space Environment*

- **Bottom-line:** Not human friendly. For example…
  - **Vacuum:** No atmosphere; no air
  - **Gravity**
    - Holds Earth in orbit w/ sun, and moon in orbit around Earth
    - Gravity reduces w/ distance. ISS (@ ~200-250 mi) feels 90% of Earth’s gravity…But…
    - ISS moves at ~17,500 mph, in constant freefall = “Microgravity”
  - **Temperature extremes**
  - **Ionizing (high energy) radiation:** Galactic cosmic rays, solar proton events
  - **Orbiting space junk/debris:** >550K larger than 1cm
Background: *U.S. Space Flight*

- “We choose to go to the moon…”
  - **Mercury**
    - $n = 6$
    - Duration: 15m to 1.5d

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- **Space Shuttle**
  - $^*n = 710$
  - Duration: ~2wk

- **Shuttle-Mir**
  - $n = 7$
  - Duration: ~0.5yr

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Background: *U.S. Space Flight*

- **International Space Station**
  - In use since 2000
  - *n = 58 (as of 31Jan17)*
  - Duration: ~0.5 to 1y
  - International partners
    - United States
    - Russia
    - European Union
    - Canada
    - Japan
  - Crew: Typically 5-6
  - “Low Earth orbit”

* Person flights; may include multiple-time flyers w/in program
Background: **U.S. Space Flight**

- **International Space Station**

![Diagram of the International Space Station](image-url)
Background: **U.S. Space Flight**
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Background: *U.S. Space Flight*

- International Space Station
  - Slight larger than football field.
  - Living space ≈ 6-bedroom house.
Background: **U.S. Space Flight**

- International Space Station
  - Slight larger than football field.
  - Living space ≈ avg 6-bedroom house
The Future…

- NASA to send humans to: An asteroid by 2025; Mars in the 2030s
We are just entering, relatively speaking, the long-duration phase of space exposure…

**Next Generation Missions**

- Mercury: *n = 6*
- Gemini: *n = 20*
- Apollo: *n = 33*
- Skylab: *n = 9*
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* Person-flights; may include multiple-time flyers w/in program.
Physiological challenges to astronauts are substantial, especially outside of Low Earth Orbit. For example…

**Muscle Density & Function**
- Impacted w/in days in space
- During 2-wk Shuttle missions: reduction in fiber mass
- Long-term space flight could result in ~40% loss in overall muscular function
  - Increased risk of injury
  - Impeded ability to operate spacecraft & equipment
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- **Muscle Density & Function**
  - Impacted within days in space
  - During 2-2.5 wk Shuttle missions: reduction in fiber mass
  - Long-term space flight could result in ~40% loss in overall muscular function
  - Increased risk of injury
  - Impeded ability to operate spacecraft & equipment

- **Bone Health**
  - In space, bone density lost at ~24x the avg rate on Earth
  - Can lead to kidney stones, fractures, hip/spine problems, impaired healing
Physiological challenges to astronauts are *substantial*, especially outside of Low Earth Orbit. For example…

- **Muscle Density & Function**
- **Bone Health**
- **Ionizing (High Energy) Radiation**
  - Filtered by Earth’s magnetic field
  - Galactic cosmic radiation
  - Bare atomic nuclei (as heavy as iron atoms) traveling at speed of light
  - Mars mission may expose ~90x the max annual dose recommended on Earth
  - Cataracts??
- **Solar flares**
  - Can produce unexpected, lethal radiation spikes
Physiological challenges to astronauts are substantial, especially outside of Low Earth Orbit. For example…

“Vision Issues”

- For >40 yrs, anecdotal reports indicated VA impairments w/ spaceflight
- NASA survey (n > 300) showed 29% of short- & 60% of long-duration (ISS) crew experienced “degradation” of dist or near VA
  - Some ISS cases did not resolve post-flight
- In 2005, a more serious disorder was identified. Termed:
  - Vision Impairment Intracranial Pressure (VIIP) --or--
  - Microgravity Ocular Syndrome (MOS)
VIIP/MOS Clinical Findings
To date, 24 USOS ISS long-duration spaceflight astronauts have developed some or all of the following findings:

- Hyperopic shift
- Globe flattening
- Choroidal folds
- Cotton wool spots
- Optic disc edema
- Optic nerve sheath distention

**Ocular**

All these findings are potential signs of elevated intracranial pressure (ICP).

- Mildly elevated post-flight intracranial pressure
  - 21 - 29 cm H$_2$O range
    - Upper limit of normal: ~20 cm H$_2$O
    - Gray zone: 20.1 – 24.9 cm H$_2$O
USOS Individuals w/ VIIP/MOS Findings:
Expeditions 1-48

24 crewmembers presented with one or more of these findings

- **Disc Edema** = Modified Frisen Scale Grade >/= 1 at first post-flight eye exam (via fundoscopy)
- **Globe Flattening** = A change compared to preflight (via MRI or ultrasound)
- **Choroidal Folds** = New or worsened compared to pre-flight (via OCT)
- **Cotton Wool Spot** = Presence in-flight or post-flight (via fundoscopy)
- **Refractive Error** = Change in cycloplegic (spherical) refraction ≥0.75D from preflight to first post-flight eye exam
Clinical Findings: *Hyperopic Shift*

- Of the active astronaut population...
  - 80% wear vision correction (32% contact lenses)
  - Mean age = 47 yrs
  - Majority are presbyopic (i.e., a normal, age-related, progressively worsening inability to focus clearly on near objects)

- From postflight questionnaires (1989 - 2011): 29% of short-duration (Shuttle) & 60% of long-duration (ISS) mission astronauts report a subjective degradation in vision, especially at near
  - Provided “Space Anticipation Glasses”
Subjective Degradation in Vision (cont):

- Associated with **Hyperopic Shifts** in refractive error due to **Globe Flattening**
  - A 1 mm decrease in axial length will produce a ~2.7 diopter hyperopic shift
  - Largest shift to date is +1.75 diopters
  - In presbyopes: Typically decreases near visual acuity (VA), but leaves distant VA intact
Clinical Findings: *Globe Flattening*

- **Case Example:**
  - Male, mid 40s at time of flight
  - No significant PMH/PSH/PFH
  - No meds
  - Normal BP (118/64)
  - Normal lipids
  - ECG Stress test normal w/ VO₂ max of 51ml/kg

- *Terrestrially:* Globe flattening associated w/ papilledema (i.e., disc edema 2° to increased intracranial pressure); typically bilateral
Clinical Findings: *Globe Flattening*

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6 days post-flight
Clinical Findings: *Globe Flattening*

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1 year post-flight
Clinical Findings: *Globe Flattening*

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  - ECG Stress test normal
    - w/ VO$_2$ max of 51ml/kg

- *Terrestrially:* Globe flattening associated w/ papilledema (i.e., disc edema $2^\circ$ to increased intracranial pressure); typically bilateral
Clinical Findings: *Choroidal Folds*

- Choroidal thickening due to vessel engorgement → induces choroidal (and sometimes retinal) folds
- Can resolve post-flight or can persist (for 5+ yrs)
- So far, no clinically-significant impact on BCVA

*Terrestrially:* Assoc. w/ choroidal tumors, scleritis, retrobulbar mass, papilledema/IIH
Clinical Findings: **Cotton Wool Spots**

Posterior pole fundoscopic images OD & OS for two ISS crewmembers
- Top arrows: **Choroidal folds**
- Bottom arrows: **Cotton wool spots**

- **Cotton wool spots**
  - Abnormal retinal finding
  - Accumulations of axoplasmic material w/in retinal nerve fiber layer
  - Caused by ischemia → reduced axonal transport → swelling of axon → damaged nerve fibers
  - **Terrestrially:** Associated w/ diabetes, HTN, central retinal vein occlusion
Clinical Findings: *Cotton Wool Spots*

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Clinical Findings: Optic Disc Edema

Pre-flight fundoscopic images of the right (OD) & left (OS) optic discs

Post-flight images of optic discs, showing Grade 3 edema OD & Grade 1 edema OS
Clinical Findings: *Optic Disc Edema*

- **Terrestrially:** Optic disc edema is associated with:
  - **Unilateral:** Optic neuritis, optic neuropathy, retinal artery/vein occlusion
  - **Bilateral:** Increase in ICP…
    - IIH (→ “papilledema”)
    - Intracranial mass
    - Cerebral edema
    - Increased CSF production
    - Decreased CSF absorption
    - Obstructive hydrocephalus
    - Venous outflow obstruction
  - Typically reduces VA, enlarges blind spot, causes relative afferent pupillary defect & color impairment

Fundoscopic image of optic disc OD, 10 days after return to Earth

- Arrows: “C” shaped halo of edema
Clinical Findings: *Optic Nerve Sheath Distention*

Post-flight ultrasound image of globe, optic nerve (ON; purple), and optic nerve sheath (green). Showing:

- ON Sheath distention
- ON tortuosity

- **ON Sheath terrestrially:**
  - Normal diameter (ONSD) < 5.9 mm
  - Enlargement typically associated w/ increased ICP

Post-Flight OD

12 mm
Common Characteristics of the Cases
Common Characteristics of the Cases

- Almost all were ~6 month duration ISS mission crewmembers
  - One short-duration case w/subtle disc edema (discovered retrospectively)
  - Severity related to flight duration?
    - What about a 3-yr Mars mission??

- All had normal pre-flight eye exams

- Normal past medical history:
  - Negative for systemic disease
  - None had used medications before/during their mission that could increase ICP (e.g., vitamin A, tetracycline, corticosteroids, or nalidixic acid)
None complained of headaches, transient vision obscurations, double vision, pulsatile tinnitus, or vision changes during eye mvmts (i.e., classic symptoms of idiopathic intracranial hypertension)

None experienced loss in BCVA, color vision, or stereopsis

OD affected more than OS *in all cases*. If only one eye affected, always OD

ISS cabin
- Normal pressure & oxygen
- Elevated CO\(_2\)
  - ~0.33-0.5% avg, w/ avg peak ~0.7%
  - 10x terrestrially: ~0.03-0.04%
Why is this Happening?
Why is this Happening?

- Terrestrially → Fluid is pulled downward by gravity (i.e., hydrostatic pressure)
- Microgravity → Fluid is free to uniformly distribute (i.e., hydrostatic pressure is eliminated)

Consider how hydrostatic pressure affects fluid/blood distribution in humans…

And what happens in its absence…
Why is this Happening?

Microgravity $\rightarrow$ Cephalad fluid shift $\rightarrow$ Cerebral venous congestion

Adapted from Hargens & Richardson, Respiratory Physiology & Neurobiology. 2009
Current Risk Statement:

“Visual Impairment Intracranial Pressure” (VIIP)

"Given that the microgravity environment causes cephalad fluid shift in astronauts, there is a probability that astronauts will have intracranial hypertension (IHT) to some degree, which if left untreated, could lead to deleterious health effects.”
Why is this Happening?

- **Hypothesis #1**: Increased intracranial pressure
  - The original theory, hence “Visual Impairment Intracranial Pressure”
  - Support:
    - Optic nerve edema & ONSD distention
    - Lateral & 3rd ventricle enlargement (like hydrocephalus) post-flight
    - Crowding of superior sagittal sinus post-mission
  - However:
    - Signs often unilateral & right-biased
    - If ICP increases, may increase only modestly
    - Globe flattening & choroidal folds can persist for years post-flight, despite a return to normal ICP
Hypothesis #2: This is a local ocular eye problem

- CSF cul-de-sac bathing ON might act as one-way valve for CSF flow during spaceflight → may increase local ICP around ON

Why is this Happening?
Hypothesis #3: Slight IOP reduction + slight ICP increase
  • Variation of original VIIP theory (i.e., ↑ ICP)
Hypothesis #4: Individual anatomical or genetic factors

- For example: VIIP may be associated with atypical folate-dependent 1-carbon metabolic pathway in some astronauts
  - May increase local toxin concentration within ON sheath
Why is this Happening?

- **Hypothesis #5**: Vessel congestion places local pressure in choroid & around optic nerve (“Circle of Zinn-Haller” theory)

  - In µGravity, head venous pressure $\approx 15-20$ mmHg (vs. standing terrestrially $\approx -20$ mmHg)
  
  - Choroid engorges & thickens, even in non-VIIP cases
  
  - Choroidal blood supply forms an anastomosis around ON. If engorged & pressurized, may place *noose-like strain* around ON
In-flight Exacerbating Factors??

**Resistive Exercise**

**High Oral Sodium Intake**
- Prepackaged Foods…
- Up to 5000+ mg/day

**High CO₂**
- ~10x terrestrial levels

**In-flight Pharmaceuticals**
Medical Surveillance
Surveillance & Medical Data Collection

- 49 ISS expedition missions have been completed (since 2000)
- **Seminal VIIP case** occurred in 2005
  - Choroidal folds & cotton wool spot OD; OS unremarkable
- Surveillance/medical data collection is ongoing and has evolved
  - Began *some* “VIIP” related testing in 2008 (w/ Exp 18)
  - Inconsistent testing until Feb 2010 (Exp 23) when standardized medical monitoring (i.e., “Eye MED B”) came into effect
**Surveillance & Medical Data Collection**

**Terrestrially (pre- & post-flight)**
- 3T MRI – Special “NASA Astronaut” protocol
- Comprehensive eye exam. **Highlights:**
  - Refraction (manifest & cycloplegic); Amsler
  - Threshold VF; Contrast sensitivity
  - Optical biometry; Applanation tonometry
  - Optical Coherence tomography (OCT)

**On-Orbit**
- Visual Acuity (Dist & Near)
- Amsler Grid
- Vision Questionnaire
- Ocular Ultrasound
- Fundoscopy
- OCT
- Tonometry (when clinically indicated)
Surveillance & Medical Data Collection

On-orbit Visual Acuity & Amsler Grid
On sheath distention

On tortuosity

On-orbit Ultrasound Imaging

(Post-flight)
On-orbit Ultrasound Imaging

ON tortuosity

Elevated optic disc

ON sheath distention
Surveillance & Medical Data Collection

On-orbit Fundoscope
Surveillance & Medical Data Collection

On-orbit Optical Coherence Tomography (OCT)
Nominal OCT Protocol

- Circular ONH Scan
- Radial ONH Scan
- Vertical Macula Scan
- Single Scan through ONH & Fovea
- Vertical Scan Between Disk Edge & Fovea
- Horizontal ONH Scan
Post-flight OCT scan showing RNFL thickening consistent with observed optic disc edema OU
Surveillance & Medical Data Collection

On-orbit Optical Coherence Tomography (OCT)

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ILM: Inner limiting membrane
IPL: Inner plexiform layer
INL: Inner nuclear layer
OPL: Outer plexiform layer
ONL: Outer nuclear layer

ELM: External limiting membrane
IS/OS: Junction of inner and outer photoreceptor segments

OPR: Outer segment PR/RPE complex

NFL: Nerve fiber layer
GCL: Ganglion cell layer
RPE: Retinal pigment epithelium

+ Bruch’s Membrane
Surveillance & Medical Data Collection

On-orbit Optical Coherence Tomography (OCT)

Pre-flight OD

Post-flight OD
Surveillance & Medical Data Collection

On-orbit Tonometry

[Image of a Tono-Pen AVIA+ device]
[Image of a person taking an eye measurement]

NASA
Ongoing clinical work

- Correlation between “Form & Function”: RNFL thickness changes (OCT) and their impact on visual sensitivity (VF)
- Correlations between VIIP/MOS signs and:
  - Subcortical white matter hyperintensities (WMH) found on MRI
  - Cardiovascular parameters (e.g., general fitness levels)
- Evaluation of next-generation OCT (“OCT2”): Will it enhance on-orbit imaging/data acquisition?
What We Are Watching Coming From Our Research Colleagues

- Ocular Health Study & Fluid Shifts Study
  - Both finish data collection in Summer 2017
- Clinical relevance of MRI-based findings
- Implementation of direct ICP measures (pre- & post-mission)
- Correlation btwn VIIP/MOS & CO₂ using HDT (EnviHab)
What We Are Watching Coming From Our Research Colleagues

- Fluid Shifts Study: OCT scan w/ lower body negative pressure
  - Not your typical clinical environment…!
Questions?

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