# THE VISUAL IMPAIRMENT INTRACRANIAL PRESSURE RISK IN LONG DURATION U.S. ASTRONAUTS: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

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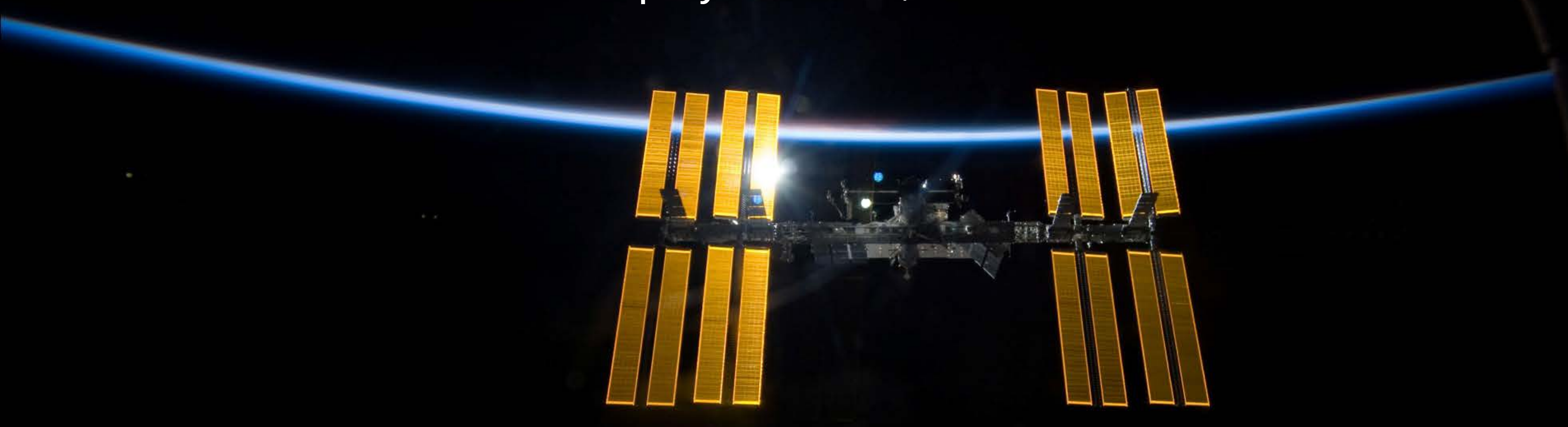


NSBRI Headquarters, Biosciences Collaborative
Houston, TX
Monday February 10, 2014.

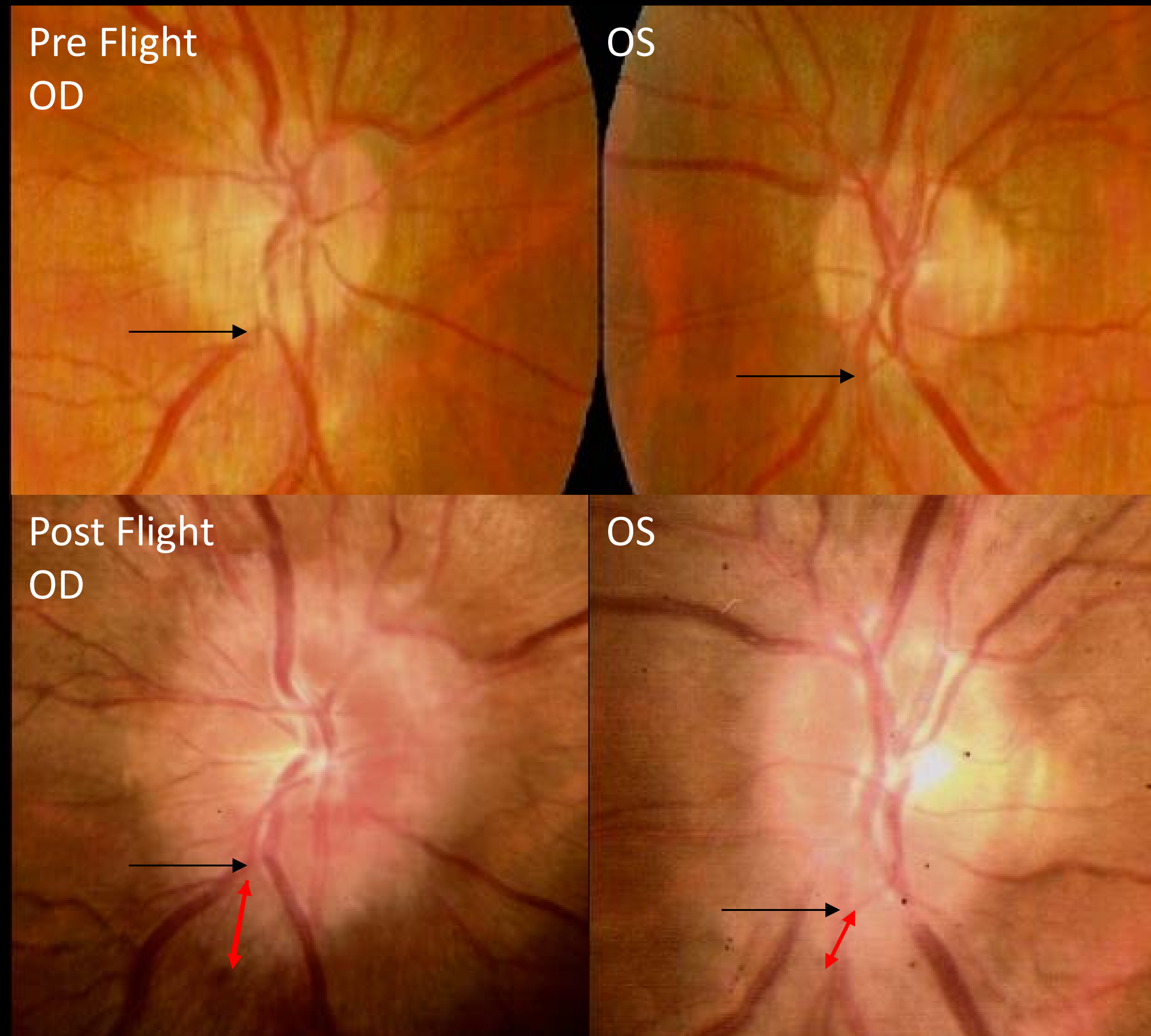
# Pre to Post Flight Papilledema
## (First case 2005. N=6)

**<u>Pre Flight</u>**

Fundoscopic images of the right and left optic disc.

**<u>Post Flight</u>**

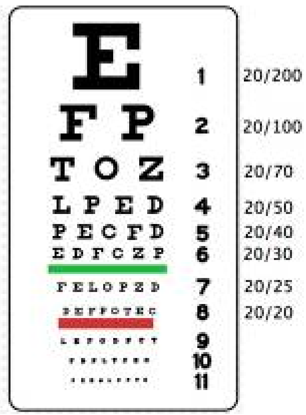
Fundoscopic images of the right and left optic disc showing **Grade 3 edema right** and **Grade 1 edema left** .



# Visual Impairment Intracranial Pressure Syndrome Signs

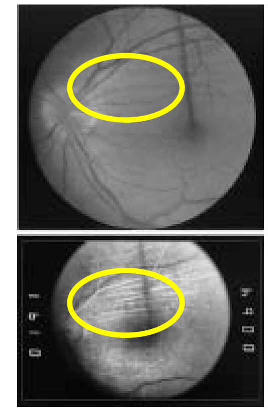
**•Hyperopic Shifts**

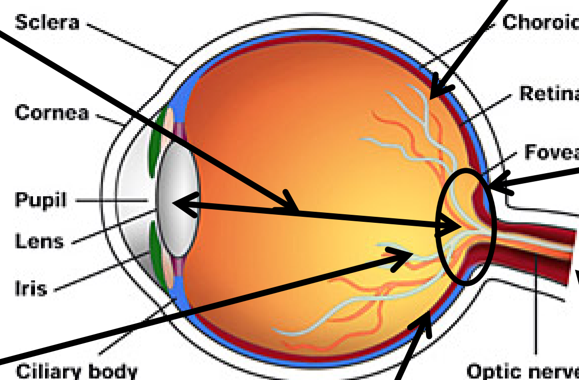
-Up to +1.75 diopters




**•Choroidal Folds**

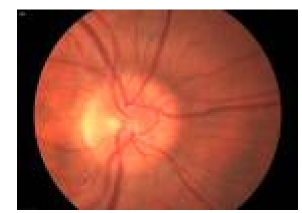
- parallel grooves in the posterior pole






**•Optic Disc Edema (swelling)**

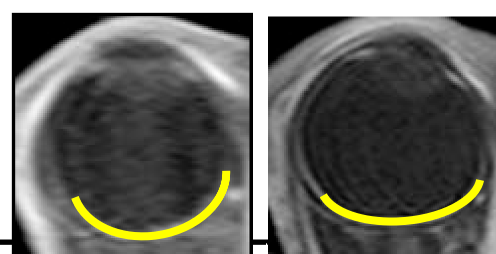
ICP



**•Altered Blood flow**

•"cotton wool" spots

**•Globe Flattening**



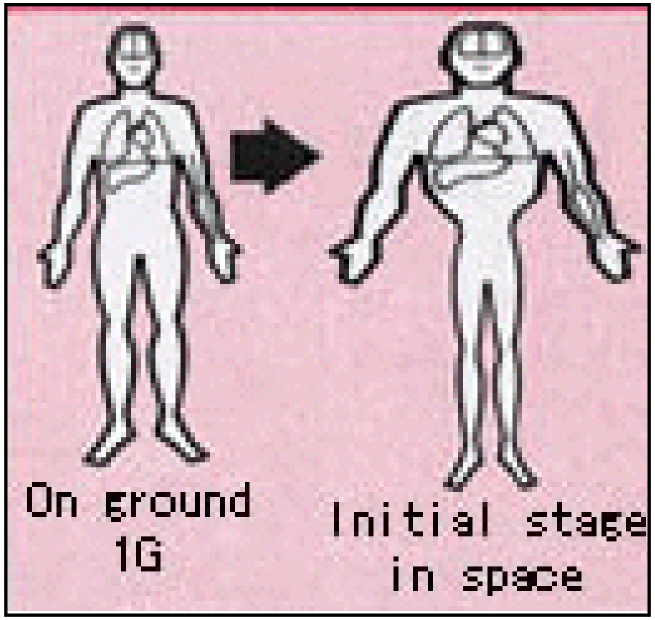
MRI Orbital Image showing globe flattening

Normal Globe Flatten Globe

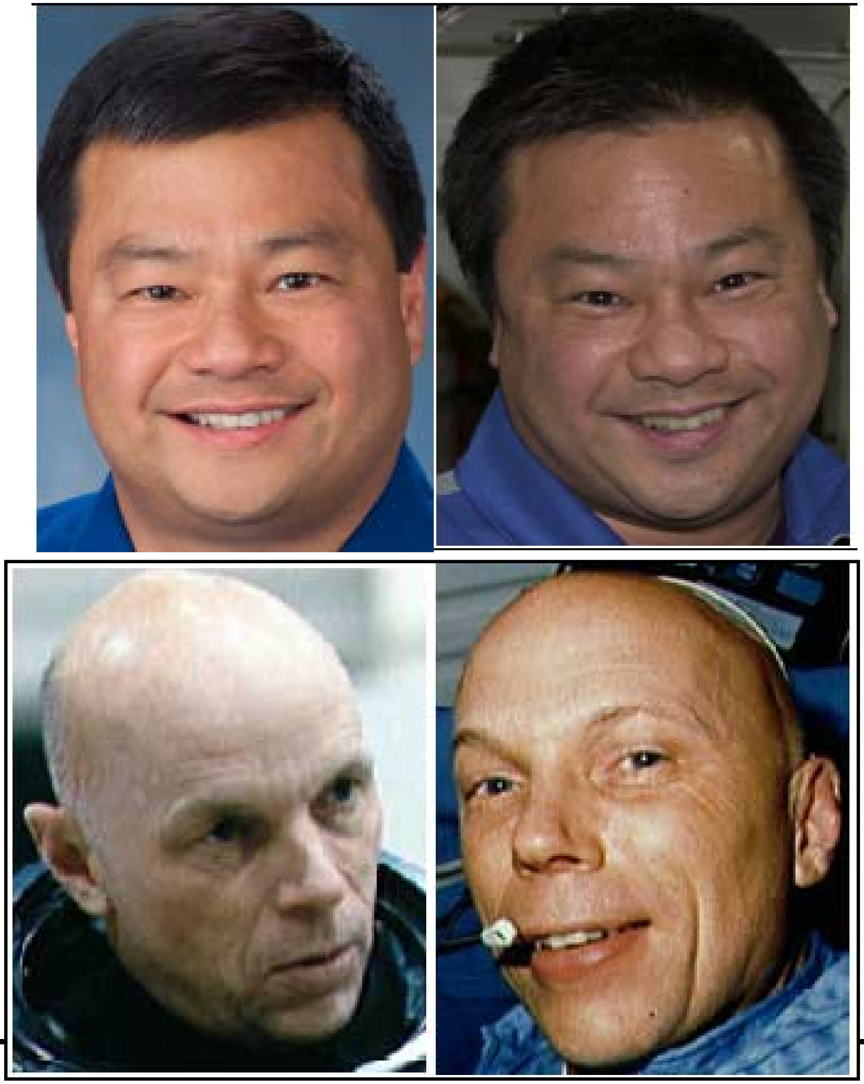
**•Increased Optic Nerve Sheath Diameter**

# How do these clinical signs fit together?

# Cephalad Fluid Shift



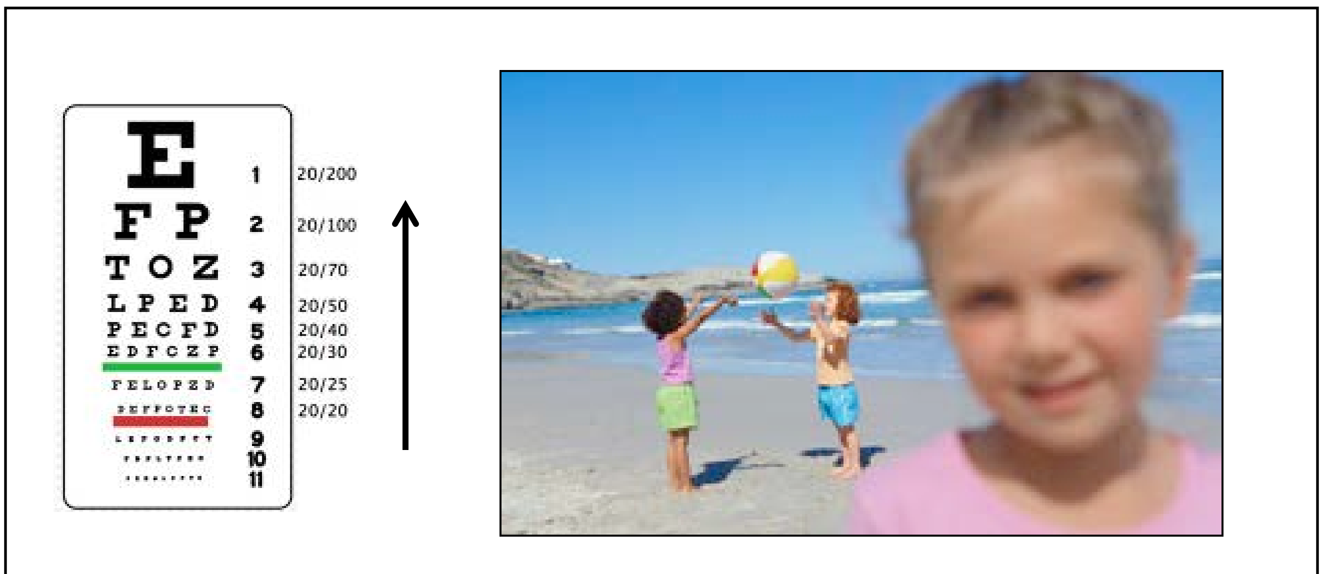

1G 0G



# Initial Identification of the VIIP: Subjective Changes in Vision

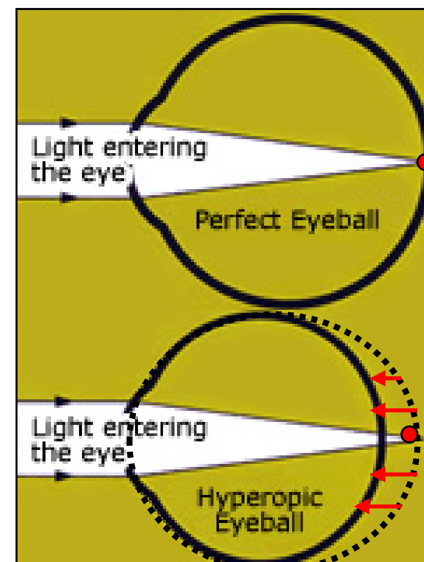
- 50% of long-duration (ISS) astronauts report a subjective degradation in vision, primarily increasing *farsightedness*
- ***Hyperopic shift***

**Decreased near visual acuity, distant vision intact**



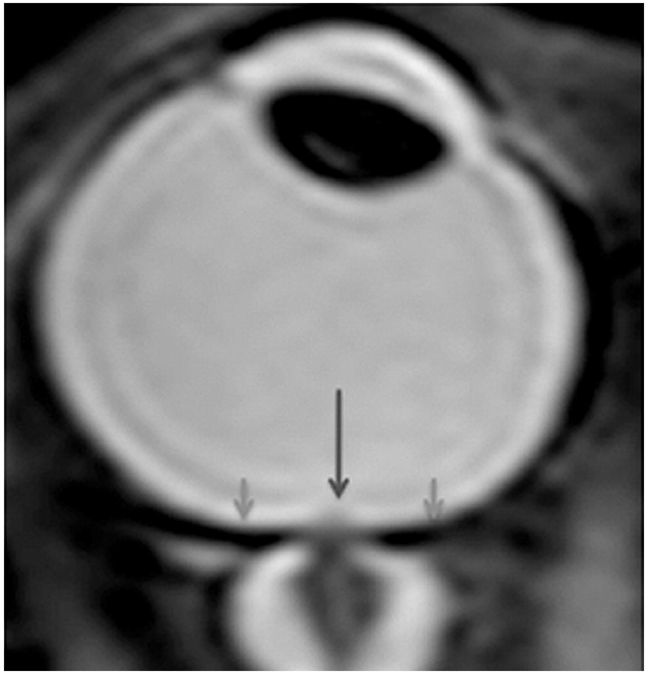

(1 mm decrease in axial length is equivalent to a 3 diopter hyperopic shift)

**Normal Eye**




**Hyperopic Eye**

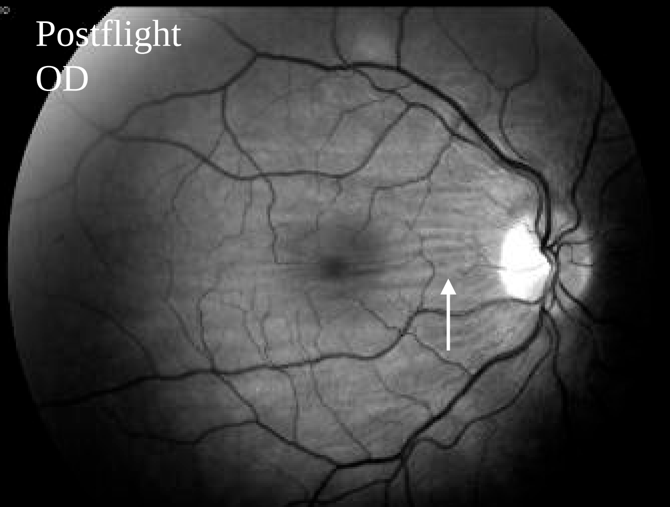
# Causes of Globe Flattening

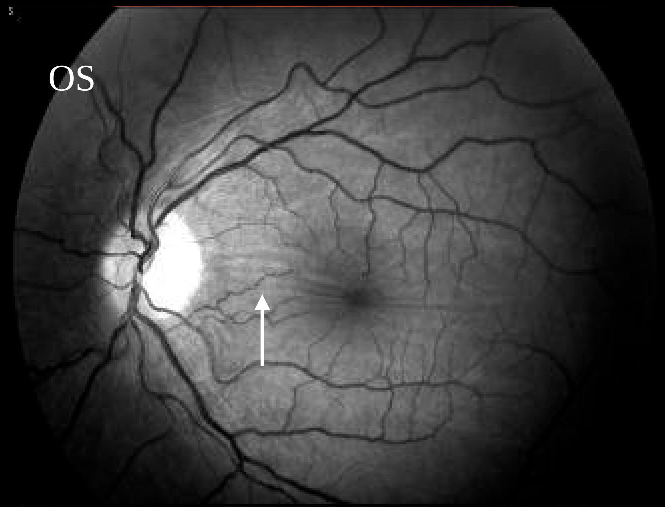


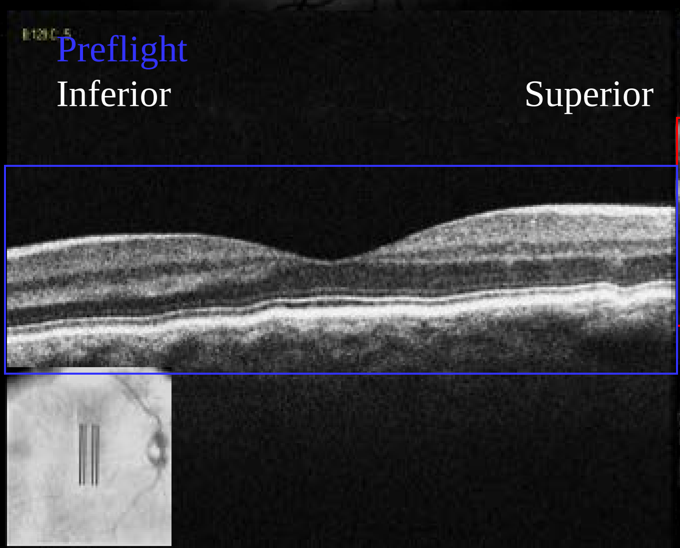

| | |
|---|---|
| *Structural √<br>Intracranial Hypertension<br>IIH<br>Head Trauma X | *Infectious X<br>Meningitis (bacterial or viral)<br>Lyme disease<br>HIV<br>Poliomyelitis<br>Coxsackie B encephalitis<br>Guillain-Barre syndrome<br>Infectious mononucleosis<br>Syphilis<br>Malaria |
| Tumors X<br>Orbital mass<br>retrobulbar tumours | *Metabolic/endocrine X<br>Lupus<br>Sarcoidosis<br>Hypoparathyroidism<br>Addison's disease |
| *Vascular X<br>Subarachnoid hemorrhage<br>Sinus thrombosus | *Drugs X<br>Tetracycline<br>Minocycline<br>Isotretinoin (Accutane)<br>All-trans retinoic acid<br>Excessive ingestion of Vitamin A<br>Amiodarone<br>Nitofurantoin<br>Lithium<br>→Levonorgestral (Norplant)<br>Growth hormone treatments<br>Steroid withdrawal |
| *Inflammatory X<br>Long-standing orbital inflammation<br>Uveitis<br>Disciform degeneration<br>Posterior scleritis | |

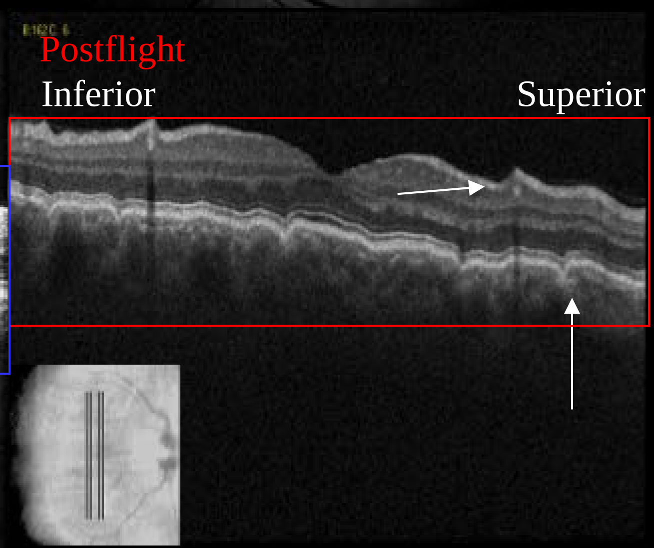
* Raised Intracranial Pressure

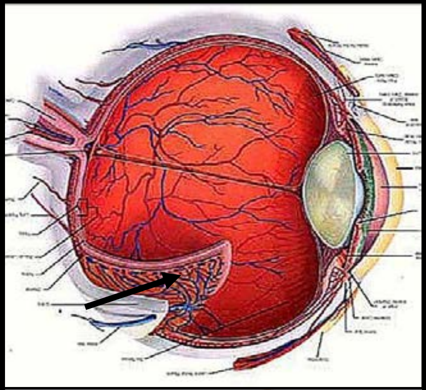
# Choroidal Folds

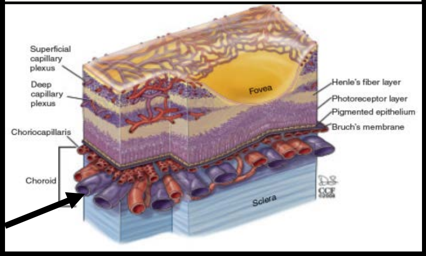





Thickening of the choroid secondary to venous blood engorgement from uG fluid shift

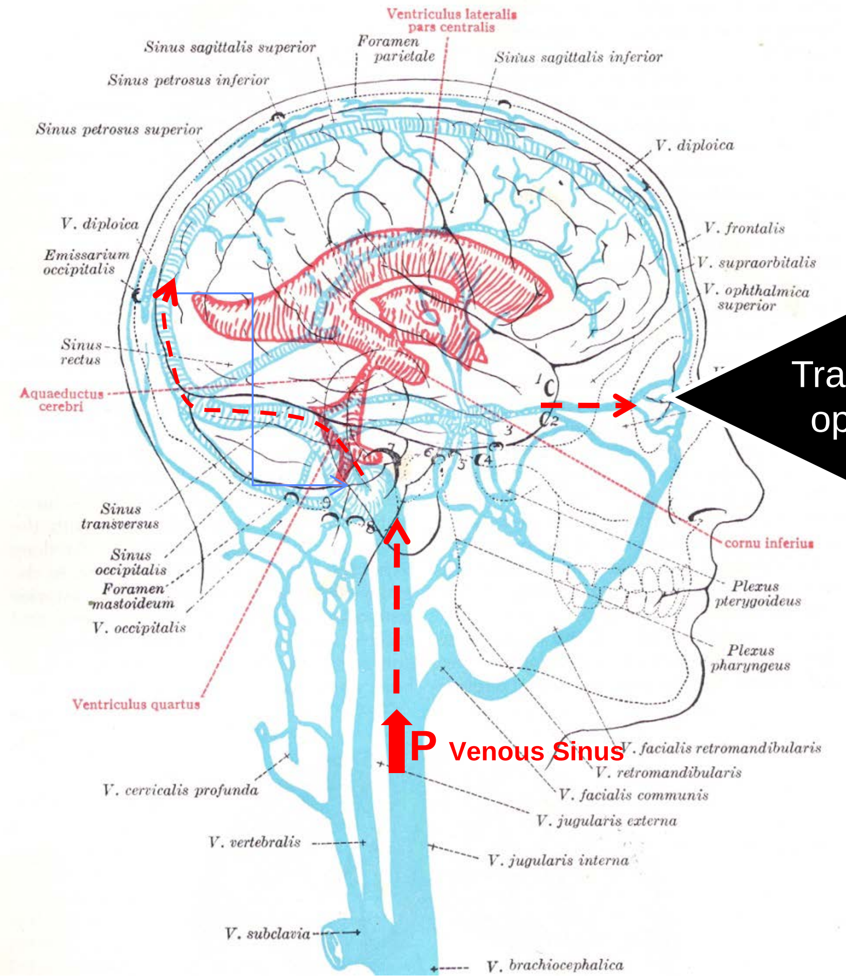
# Causes of Choroidal Folds

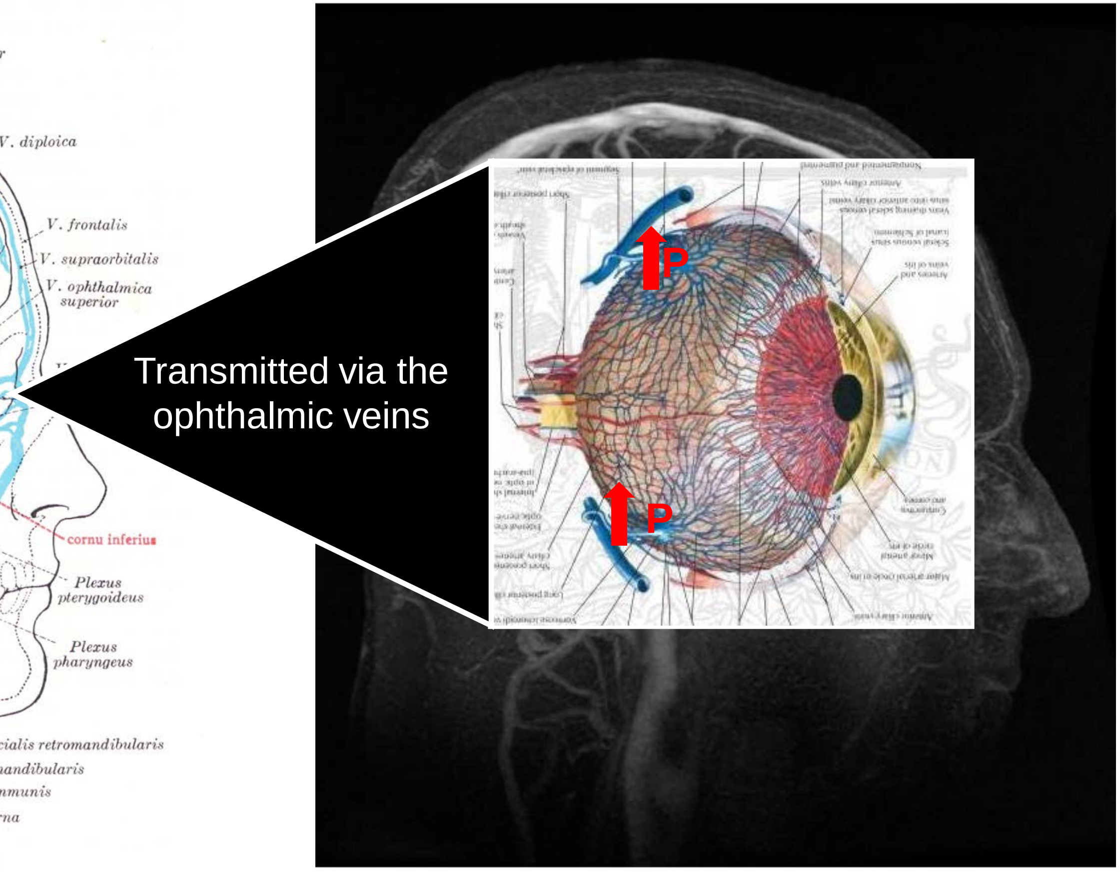
- Choroidal folds are folds of the posterior pole, at the level of the choroid

| | |
|---|---|
| **Structural**<br>Exophthalmos<br>High hyperopia<br>Ocular hypotony<br>Posteriorly located choroidal detachment<br>Primary retinal detachment<br>Postoperative condition (scleral buckle) | **Inflammatory**<br>Long-standing orbital inflammation<br>Uveitis<br>Disciform degeneration<br>posterior scleritis |
| **Tumors**<br>Choroidal tumor, such as a melanoma<br>Orbital mass<br>retrobulbar tumours<br>Massive cranioorbital hemangiopericytoma | **Infectious**<br>Infection of paranasal sinuses |
| **Vascular**<br>Subretinal neovascularization | **Metabolic/endocrine**<br>Graves disease (Basedow syndrome) |
| | **Idiopathic** |
| | **Increased ICP**<br>Papilledema<br>intracranial hypertension |

# Venous Congestion & Elevated ICP: Transmitted to the Choroid?

- **Ansari et al. 2003. Measurement of Choroidal blood flow in Zero Gravity** KC135 parabolic flight experiment.
  - Choroidal volume and flow increase significantly in low G environment when compared with the baseline data (1G): 75% increase for volume, and 105% for flow.

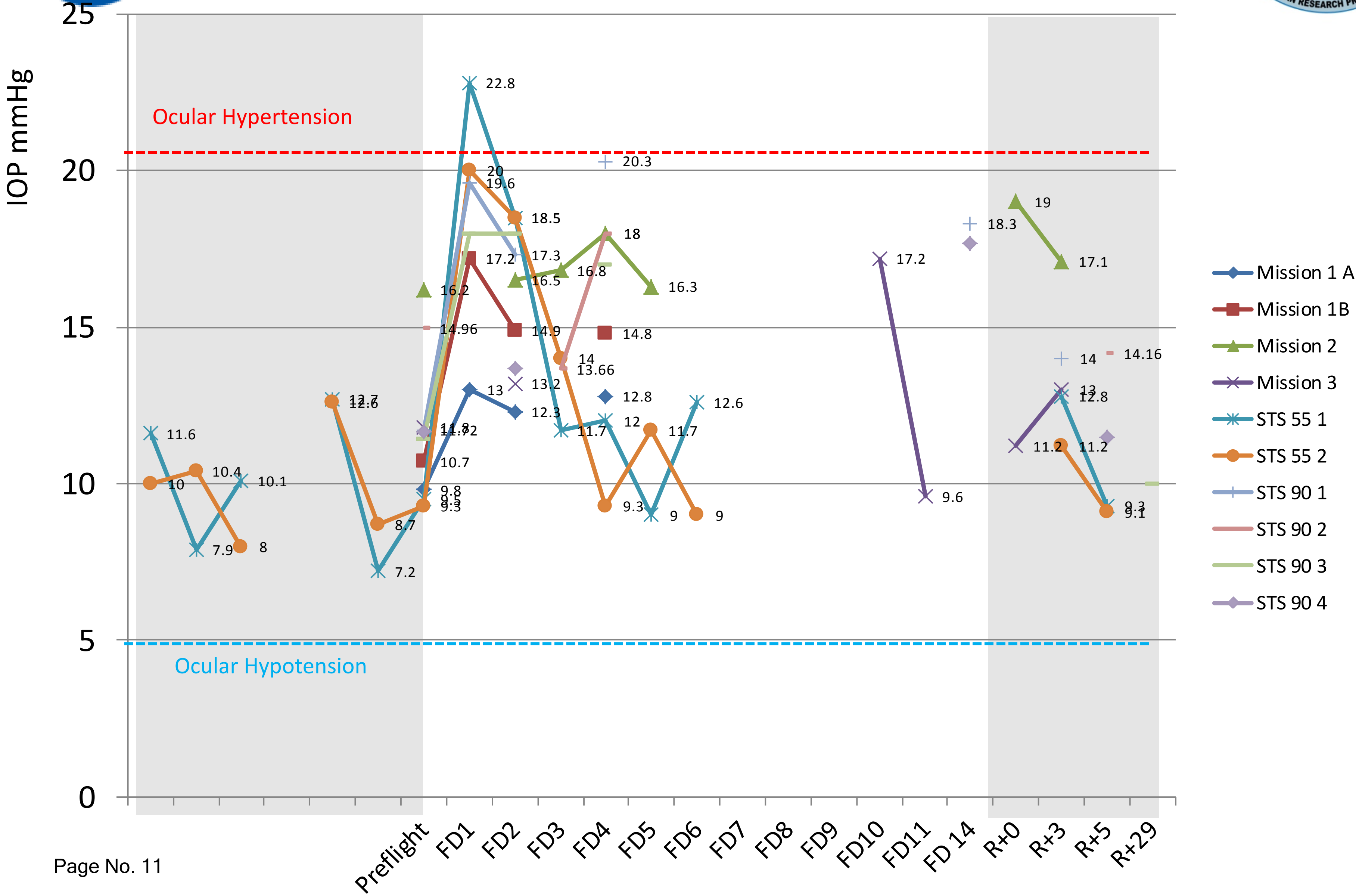


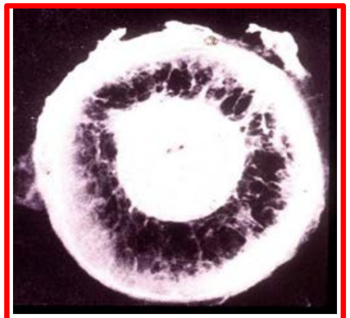

MRI Brain Venogram

# IOP for Five Shuttle Missions (10 Subjects)

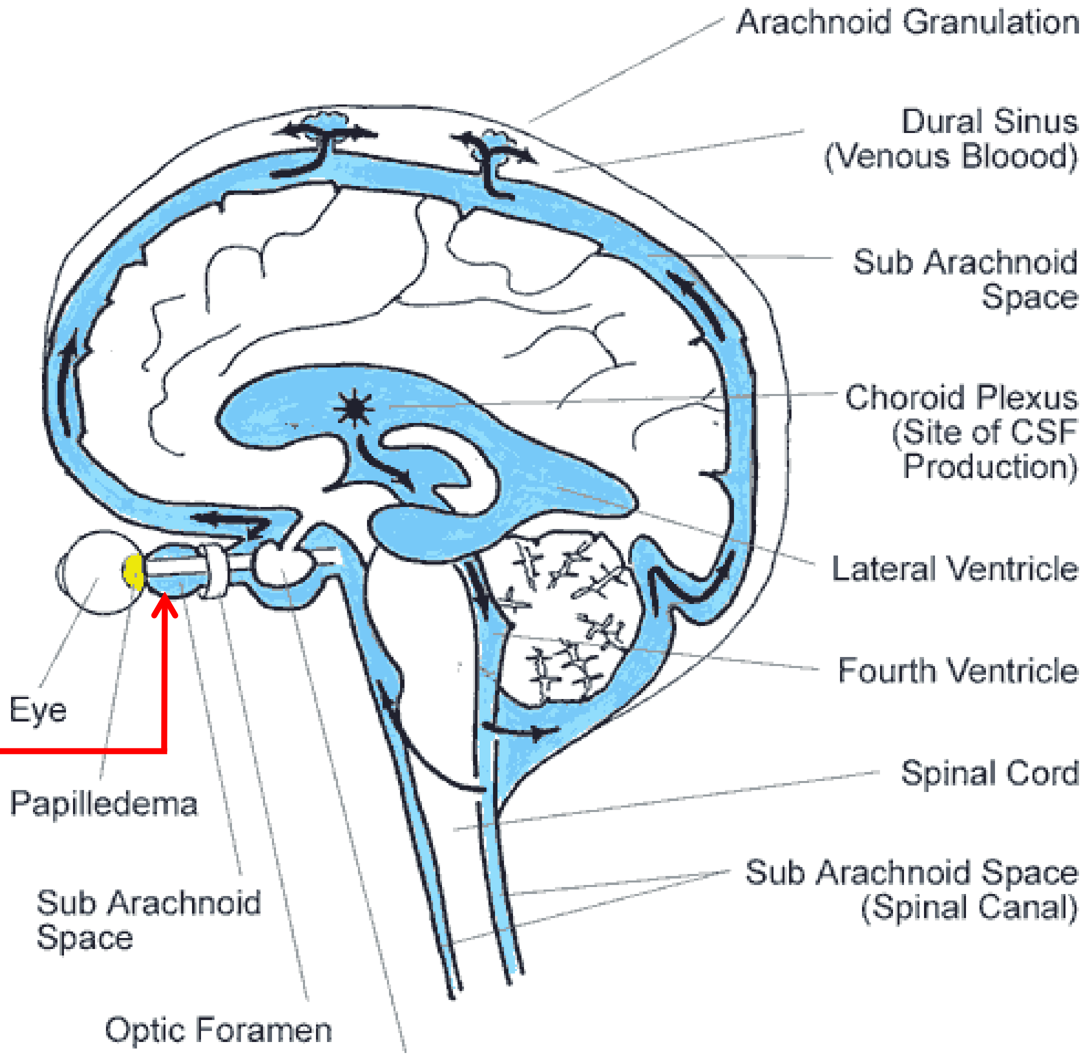
## Pre-flight, In-flight-Post-flight



# Raised Intracranial Pressure-Qualitative Measurement with ONSD

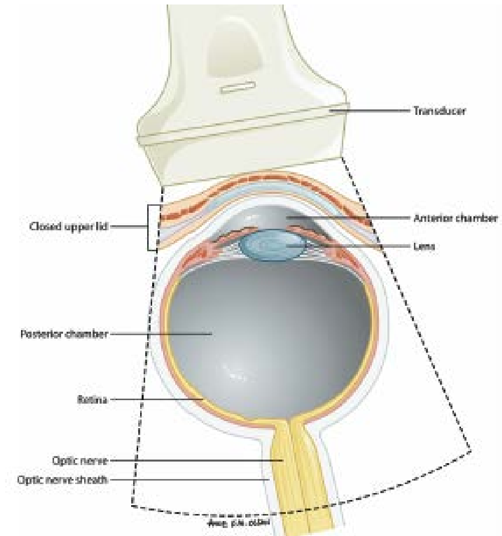


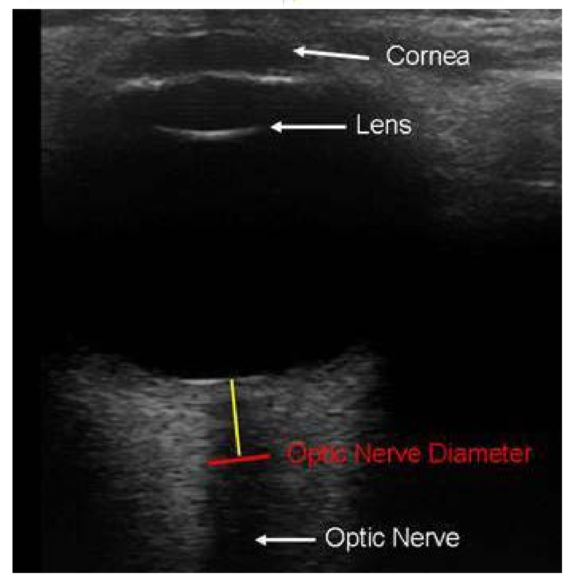
Elevated ICP transmitted to optic nerve



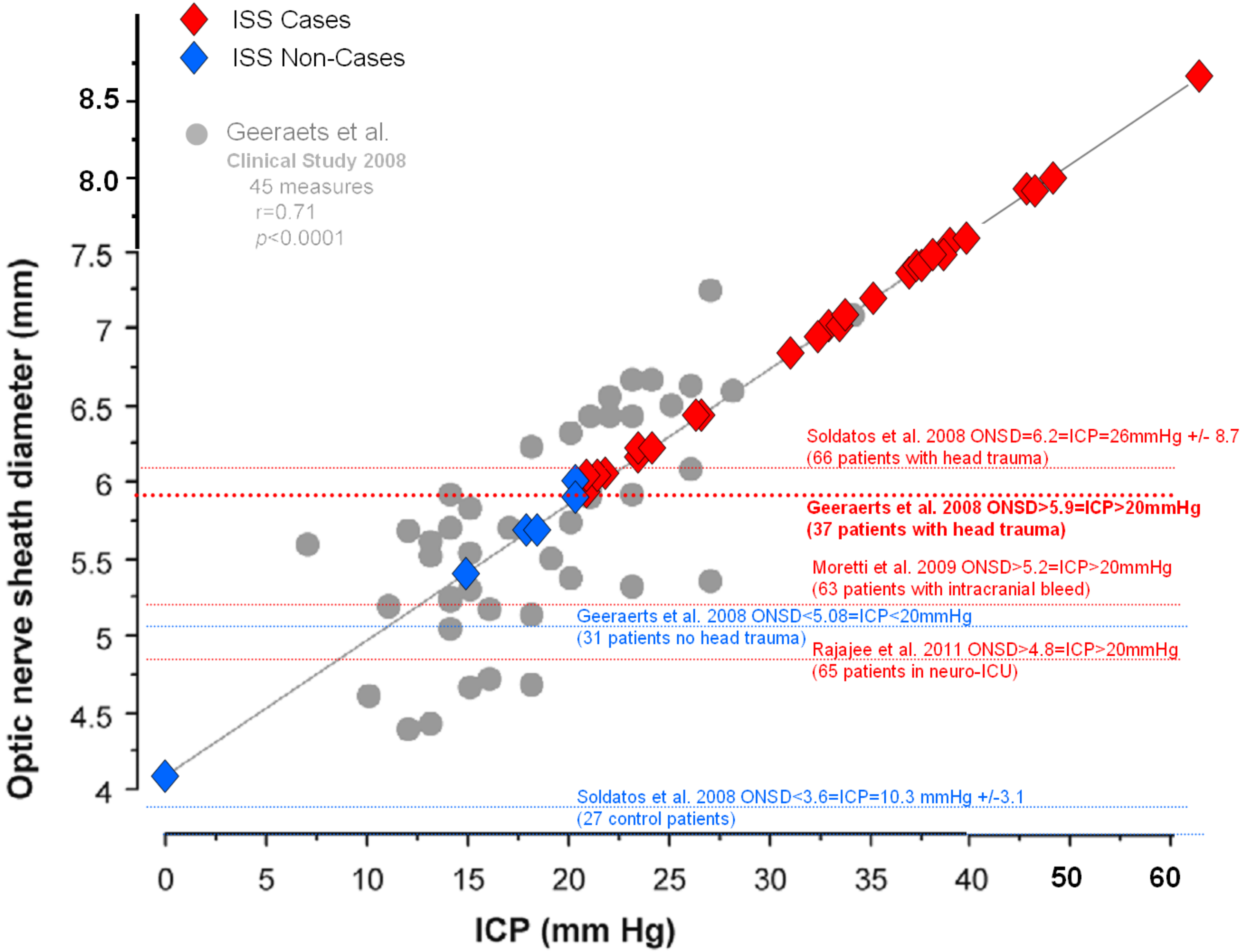
# In Flight B-scan Ultrasound

Shalizan Sharipov & Leroy Chiao

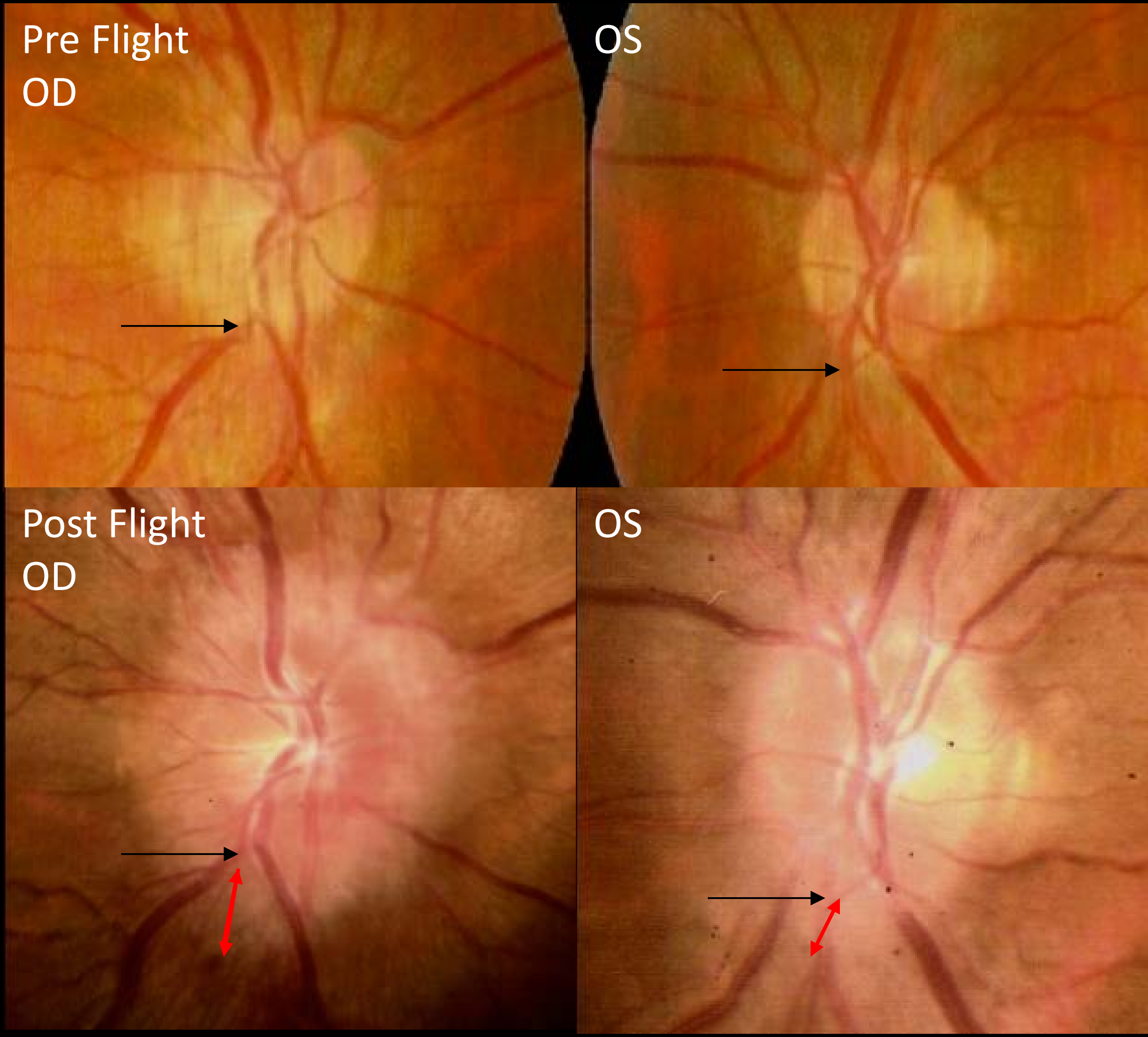


# ISS In-Flight ONSD for VIIP Cases & Non-Cases Plotted Against Ground Study of ONSD & ICP



# Pre to Post Flight Papilledema
## (First case 2005. N=6)




## Pre Flight

Fundoscopic images of the right and left optic disc.

## Post Flight

Fundoscopic images of the right and left optic disc showing **Grade 3 edema right** and **Grade 1 edema left** .

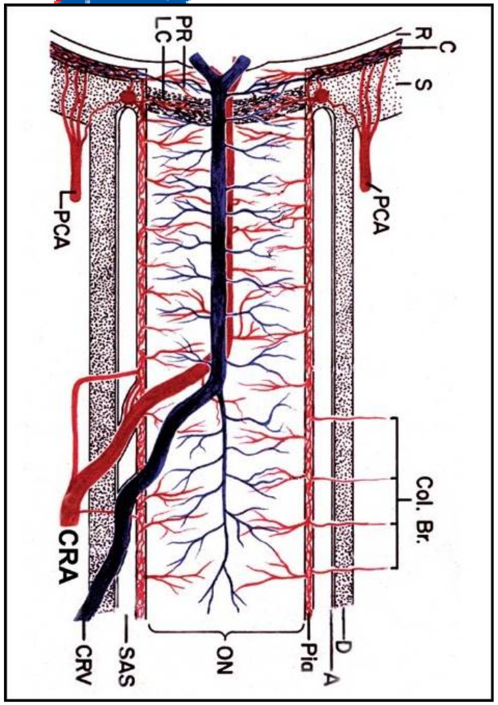
| General causes of optic disc edema | Specific causes |
|---|---|
| Increased ICP | Brain tumors<br>*Idiopathic intracranial hypertension*<br>Dural sinus obstruction/thrombosis<br>Carotid-cavernous fistulae<br>AVMs (dural or parenchymal) |
| Structural | Optic disc drüsen<br>Glial remnants |
| Vascular/ circulatory | Hypertension<br>Nonarteritic AION<br>Arteritic AION (temporal arteritis)<br>Congestive heart failure<br>COPD/emphysema<br>Congenital heart disease<br>Pickwickian syndrome/obstructive sleep apnea<br>Hypoxia<br>Ocular ischemia<br>Central retinal vein occlusion<br>Papillophlebitis<br>Radical neck dissection |
| Hematological | Anemia<br>Acute hemorrhage/acute hypotension<br>Polycythemia vera<br>Idiopathic thrombocytopenic purpura<br>Hyperviscosity syndrome<br>Waldenström's macroglobulinemia |
| Tumors | Meningiomas<br>Gliomas<br>Hemangiomas<br>Hemangiopericytomas<br>Metastases<br>Orbital tumors<br>Spinal tumors, especially paragangliomas |
| Infiltrative tumors | Lymphomas/leukemia<br>Multiple myeloma<br>Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes<br>Histiocytosis syndromes<br>Meningeal carcinomatosis<br>Paraneoplastic syndromes |
| Disc tumors | Hemangiomas<br>Hamartomas<br>Gliomas<br>Hemangioblastomas<br>Astrocytomas |
| Collagen vascular disease | Systemic lupus erythematosus<br>Polyarteritis nodosa<br>Lupus anticoagulant syndromes<br>Wegener's granulomatosis |
| Inflammatory | Uveitis (HLA-B27, Behçet's syndrome, or Vogt-Koyanagi-Harada syndrome)<br>Ocular hypotony<br>Orbital pseudotumor/myositis<br>Sarcoidosis<br>Pachymeningitis<br>Granulomatous meningitis<br>Inflammatory bowel disease |
| Infectious | Tuberculosis<br>Hansen's disease (leprosy)<br>Syphilis<br>HIV<br>Viral and postviral (polio, CMV, coxsackievirus, HSV, EBV, rubella)<br>Orbital cellulitis<br>Bacterial meningitis<br>Fungal/parasitic diseases (*Aspergillus*, *Candida*, *Cryptococcus*, *Mucor*, *Coccidioides*, *Histoplasma*, *Toxoplasma*)<br>Cat scratch disease (*Bartonella*)<br>Sinusitis<br>Mucocele<br>Neuroretinitis<br>Big blind spot syndrome/MEWDS<br>Whipple's disease (*Tropheryma whippelii*)<br>Leptospirosis<br>Brucellosis<br>Lyme disease (*Borrelia burgdorferi*) |
| Demyelinating | Optic neuritis (associated with multiple sclerosis)<br>Schilder's disease |
| Hereditary | Leber's optic neuropathy<br>Mucopolysaccharidoses |
| Metabolic/ endocrine | Diabetic papillopathy, diabetic ketoacidosis<br>Eclampsia<br>Hypoparathyroidism<br>Thyrotoxicosis<br>Graves' orbitopathy (compressive)<br>Uremia<br>Puberty/menarche |
| Toxic | Hypervitaminosis A, ethambutol, methanol, ethylene glycol, lithium, tetracycline, radiotherapy |

[a] ICP, intracranial pressure; AVM, arteriovenous malformation; HIV, human immunodeficiency virus; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; COPD, chronic obstructive pulmonary disease; AION, anterior ischemic optic neuropathy; MEWDS, multiple evanescent white dot syndrome.

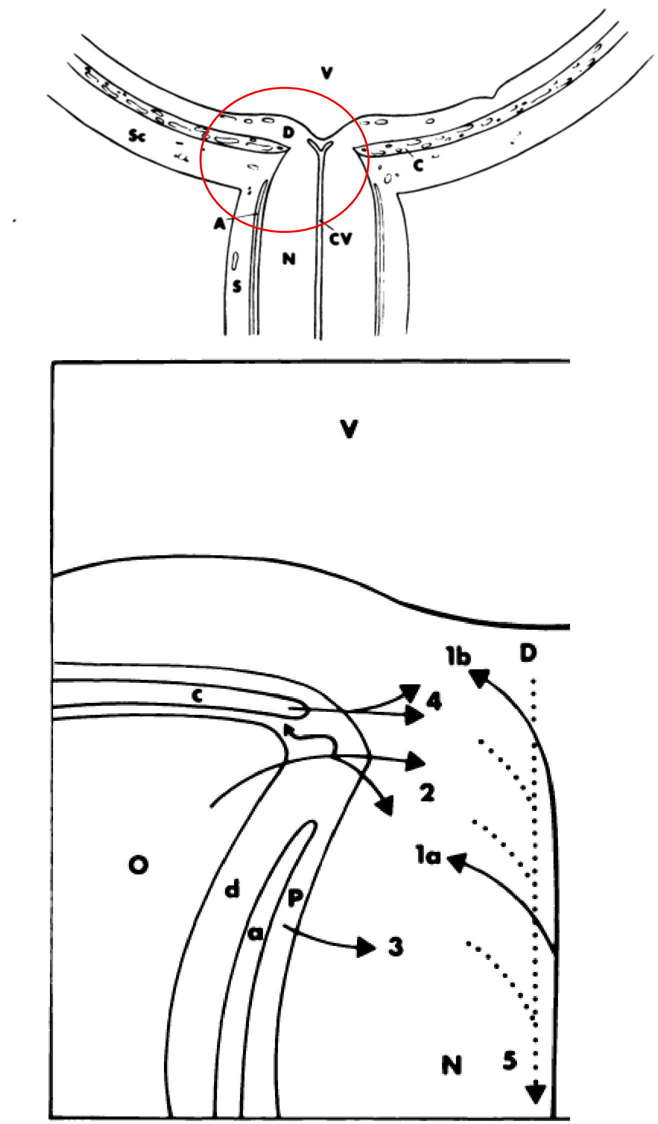
HUMAN RESEARCH PROGRAM

Jinkins et al. 1987

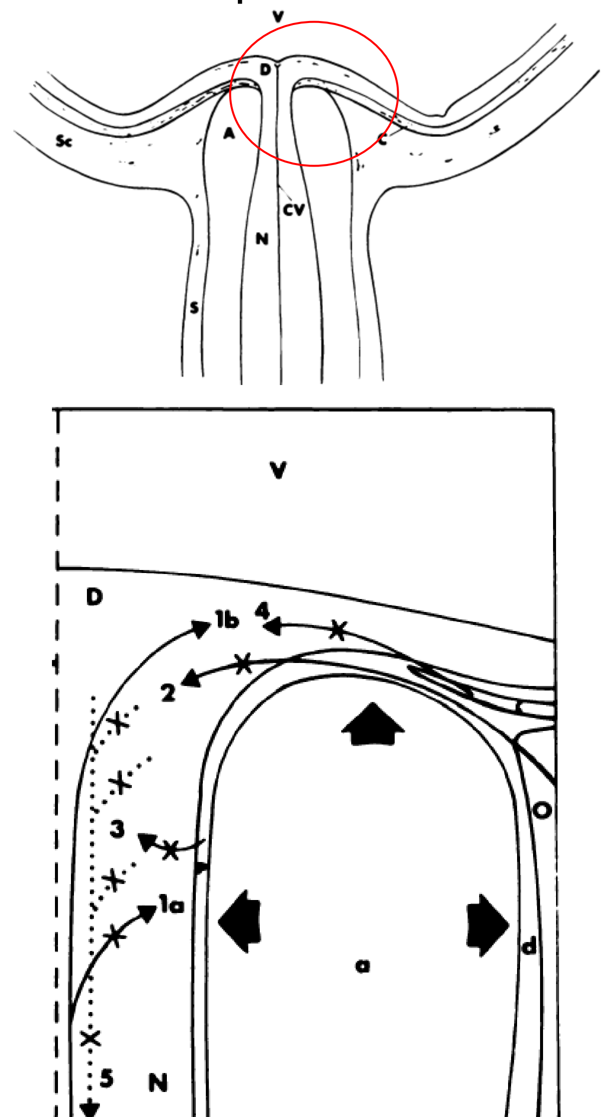
# Papilledema Mechanism




Normal




Papilledema




1a central retinal artery in optic nerve
1b central retinal artery in optic disc
2 short ciliary arteries
3 plial arterioles
4 arterioles from choroid layer
5 Central retinal vein
a subarachnioid space
d dura
D optic disc
N optic nerve
V vitreous
X compromised perfusion

# ICP Related Disc Edema (Papilledema) Pathophysiology

C. M. Schirmer and T. R. Hedges , 2007

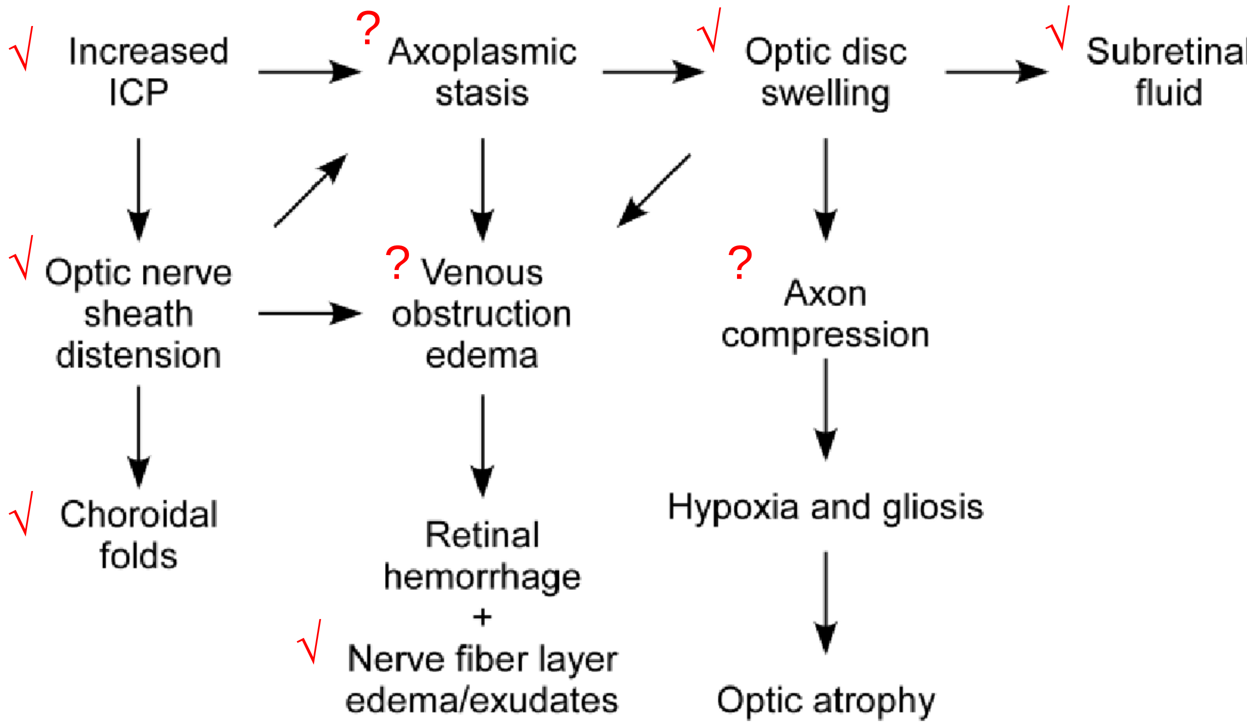
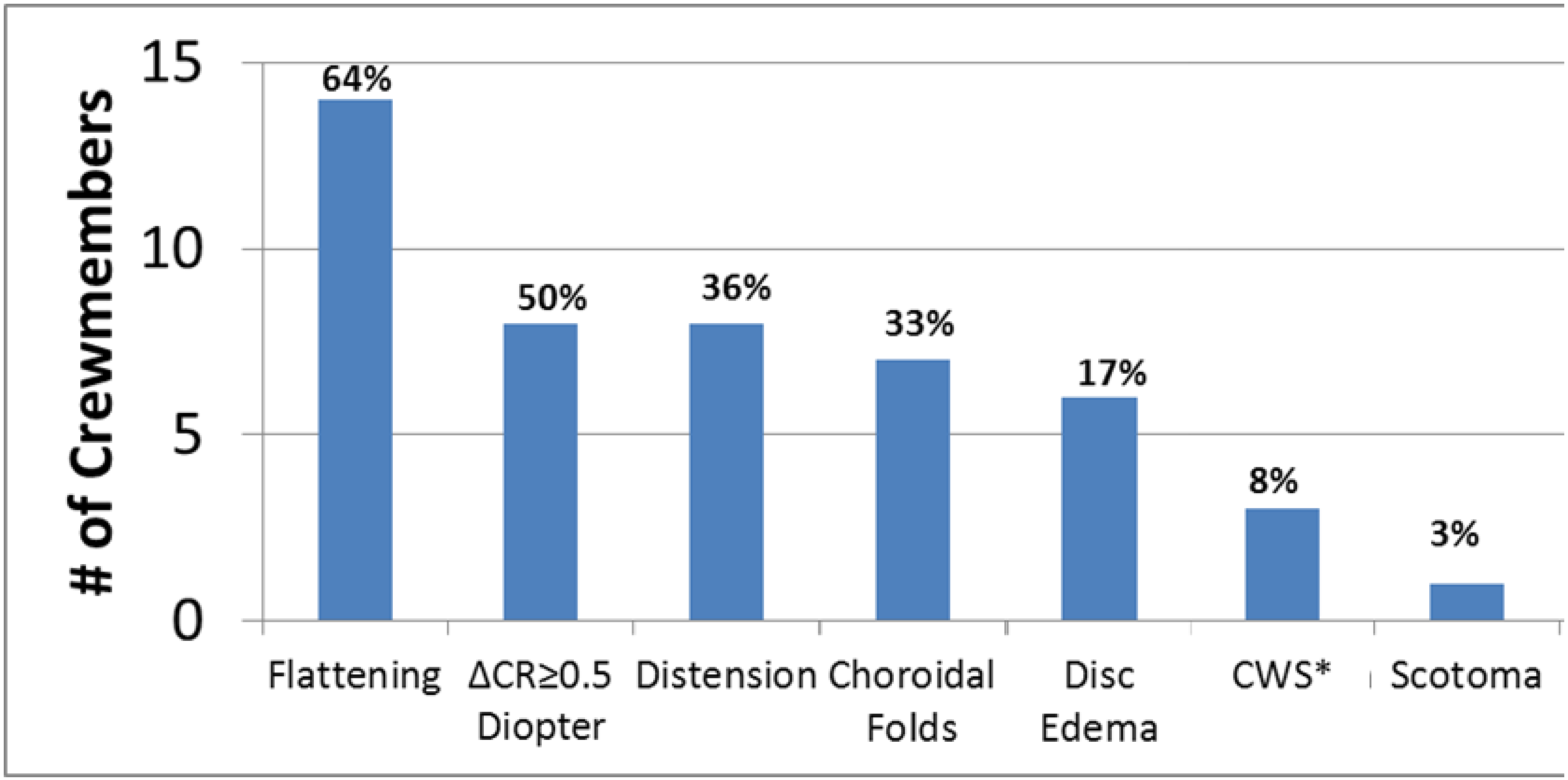


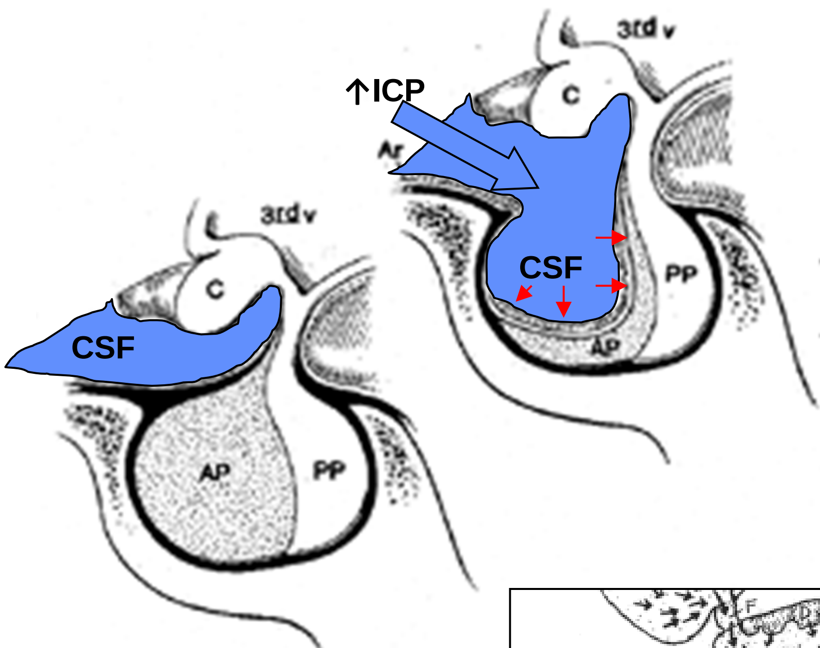

FIG. 1. Schematic diagram of the pathogenesis of papilledema based primarily on the literature dealing with its pathophysiology.

# VIIP Ocular Findings in ISS Astronauts

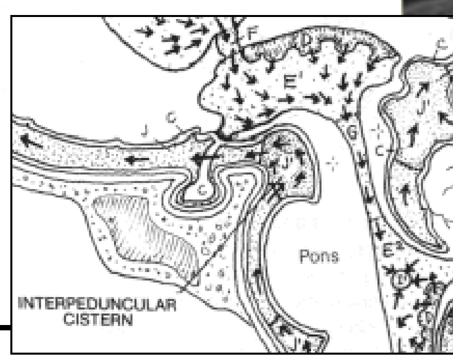


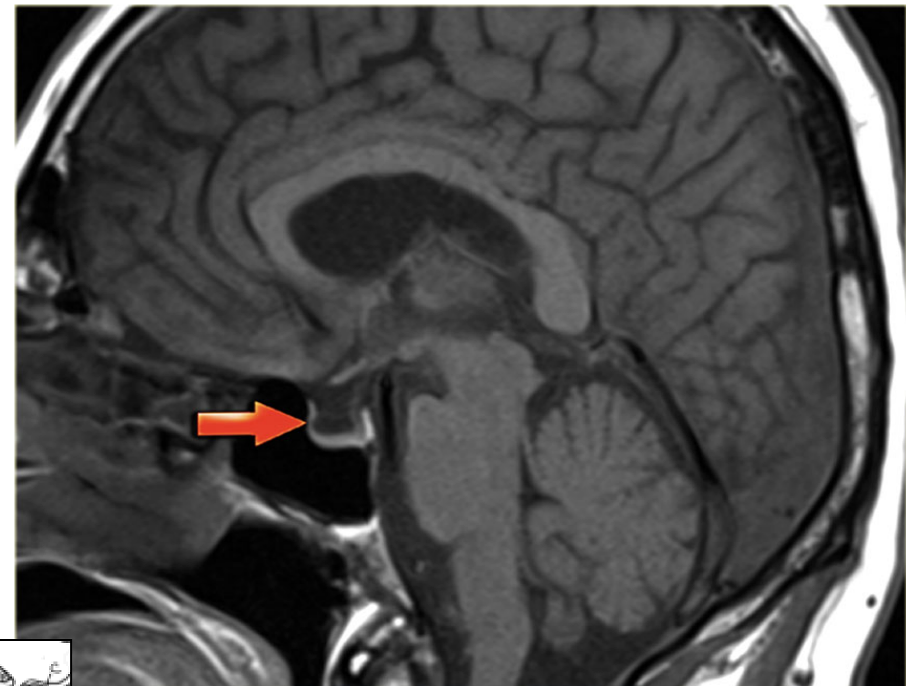
# Partially Empty Sella (Turcica)

Pituitary compressed by CSF
“Partially empty sella”




Normal Pituitary



Documented in 5 crew members

# Current U.S. ISS VIIP Incidence:

45 U.S. ISS astronauts :

- *Unclassified astronauts N=16 (No* MRI, OCT or ocular US)
- Known Non-cases: N=8
- Confirmed cases: N= 21

**Clinical Classification:**

- Class One: N=2
- Class Two: N=13
- Class Three: N=2
- Class Four : N=4

71.2 % Class 1&2

28.6 % Class 3&4

Increasing severity

**Current VIIP Incidence as a % of U.S. ISS astronauts tested= 72.4%**

# VIIP Clinical Practice Guideline
# Case Definition

**Class 1** ≥ .50 diopter cycloplegic refractive change and/or cotton wool spot

**Class 2** ≥ .50 diopter cycloplegic refractive changes or cotton wool spot

- Choroidal folds and/or optic nerve sheath distension and/or globe flattening and/or scotoma

**Class 3** ≥ .50 diopter cycloplegic refractive changes and/or cotton wool spot

- Optic nerve sheath distension, and/or globe flattening and/or choroidal folds and/or scotoma
- Papilledema of Grade 0-2.

**Class 4** ≥ .50 diopter cycloplegic refractive changes and/or cotton wool spot

- Optic nerve sheath distension, and/or globe flattening and/or choroidal folds and/or scotoma
- Papilledema Grade 2 or above.
- Presenting symptoms of new headache, pulsatile tinnitus and/or transient visual obscurations
- CSF opening pressure >25 cm $H_2O$

# VIIP Clinical Findings

- To date 21 U.S. ISS long-duration spaceflight astronauts have developed some or all of the following findings:

*Eye Findings*

- Hyperopic shift
- Cotton wool spots
- Choroidal folds
- Optic Nerve Sheath Distention
- Globe flattening
- Edema of the Optic disc (papilledema)
- Partially empty sella

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- Partially Empty Sella

*Signs of elevated intracranial pressure*

# NASA ISS Astronaut LPs to Date

- LPs conducted if clinically indicated
- 5 LPs postflight in crewmembers with optic disc edema, no preflight LP as baseline
- Results: Mild to moderate elevation in ICP, normal composition
- Postflight measure is inadequate surrogate to in-flight measurement of ICP (cephalad fluid shift & CO2 challenge absent)

| Case | Opening pressure (cm $H_2O$) Normal range 10-20 cm $H_2O$ | Opening pressure (mmHg) Normal range 5-15 mm $H_2O$ | Time after flight (days) |
|---|---|---|---|
| A | 22 | 16.2 | 66 |
| B | 21 | 15.4 | 19 |
| C | 28 | 20.6 | 12 |
| D | 28.5 | 21.0 | 57 |
| E | 18 | 13.2 | 8 |

# Idiopathic Intracranial Hypertension Diagnostic Criteria:

Modified Dandy Criteria

1. Symptoms of raised intracranial pressure (headache, nausea, vomiting, transient visual obscurations, or papilledema)

2 No localizing signs with the exception of abducens (sixth) nerve palsy

3 The patient is awake and alert

4 Normal CT/MRI findings without evidence of thrombosis/tumor

5 LP opening pressure of >20 $cmH_2O$ (non obese) and normal CSF composition

6 No other explanation for the raised intracranial pressure

Maybe VIIP is not IIH? However, the pathophysiology may be closely related re: CVP & ICP

**Table 1: Confounding conditions that may present as similar to IIH[a]**

| |
|---|
| **Medical disorders** |
| Addison disease |
| Hypoparathyroidism |
| Chronic obstructive pulmonary disease |
| Right heart failure with pulmonary hypertension |
| Obstructive sleep apnea |
| Pickwickian syndrome |
| Polycystic ovary syndrome |
| Systemic lupus erythematosus |
| Uremia |
| Severe iron deficiency anemia |
| **Medications** |
| Tetracycline and related compounds (minocycline, doxycycline) |
| Vitamin A (at doses >25 000 IU daily) and related compounds (isotretinoin [Accutane], vitamin supplements, excessive intake of liver, all-trans retinoic acid) |
| Anabolic steroids |
| Corticosteroid withdrawal following prolonged administration |
| Growth hormone administration in deficient patients |
| Nalidixic acid |
| Lithium |
| Oral contraceptive use |
| Levonorgestrel implant system |
| Amiodarone |
| Cyclosporine |
| Cytarabine |
| **Obstruction to venous drainage** |
| Cerebral venous sinus thrombosis |
| Jugular vein thrombosis |
| Superior vena cava syndrome |
| Jugular vein ligation following bilateral radical neck dissection |
| Increased right heart pressure |
| Glomus tumor |
| Compression by tumor process (eg, meningioma) |
| **Infections** |
| HIV infection, borreliosis |
| Postvaricella infection in children |

[a] Adapted from Friedman and Jacobson,[7] Szitkar,[8] Wall,[22] and Alperin et al.[79]

Annotations: ↑CVP/ICP (Chronic obstructive pulmonary disease; Right heart failure with pulmonary hypertension; Obstructive sleep apnea; Pickwickian syndrome); ↑ICP (Medications); ↑ICP/CVP (Cerebral venous sinus thrombosis; Jugular vein thrombosis; Superior vena cava syndrome; Jugular vein ligation following bilateral radical neck dissection; Increased right heart pressure)

# Qualitative Evidence for Elevated ICP:
# Similarity of Findings Between IH, IIH & VIIP

| Finding | Present in IH |
|---|---|
| **Elevated ICP** | √ (>15mmHg) |
| **Normal CSF** | X |
| **Papilledema** | √ |
| **Flattening of Posterior Globes** | √ 64%/78% |
| **Optic Nerve Protrusion** | √ 33%/100% |
| **Partially Empty Sella** | √ 56%/97% |
| **Optic Nerve Sheath Distension** | √ 92%/89% |
| **Optic Nerve Tortuosity** | √ |
| **Optic Nerve Enhancement** | -- |

# Qualitative Evidence for Elevated ICP:
# Similarity of Findings Between IH, IIH & VIIP

| Finding | Present in IH | Present in IIH | Present in VIIP |
|---|---|---|---|
| **Elevated ICP** | √ (>15mmHg) | √ (>15mmHg) | √*(15-21mmHg) |
| **Normal CSF** | X | √ | √ |
| **Papilledema** | √ | √ | √ |
| **Flattening of Posterior Globes** | √ 64%/78% | √<br>54%/100%<br>43%/--<br>80%/--<br>63%/-- | √ |
| **Optic Nerve Protrusion** | √ 33%/100% | √<br>37/100<br>3%/--<br>30%/-- | √ |
| **Partially Empty Sella** | √ 56%/97% | √<br>65/95<br>53%/--<br>80%/--<br>70%/ | √ |
| **Optic Nerve Sheath Distension** | √ 92%/89% | √<br>49%/88%<br>67%/--<br>45%/-- | √ |
| **Optic Nerve Tortuosity** | √ | √<br>35%/86%<br>40%/--<br>40%/-- | √ |
| **Optic Nerve Enhancement** | -- | √<br>4.3%/100%<br>7%/--<br>50%/-- | √ |

# There is a rational hypothesis for the physiology.

# Dose Response for the VIIP? Shuttle vs ISS

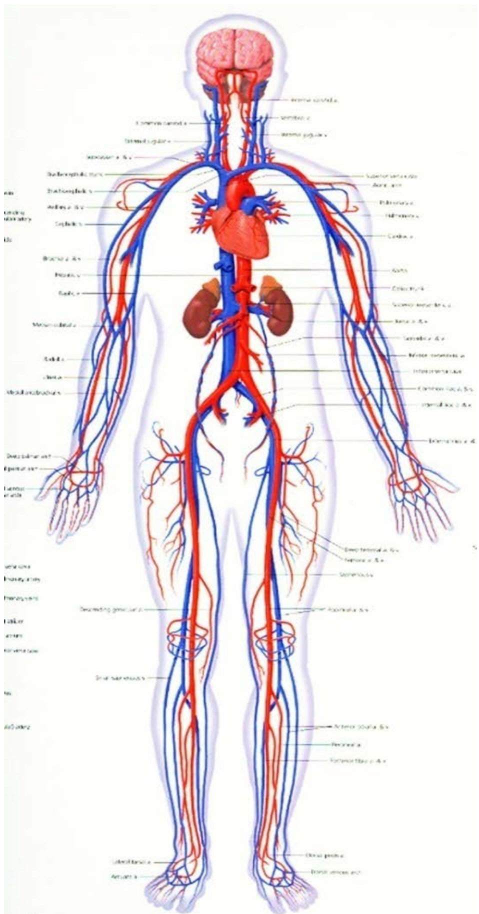
- Kramer et. al. *Orbital and Intracranial Effects of Microgravity: Findings at 3-T MR Imaging.* Radiology: Vol 263:3 2012
- N=27 Astronauts
- Consistently higher percentage of findings for group with greater microgravity exposure, and increased severity of findings.

| Cumulative Lifetime Exposure to Microgravity Relative to Imaging Findings | | | | | | | |
|---|---|---|---|---|---|---|---|
| Time in UG | No. Subjects | Globe Flattening | Optic Nerve Sheath Kinking | ONSD>5.9mm | Optic Disc Protrusion | Moderate or Greater Pituitary Concavity | Papilledema |
| **<30d (Short)** | 12 | 1 | 1 | 5 | 0 | 0 | 0 |
| **>30d (Long)** | 15 | 6 | 3 | 9 | 4 | 3 | 3 |

# Visual Impairment and Elevated Intracranial Pressure in Spaceflight

## *Primary Systems Involved*

### Cardiovascular



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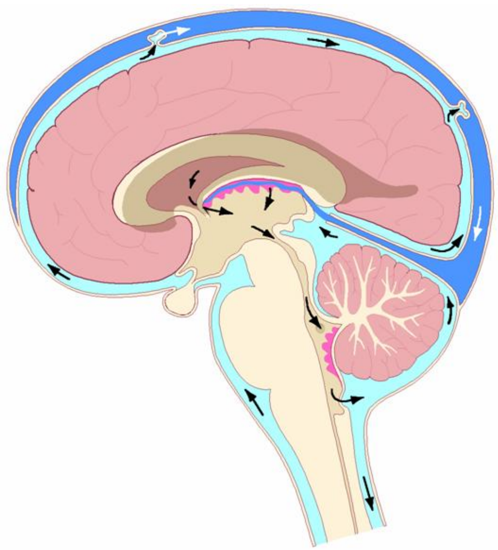
### CNS



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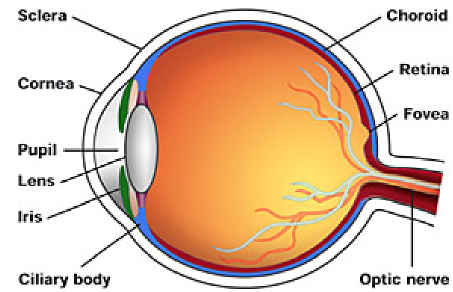
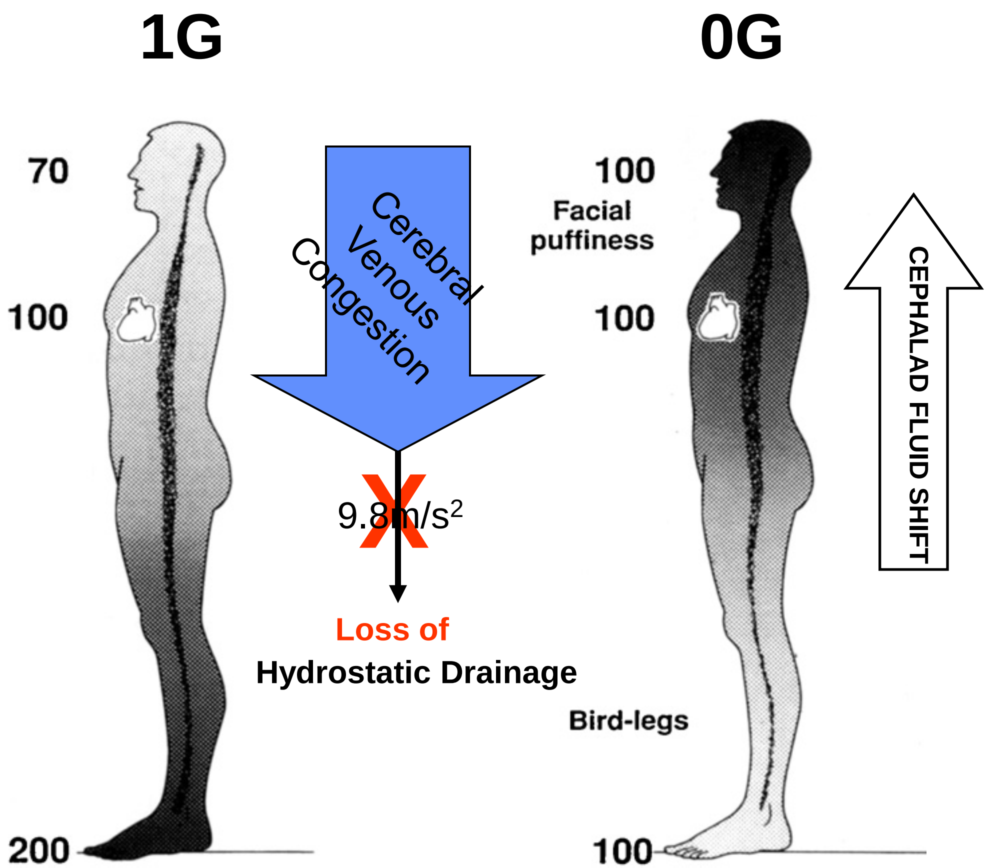
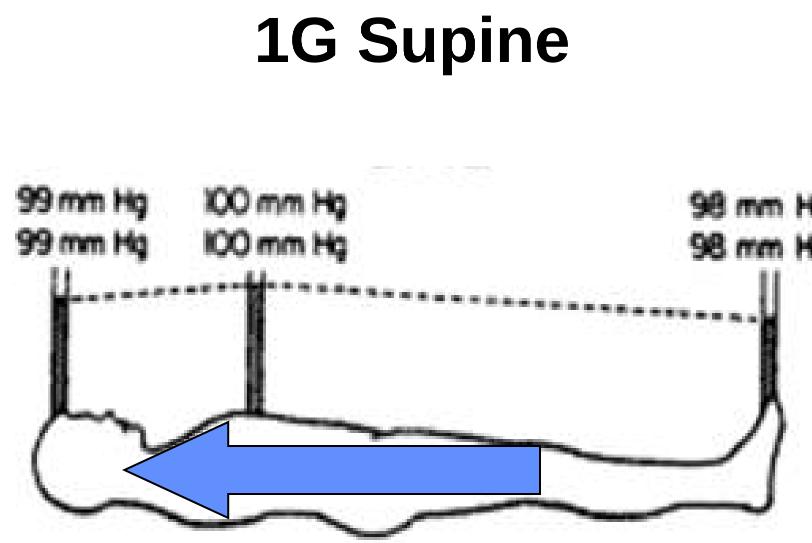
### Ocular



# Loss of Hydrostatic Drainage & Cerebral Venous Congestion



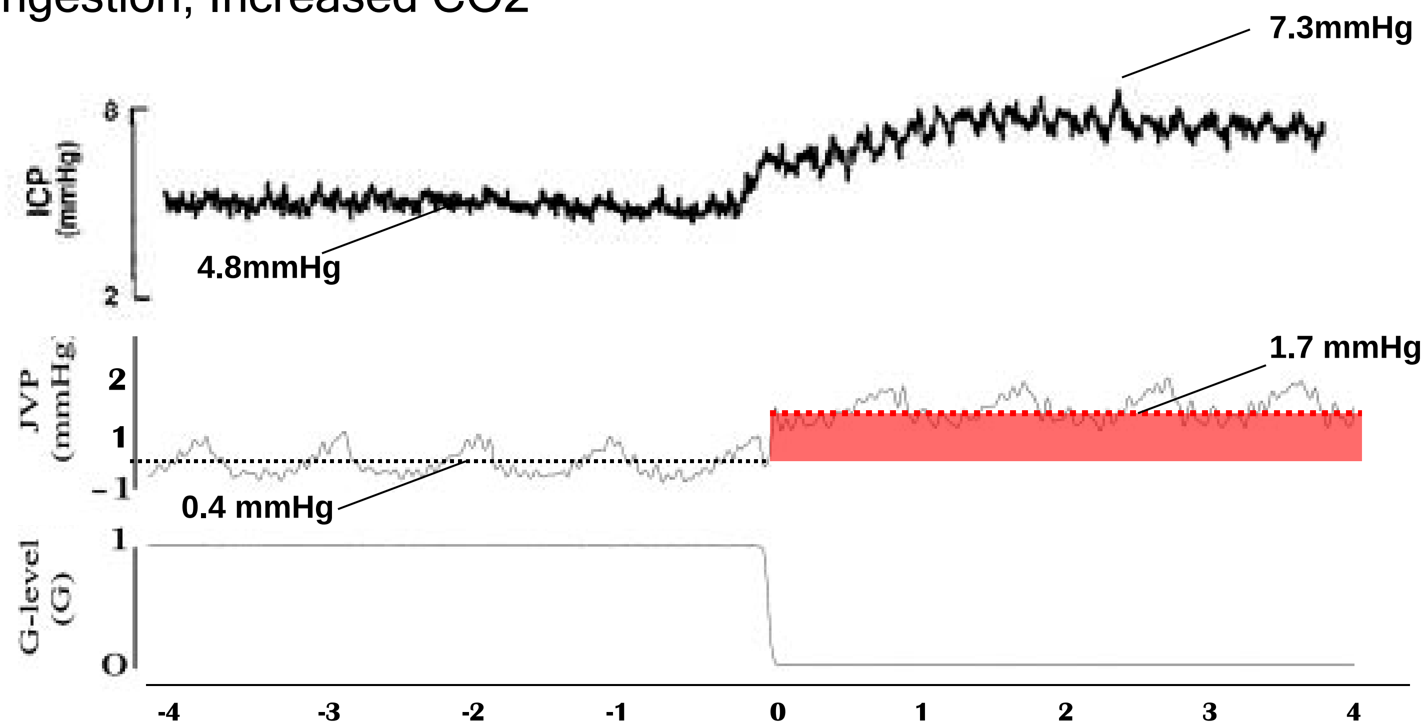

Adapted from Hargens & Richardson, Respiratory Physiology & Neurobiology. 2009




Adapted from Rowell, 1988

# Elevated ICP in Simulated Microgravity

- ICP measured during 4.5s free drop (N=5)
- ICP increased 52%, 4.8 to 7.3 mmHg
- Jugular bulb pressure ↑ 325% (N=7) i.e. loss of hydrostatic assisted venous drainage
- Factors that may further raise ICP: Complete cephalad fluid shift, lymphatic congestion, Increased CO2

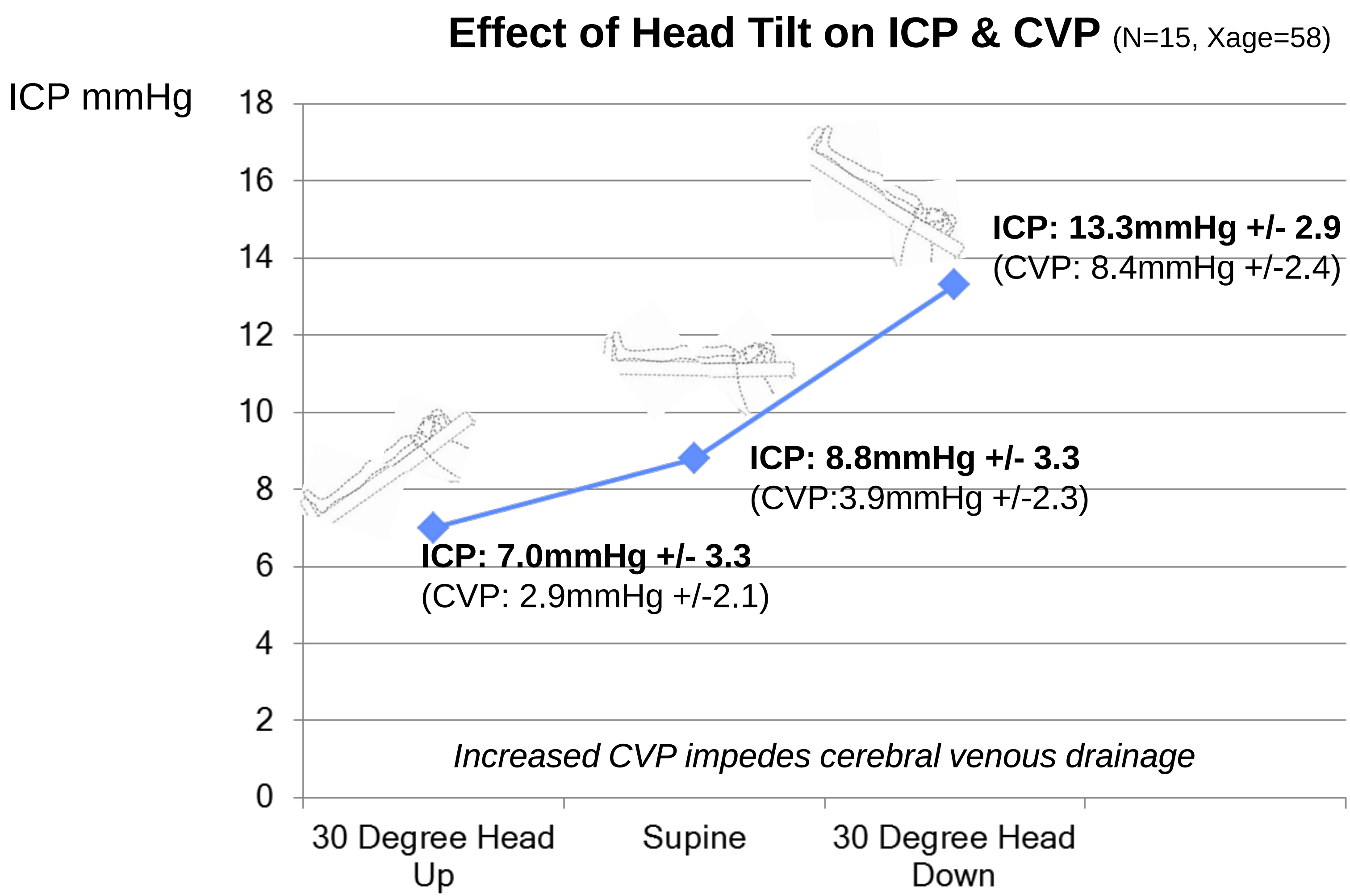




1. Gotoh et al. *Acute hemodynamic responses in the head during microgravity induced by free drop in anesthetized rats.* Am J Physiology-Regulatory Integrative & Comparative Physiology. 2004

2. GOTOH et al. Cerebral Circulation during Acute Microgravity Induced by Free Drop in Anesthetized Rats *Japanese Journal of Physiology*, **53**, 223–228, 2003

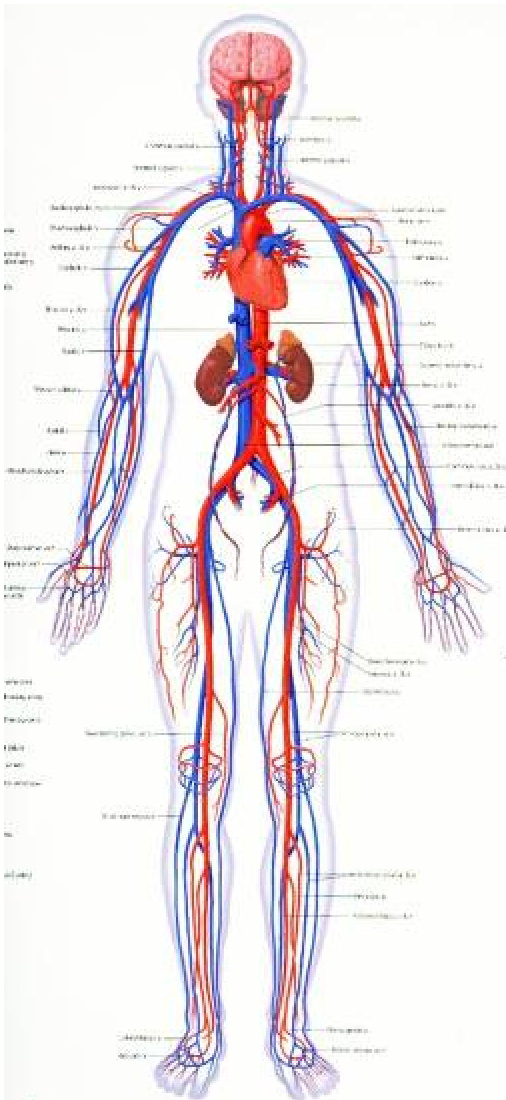
# CVP & ICP Increases with Acute Cephalad Fluid Shift

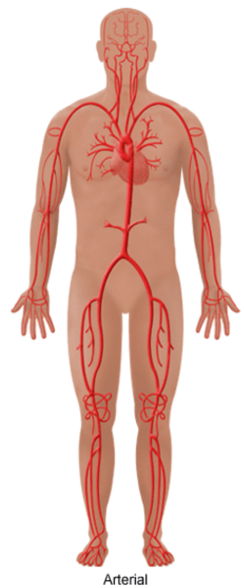




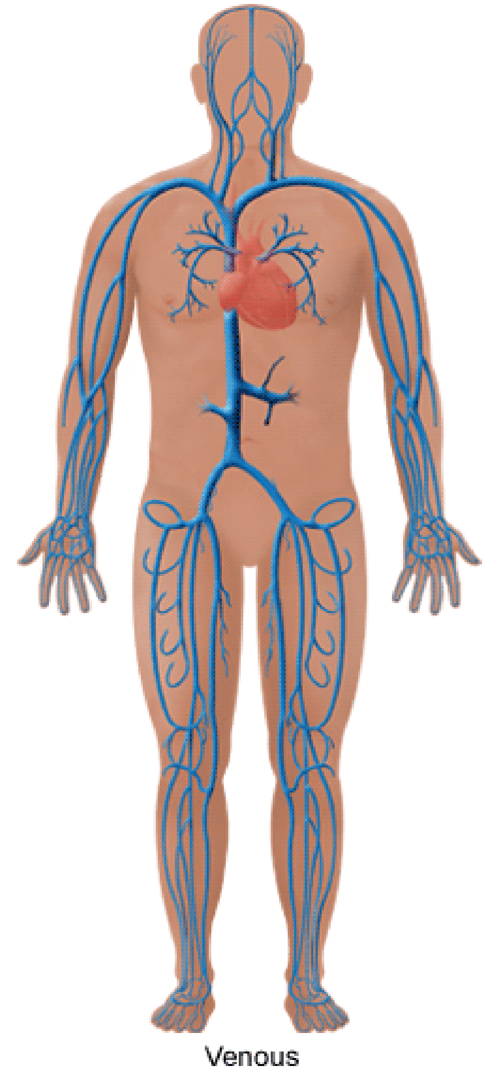

Mavrocordatos et al. Effects of Neck Position and Head Elevation on Intracranial Pressure in Anaesthetized Neurosurgical Patients: Preliminary Results. J. Neurological Anesthesia. 2000 Jan;12(1):10-4.

# Vascular Capacitance: Venous & Arterial





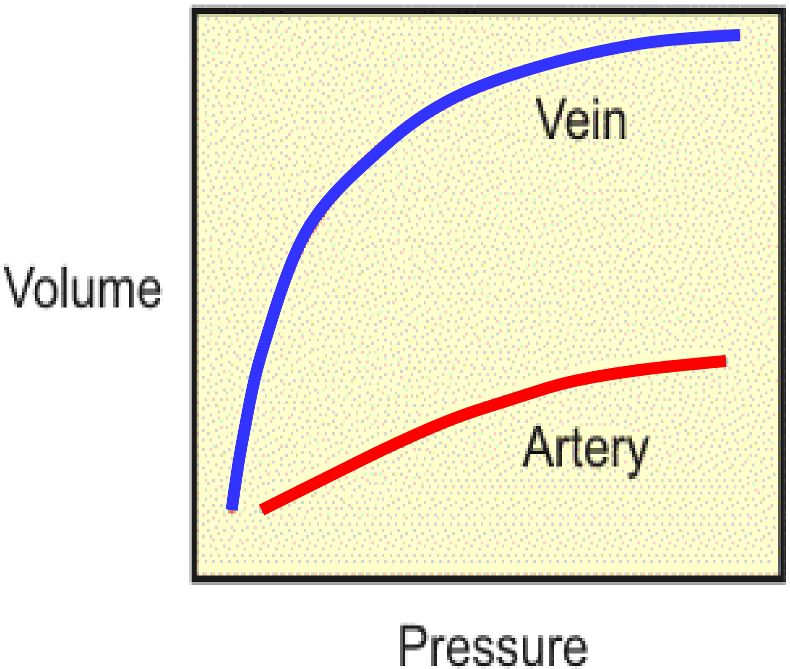

**20%=1L**

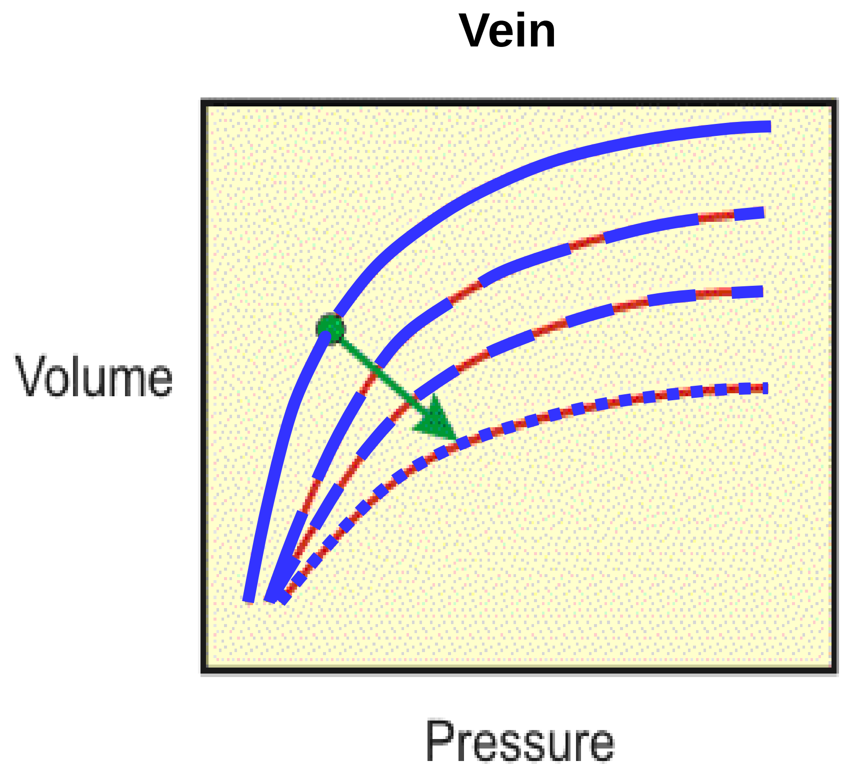



**70-80%=4L**

# Venous Compliance

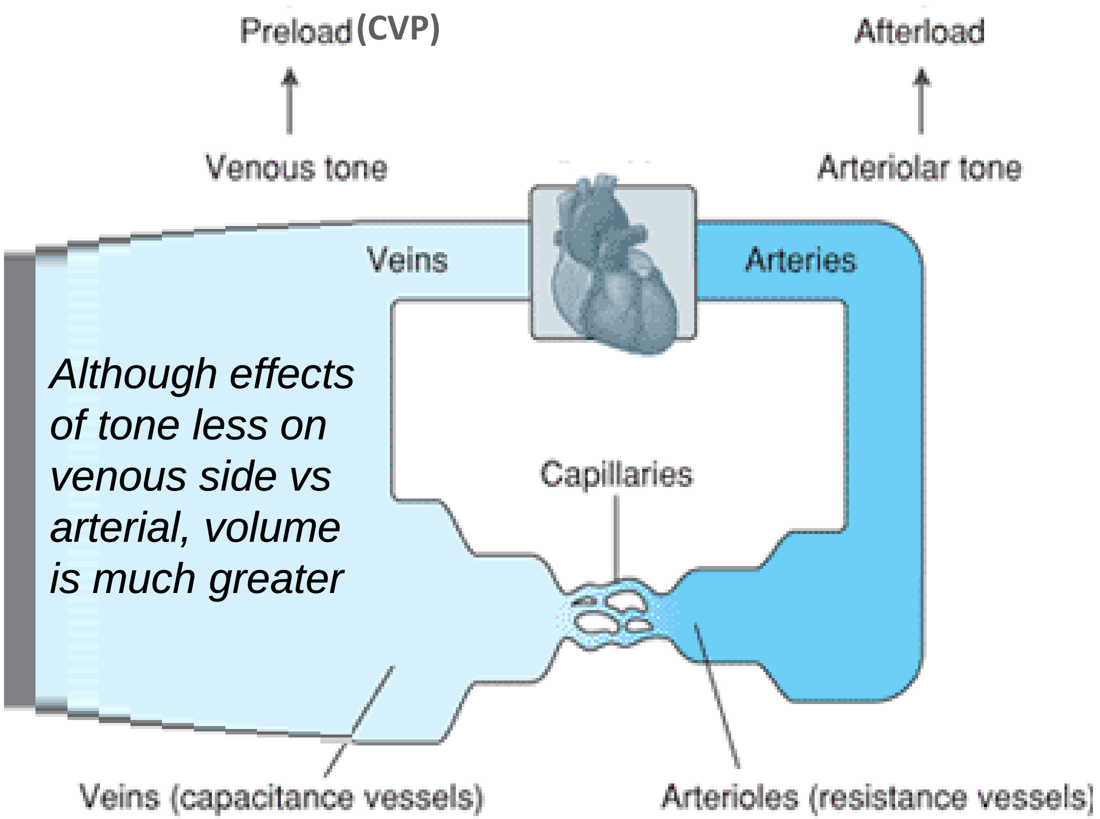
$$C = \frac{\Delta V}{\Delta P}$$



# Factors Increasing Venous Tone will Increase Cerebral Venous Outflow Resistance

- **Resting Tone of Venous Vessels Influenced by**:
  - SNS tone↑
    - ✓ Resting Blood Pressure
  - Endothelin↑
  - Nitric oxide↓
  - Inflammatory cytokines ↑

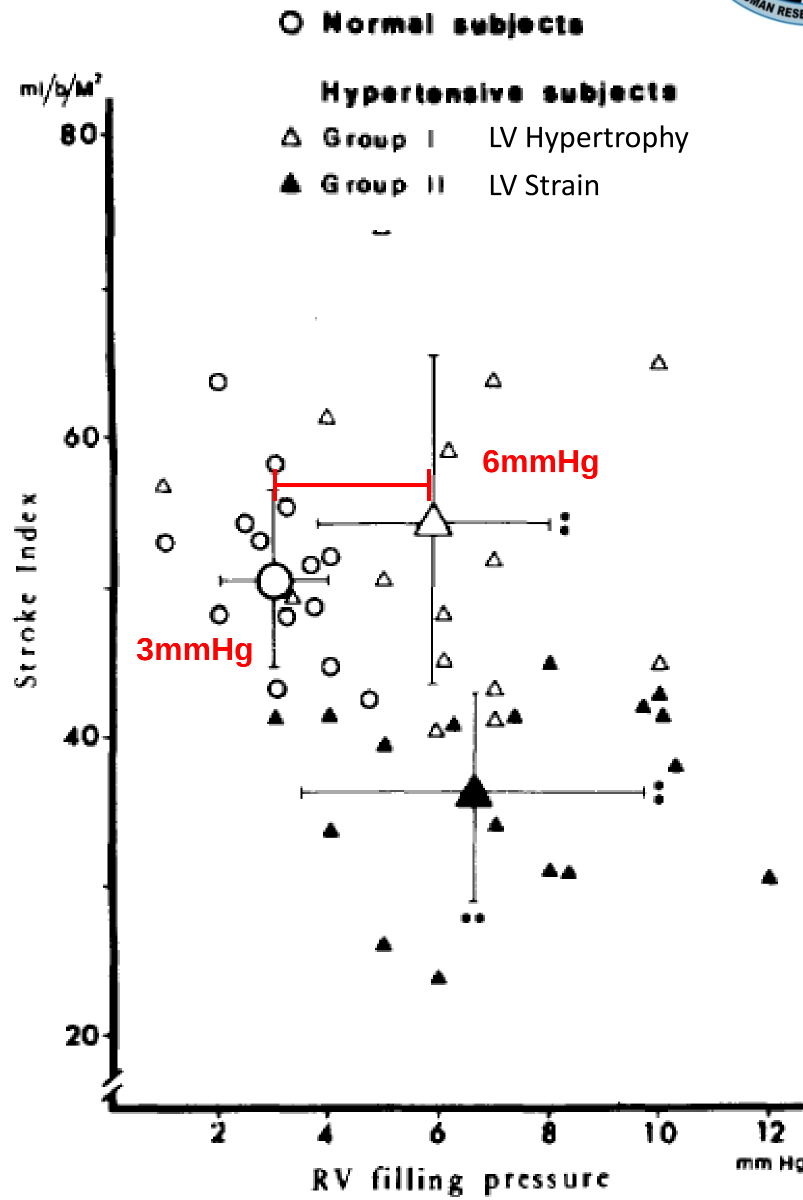


# Decreased Venous Compliance and Elevated CVP in Hypertensives

- Normal CVP=2-6mmHg
- A change in CVP determined by: change in volume (ΔV) of blood within the thoracic veins divided by the compliance of those veins:

$$\Delta CVP = \Delta V / Cv$$

- CVP, measured in patients with essential hypertension is modestly **increased**, even with normal pumping ability of the heart
- Decreased venous compliance contributes to the increase in CVP in hypertensive patients

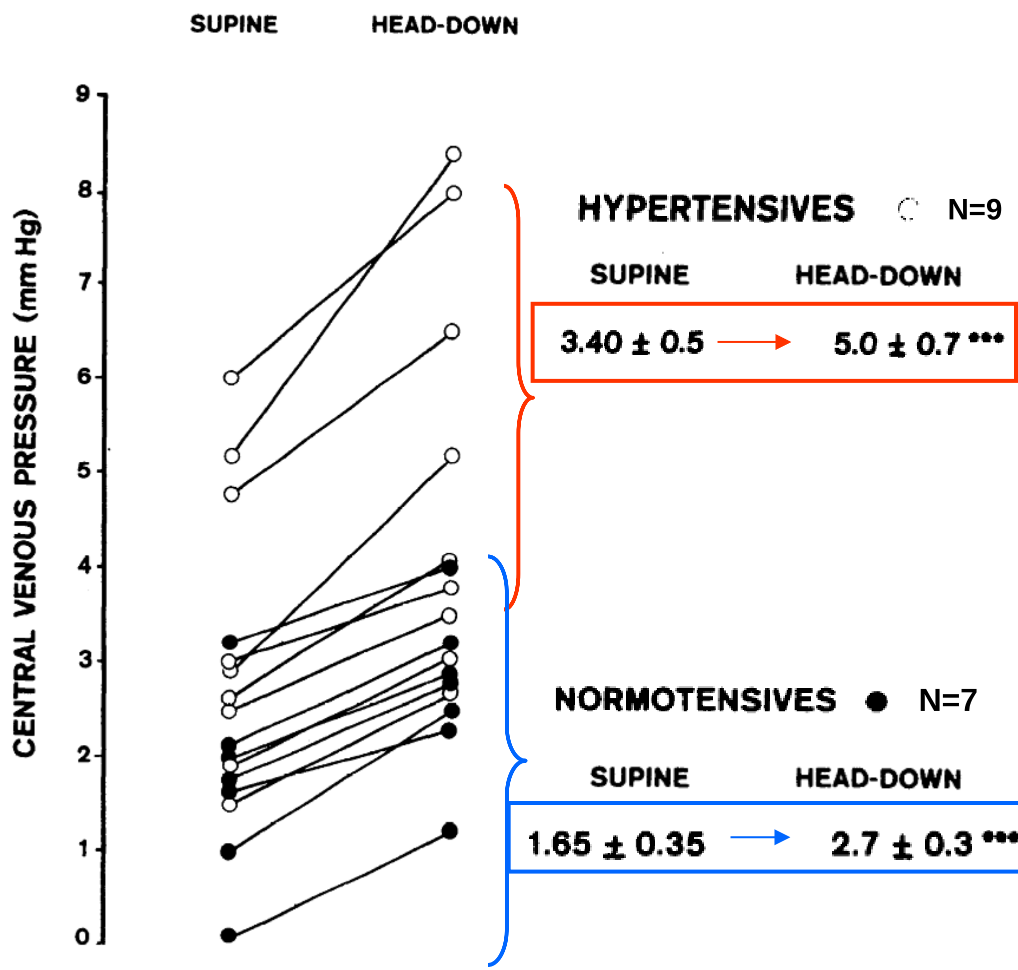




- *Olivari et al. Pulmonary hemodynamics and right ventricular function in hypertension. Circulation 1978;57:1185-1190*
- *Safar et al. Venous system in essential hypertension. Clin Science 1985 Nov;69(5):497-504.*
- *London et al. Hemodynamic effects of head-down tilt in normal subjects and sustained hypertensive patients Am J Physiol Heart Circ Physiol August 1, 1983 245:(2) H194-H202*

# CVP in Normotensives vs Hypertensives During 10° HDT

- A **<u>decrease in venous vascular resistance</u>** among **<u>normotensives,</u>** due to inhibition of vasoconstrictor tone (-SNS +PNS), led to partial relief of the congestion; minimizing the impact of blood volume redistribution.
- **Hypertensives did not demonstrate a decrease in venous tone**
  - The absence of this buffering effect of the veins in hypertensives may be contributing to the higher CVP and CO.





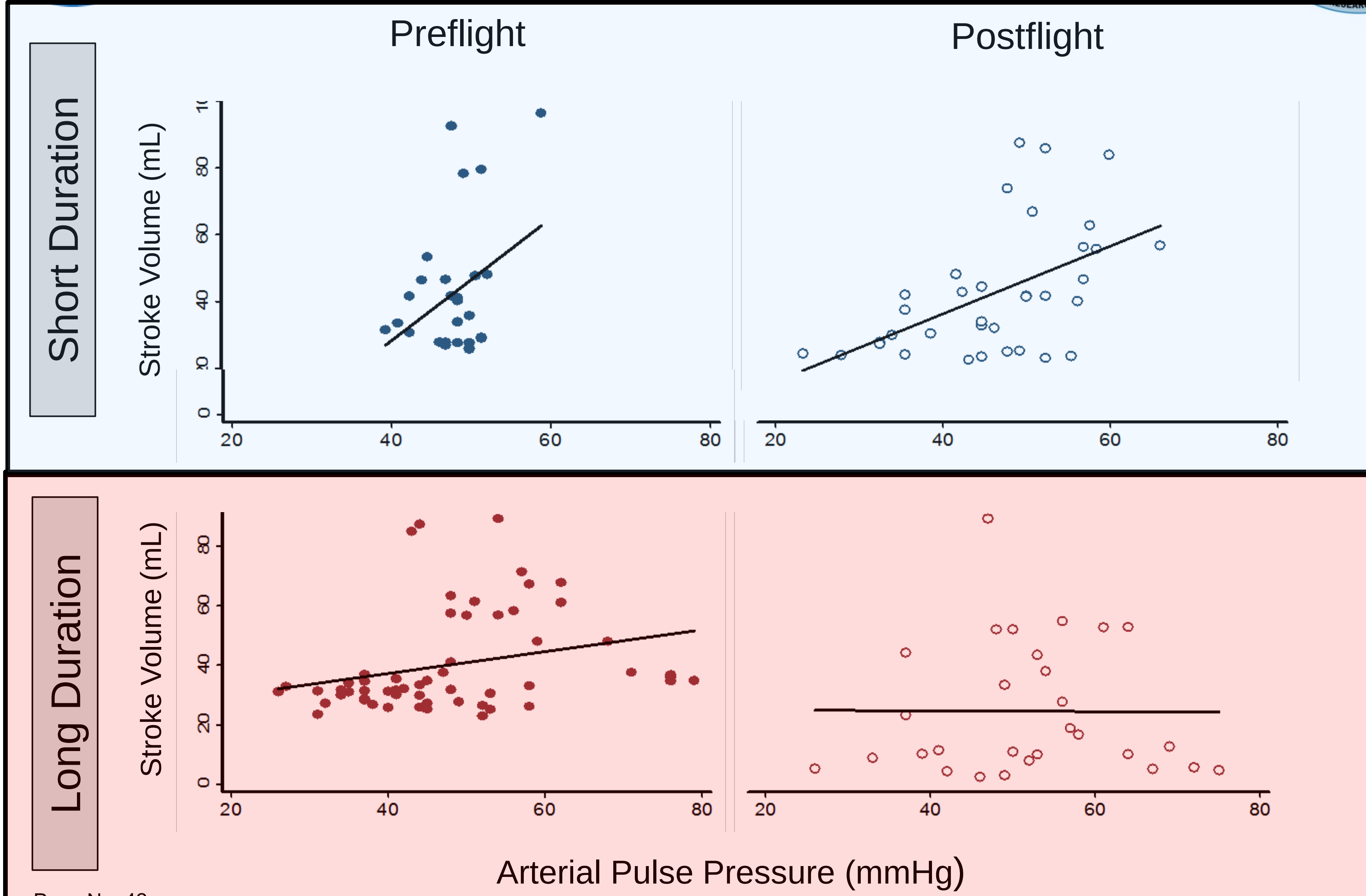

*London et al. 1983. Hemodynamic effects of head-down tilt in normal subjects and sustained hypertensive patients. Am J Physiol.*

# VIIP CPG Class & Blood Pressure

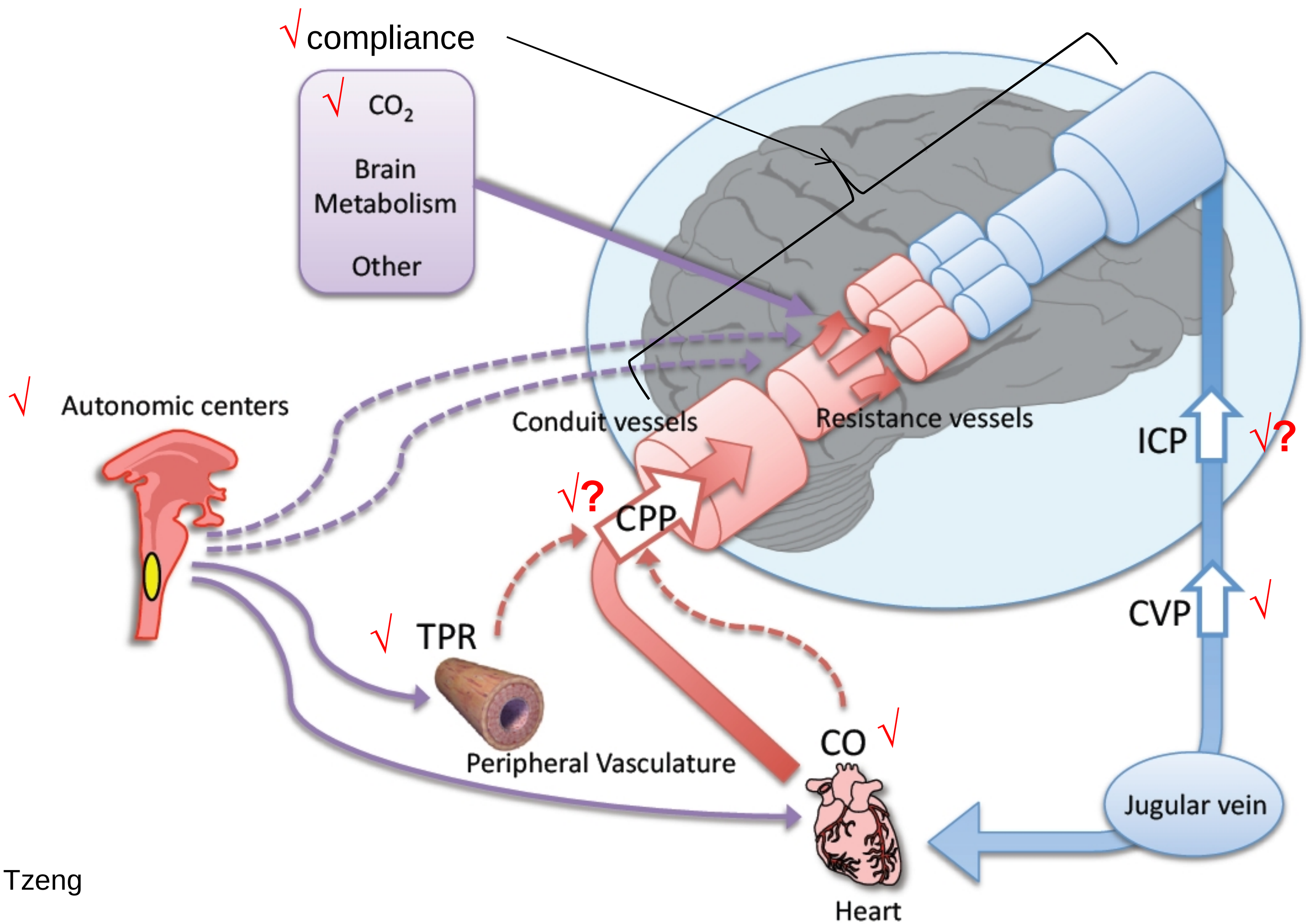
| CPG Classification | N | Mean Systolic BP | Mean Diastolic BP |
|---|---|---|---|
| 3-4 | 5 | 130.1* $P<0.001$ | 82.3* $P<0.05$ |
| 1-2 | 10 | 117.3 | 76.8 |
| 0 | 5 | 118.1 | 76.7 |

**Resting blood pressure averaged over 3-4 annual exams, preflight ISS**

# Vascular Compliance in Astronauts following Short & Long Duration Missions- Estimated by Pulse Pressure and Stroke Volume During Tilt Testing.

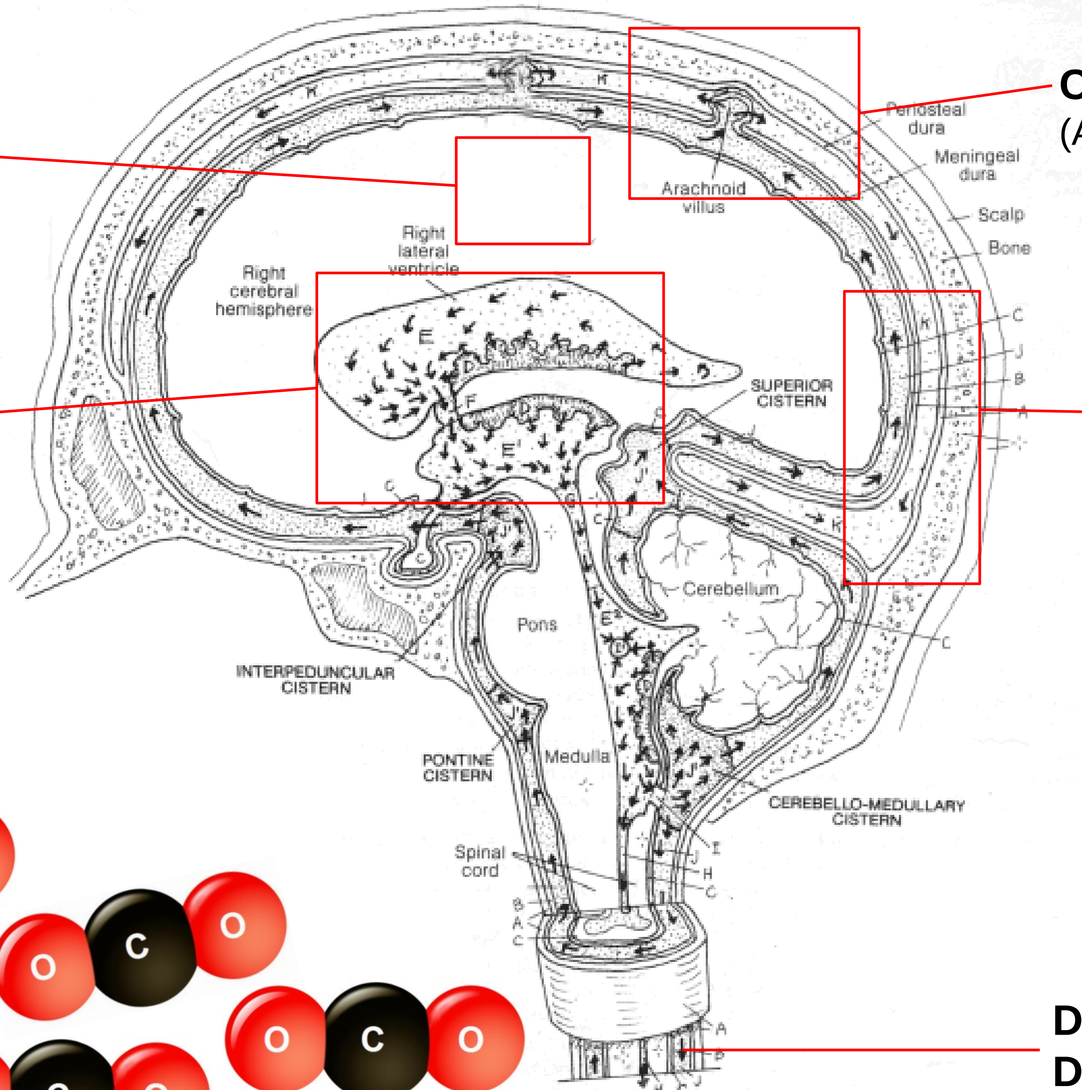


# Cardiovascular Impacts to Cerebral Autoregulation




S. Tzeng

# Key Brain Areas Affected by Fluid Shift



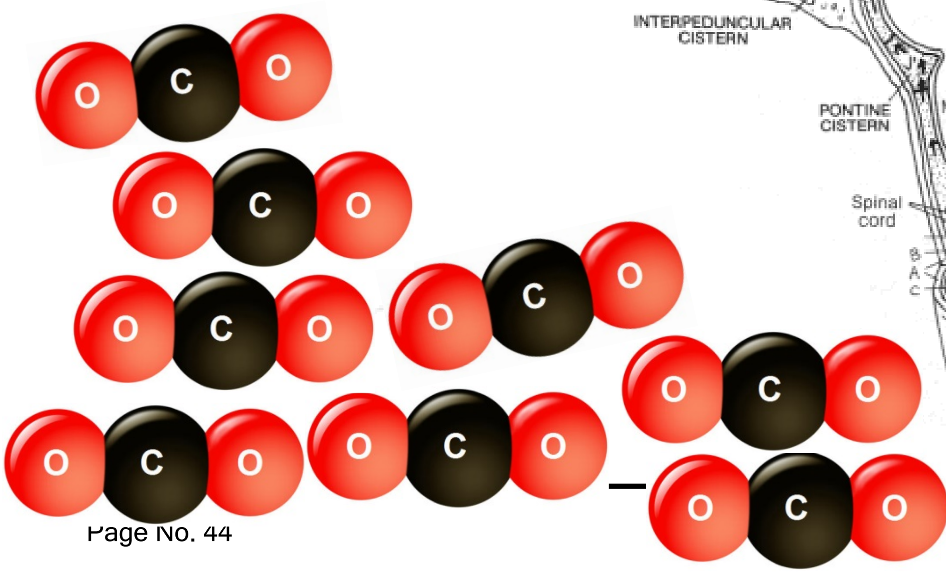

**Interstitial fluid**

**CSF Resorbtion**
(AG-Venous)

**CSF Production**

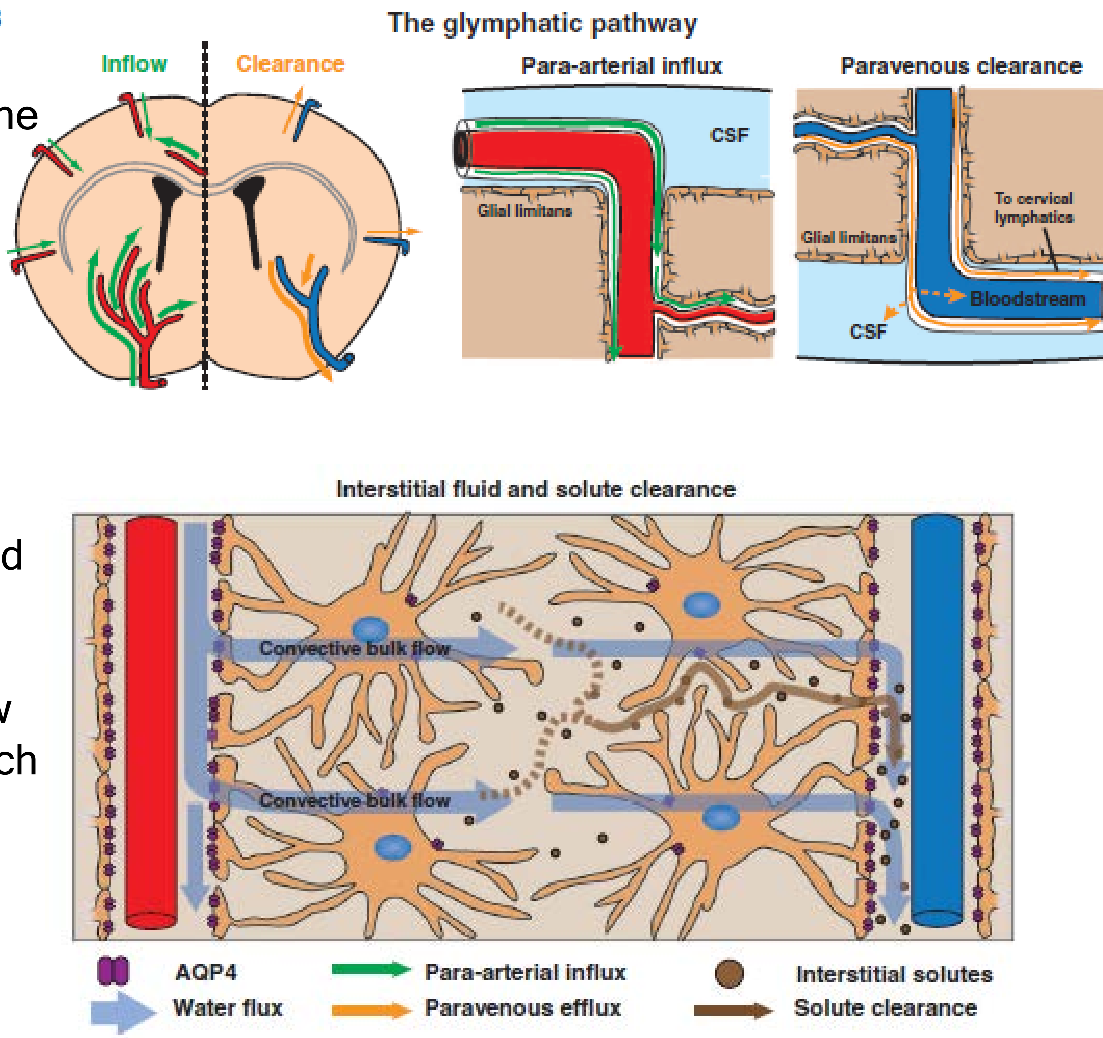
**Venous Congestion**

**Decreased CSF Displacement (Compliance Effect)**



# The Glymphatic Pathway: A Paravascular Pathway Facilitating CSF Flow through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid b

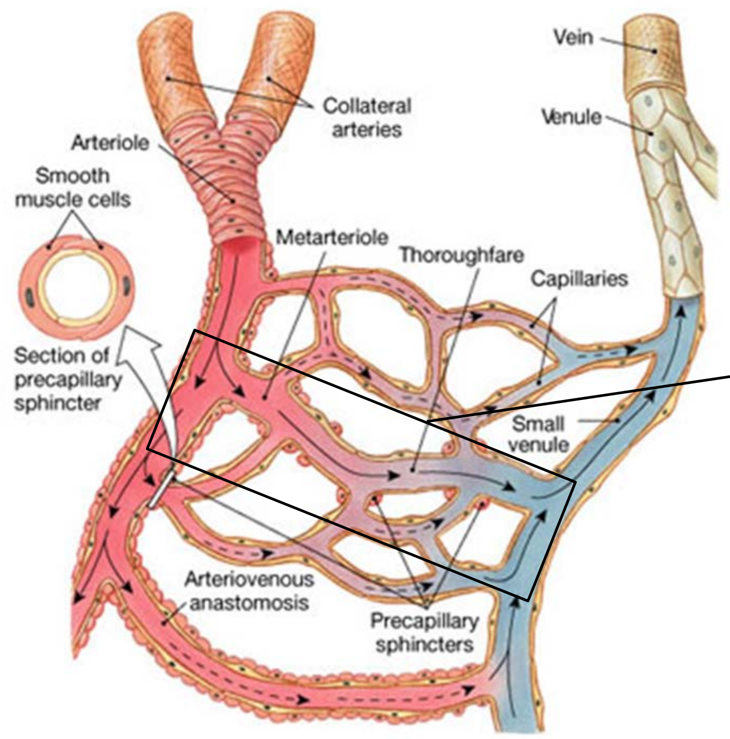
- CSF enters the brain along para-arterial routes, ISF is cleared from the brain along paravenous routes.
- Convective bulk ISF flow between these influx and clearance routes is facilitated by AQP4-dependent astroglial water flux and drives the clearance of interstitial solutes and fluid from the brain parenchyma.
- Solutes and fluid may be 1. dispersed into the subarachnoid CSF, 2. enter the bloodstream across the postcapillary vasculature, or 3. follow the walls of the draining veins to reach the cervical lymphatics.

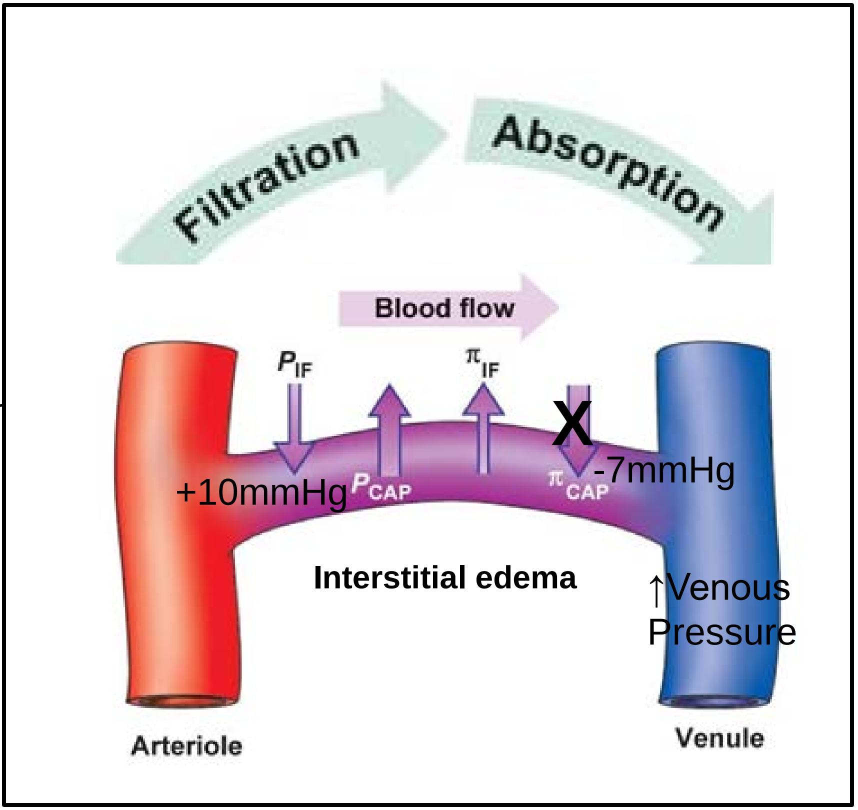




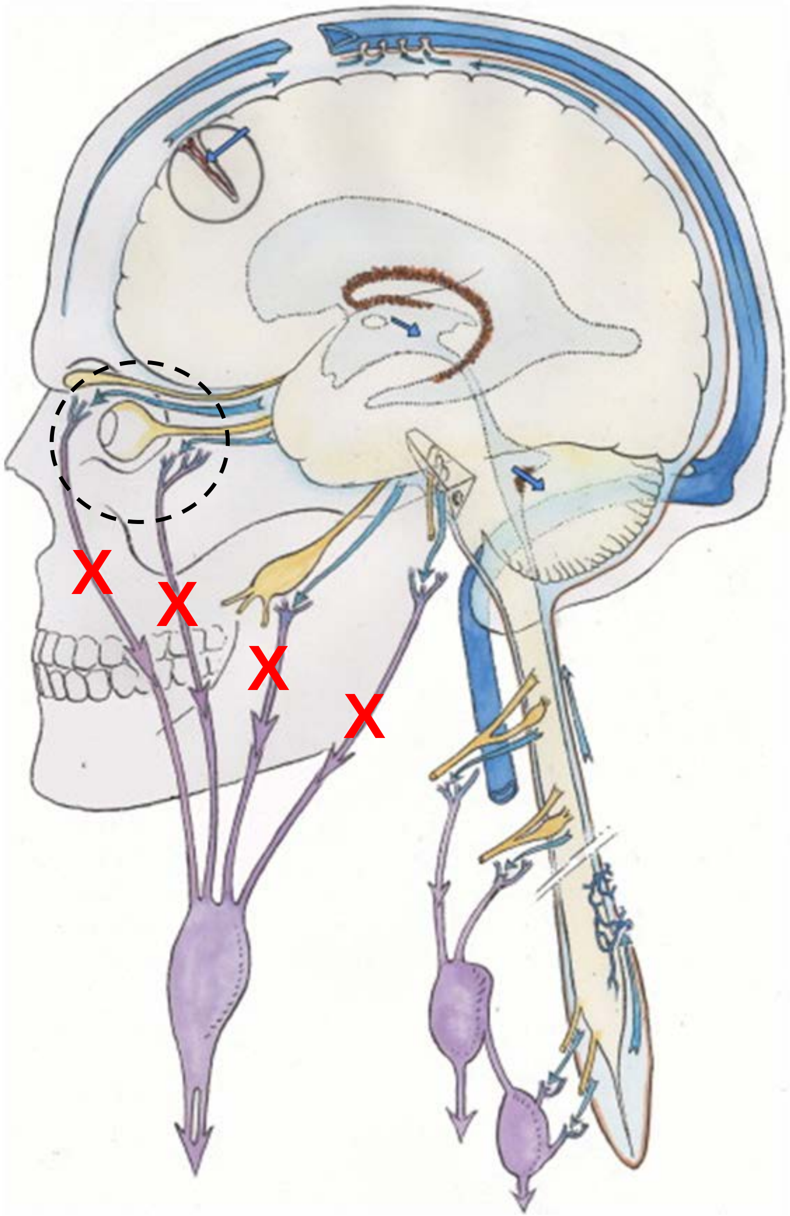

Iliff et al. *Science*. 2012

# Venous Congestion May Cause Increased Transcapillary Pressure & Decreased Absorbtion

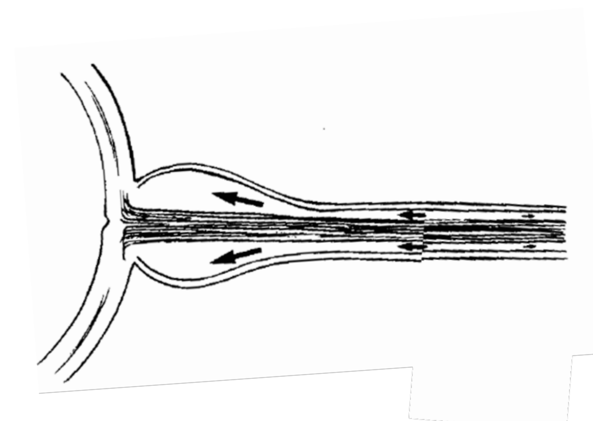


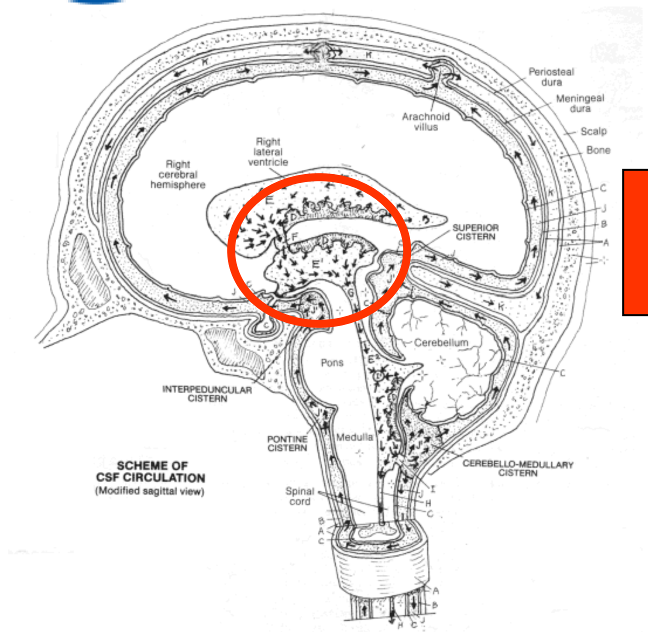
# Venous Congestion & Interstitial Edema May Inhibit Lymphatic CSF Drainage

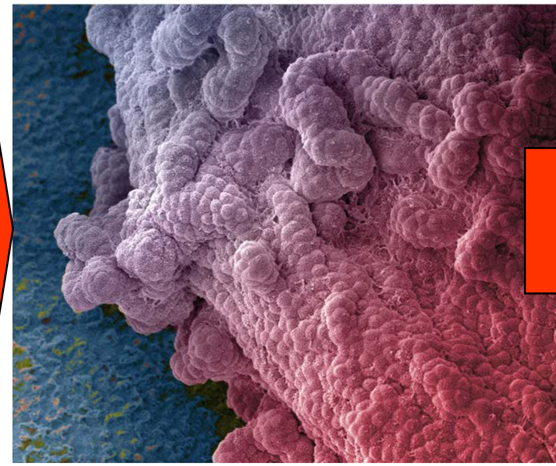


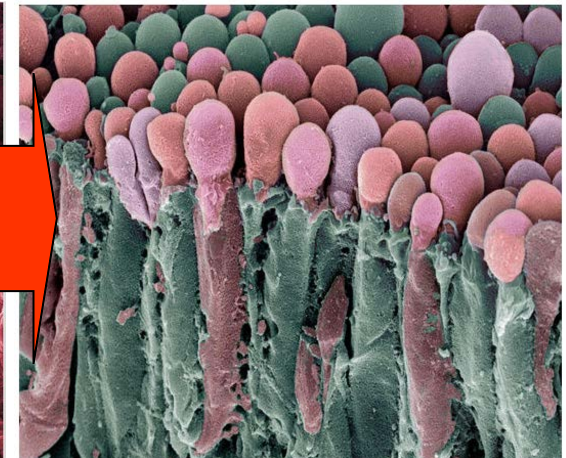
40% of CSF drained via the cranial nerve lymphatics



# CSF Production: Choroid Plexus

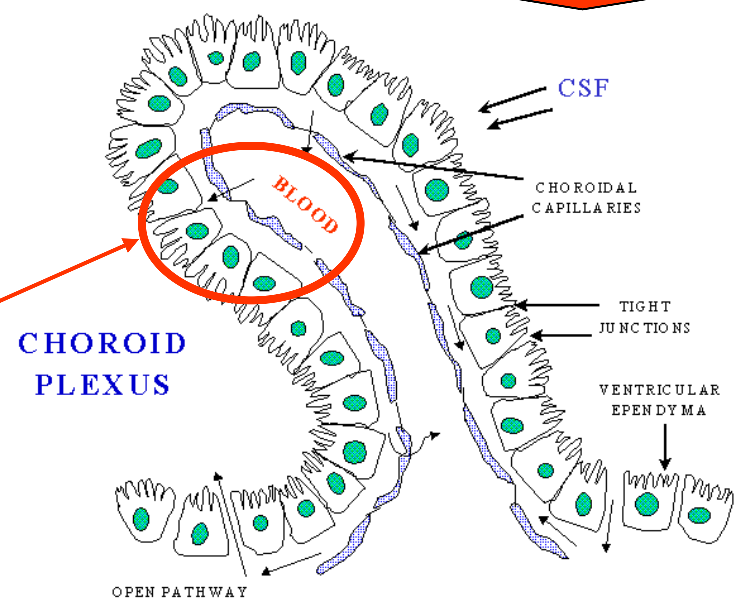




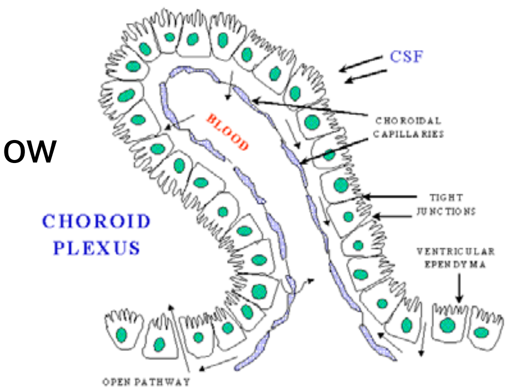
Choroid plexus in lateral, third & fourth ventricle produces 70-90% of CSF in brain

Increased filtration?



# Hypertension Increases CSF Formation

- Ruchoux et al. 1992 found ultrastructural changes in the choroid plexus of SHR reflecting increased secretory activity
- Chronic hypertension increases choroidal blood flow
- CSF production is directly correlated to choroid plexus blood flow




- In a study of hypertension on CSF dynamics, Al-Sarraf et al:

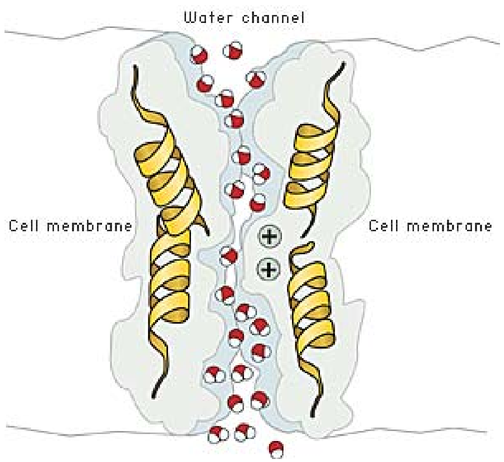
| | JVP (cm $H_2O$) | Choroidal Blood Flow (ml $min^{-1}g^{-1}$) | CSF Secretion (ul $ml^{-1}$) | CSF Pressure (cm $H_2O$) |
|---|---|---|---|---|
| WKY | 2.4 +1.1 | 2.41 +/- 0.08 | 2.61+/- 0.21 | 8.4 +/-2.3 |
| SHR | 7.6 + 2.8* | 2.82 +/- 0.21** | 3.38 +/-0.11** | 16.8 +/- 5.1* |



*Al-Sarraf et al. Effect of hypertension on the integrity of the blood brain barrier and blood CSF barriers, cerebral blood flow and CSF secretion in the rat. Brain Research 2003; 975:179-188.*

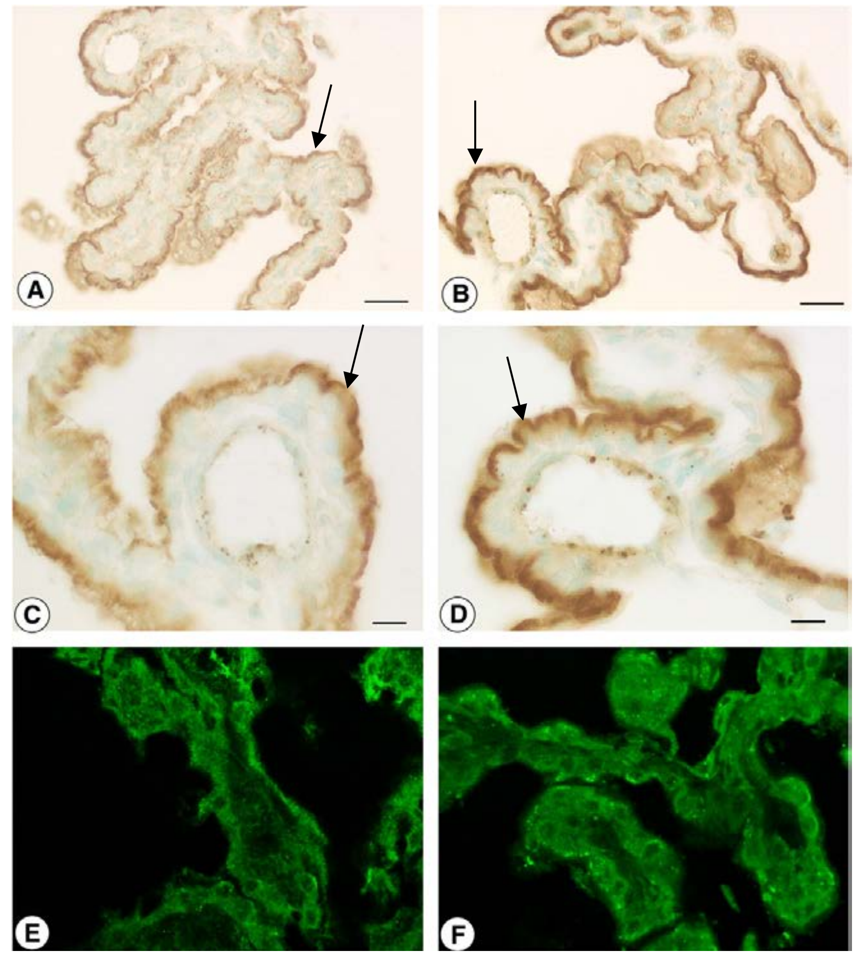
# Increased AQP1 Expression in the Choroid Plexus of Hypertensive Animals

Aquaporin 1-Membrane Protein




- Tomassoni et al. Brain Research 2010
  - Stronger staining in the choroid plexus apical membrane of 6 month  SHR vs normotensive controls
  - AQP1 expression

**Normotensive** **Hypertensive**



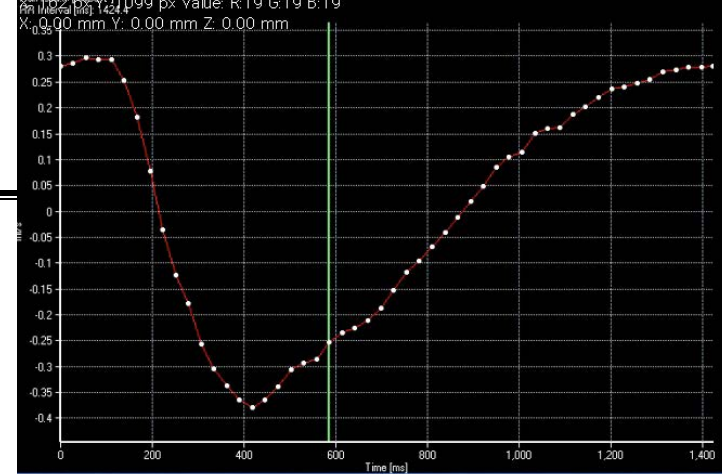

Immunohistochemistry

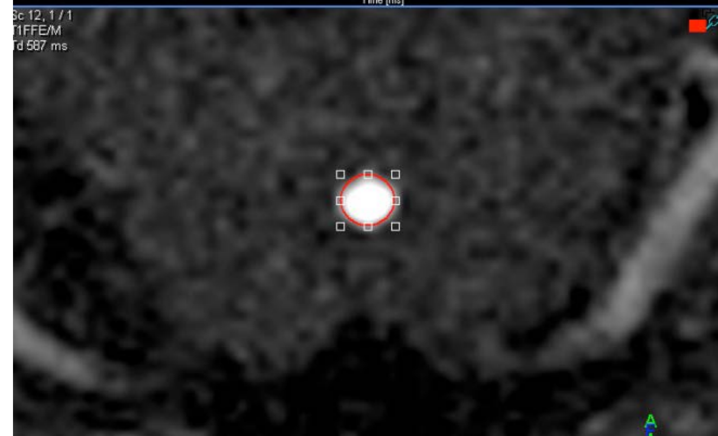


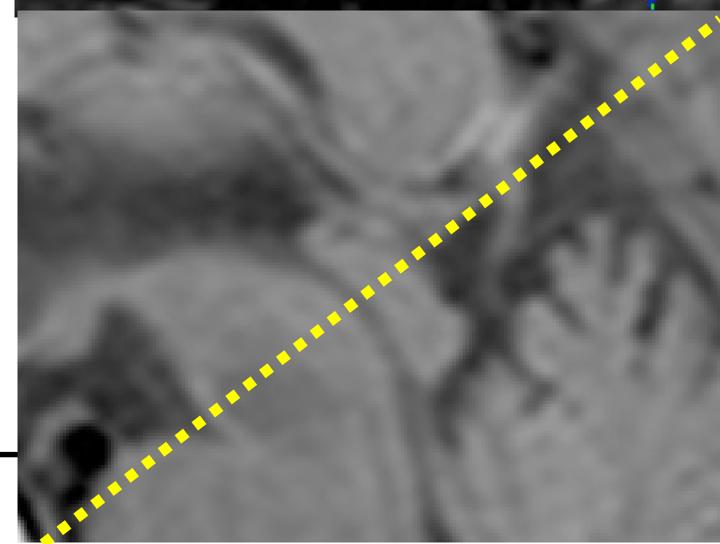
*Tomassoni et al. Expression of aquaporins 1 and 4 in the brain of spontaneously hypertensive rats. Brain Research 2010; 1325:155-163.*

# Flow analysis of CSF through the aqueduct

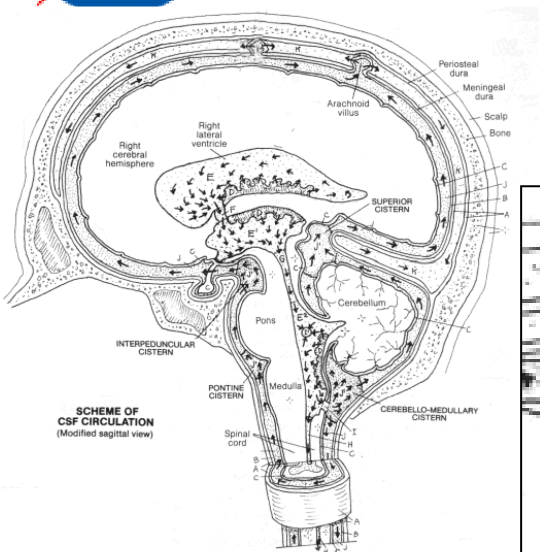
- The flow analysis of CSF through the aqueduct (axial oblique section noted as dashed line --Bottom).
- A CINE phase contrast sequence obtained perpendicular to the mid cerebral aqueduct showing velocity versus time after the QRS wave (graph --- top left) Case #5:
    - R+30: CSF production rate=**305** 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
- 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



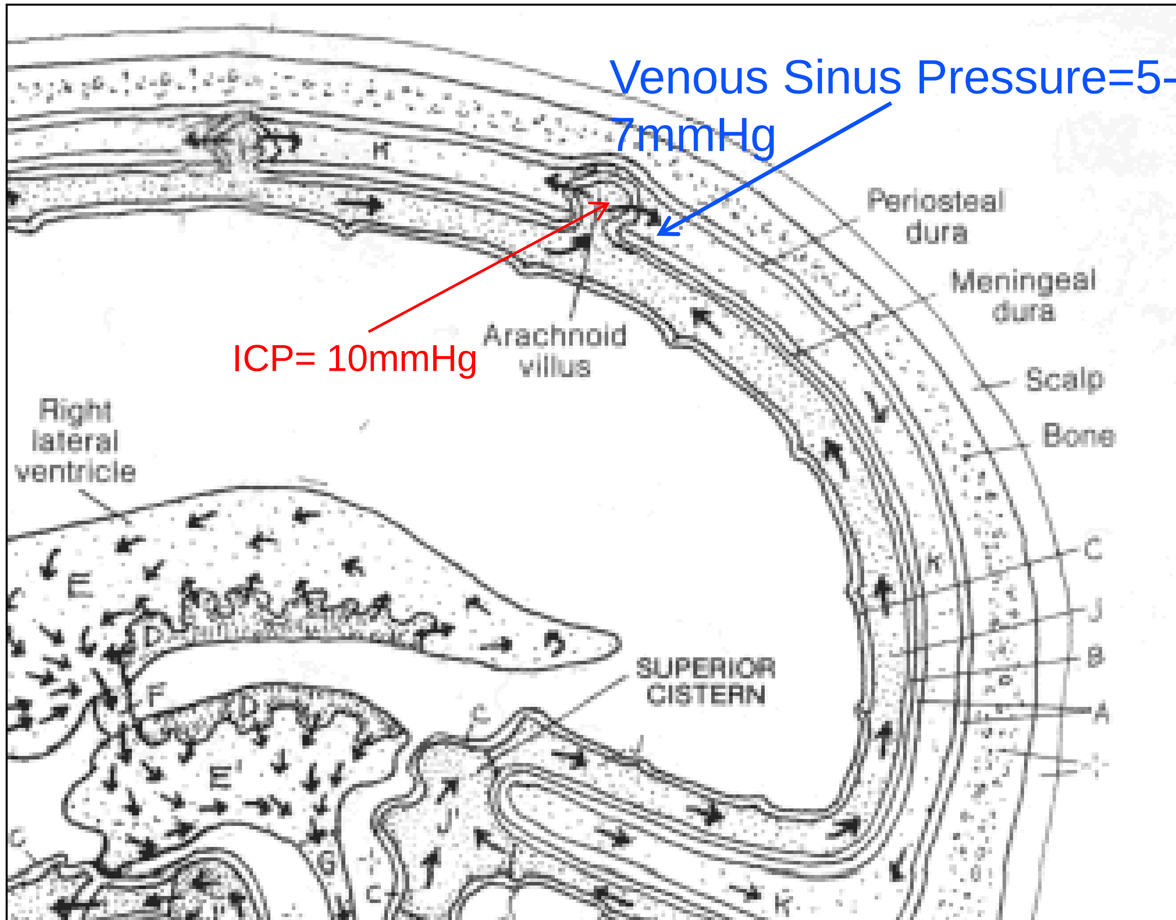





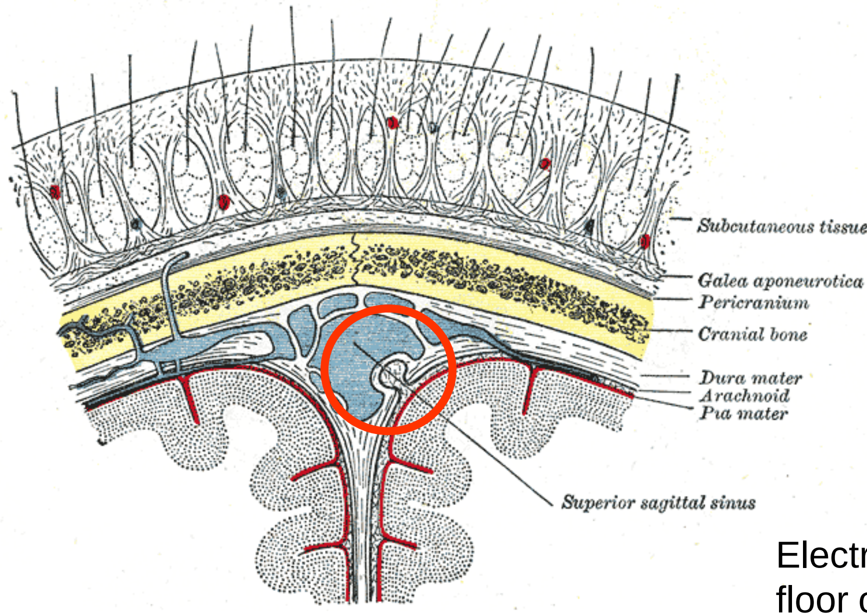
# Normal CSF Diffusion Gradient

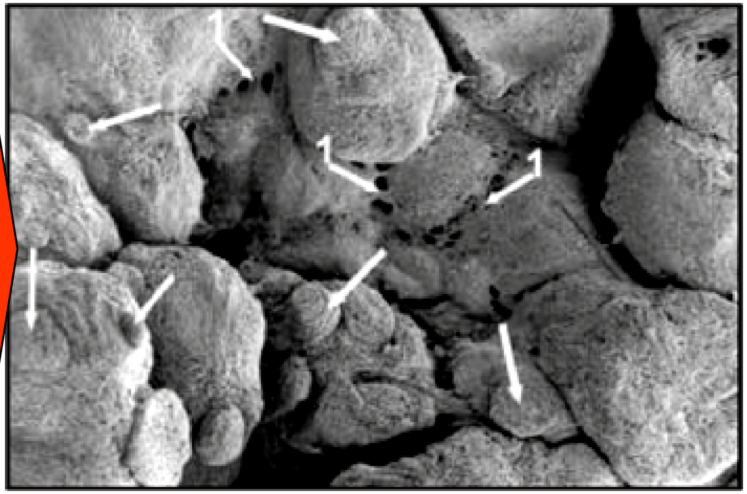



Normal SSVP:CSFP= 0.60
Therefore delta driving pressure only~3-5mmHg



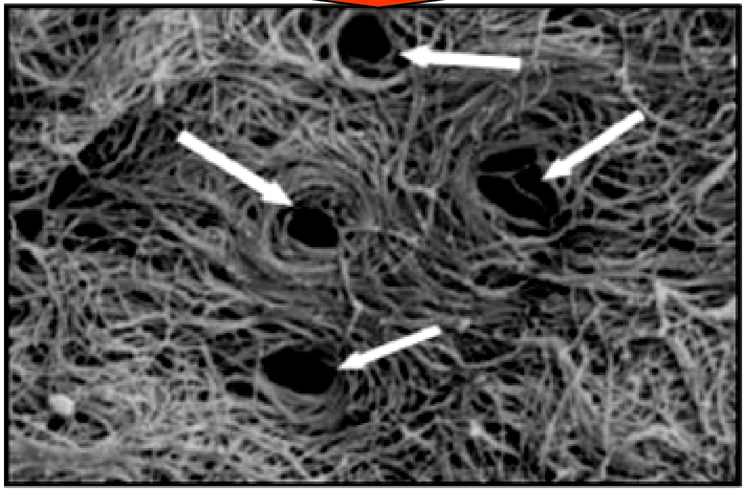
# CSF Resorption: Arachnoid Granulations



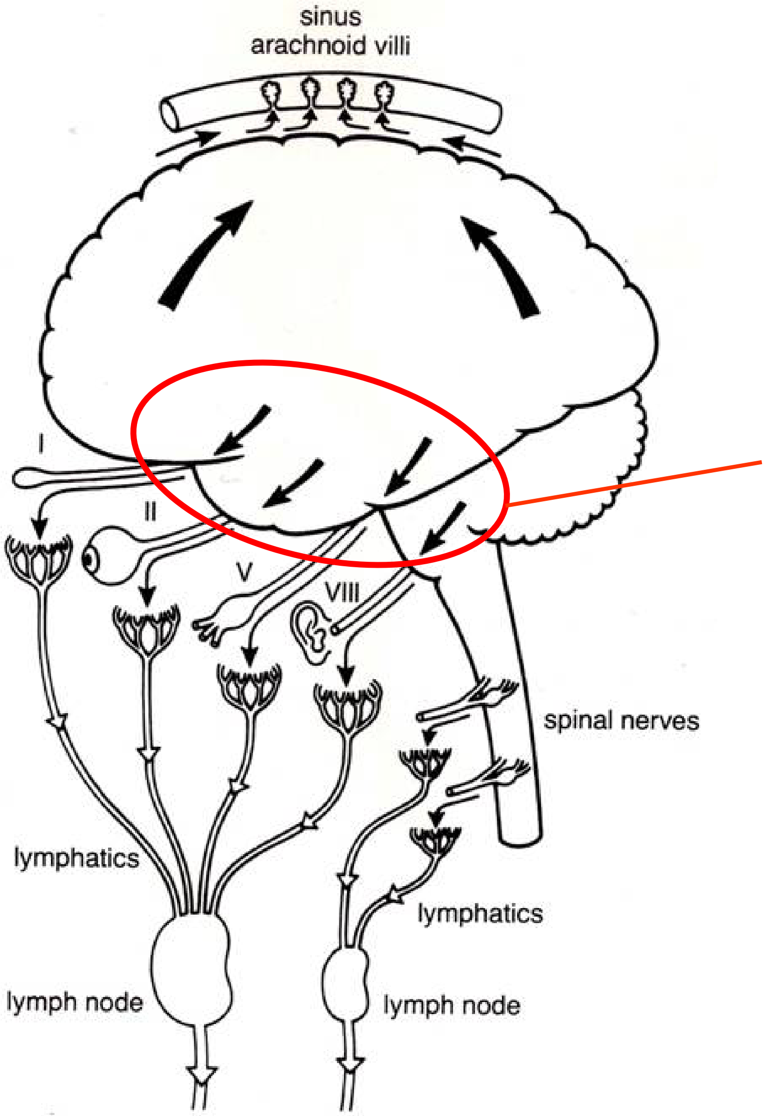
Electron Micrograph of clustered arachnoid granulations from the floor of the superior sagital sinus. Arrows pointing to lobules

***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

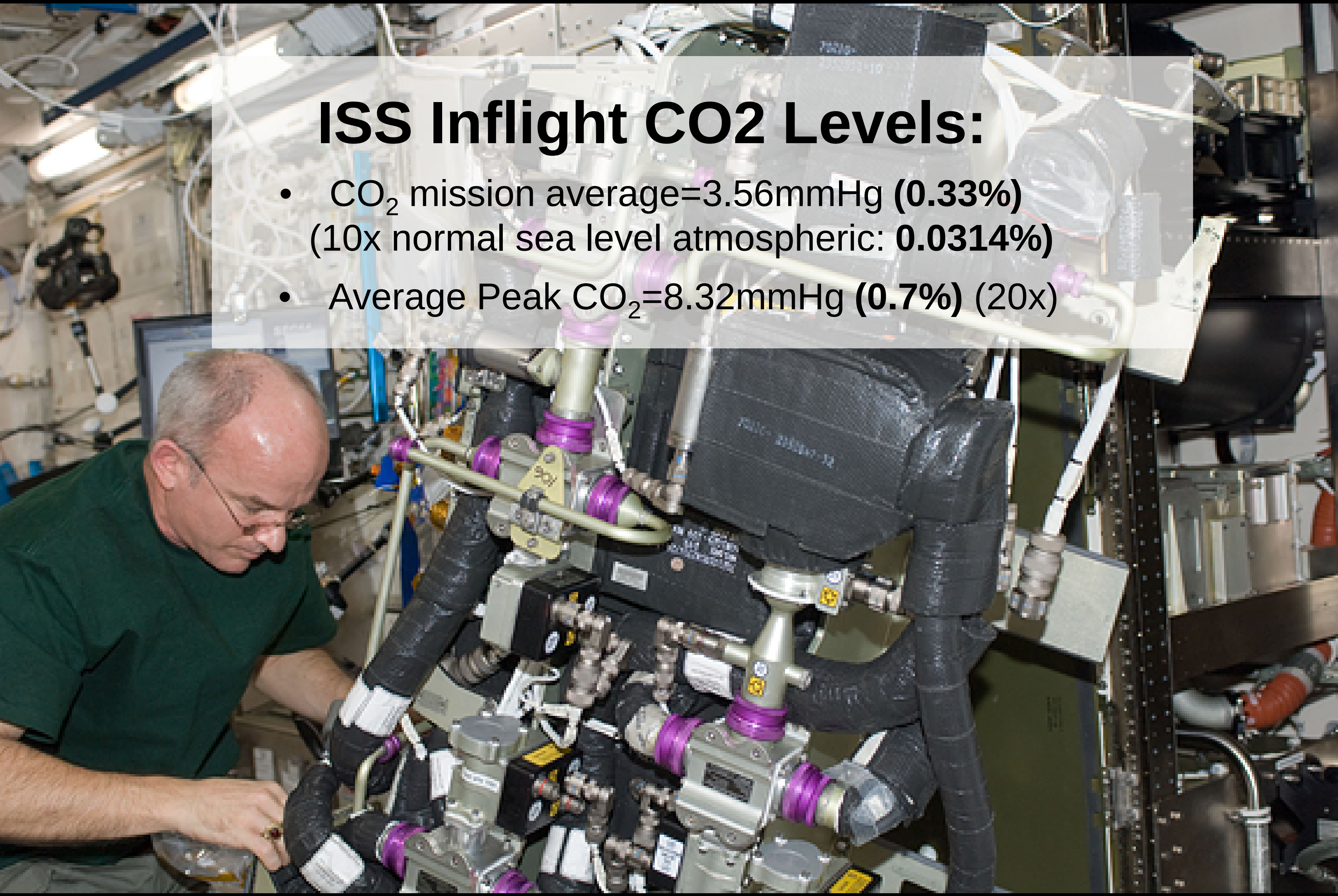
# Blocked Lymphatic Drainage of CSF




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

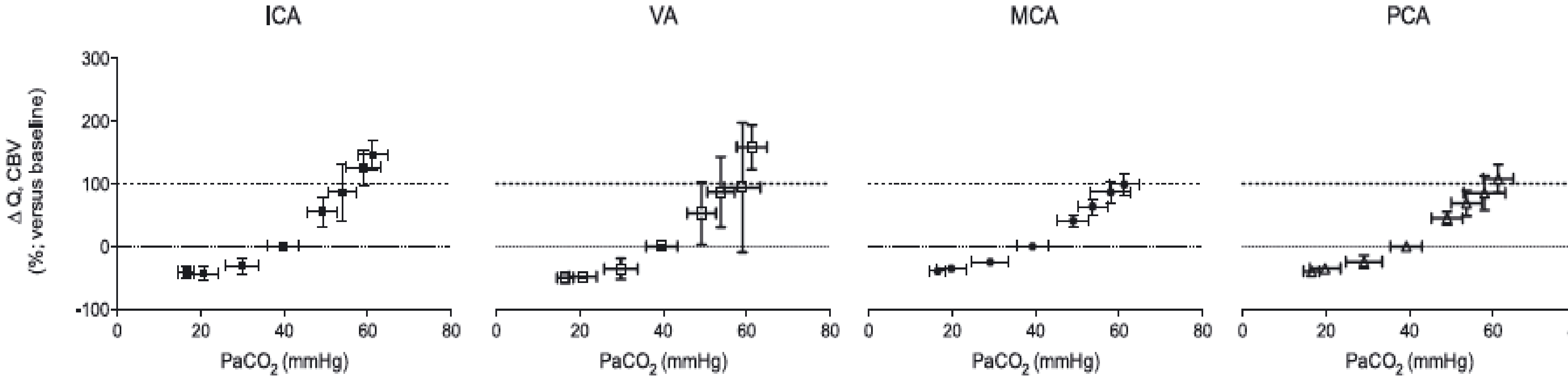
# ISS Inflight CO2 Levels:

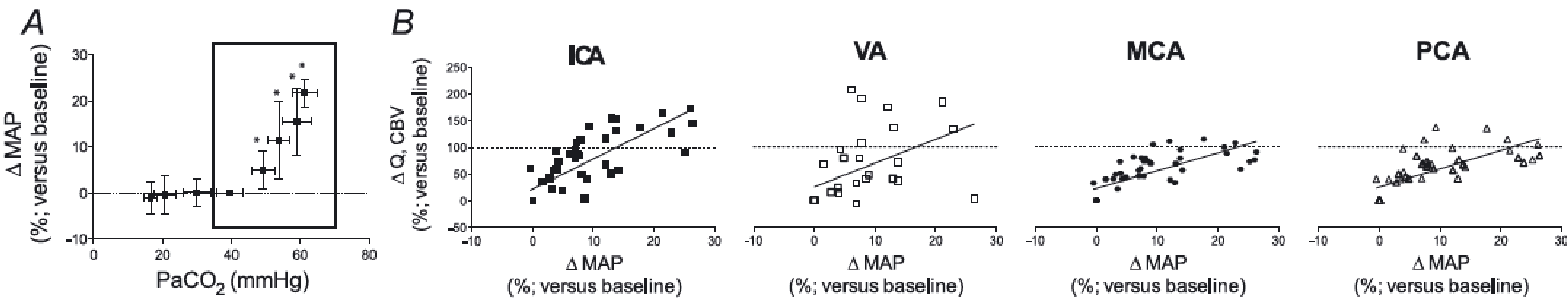
- $CO_2$ mission average=3.56mmHg **(0.33%)** (10x normal sea level atmospheric: **0.0314%)**
- Average Peak $CO_2$=8.32mmHg **(0.7%)** (20x)



*ISS Commander Jeff Williams working on CDRA unit*

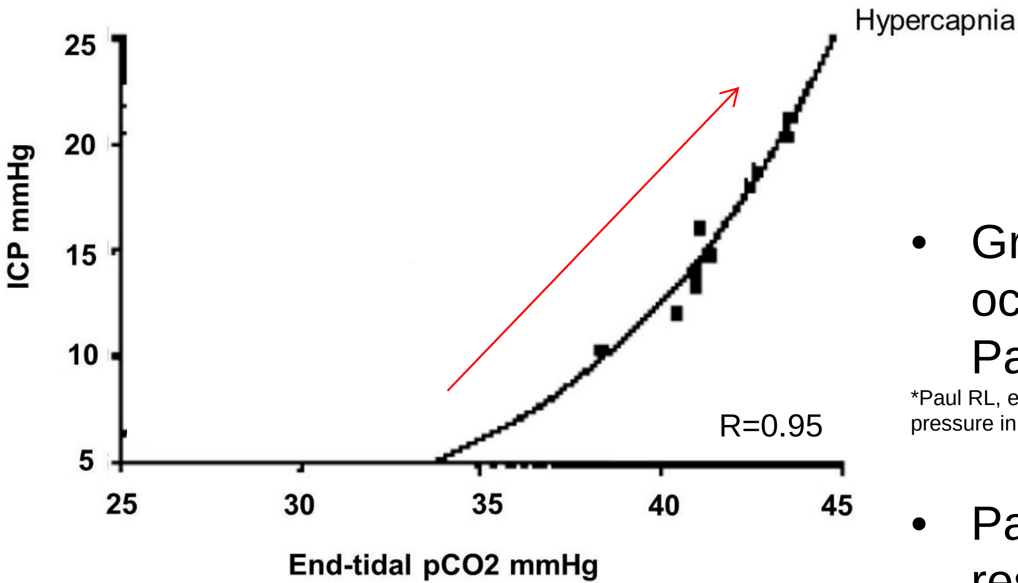
# Increasing PaCO2 Increases Cerebral Blood Flow, & Mean Arterial Pressure




**CPP=MAP-ICP**

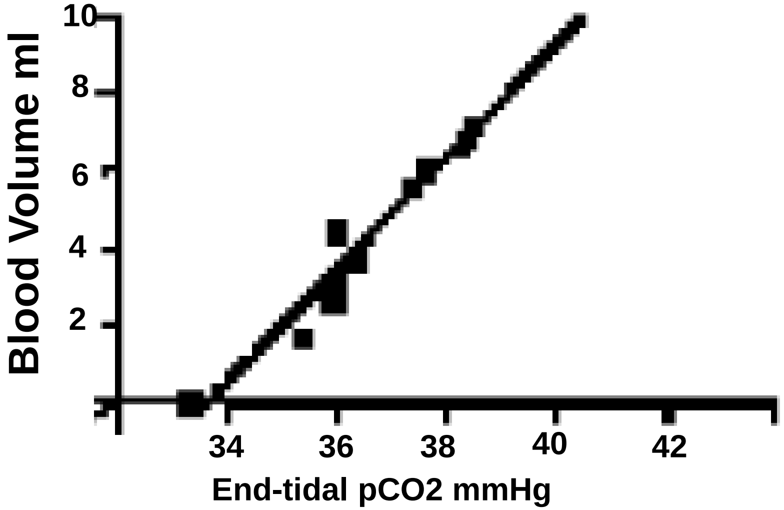
# Intracranial Blood Volume Increases in Direct Proportion to Increasing PaCO2




- Greatest rate of change in ICP occurs between **30-50mmHg*** PaCO2-*steepest portion of curve*

*Paul RL, et al: Intracranial pressure responses to alterations in arterial carbon dioxide pressure in patients with head injuries. **J Neurosurg 36:**714–720, 1972

- PaCO2 Increased 7.0mmHg, resulted in more than doubling of ICP from 10→21mmHg





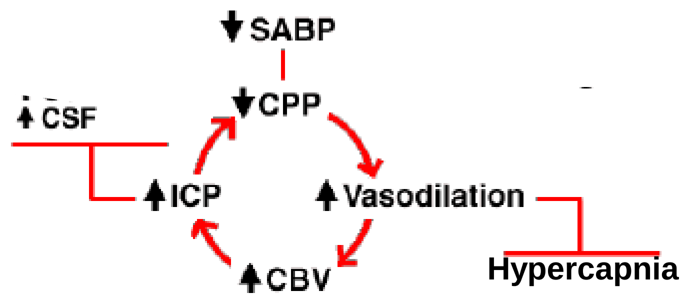

**Yoshihara et al.** Cerebrovascular carbon dioxide reactivity assessed by intracranial pressure dynamics in severely head injured patients. **J Neurosurg 82**:386–393, 1995

# Potential Impact of Acutely Elevated pCO2 on ICP

ISS Lowest average CO2=**3.5 mmHg**

- *High Compliance Crewmember:*
  - 1mmHg PaCO2/ 1.4mmHg ICP
  - **4.9mmHg ↑ ICP, 2º to CO2**

- *Low Compliance Crewmember:*
  - 1mmHg PaCO2/ 2.6mmHg ICP
  - **9.1mmHg ↑ ICP, 2º to CO2**

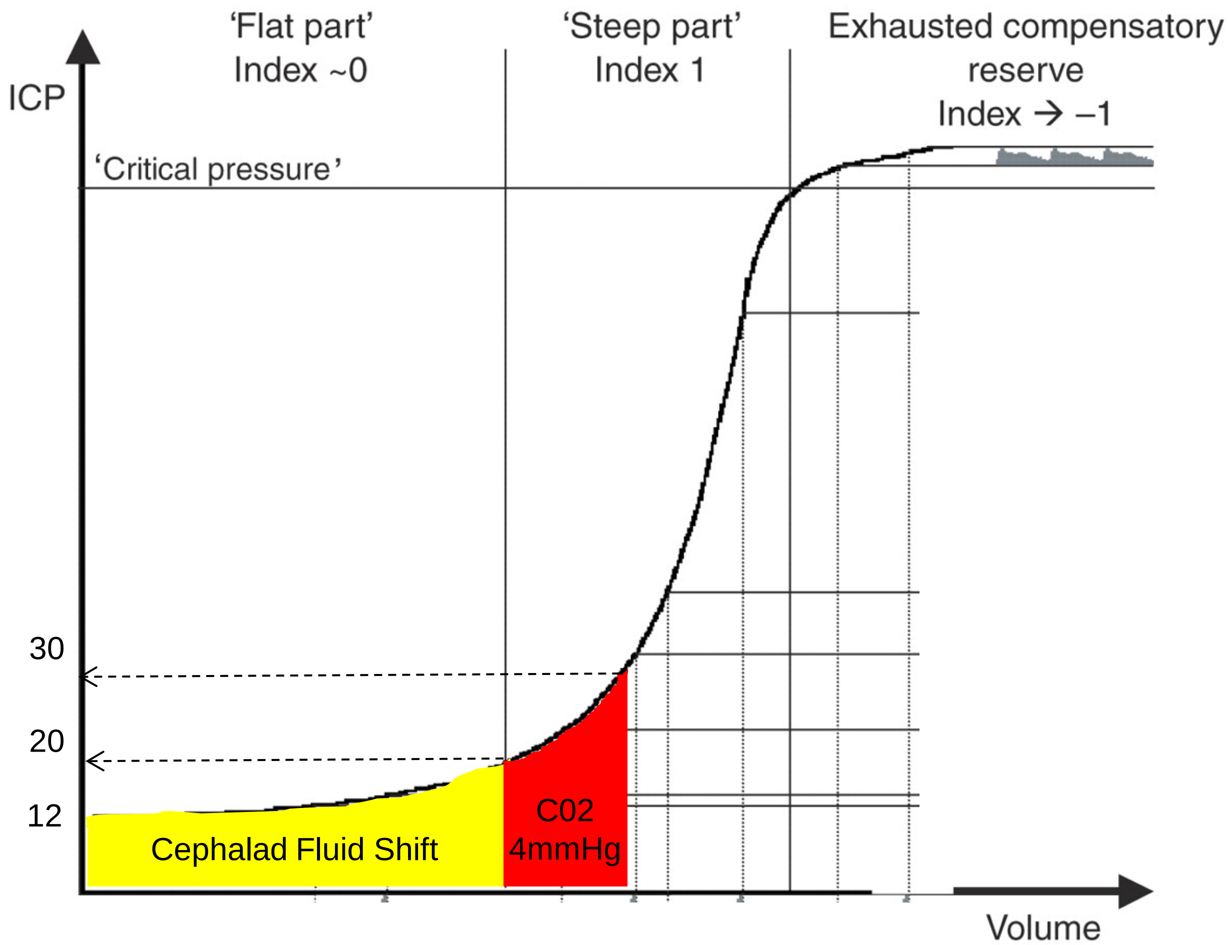




**Yoshihara et al.** Cerebrovascular carbon dioxide reactivity assessed by intracranial pressure dynamics in severely head injured patients. **J Neurosurg 82**:386–393, 1995

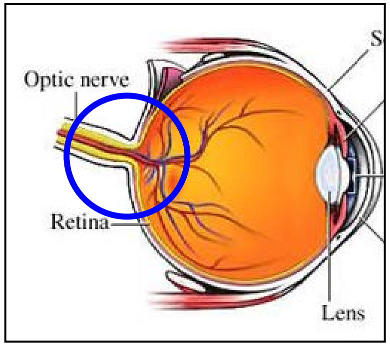
Greenberg JH et al: *Local cerebral blood volume response to carbon dioxide in man*. Circ Res 43: 324–331, 1978

# Cephalad fluid Shift Exacerbates CO2 Challenge on ISS

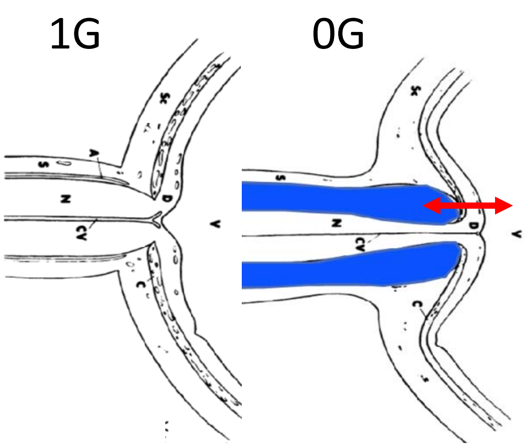


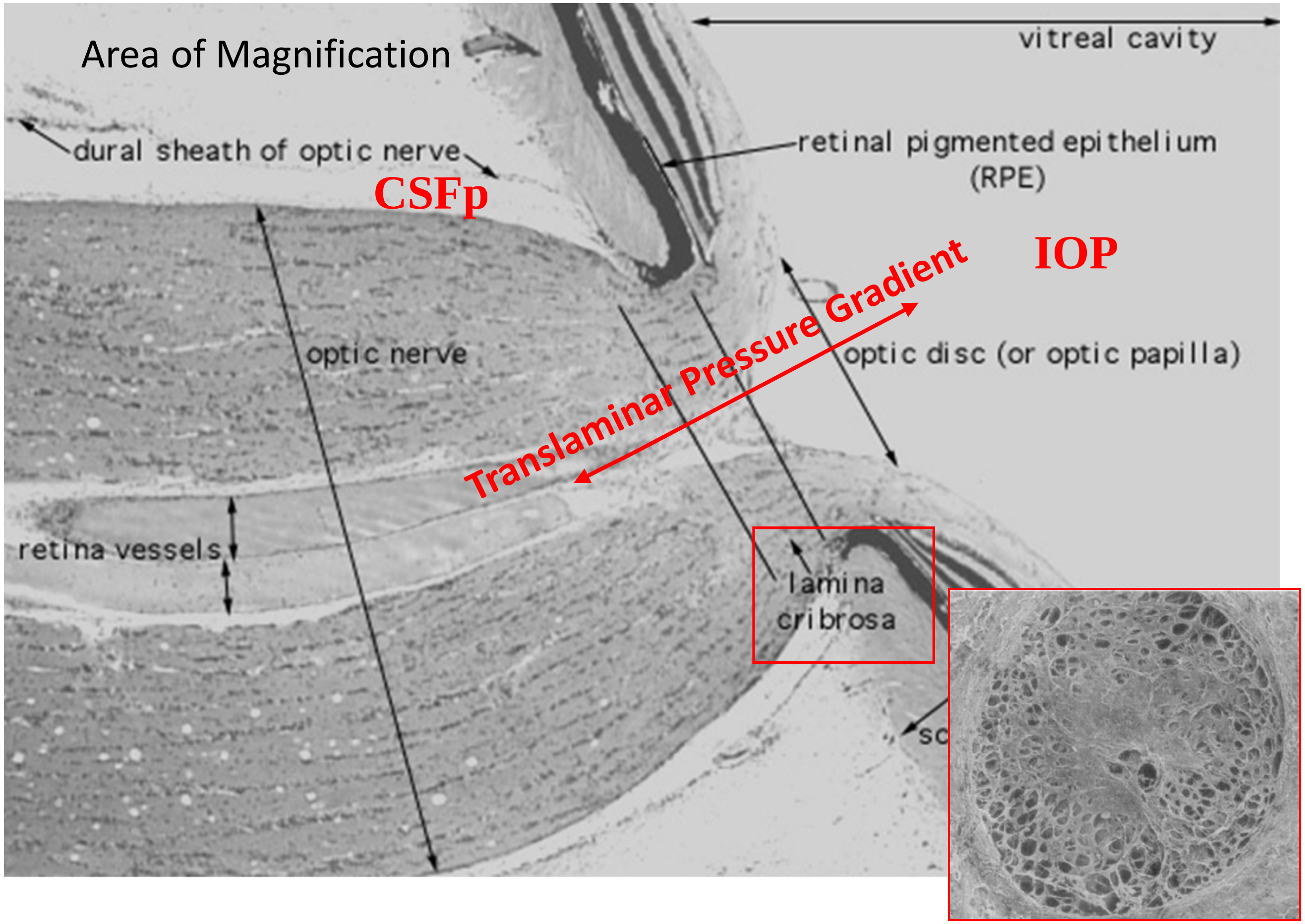
# The Translaminar Pressure Gradient: A Mechanism for Papilledema

Area of Interest:

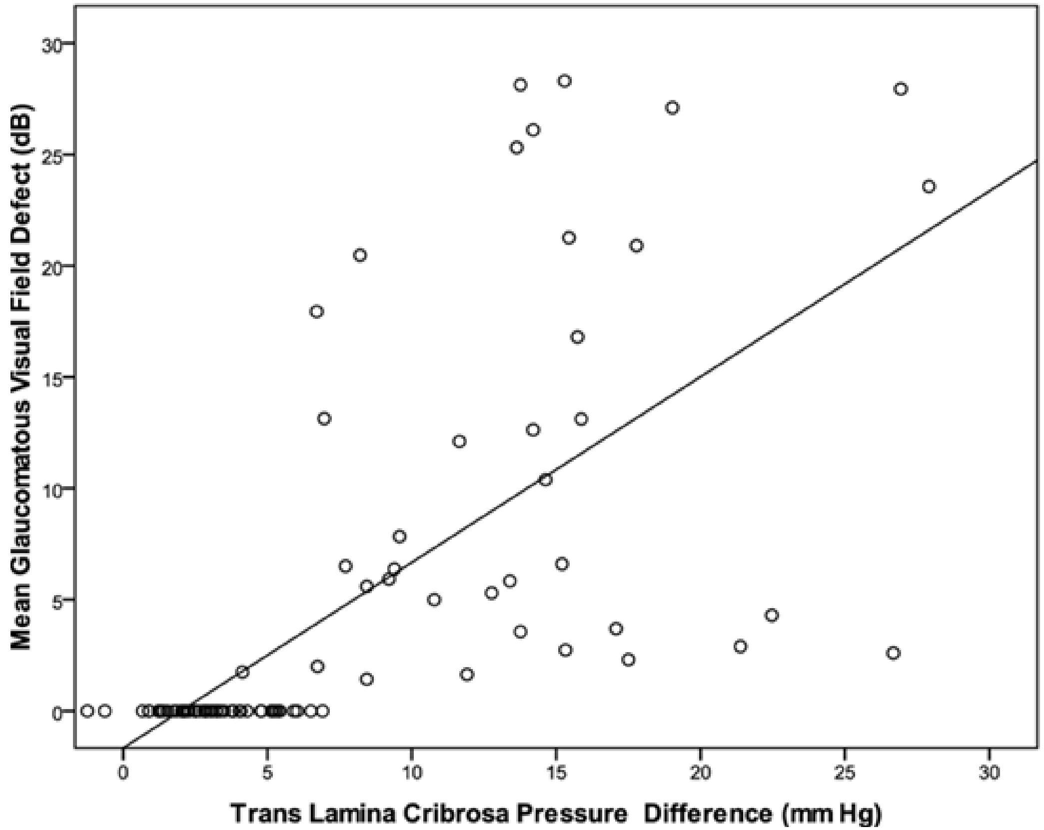



Translaminar Pressure Gradients:



# Translaminar Pressure Difference & Visual Field Defect

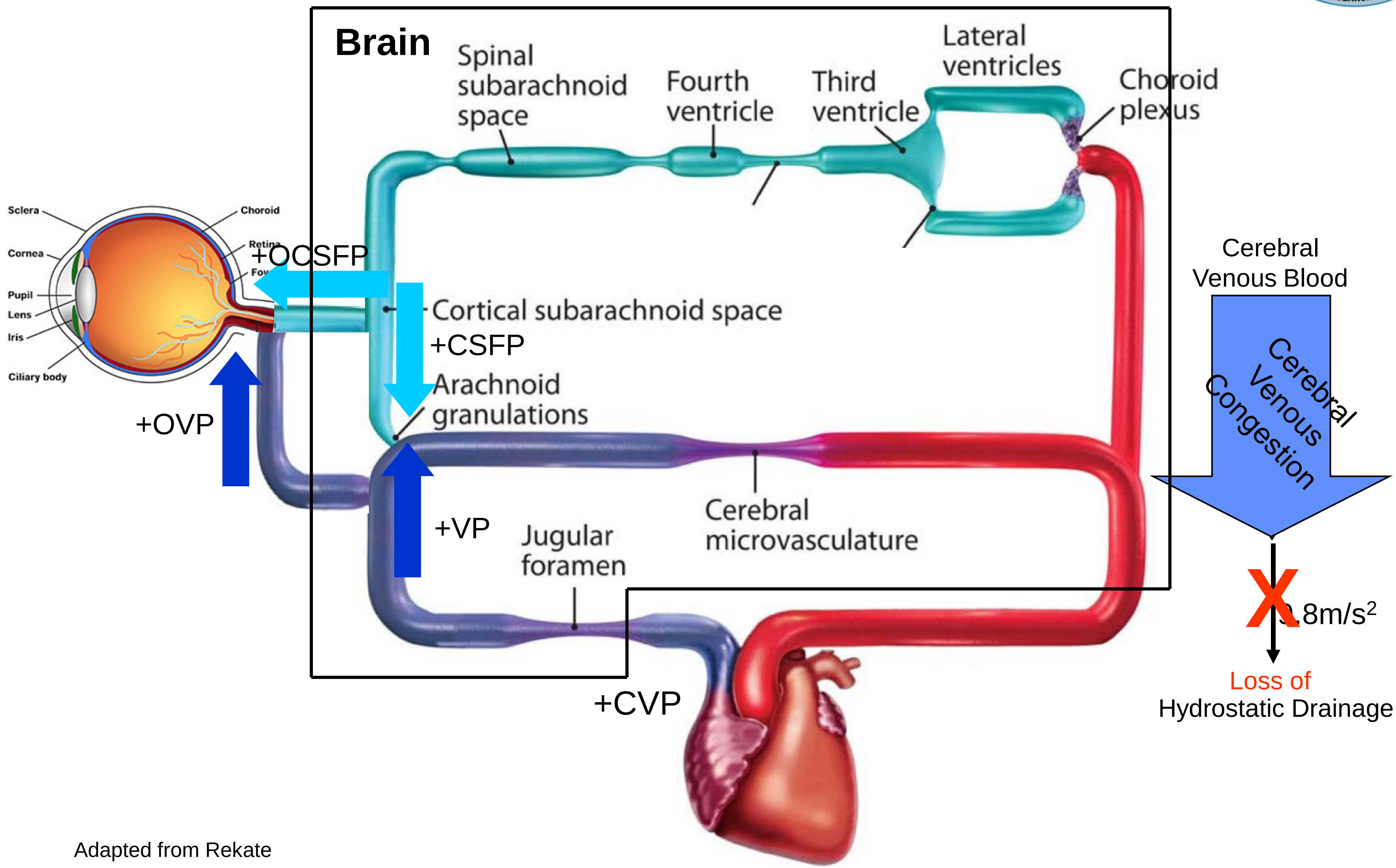



Examples:

| ICP | IOP | TLP | Delta |
|---|---|---|---|
| 10 | 15 | -5 | 5 |
| 25 | 17 | +8 | 13 |
| 35 | 17 | +18 | 23 |

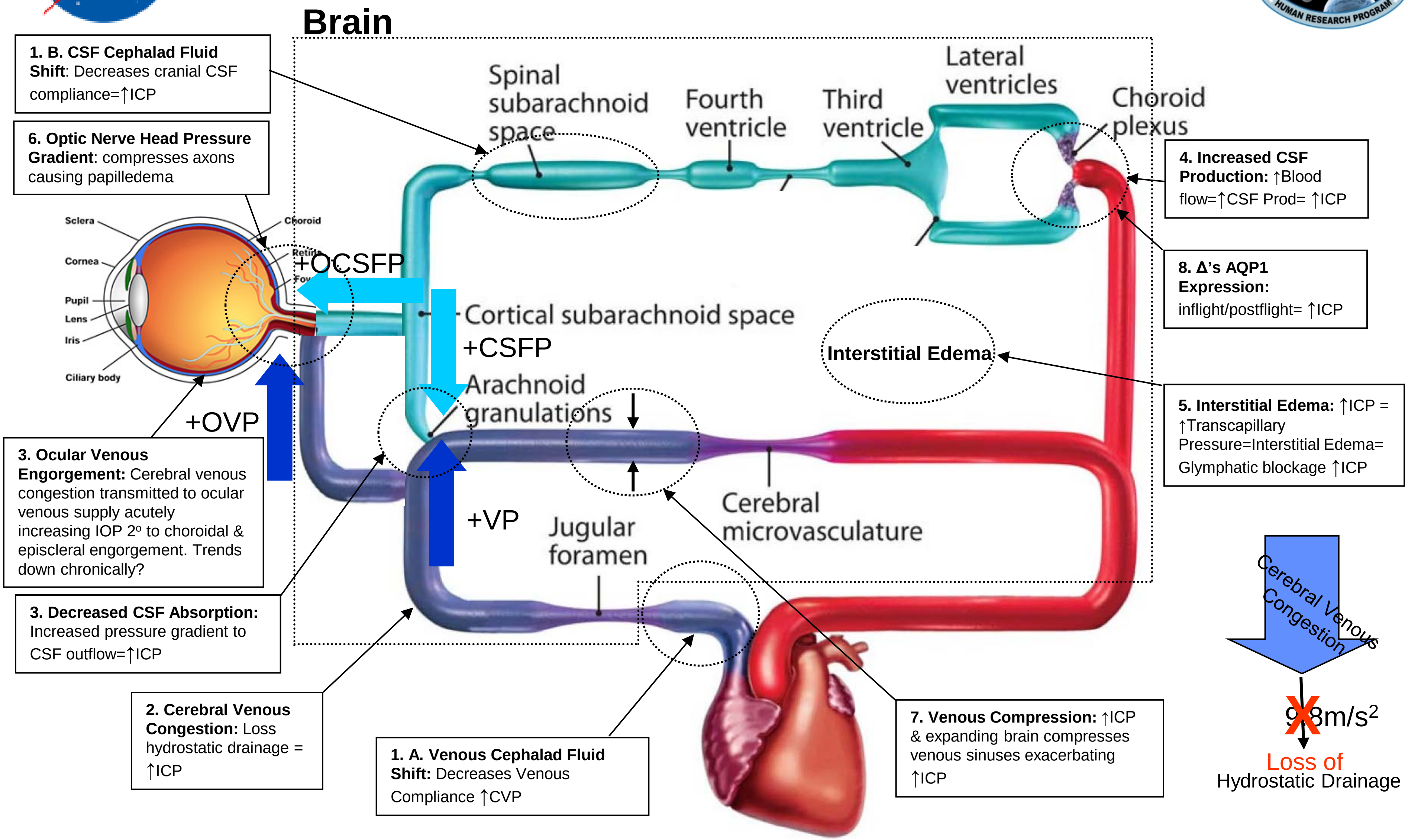
➢ Amount of glaucomatous visual field defect correlated positively with the TLP pressure difference (*P* _ 0.005) r=0.69

# A Working Model: Potential Interaction of the CNS, Vascular, & Ocular System in the VIIP




Adapted from Rekate

# VIIP Pathophysiological Hypotheses: Vascular, CNS & Ocular



# Risk of Spaceflight-Induced Intracranial Hypertension/Vision Alterations

- **Risk Statement**
- 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, and if left untreated, could lead to deleterious health effects.

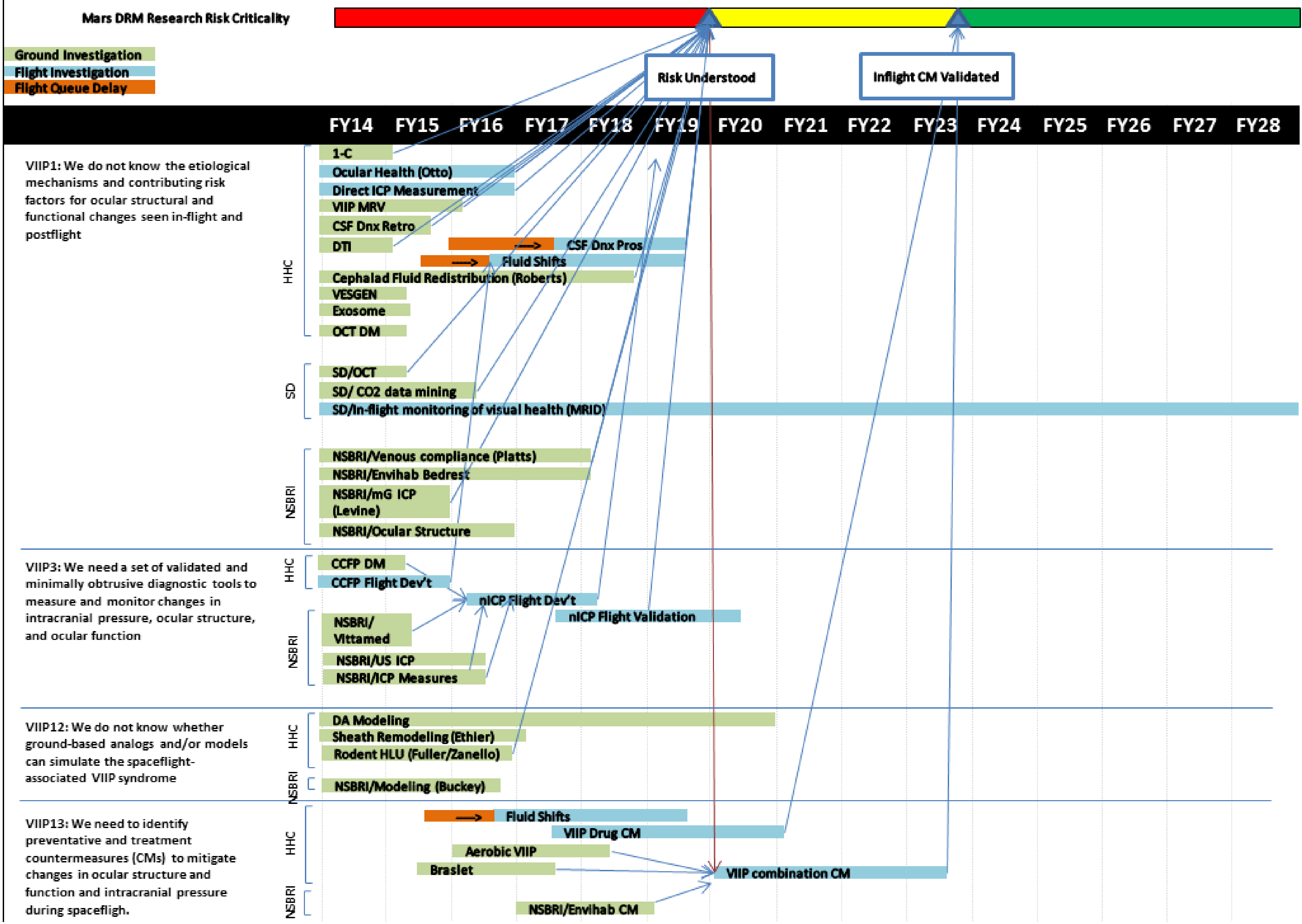
# Operational Relevance

- Vision disturbance and potential elevated intracranial pressure (ICP) in spaceflight are serious health risks to the astronaut population. Evidence to date from short-duration and long-duration space flights supports a dose-response relationship. NASA is planning exploration missions that will involve a longer duration of microgravity exposure. Therefore, the likelihood and consequence of VIIP may be higher.  Changes to vision may impact a crewmember's ability to function nominally onboard, for example: reading computer displays, or working with robotic arms external to the spacecraft. Permanent visual acuity losses may result in lifetime disability to various degrees. In addition, the scientific literature suggests that some patients with the terrestrial condition of idiopathic intracranial hypertension (IIH), thought to be the closest condition analogous to VIIP, may suffer from mild cognitive impairment, which would be of concern to astronaut functioning and well-being.

# Gaps

- VIIP1: We do not know the **etiological mechanisms** and contributing risk factors for ocular structural and functional changes seen in-flight and postflight.
- VIIP3: We need a set of validated and minimally obtrusive **diagnostic tools** to measure and monitor changes in intracranial pressure, ocular structure, and ocular function.
- VIIP12: We do not know whether **ground-based analogs** and/or models can simulate the spaceflight-associated VIIP syndrome.
- VIIP13: We need to identify preventative and treatment **countermeasures (CMs)** to mitigate changes in ocular structure and function and intracranial pressure during spaceflight.

# Risk of Spaceflight-Induced Intracranial Hypertension/Vision Alterations



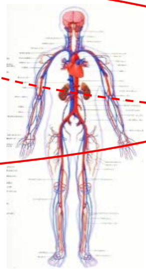
# VIIP1: We do not know the etiological mechanisms and contributing risk factors for ocular structural and functional changes seen in-flight and postflight.

- The rVIIP project considers the VIIP 1 knowledge gap to be its highest priority
- The leading hypothesis is that the VIIP syndrome is caused by increased intracranial pressure resulting from a cephalad (headward) fluid shift resulting from microgravity exposure.

- **Target for closure:**
  Establish the etiology of VIIP syndrome development and the relative contribution of its hypothesized risk factors to a level suitable (as determined by the RCAP) to direct and focus upcoming countermeasure development efforts.

# VIIP1 Tasks: Etiological Mechanisms and Contributing Risk Factors

- ✓ VIIP Data Mining
- ❑ Venous/Arterial Compliance

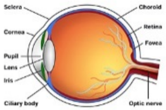


- ➢ ICP in Microgravity

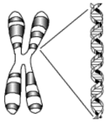
- ❑ CSF Dynamics pre/postflight
- ➢ Venous Sinus Evaluation
- ❑ Cerebral Vascular Autoregulation
- ➢ Diffusion Tensor Imaging
- ❑ Brain Gene Expression Signatures
- ❑ CSF Production and Outflow

- ✓ Evidence Report
- ➢ Occ. Surveillance Data Mining
- ➢ ISS Ocular Health
- ➢ SD/Visual Health (MRID)
- ❑ Fluid Shifts
- ➢ Digital Astronaut Modelling
- ➢ Cranio-Venous Modelling

- ❑ Data Mining – Ocular structure
- ❑ Ocular structure, biomechanics
- ✓ Phase I: SD-OCT Analysis
- ❑ Mapping by VESGEN-Bed Rest



- ✓ Retinal gene expression during uG
- ✓ Retinal gene changes in HLS
- ➢ 1-carbon polymorphism

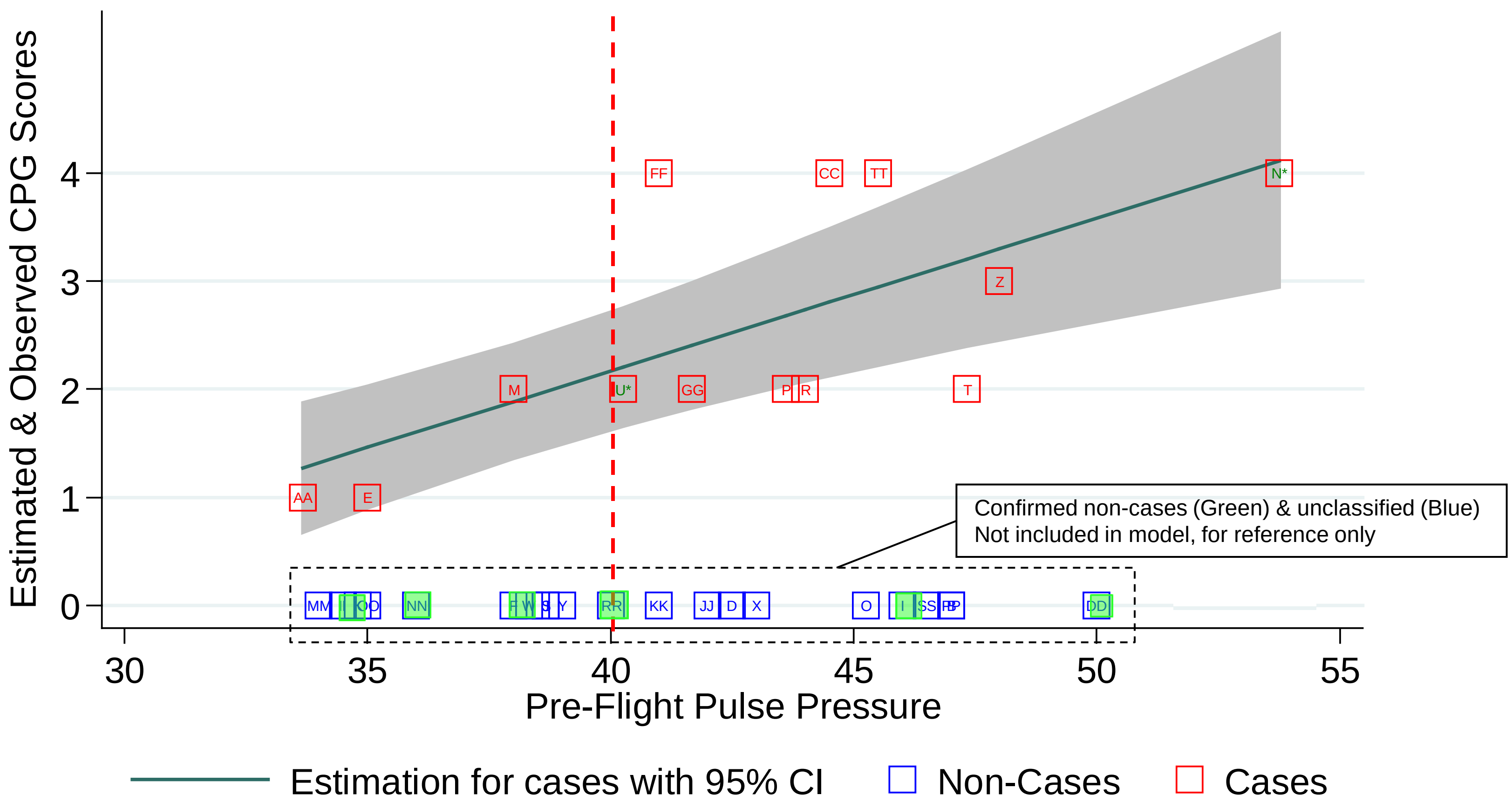


HHC
NSBRI
SD

- ✓ Completed
- ➢ Ongoing
- ❑ To start

# Occupational Surveillance Data Mining: Resting Pulse Pressure (Sitting)

## Cases per CPG vs Pulse Pressure
(Annual Preflight Exam 4-Year Mean)

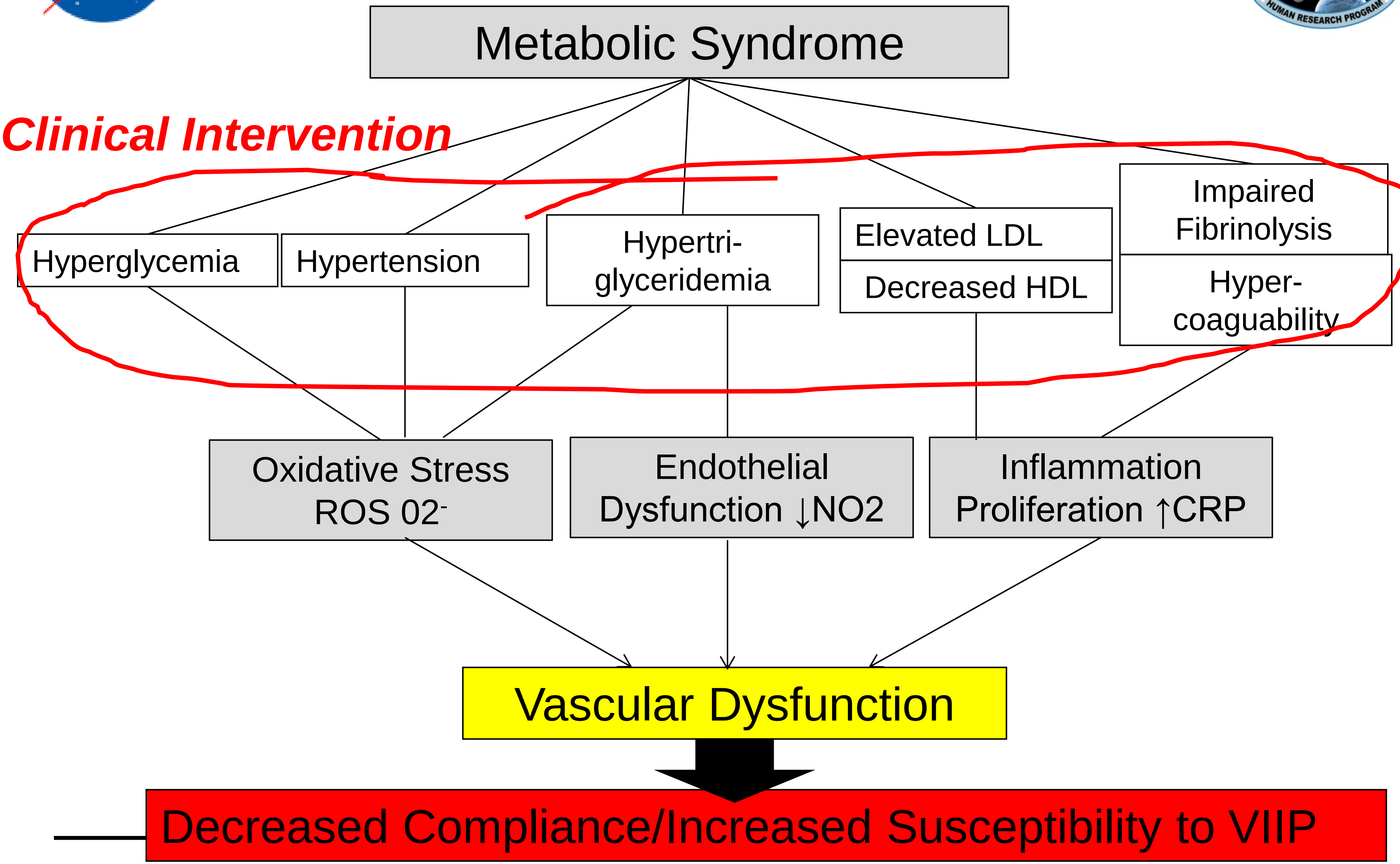



Best Fit (curvilinear) for Cases; $R^2$=.45 (including BP meds predictor), p<.01

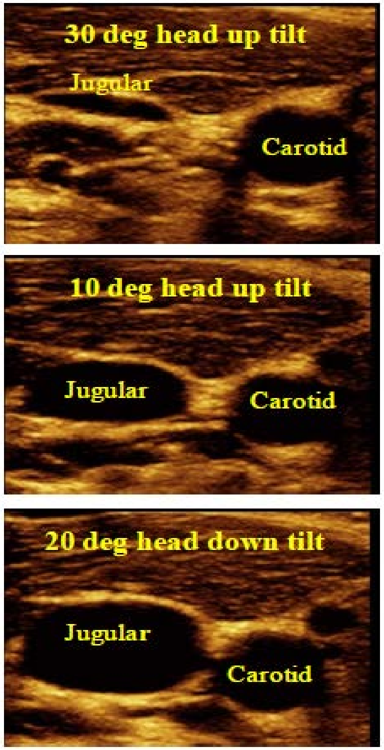
# Occupational Data Mining in ISS Astronauts: Cardiovascular Variables Correlating with CPG

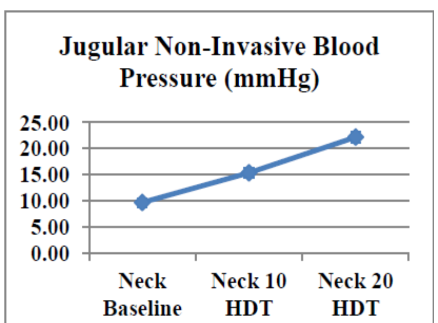
| Cardiovascular Variable | Significant Correlation Across CPG Classification | $R^2$ | P value |
|---|---|---|---|
| **Biochemistry:** | | | |
| LDL | √ | 0.43 | P<0.02 |
| HDL | - | 0.22 | P<0.09 |
| Triglycerides | - | - | |
| Hemoglobin A1c | √ | - | P<0.01 |
| Fasting serum glucose | √ | 0.125 | P<0.008 |
| Homocysteine | √ | - | P<0.01 |
| Oral sodium intake | √ | 0.22 | P<0.05 |
| **Body Composition:** | | | |
| Body Mass Index | √ | 0.41 | P<0.01 |
| Percentage Body Fat | √ | 0.38 | P<0.01 |
| **Cardiac:** | | | |
| Resting systolic blood pressure (pre-in-post flight) | √ | 0.31 | P<0.0002 |
| Pulse Pressure (pre-in-post flight) | √ | 0.45 | P<0.01 |
| CT Coronary Calcium Score | - | - | - |
| **Aerobic Capacity:** | | | |
| Decreased Maximal Oxygen Uptake | √ | - | P<0.04 |

# Metabolic Syndrome-Vascular Relationship

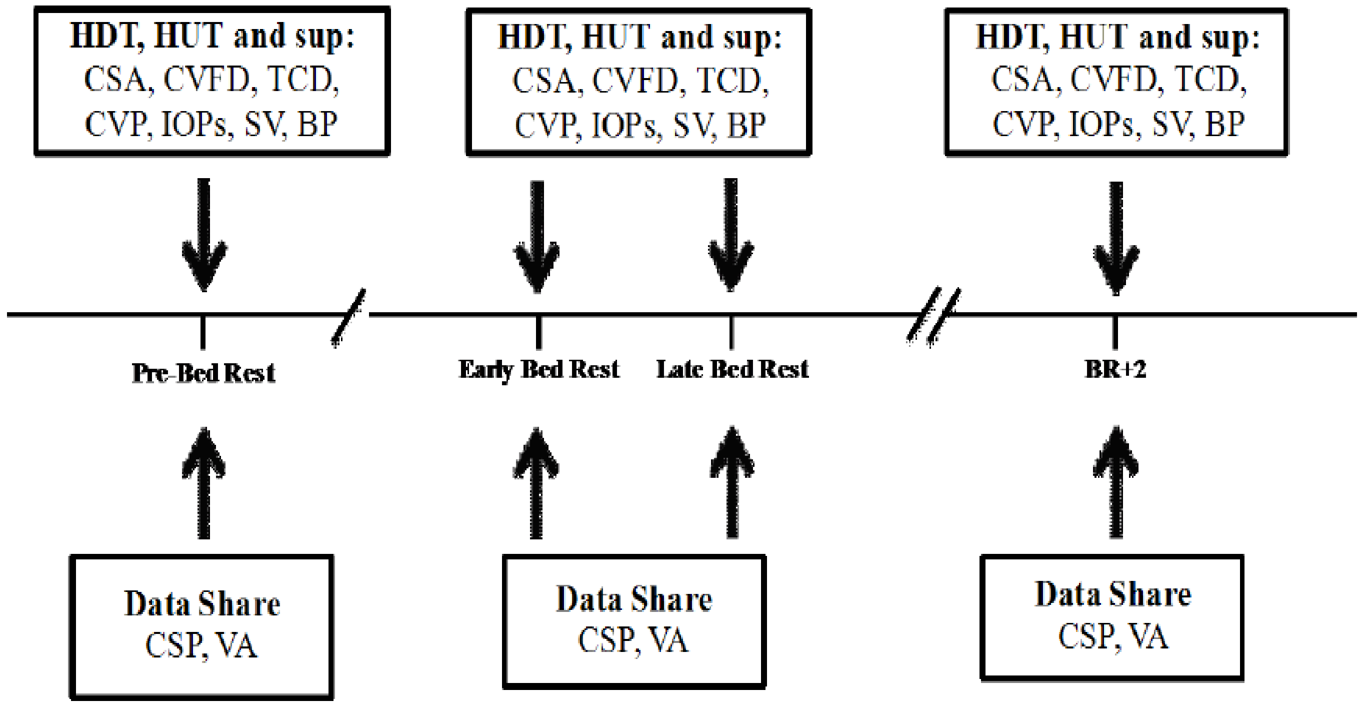


# Platts-Venous Compliance *Bed Rest*



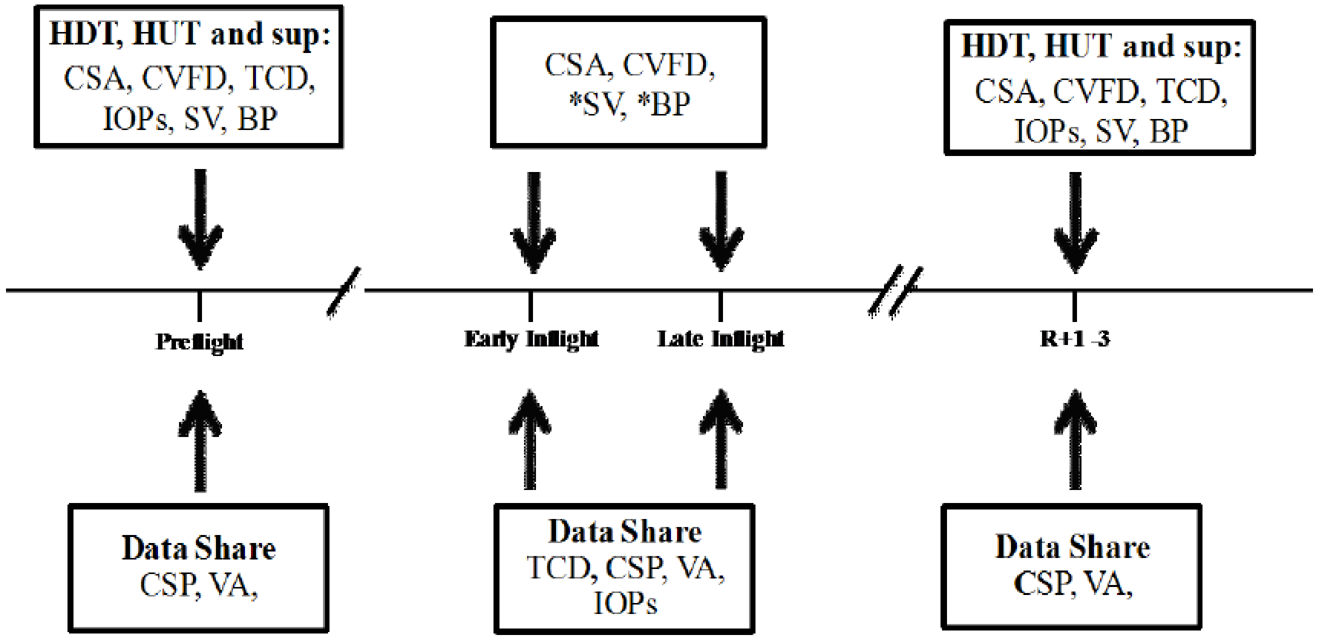

Aims: To track changes in venous and arterial compliance in the head and neck vasculature due to bed rest and determine relationship to morphological alterations of the eye. *Is bed rest an adequate model?*




HDT - head-down tilt (@ -10/20/30 ) HUT - head-up tilt (@ 10/20/30 ) sup - supine
CSA - venous cross-sectional area SV - stroke volume BP - blood pressure
TCD - transcranial Doppler IOPs - intraocular pressure surrogate VA - visual acuity
CSP - cerebrospinal fluid pressure CVFD - carotid & vertebral flow/diameter
CVP - central venous pressure

# Platts-Venous Compliance *Inflight*

Aims: ***Are venous compliance changes inflight contributing to VIIP?***

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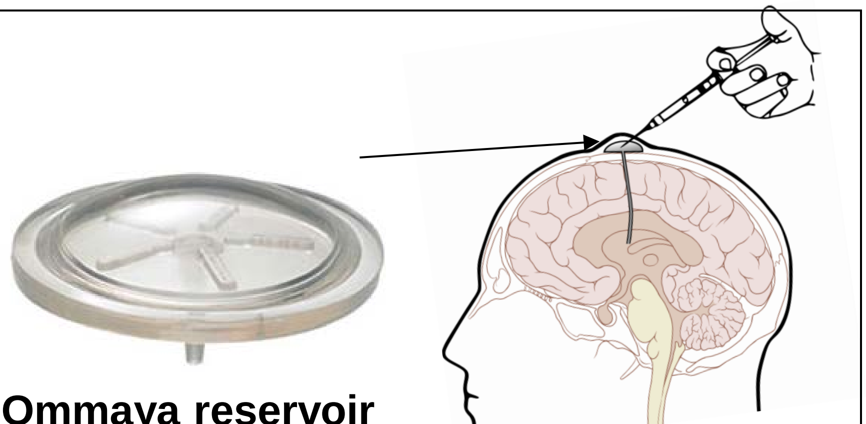
* = data share if Ocular Health subject

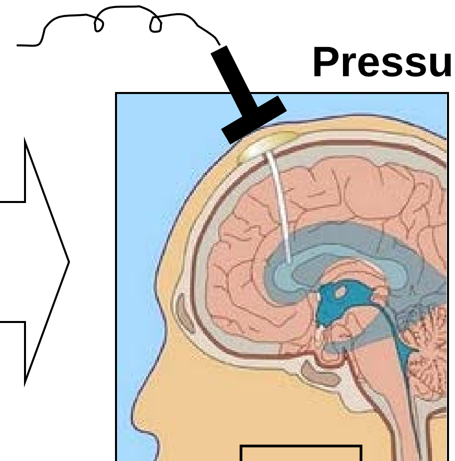
# Effects of Microgravity on Central Venous Pressure & Intracranial Pressure

PI: Dr. Ben Levine:

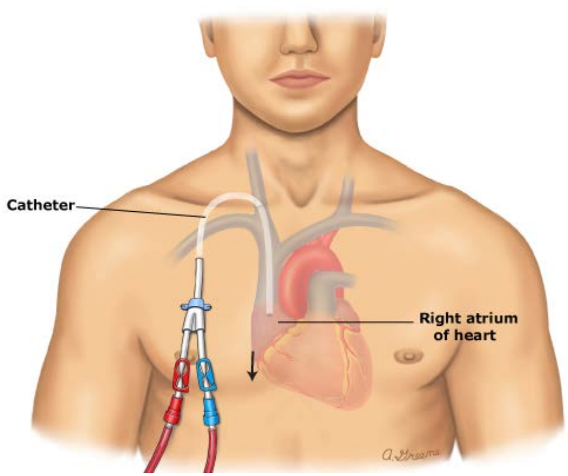


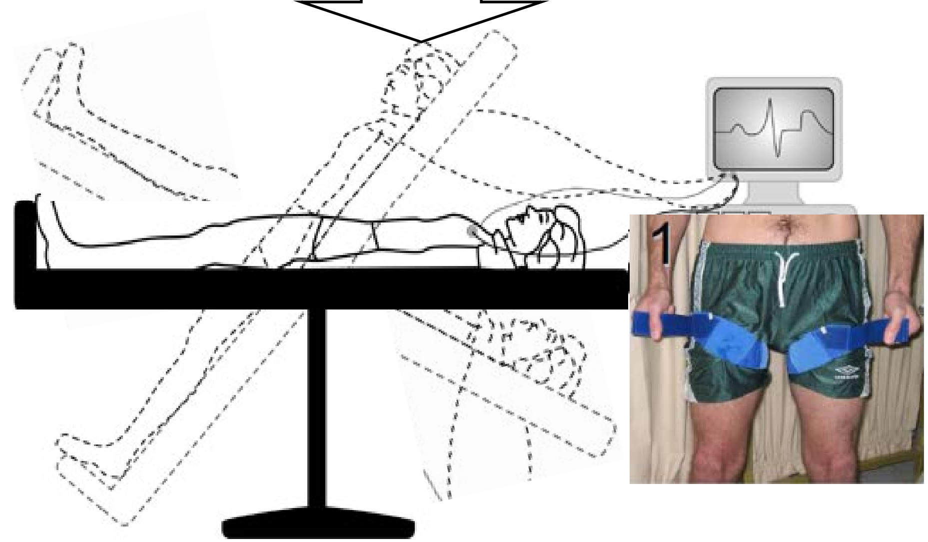
**Ommaya reservoir**
**Utilized for CNS drug delivery**

**Pressure Transducer Measures ICP**



**Right Heart Catheterization to measure CVP**

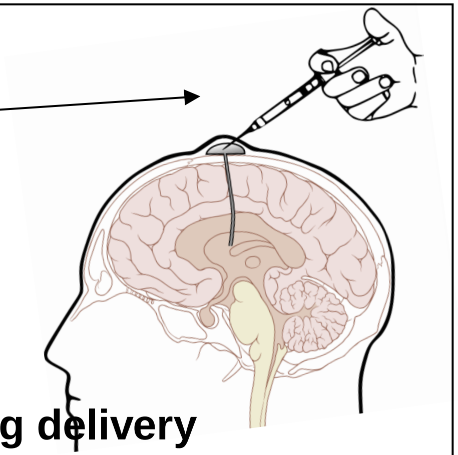


**Measurement of ICP & CVP during 24hr tilt testing +/- Braslet, +/- CO2 with ocular ultrasound**

# Effects of Microgravity on Central Venous Pressure & Intracranial Pressure

*How do alterations in CVP in uG impact ICP?*



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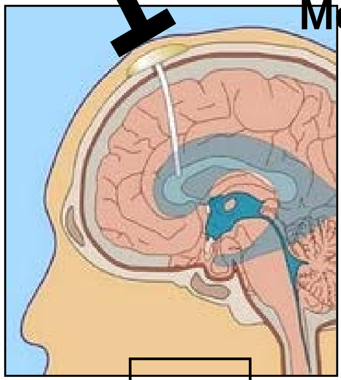

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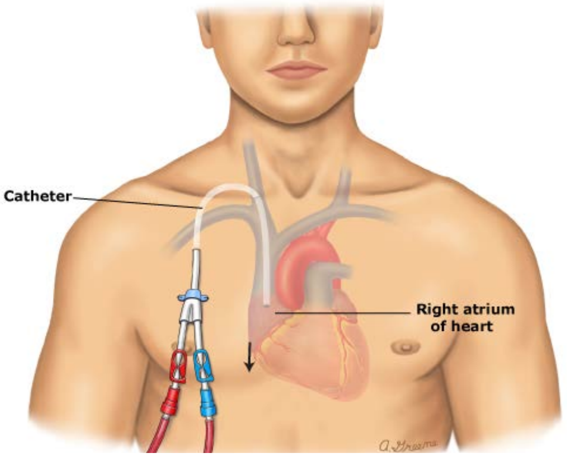


Measurement of ICP & CVP during parabolic flight and with CO2, and strength challenge

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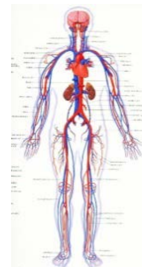

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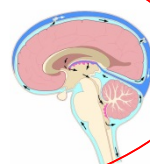

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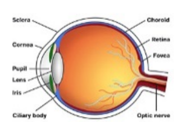


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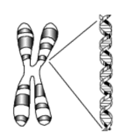


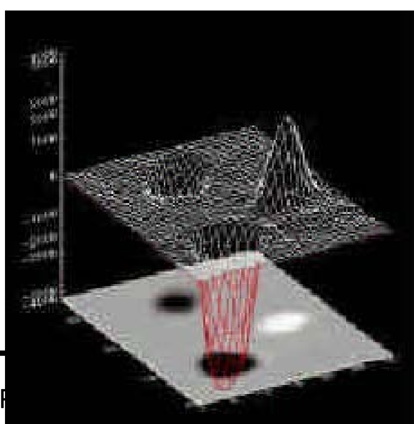
| Color key | Symbol key |
|---|---|
| HHC | ✓ Completed |
| NSBRI | ➢ Ongoing |
| SD | ❑ To start |

# Pre and Postflight Measurement of Cerebrospinal Fluid (CSF) Dynamics & ICP

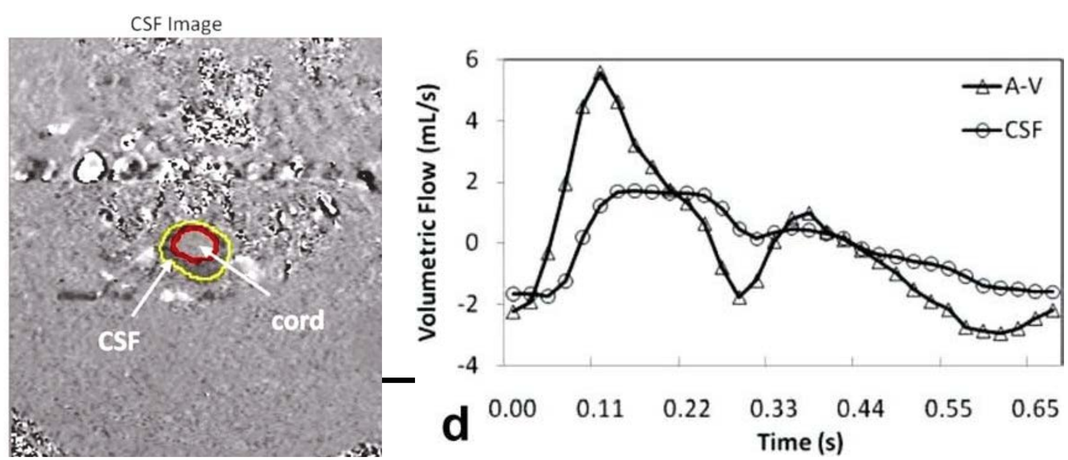
- **PI:** Noam Alperin, Ph.D.
- **Aims:** Retrospective study will evaluate pre and postflight MRI data from long-duration crew members to determine cerebrospinal fluid (CSF) dynamics & ICP, to identify changes due to space flight.
- **Clinical Applications:**
  - Non-invasive ICP measurement- *diagnosis & treatment*
    - Non-invasive craniospinal compliance *-susceptibility*

- *Is ICP altered in ISS crew following flight?*

3D plot of the blood flow velocities: right carotid artery, vertebral artery and jugular vein.



Velocity encoded MRI images of CSF flow(b) used for derivation of the blood CSF volumetric flow rate waveforms



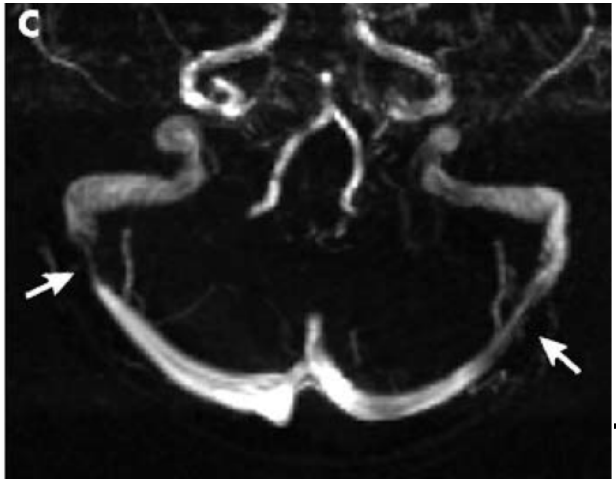
# Pre & Postflight MRV Review (Central Venous Congestion/Stenosis)

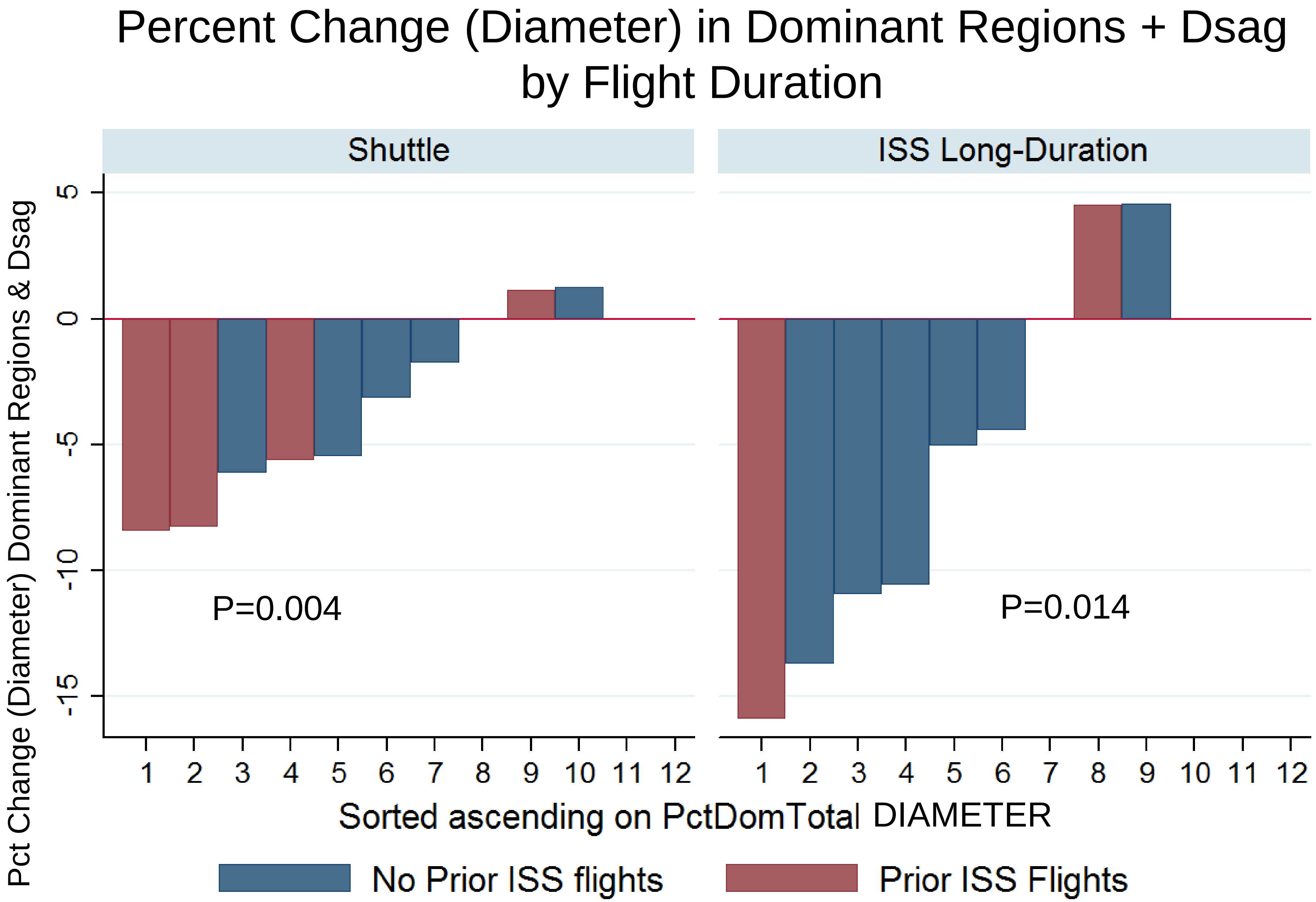
- **PI:** Riascos-Casteneda
- **Aims: E**valuate central venous congestion and stenosis in astronauts pre and postflight.

- **Clinical Applications:**
  - Determination of whether or not astronauts present with signs of cerebral venous compression following flight

- *Is venous compression secondary to elevated ICP present in crew following flight?*

Focal narrowing in right & left transverse sinus in Idiopathic Intracranial Hypertension

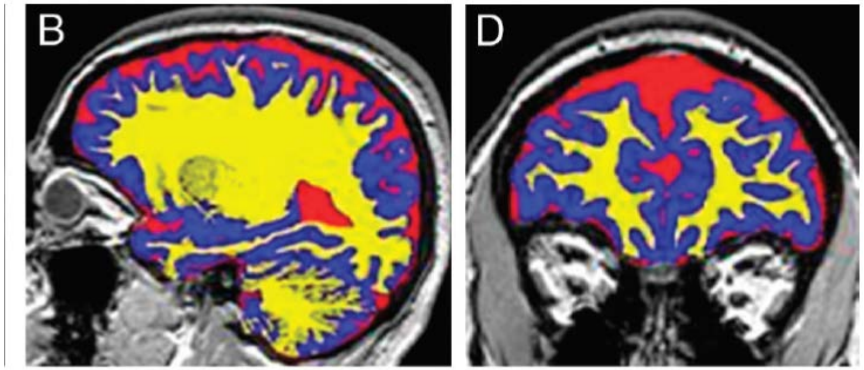


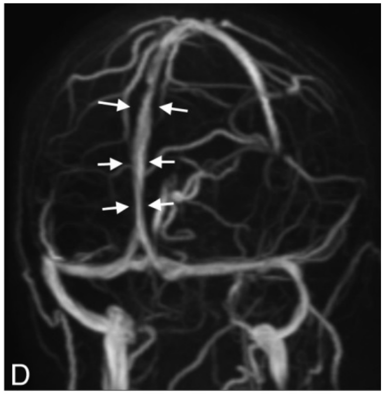


Percent Change (Diameter) in Dominant Regions + Dsag
by Flight Duration
Shuttle
ISS Long-Duration
Pct Change (Diameter) Dominant Regions & Dsag
5
0
-5
-10
-15
P=0.004
P=0.014
1 2 3 4 5 6 7 8 9 10 11 12
1 2 3 4 5 6 7 8 9 10 11 12
Sorted ascending on PctDomTotal DIAMETER
No Prior ISS flights
Prior ISS Flights

# Cephalad Fluid Redistribution
# PI: Donna Roberts

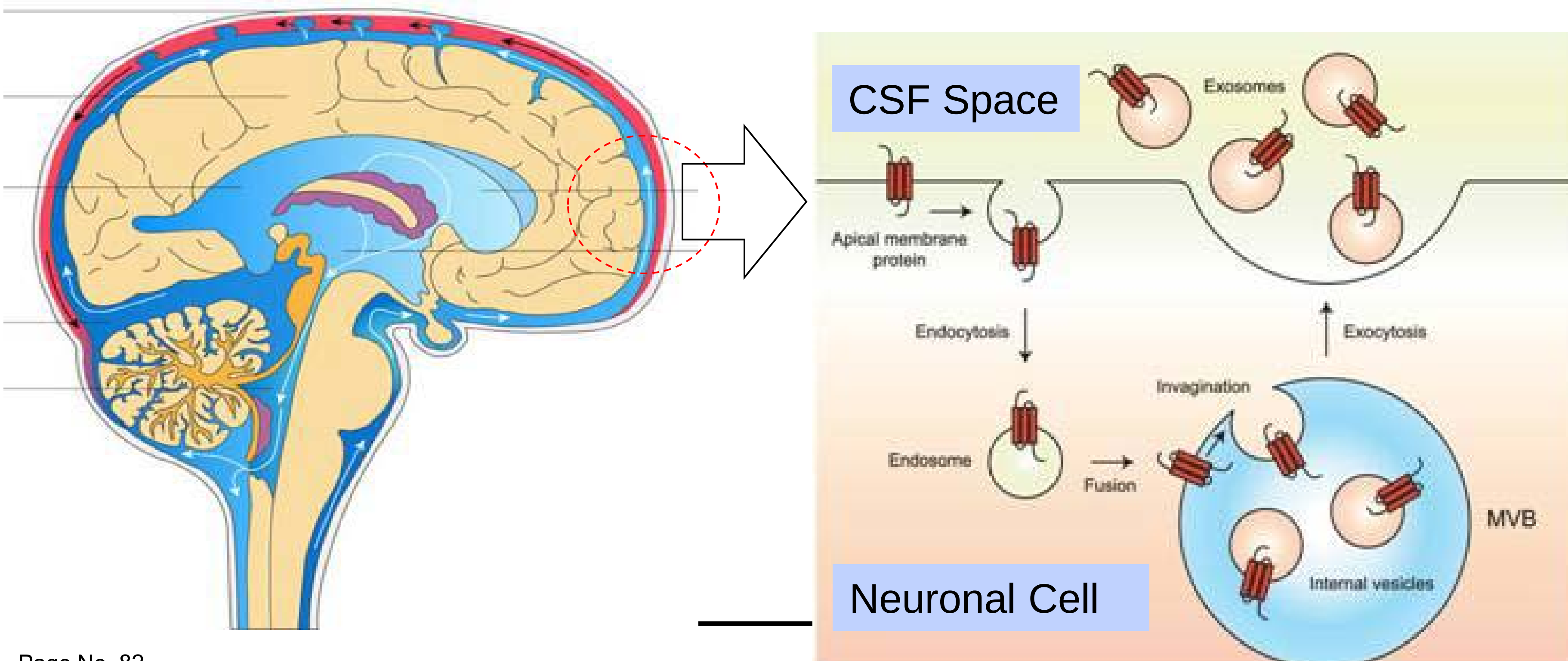
- ***Specific Aim #1:*** Characterize weightlessness-induced intracranial compartmental fluid volume changes.
- ***Specific Aim #1a (Macroscopic Fluid Volume Changes):*** Perform a volumetric analysis of the brain and CSF to assess for any potential shifts in brain and intracranial CSF volume induced by microgravity exposure.
- ***Specific Aim #1b (Arterial and Venous Fluid Volume Changes):*** Perform volumetric analysis of the regional arterial cerebral blood volume and venous outflow to assess for evidence of cerebral venous insufficiency
- ***Specific Aim #2:*** Evaluate the impact that exposure to microgravity has on human cerebral hemodynamics including cerebral perfusion.
- *<u>Do volume changes and compartment volume shifts occur in the brain following flight?</u>*



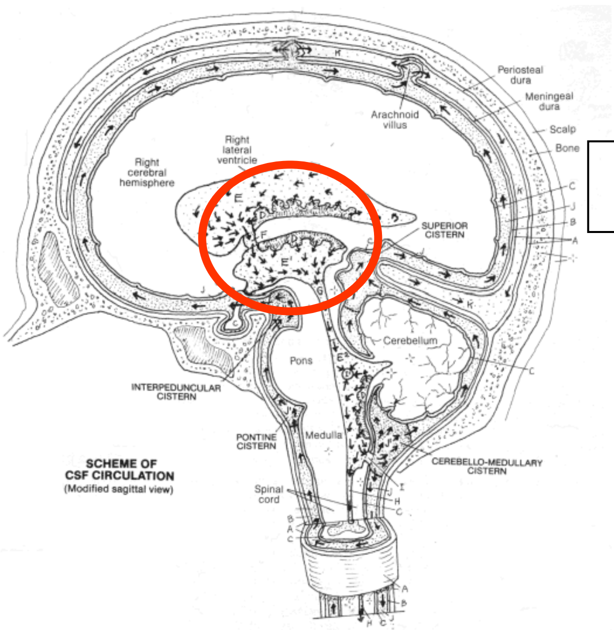
# Brain Gene Expression Signatures

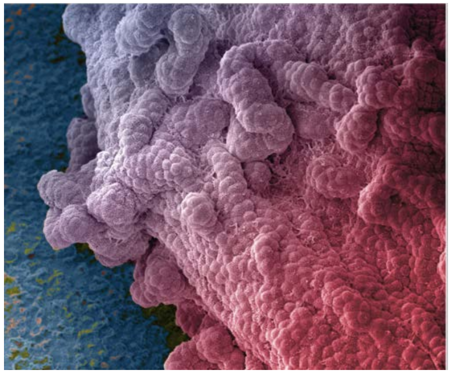
- PI: Zanello
- Aims: Sample CSF in IIH patients to examine neuronal cell RNA exosomes to determine if white matter disease genetic changes are present?
- *<u>Does chronically elevated ICP damage neuronal cells and predispose to white matter disease?</u>*

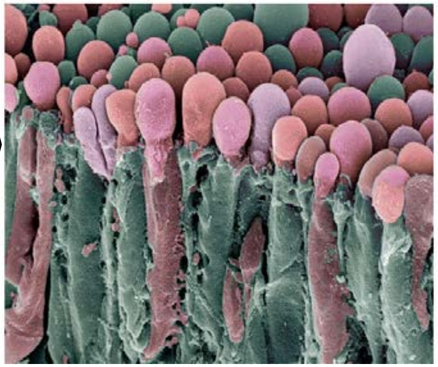


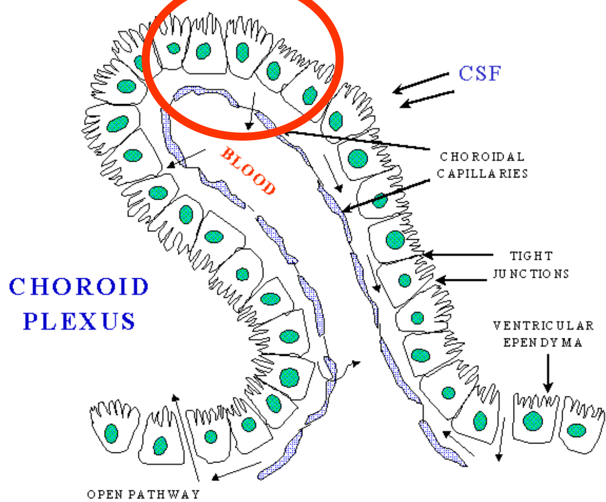
# CSF Production: Choroid Plexus

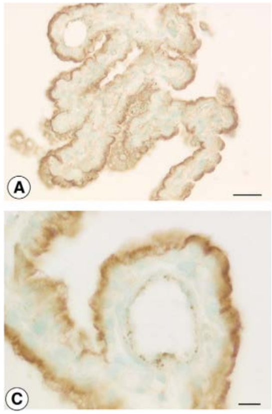
***Is CSF production altered as a consequence of cephalad fluid shift?***

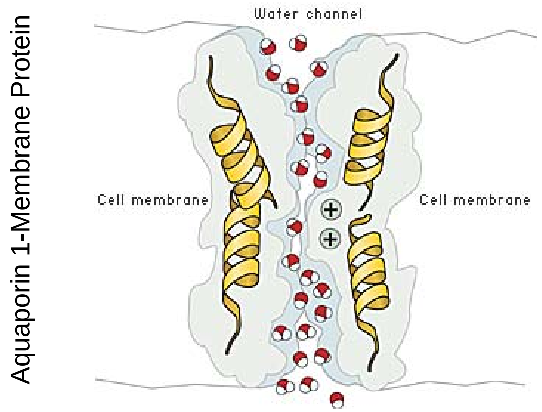






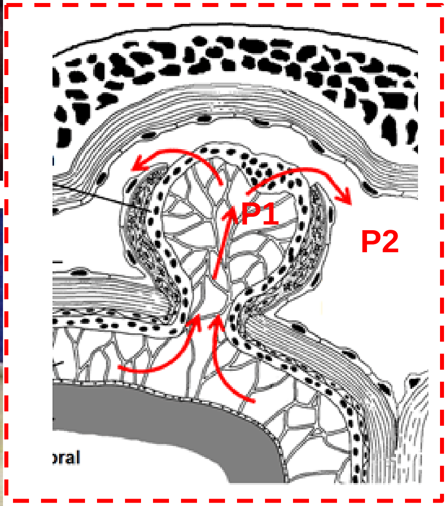



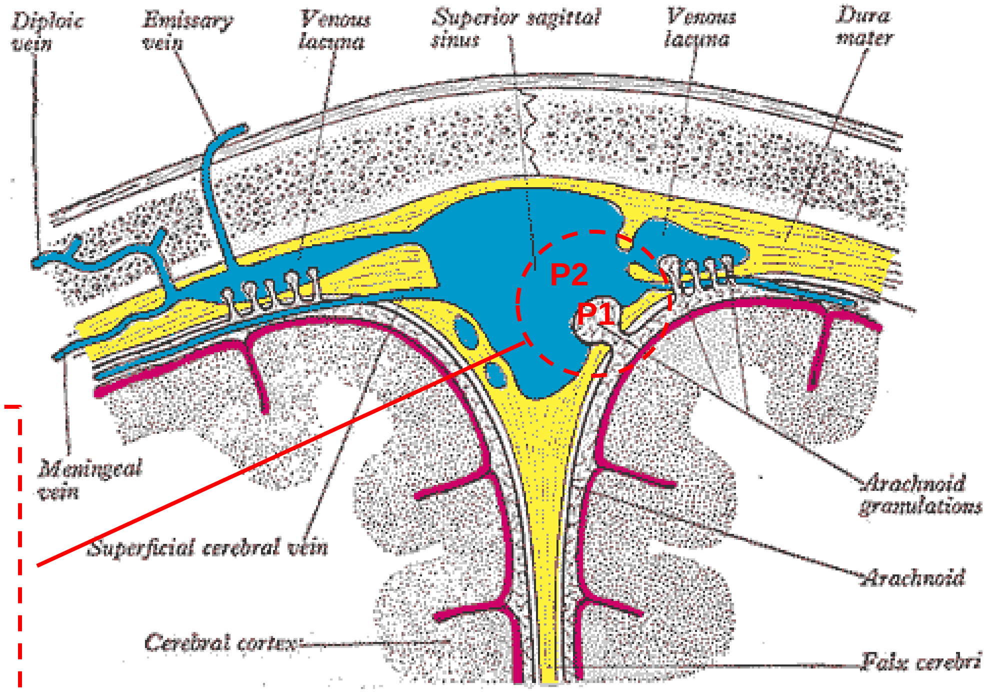



Choroid plexus in lateral, third & fourth ventricle produces 70-90% of CSF in brain

# CSF Resorbtion: Arachnoid Granulations

<u>*Is CSF resorbtion altered as a consequence of cephalad fluid shift?*</u>



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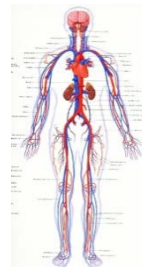

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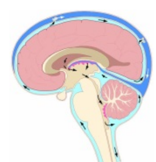

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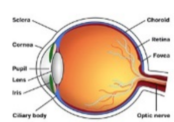

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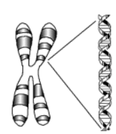

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- ➢ SD/Visual Health (MRID)
- ❑ Fluid Shifts
- ➢ Digital Astronaut Modelling
- ➢ Cranio-Venous Modelling

HHC
NSBRI
SD

- ✓ Completed
- ➢ Ongoing
- ❑ To start

# Astronaut Data Mining: Ocular Structure, Retrospective

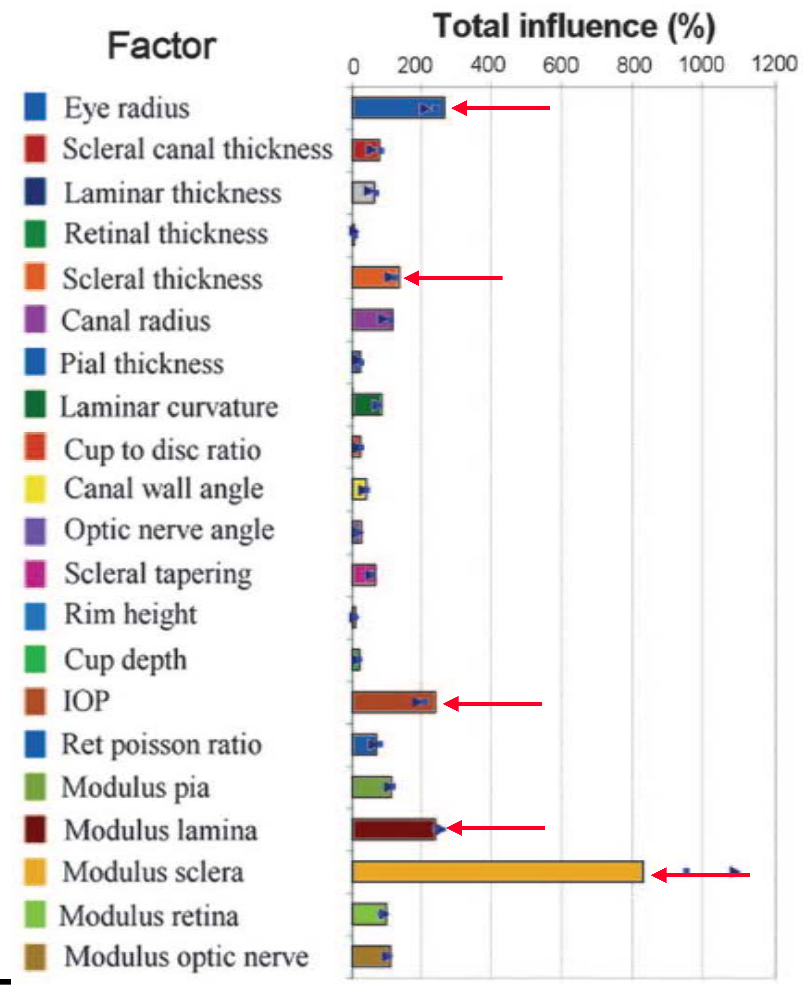
Gap: VIIP 1 (Etiology/Risk Factors)

Timeframe: FY14

**Aim:** Evaluate the changes in ocular structure and biomechanics during space flight, such as crowded disc, posterior eye radius, degree of refraction, intraocular pressure (IOP), corneal thickness, retinal pigmented epithelial angle (RPE), and translaminar pressure gradient.

- ***Do biomechanical factors of the eye predispose certain crew to developing VIIP?***

Input factors in Modeling Strain on the ONH



# Ocular Structure - Flight

Gap: VIIP 1 (Etiology/Risk Factors)

Funding Status: Not funded

- **Aim:** This prospective flight study will examine pre- and postflight measures of ocular structure and biomechanics (e.g. crowded disk, scleral thickness, optic canal opening, posterior eye radius, degree of myopia, intraocular pressure (IOP), corneal thickness, retinal pigmented epithelial angle (RPE), and translaminar pressure gradient). The task will contribute to gap closure by characterizing any pre/postflight changes in ocular structure and correlating these measures to the incidence and magnitude of symptoms of the VIIP syndrome.

  *This work is a follow-up to the task “Ocular Structure Data Mining.”

# SD OCT Data mining

- PI: N. Patel
- Aim: Are OCT changes of the optic nerve head present in ISS crew following flight?
- *Do changes in retrobulbar optic nerve CSF pressure and blood flow precipitate optic nerve head alterations?*

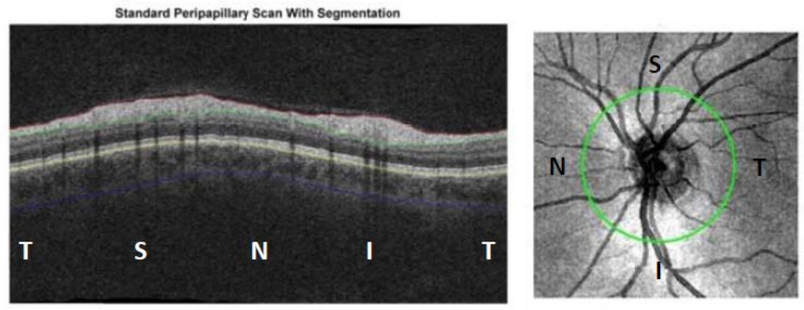
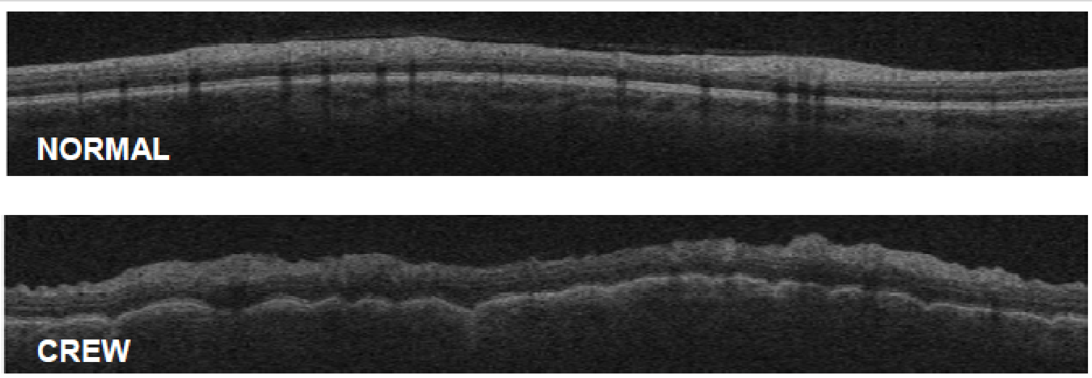



Figure 4. Circumpapillary scan used for RNFL and Choroid thickness



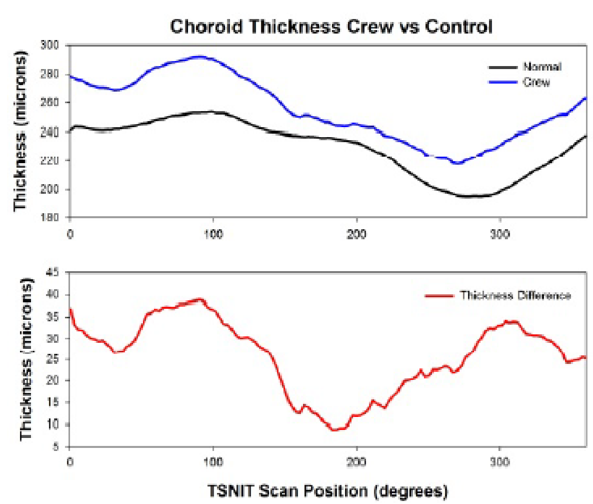




Figure 7. B-scans of crew members have significant choroidal folds compared to normals. The TSNIT plots on the right illustrate mean and differences of choroidal measures for crew and normals.

# SD OCT Data mining

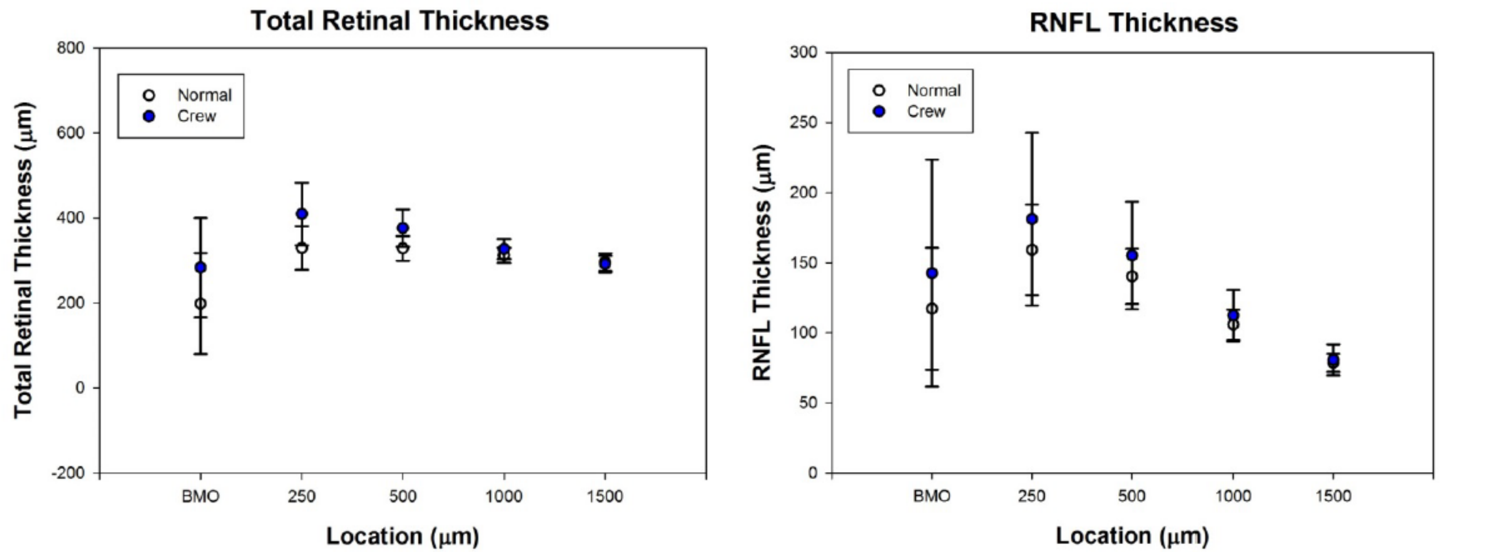



Figure 5. Average total retinal thickness and RNFL thickness at various eccentricities (fig 3B) for crew and control subjects. Significant differences are seen up to 500 microns from the BMO.

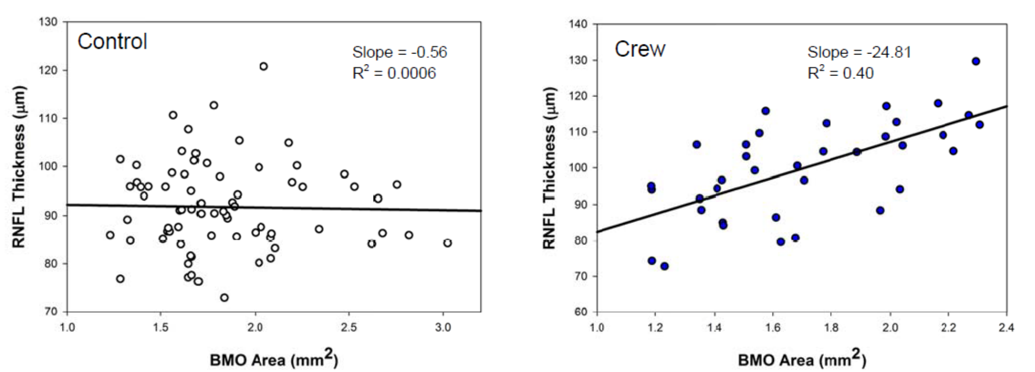
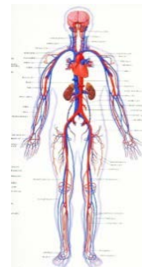



Figure 8. There us a significant relationship between RNFL thickness and BMO area in crew memebers. However, this trend is not appreciated in normal controls.

Positive relationship between scleral opening and RNFL thickness

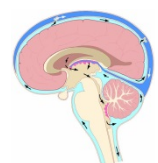
# VIIP1 Tasks: Etiological Mechanisms and Contributing Risk Factors

- ✓ VIIP Data Mining
- ❑ Venous/Arterial Compliance



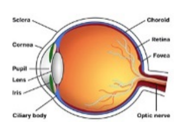
- ➢ ICP in Microgravity

- ❑ CSF Dynamics pre/postflight
- ➢ Venous Sinus Evaluation
- ❑ Cerebral Vascular Autoregulation
- ➢ Diffusion Tensor Imaging
- ❑ Brain Gene Expression Signatures
- ❑ CSF Production and Outflow

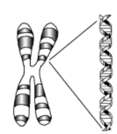


- ✓ Evidence Report
- ➢ Occ. Surveillance Data Mining
- ➢ ISS Ocular Health
- ➢ SD/Visual Health (MRID)
- ❑ Fluid Shifts
- ➢ Digital Astronaut Modelling
- ➢ Cranio-Venous Modelling

- ❑ Data Mining – Ocular structure
- ❑ Ocular structure, biomechanics
- ✓ Phase I: SD-OCT Analysis
- ❑ Mapping by VESGEN-Bed Rest




- ✓ Retinal gene expression during uG
- ✓ Retinal gene changes in HLS
- ➢ 1-carbon polymorphism



| | |
|---|---|
| HHC | ✓ Completed |
| NSBRI | ➢ Ongoing |
| SD | ❑ To start |

# Spaceflight Effects on the Mouse Retina: Histological, Gene Expression and Epigenetic Changes After Flight on STS-135

- **PI:** S. Zanello
- **Aims:** Perform histological and gene expression analysis of retinas collected from C57BL/6 mice flown in STS-135 (and from ground control counterparts). Histological and gene expression outcomes focused on cellular stress, oxidative stress, DNA damage and cellular death and survival.
- **Results :**
  - *Histological analysis for apoptosis*: 30 % more apoptotic activity in FLT vs Ground Controls
  - DNA damage caused by oxidative stress, was elevated in flight samples for the retinal ganglion cells and inner nuclear layer
- *Hypoxic stress is occuring at the optic nerve head in uG?*√

# Hindlimb Suspension (HS) as an Analog Model of Ocular Alterations Associated with Cephalad Fluid Shifts: Resveratrol as a Countermeasure

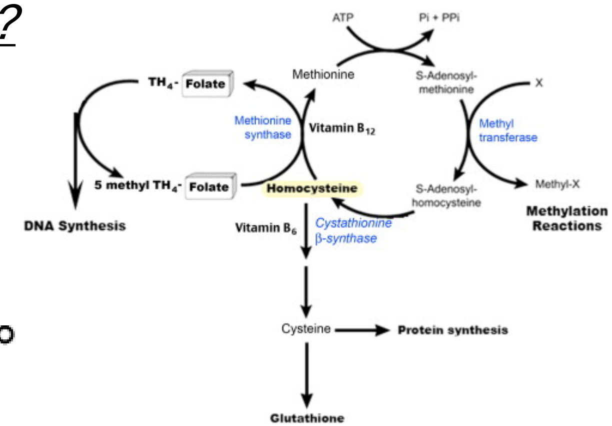
- **PI: S. Zanello**
- **Aims:** Testing the hypothesis that cephalad fluid shift represents a stress factor that induces optic disc neuroanatomical changes, as well as retinal cell deterioration and loss via oxidative stress.
- **Results:** First evidence of molecular changes (gene expression) in the retina due to hindlimb suspension

1. Egr1 (early growth response protein-1) a transcription factor responsive to mechanical stress, is induced in the retina due to HS. Egr1 induction by HS is reversed by recovery in normal posture after HS and suppressed by antioxidant-rich diet with green tea extract.
2. Shown that resveratrol diet-fed animals had thicker retinas compared to animals fed on a control diet in HS

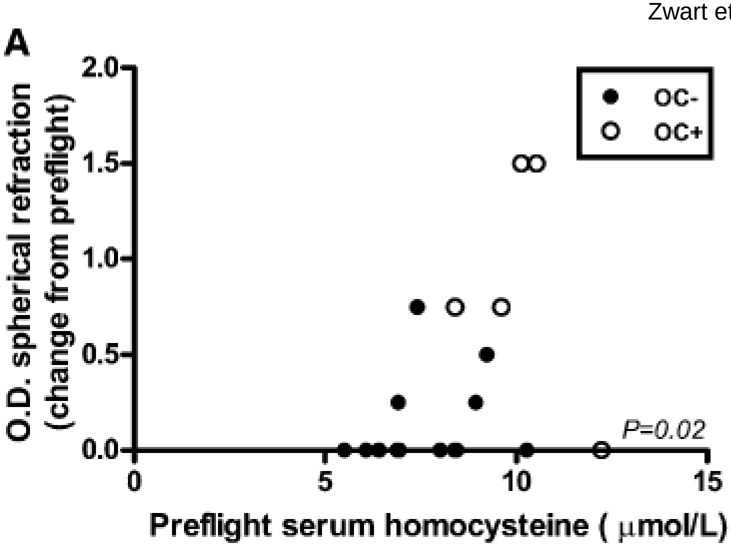
- *Cephalad fluid shift may be causing ocular changes as demonstrated by mechanical changes and oxidative stress*

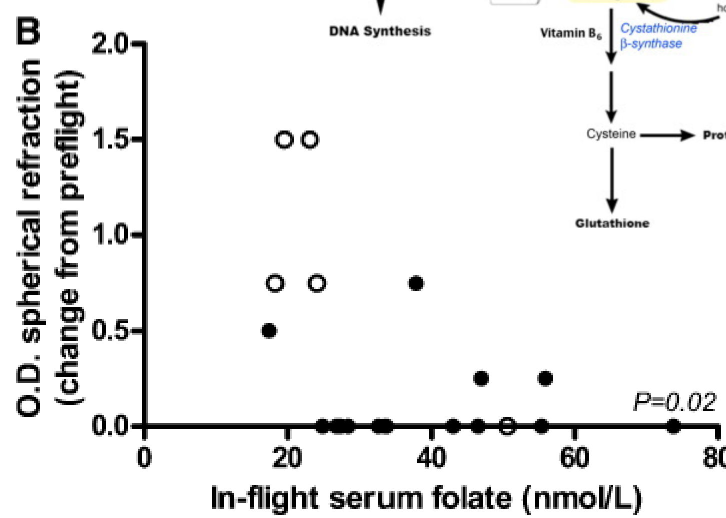
# Evaluation of the Role of Polymorphism of Enzymes Involved in 1-Carbon Metabolism on the VIIP Risk

- **PI:** S. Smith
- **Aims:** Evaluation of the Role of Polymorphism of Enzymes involved in 1-carbon Metabolism
- Elevations in 4 metabolites of the one-carbon metabolism pathway have been identified in 7 affected crew members studied to date. These elevations and related data suggest that polymorphism(s) of one or more of the enzymes in this pathway exist(s) in affected crew members.
- *Does a genetic error of metabolism contribute to VIIP?*



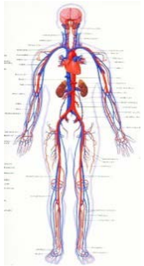

Zwart et al. Journal of Nutrition. Feb 2012.



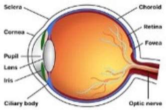
# VIIP1 Tasks: Etiological Mechanisms and Contributing Risk Factors

- ✓ VIIP Data Mining
- ❑ Venous/Arterial Compliance

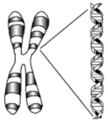


- ❑ CSF Dynamics pre/postflight
- ➢ Venous Sinus Evaluation
- ❑ Cerebral Vascular Autoregulation
- ➢ Diffusion Tensor Imaging
- ❑ Brain Gene Expression Signatures
- ❑ CSF Production and Outflow

- ❑ Data Mining – Ocular structure
- ❑ Ocular structure, biomechanics
- ✓ Phase I: SD-OCT Analysis
- ❑ Mapping by VESGEN-Bed Rest




- ✓ Retinal gene expression during uG
- ✓ Retinal gene changes in HLS
- ➢ 1-carbon polymorphism

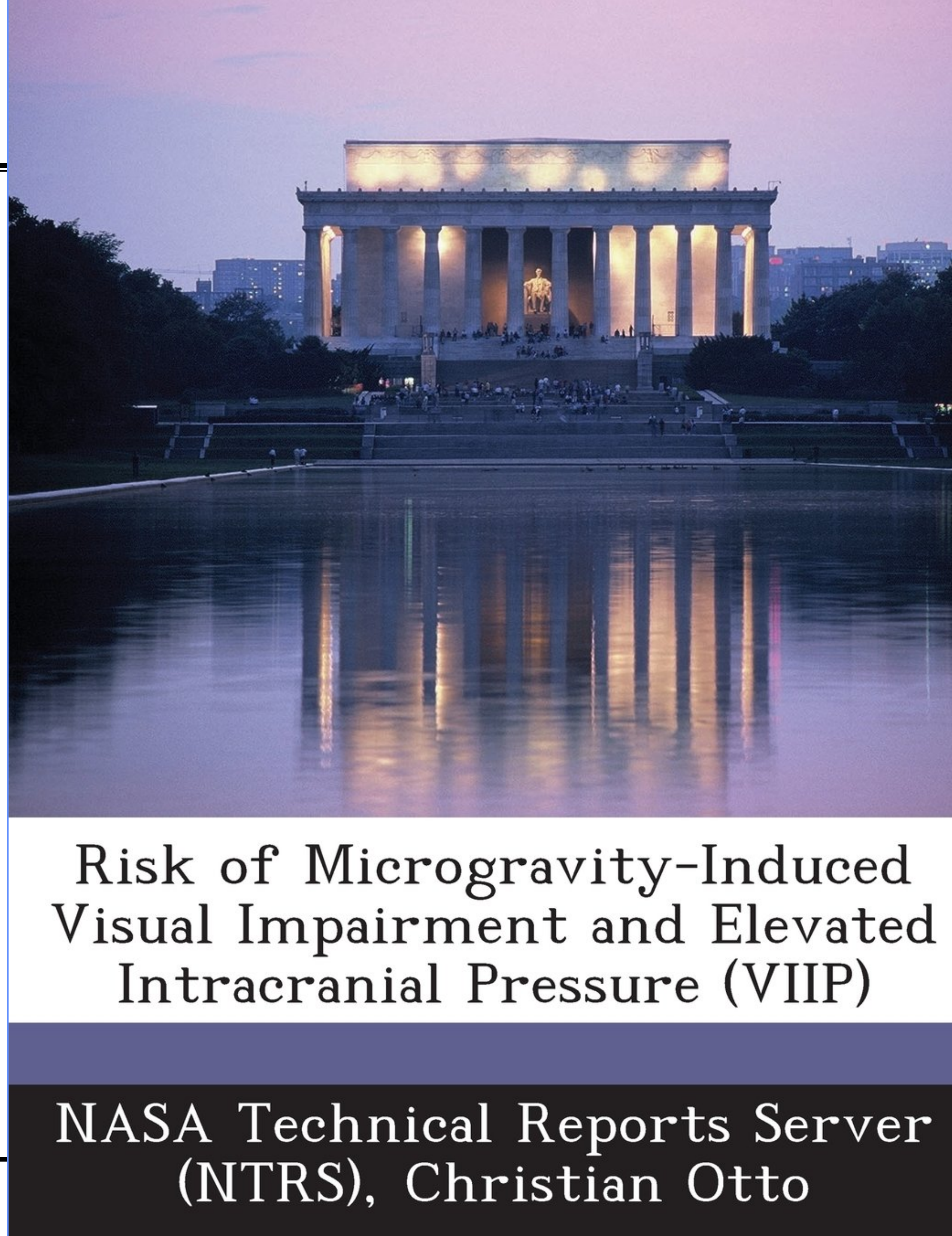


- ➢ ICP in Microgravity

- ✓ Evidence Report
- ➢ Occ. Surveillance Data Mining
- ➢ ISS Ocular Health
- ➢ SD/Visual Health (MRID)
- ❑ Fluid Shifts
- ➢ Digital Astronaut Modelling
- ➢ Cranio-Venous Modelling

| | |
|---|---|
| HHC | ✓ Completed |
| NSBRI | ➢ Ongoing |
| SD | ❑ To start |

- VIIP Evidence book published June 18, 2012
- IOM Review Dec. 19, 2013



# ISS Ocular Study

## Pre-flight Exams

L-21/18 mo — L-12-3 mo

**Victory Lakes**
MRI

Ocular Ultrasound at L-12/9 and 6/3 mo;
All other tests at L-9/6 mo

**Flt Med. Clinic** (L-21/18 mo)
- Vision Testing*
- Fundoscopy
- Refraction
- Pupil Reflexes
- Extra-Ocular Muscle Bal.
- IOP (Tonometry)
- Blood pressure for IOP

**Flt Med. Clinic** (L-12-3 mo)
- Ocular Ultrasnd
- Vision Testing*
- Fundoscopy
- Refraction
- Pupil Reflexes
- Extra-Ocular Muscle Bal.
- IOP (Tonometry)
- Blood pressure for IOP

**Coastal Eye Assoc:** (L-21/18 mo)
- OCT/A-Scan
- Biomicroscopy/ Hi Res Photogr.

**Coastal Eye Assoc:** (L-12-3 mo)
- OCT/A-Scan
- Biomicroscopy/ Hi Res Photogr.

**Bldg. 261:**
- Cardiac Ultrasnd
- Blood Pressure

## In-flight Exams

L+10 L+30 L+60 L+90 L+120 R-30

MedB allows the addition of a session without research components at L+100 if requested & as clinically indicated

- Ocular Ultrasnd
- Fundoscopy
- IOP (Tonometry)
- Blood pressure for IOP
- Vision Testing*
- Cardiac Ultrasnd
- Blood Pressure

## Post-flight Exams

R+1-3 R+30 R+90 R+180 R+365

**Victory Lakes**
MRI

**Flt Med. Clinic**
- Ocular Ultrasnd
- Vision Testing*
- Fundoscopy
- Refraction
- Pupil Reflexes
- Extra-Ocular Muscle Bal.
- IOP (Tonometry)
- Blood pressure for IOP

**Coastal Eye Assoc:**
- OCT/A-Scan
- Biomicroscopy/ Hi Res Photogr.

**Bldg. 261:**
- Cardiac Ultrasnd
- Blood Pressure

# Ocular Health Study Aims & Rationale:

- PI: C. Otto

1. Increased frequency of crew VIIP testing is required to:
   a) Define the **temporal sequence** for the appearance of signs and symptoms.
   b) Delineate the interaction between **duration** of weightlessness and severity of symptoms, i.e. the dose-response.
   c) Identify whether VIIP signs and symptoms **recover post-flight** and determine the impact of prolonged changes on crew health.

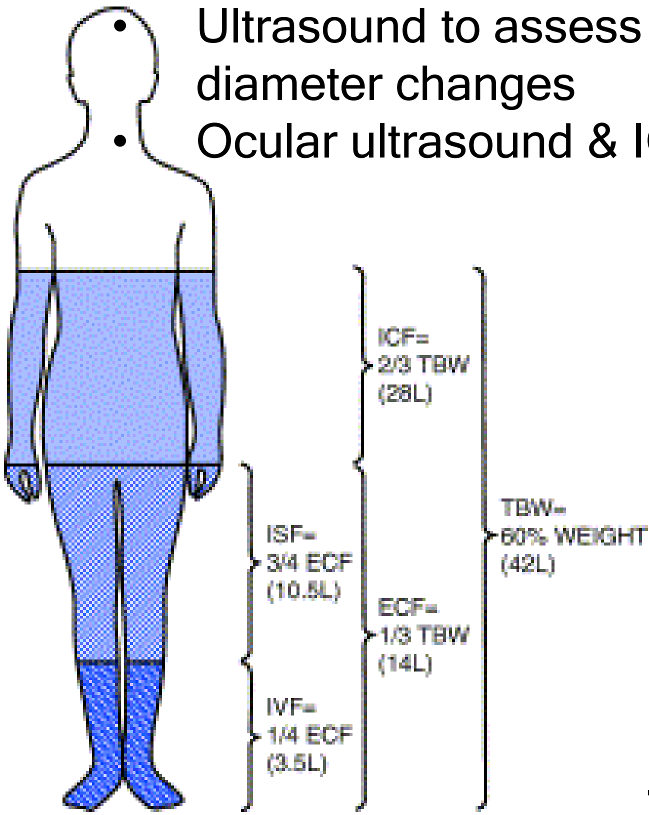
- *Outline physiological systems relationships in **VIIP** , and aid in guiding development of countermeasures and targeted treatments.*

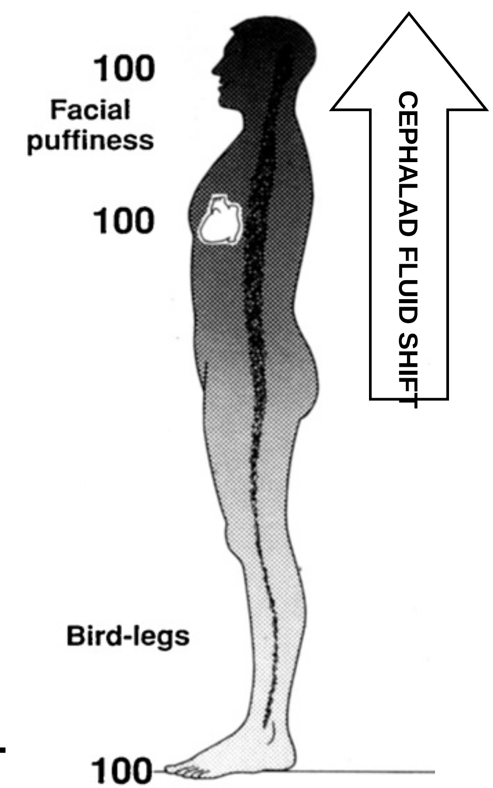
# Fluid Shifts Specific Aims

- *PI's: M. Stenger, A. Hargens & S. Dulchavsky*
- *Specific Aim I*: To **characterize fluid distribution and compartmentalization** before, during and after long-duration space flight.
- *Specific Aim II*: To **correlate in-flight alterations** of eye structure, ocular vascular parameters, and vision with headward fluid shifts, vascular dimensions and flow patterns.
- *Specific Aim III*: To **determine systemic and ocular factors of individual susceptibility** to the development of ICP elevation and/or vision alterations.
- *Outline the interaction of physiological systems in **VIIP** , and aid in guiding development of countermeasures and targeted treatments.*

# Fluid Shifts Before, During and After Prolonged Space Flight : Associations with ICP and Visual Impairment

- **PIs: Stenger, Dulchavsky & Hargens**
  - Total body water, extracellular and intracellular fluid volume will be determined by biochemical dilution techniques using Deuterium oxide and bromide ingestion
- Pre & postflight to include tilt table testing
- Ultrasound to assess upper/lower body interstitial fluid & vein diameter changes
- Ocular ultrasound & IOP measured



# Fluid Shifts Before, During and After Prolonged Space Flight : Associations with ICP and Visual Impairment

L-21/18 months — L-90 — // — FD45 — R-45 — // — R+1/3 — R+10 — R+30 — R+180

**L-21/18 months**
**MRI**
concurrent with
Med Ops schedule

**L-90**
**Day 1**
supine, upright sitting,
15° HDT baseline

**Day 2**
supine, 15° HDT
with LBNP

**FD45 / R-45**
**Day 1**
dilution measures

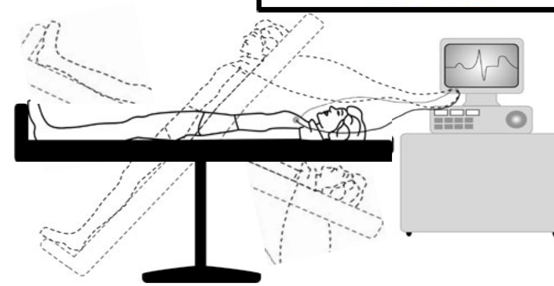
**Day 2**
all other baseline
measures

**Day 3**
Chibis LBNP - part 1

**Day 4**
Chibis LBNP - part 2

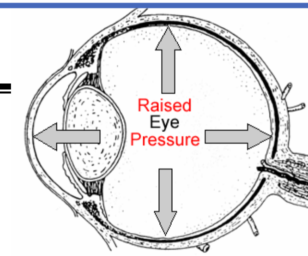
**R+1/3**
**MRI**
concurrent with
Med Ops schedule

**R+10 / R+30 / R+180**
**Single Day Sessions**
supine, upright sitting, 15°
HDT measures
No LBNP



# Fluid Shifts with In-Flight Chibis-M

Tonometry

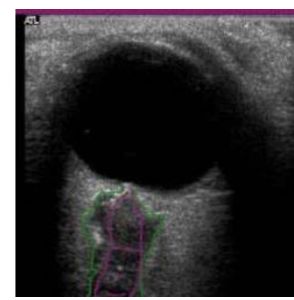



Fundoscopy

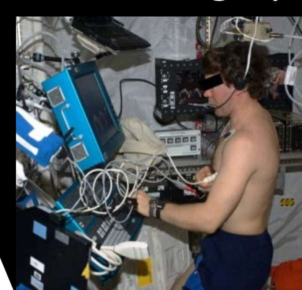
Chibis-M

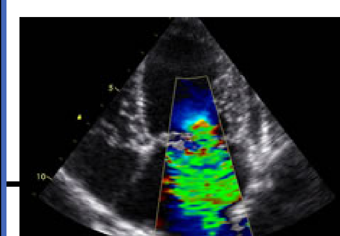
+ICP
Measurement
with CCFP

Ocular Ultrasound



Echocardiography





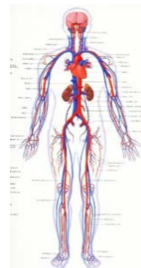
# Role of the cranial venous circulation in microgravity-associated visual changes

- PI: J. Buckey
- Problem- Cranial venous circulation may be important in microgravity-induced visual changes, but the interaction between fluid shifts and hydrostatic pressure changes in the circulation is complex.
- Overall Goal- Develop a numerical model of the cerebral venous circulation to provide an integrated understanding of the changes
  - Aim I - Develop numerical model
    - ✓ Incorporates circulatory system, CSF system, and eye
  - Aim II - Measure cranial venous changes during fluid shifts and hydrostatic pressure changes to validate the numerical model
    - ✓ Use MRI to measure cranial venous anatomy, compliance and flows during shifts
  - Aim III - Identify critical venous variants involved in maladaptation to fluid shifts
    - ✓ ID susceptible variants in Aim II and further study

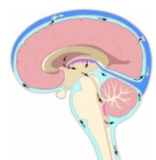
# VIIP1: Etiological Mechanisms and Contributing Risk Factors

## Environmental/Occupational

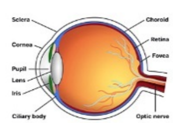
- ❑ ICP in Microgravity & resistive exercise



- ✓ CO2 Data mining headaches
- ➢ CO2 Data mining Vision



- ✓ Effects of gamma radiation on the retina

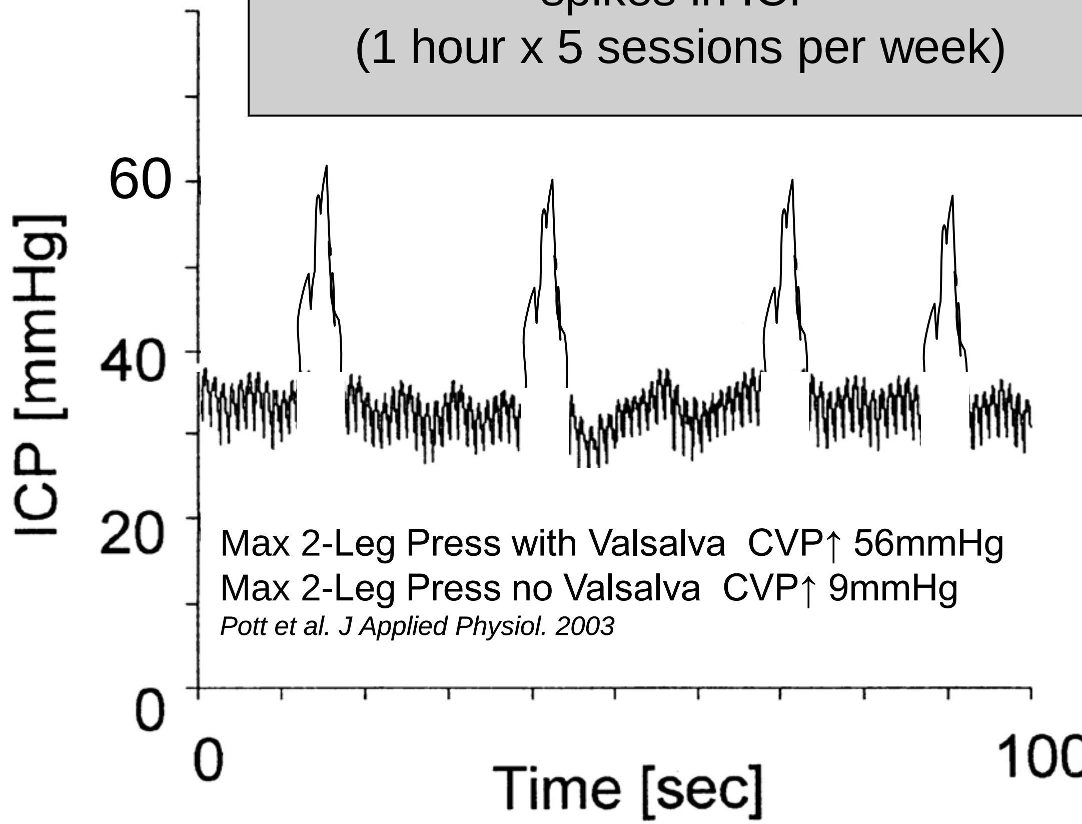

- ➢ Are Medications Involved in Vision and Intracranial Pressure Changes Seen in Spaceflight?
- ❑ Assessment of bedrest, CO2, Resistive Exercise & High Sodium (Envihab)

| | |
|---|---|
| HHC | ✓ Completed |
| NSBRI | ➢ Ongoing |
| SD | ❑ To start |

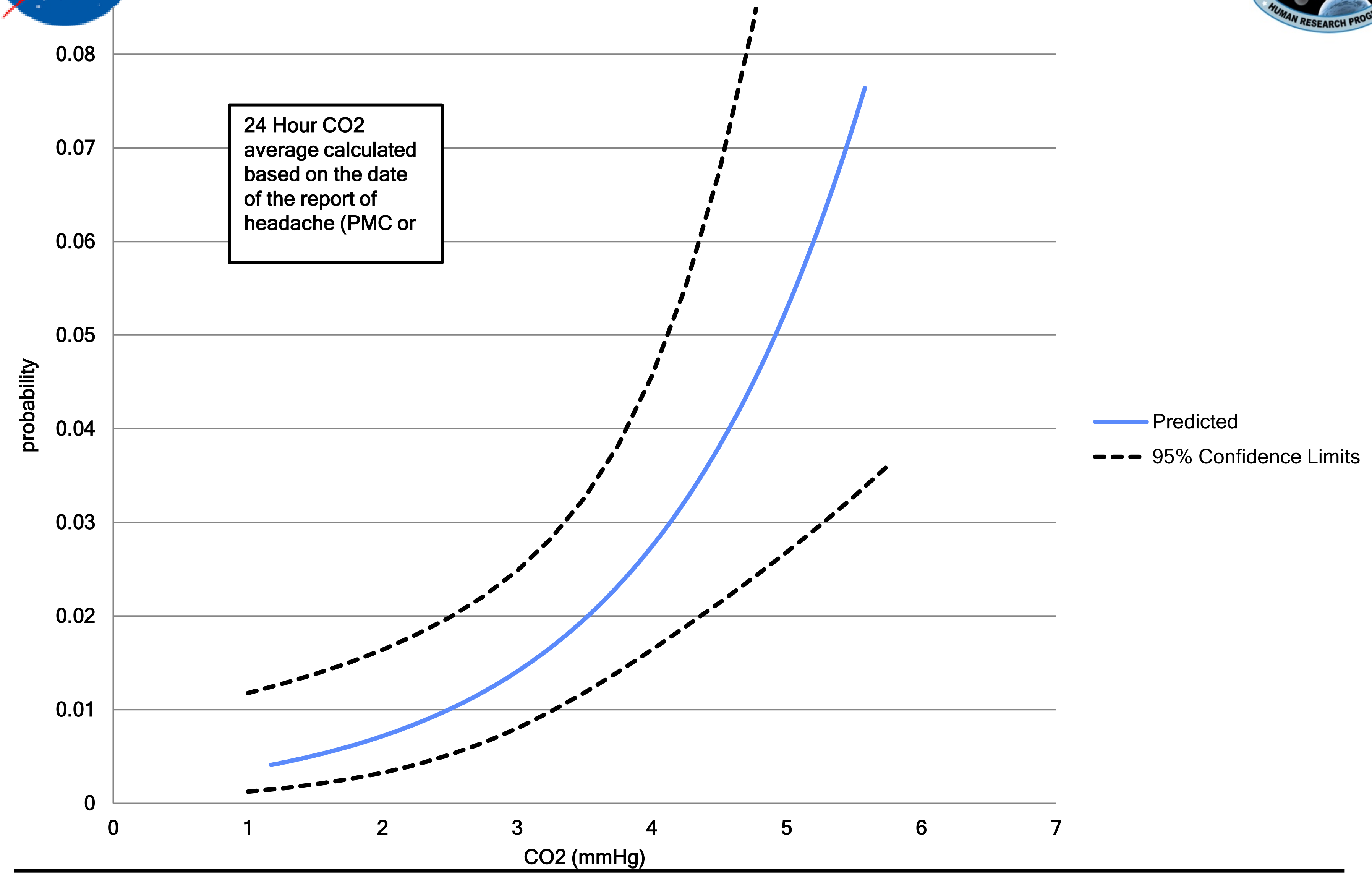
# Limit Resistive Training:

**Resistive Exercise**
Does in-flight resistance training cause additional transient elevations in ICP?

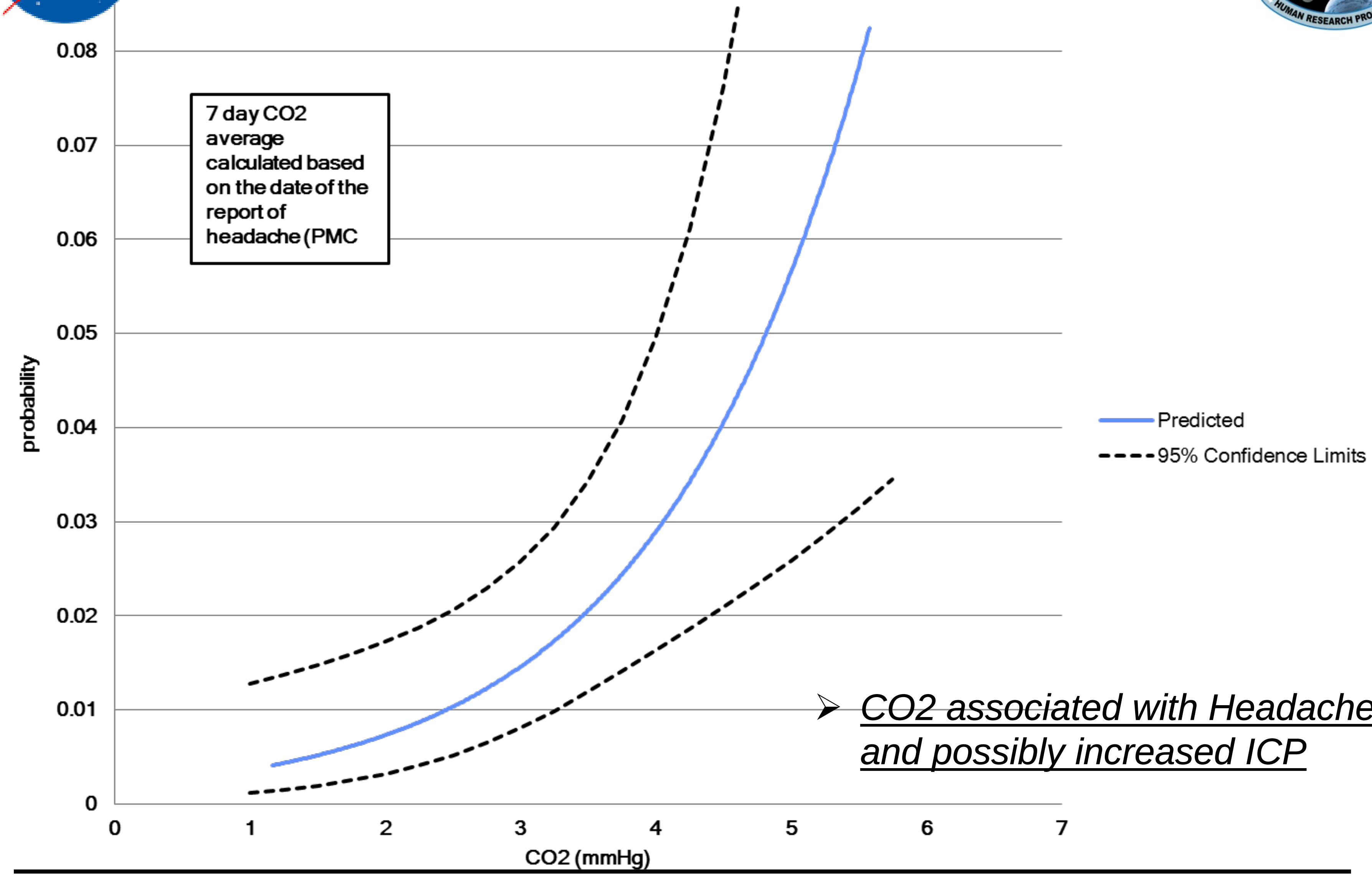
Resistive Exercise Repetitions causing spikes in ICP
(1 hour x 5 sessions per week)



# Predicted Probability of Headache Associated with 24 Hour Average CO2: Expeditions 2-31



# Predicted Probability of Headache Associated with 7 Day Average CO2: Expeditions 2-31

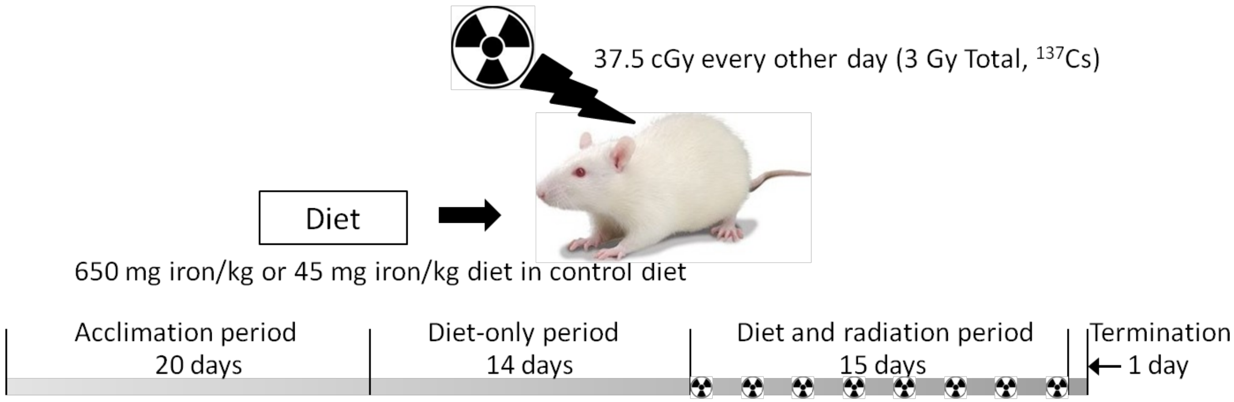


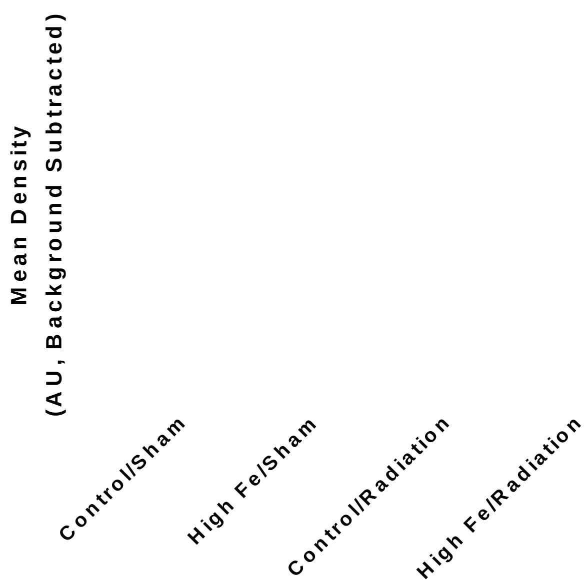

- ***CO2 associated with Headache and possibly increased ICP***

# Are Medications Involved in Vision and Intracranial Pressure Changes Seen in Spaceflight?

- **PI:** V. Wotring
- **Aims:** Determine if affected crewmembers use medications known to be associated with cardiovascular, visual changes and ICP elevations in terrestrial medical practice and to assess the likelihood of medications as causal agents in spaceflight-associated visual changes and ICP elevation. 38 medications in the ISS kit have the potential to affect BP/ICP/IOP (~ 35% of kit).
- **Clinical Applications: Treatment**
  - Avoidance of exacerbating medications, symptom reduction

# Effects of Gamma Irradiation (alone or combined with dietary iron overload) on the rat retina - (PI: S.Zanello- tissue sharing with S. Zwart)



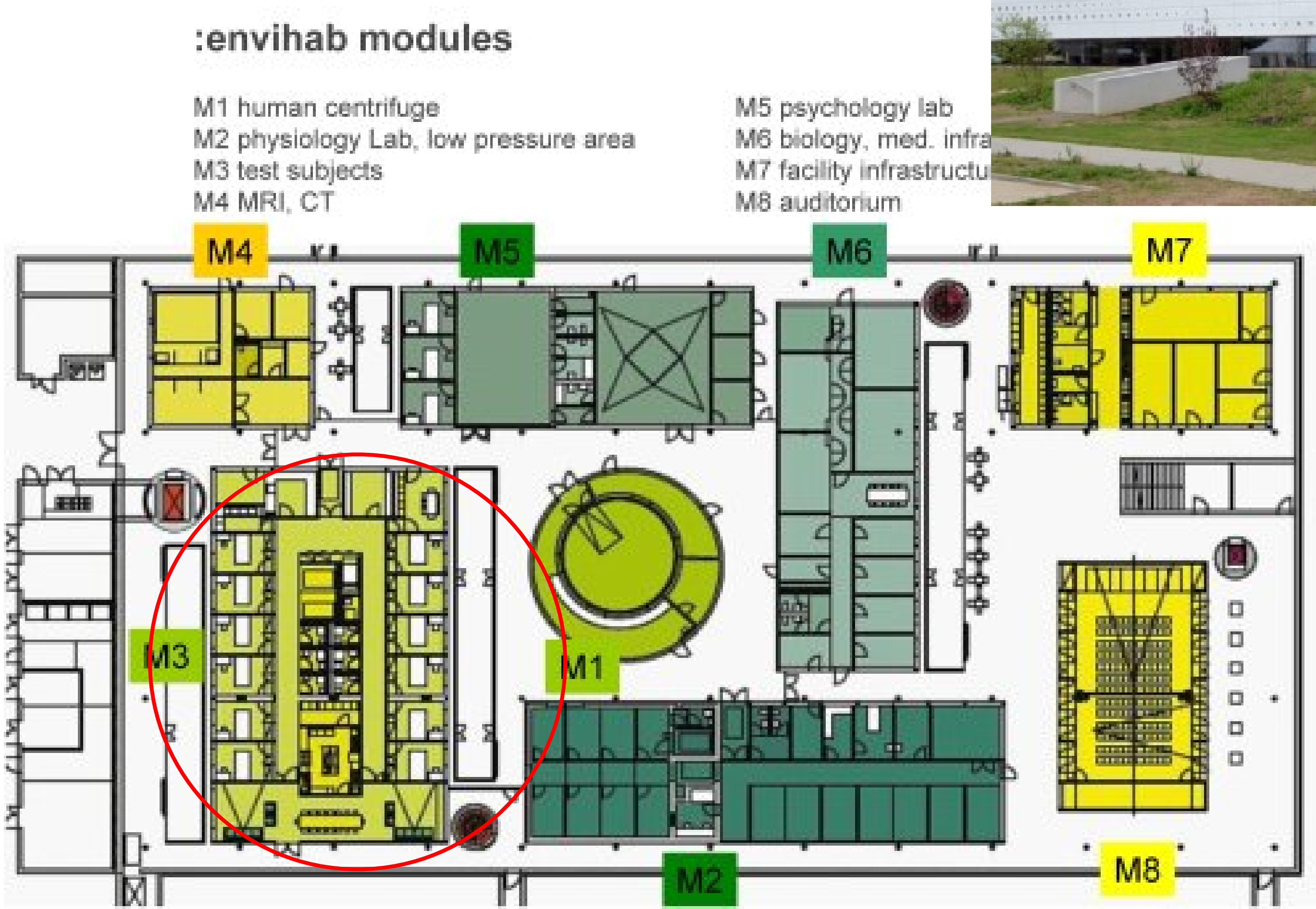

***<u>Oxidative stress-induced DNA damage</u> (measured as 8OHdG immunoreactivity <u>on retina histologic sections</u> (note the increase in 8OHdG density units for radiation compared to control). Similar results were observed on other cell layers of the retina***



(8-hydroxydeoxygaunasine (guanasine oxidative stress )

# Envihab-Bedrest

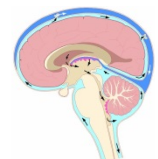
- HDT Bedrest, $CO_2$, resistive exercise, Sodium loading, & ICP measurement



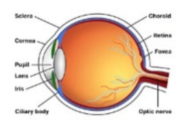
# VIIP3: Minimally Obtrusive Diagnostic Tools for Measurement and Monitoring

- ✓ Pilot-Non-invasive CVP Device

- ➢ Non-invasive ICP evaluation-Vittamed
- ➢ CCFP Clinical Database
- ➢ Comparison of Continuous Non-Invasive & Invasive ICP
- ➢ ICP Tech Search
- ❑ Validation of in-flight non-invasive ICP with LP



- ✓ SD/Upgrade Visual Acuity Software & In-flight Tonometer
- ✓ SD/Fundoscopy Trade Study
- ✓ SD/Development of In-Flight Fundoscopy
- ✓ SD/Diagnostic OCT Trade Study
- ✓ SD/Development in-flight diagnostic OCT
- ❑ Retinal Vascular Remodeling/VESGEN



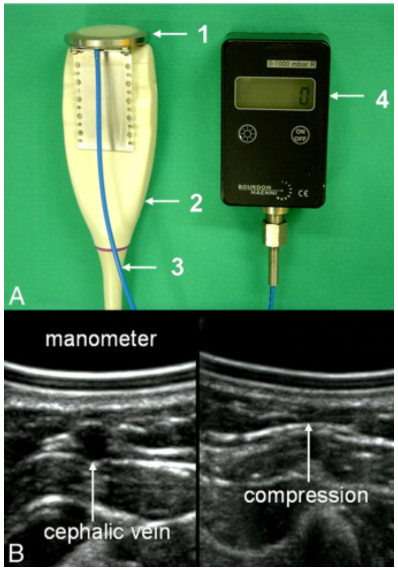

- ➢ Volumetric Ophthalmic Ultrasound

HHC
NSBRI
SD

- ✓ Completed
- ➢ Ongoing
- ❑ To start

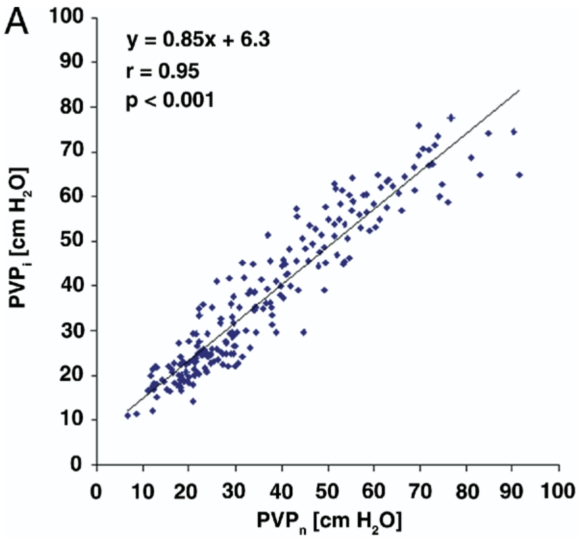
# Pilot study to Evaluate a Novel Non-Invasive Technology to Measure Central & Peripheral Venous Pressure

- **PI:** David Martin
- To confirm the relation between compression sonography as a non-invasive measure of peripheral venous pressure and CVP. Central venous pressure is one of the primary factors which have been hypothesized to contribute to the development of elevated ICPin astronauts during and after space flight.
- **Clinical Application: Diagnosis**
  - Measurement of CVP




(A) Pressure manometer connected to ultrasound transducer:
(1) translucent silicone membrane,
(2) ultrasound transducer,
(3) flexible pressure tubing,
(4) pressure meter.

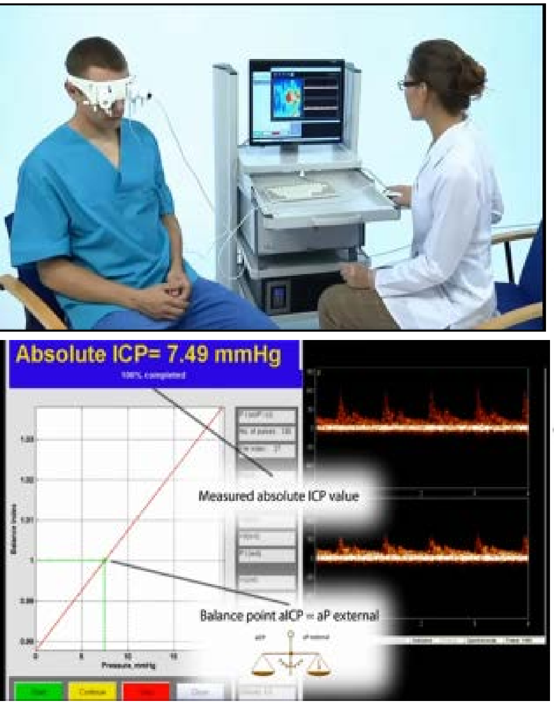
(B) Cross-sectional sonography: cephalic vein before and after compression.

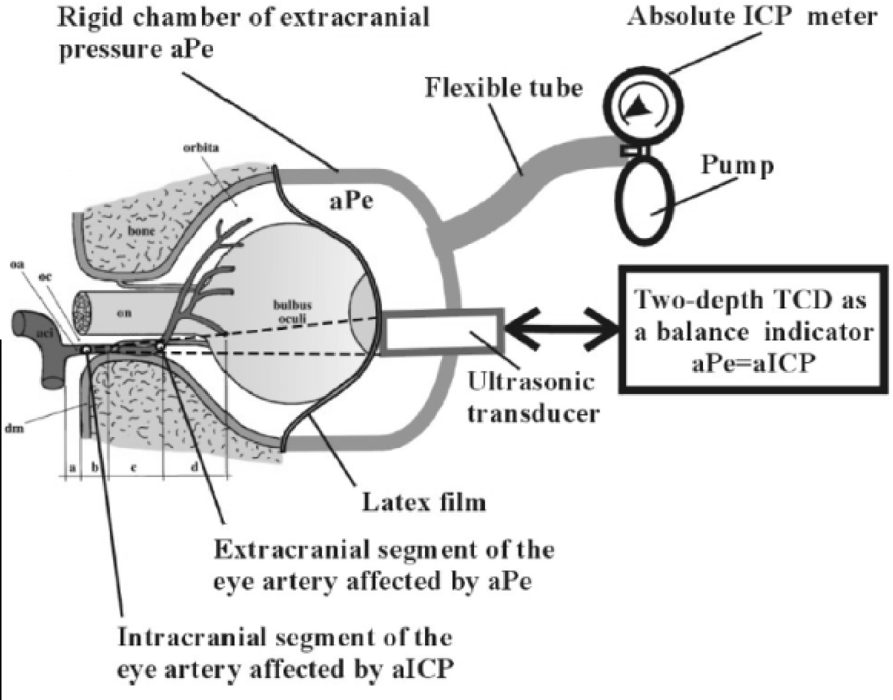


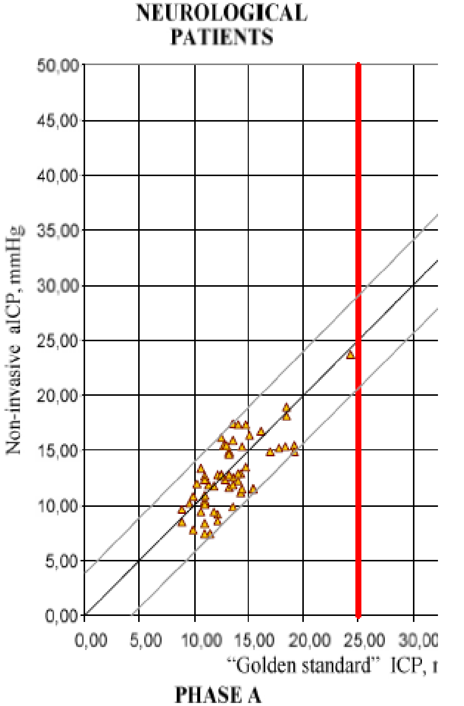

Thalhammer et al. Noninvasive CVP Measurement.
(A) Linear regression: positive correlation between PVPi and PVPn.

# Non-invasive ICP Device Purchase & Evaluation

- **PI:** Eric Bershad
- **Aims:** Evaluation and validation of the *Vittamed* non-invasive, absolute intracranial pressure measurement device
- Clinical Applications: Diagnosis & Treatment
  - Non-invasive measurement of ICP

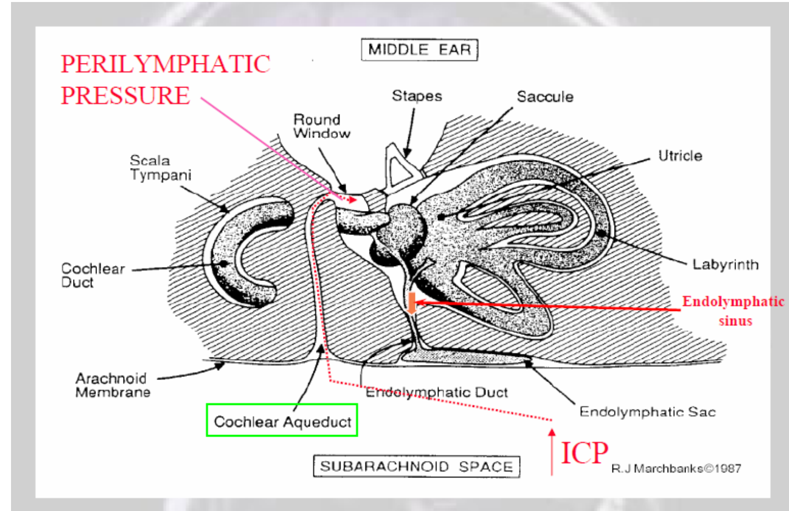


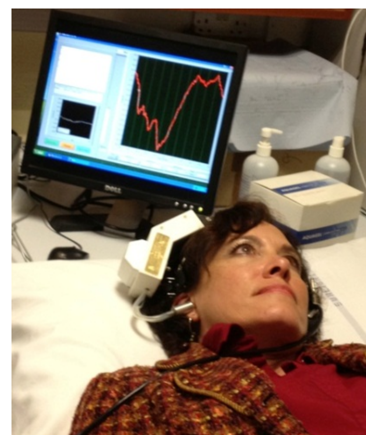
# Tympanic Membrane Displacement (TMD)

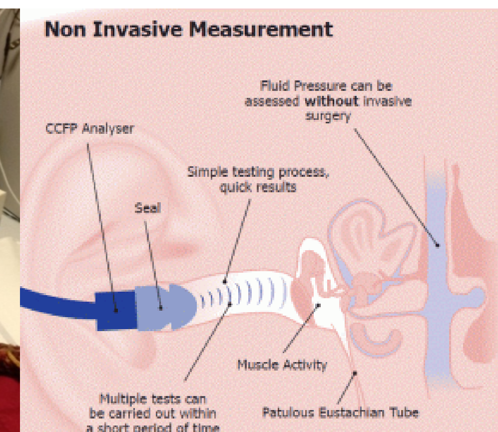
- Cerebral and Cochlear Fluid Pressure device (CCFP)




## How it works:

- Cochlear aqueduct connects perilymphatic space to subarachnoid space
- ↑ ICP distributes force to perilymph in cochlea
  - Affects resting position of Stapes via oval window
  - Alters the position of the tympanic membrane
- Measures the direction and volume in nanoliters of the tympanic membrane displacement in one of 2 modes:
  - Spontaneous (tympanic movement in response to cardiac/respiratory pulsations)
  - Elicited (in response to high intensity sound (~100 dB) which elicits the Stapedial reflex

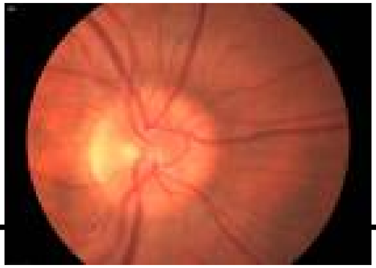




# 1. SD/Fundoscopy Trade Study
# 2. SD/Development of In-Flight Fundoscopy

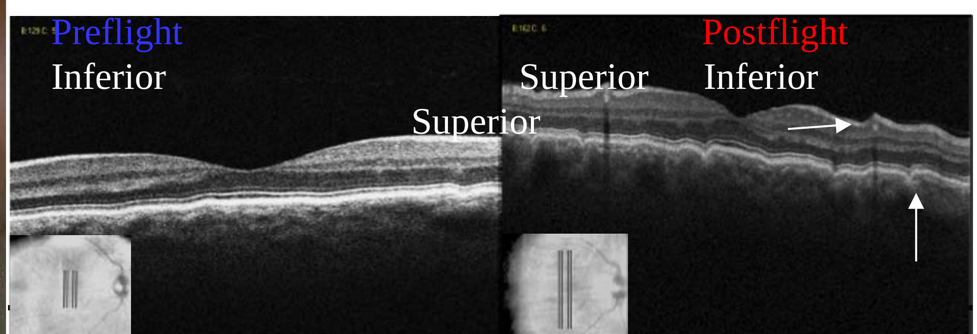
- The NASA Space Medicine group performed a trade study to identify the optimal fundoscopy device for both clinical and research use during flight.
- **Deliverables:** A fundoscopy device that can be developed into hardware for use during flight. In February 2012, HMS Hardware Team selected the MERGE EyeScan. Flight ready fundoscopy hardware.
- **Clinical Applications: Diagnosis**
  - High resolution digital imaging of the fundus

NASA Astronaut Karen Nyberg
Self-exam with Merge Eyescan fundoscope
Expedition 36

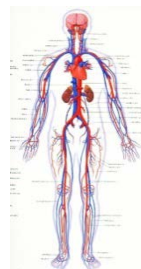


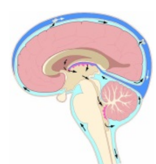
# 1. SD/Diagnostic OCT Trade Study
# 2. SD/Development of in-flight diagnostic OCT

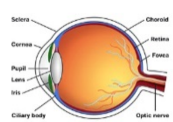
- The NASA Space Medicine group performed a trade study to identify the optimal optical coherence tomography (OCT) device
  - Heidleberg Spectralis with Eye tracking laser tomography
- The modified flight unit was delivered to ISS onboard the ESA Albert Einstein ATV that docked June 15.
- <u>Clinical Applications: Diagnosis, Treatment</u>
  - Early identification of choroidal and RNFL swelling
  - Early intervention, and treatment monitoring




# VIIP12: Ground-based Analogs & Models








- ❑ Optic Nerve/Sheath Remodeling Simulator

- ➢ Rodent HLS (Fuller/Zanello)
- ✓ Rodent HLS (Zanello)
- ➢ GRC/Digital Astronaut: VIIP modeling
- ➢ JSC/Digital Astronaut: VIIP modeling
- ✓ Cranial Venous Circulation in uG
- ❑ bedrest plus CO2, Resistive Exercise & High Sodium

HHC

NSBRI

SD

- ✓ Completed
- ➢ Ongoing
- ❑ To start

# Head-Down Tilt in Rats: A Model for Intracranial & Intraocular Pressures, & Retinal Changes During Spaceflight

**PI:** C. Fuller / S. Zanello

- 90 day HLS= 2.5 Year Mission
- Male & female
- Young and old
- $CO_2$ challenge (1%)
- Telemetry: Instrumented rodents
  - Continuous ICP monitoring
  - IOP
- MRI Pre/In/post (30,60,90d)
- OCT Pre/In/post (7,14,28,90d)
- Histology
- Post suspension recovery time
- Controls: No suspension

- Cohort 1
- 33 Young adult male rats
- 33 Controls

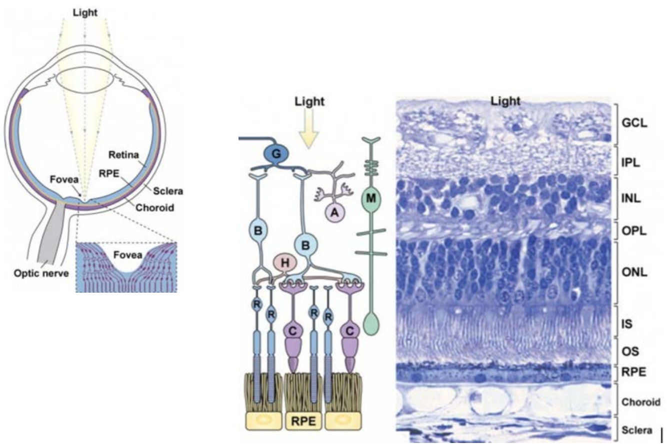
- Cohort 2
- 33 Middle age male rats
- 33 Controls

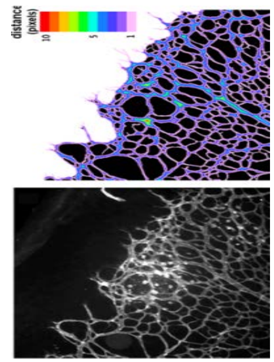
- Cohort 3
- 33 Young female rats
- 33 Controls

- Cohort 5
- 33 Middle age male rats, 1% $CO_2$
- 33 Controls

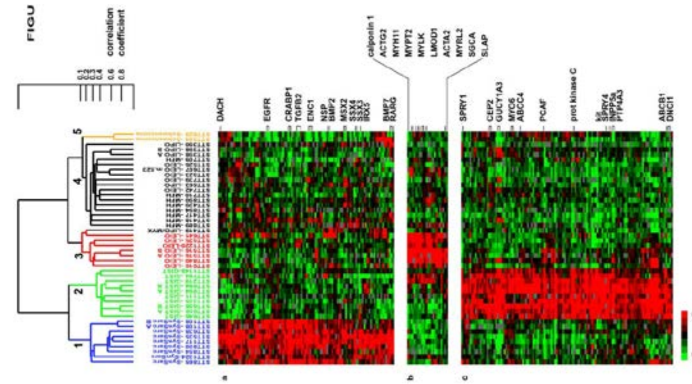
# Head-Down Tilt in Rats: A Model for Intracranial & Intraocular Pressures, & Retinal Changes During Spaceflight

**Retinal Histopathology** | **Vascular Remodelling** | **Retinal Gene Expression Analysis**



VESGEN



- **Deliverables:** A validated rodent analog and the influence of gender, age, $CO_2$ on ICP and IOP in the VIIP syndrome
- **Clinical Applications: <u>Knowledge, Diagnosis & Treatment</u>**
  - Interaction of ICP:IOP and TLPG on the retina
  - Influence of $CO_2$ on ICP:IOP
  - Aquaporin expression & CSF production in the choroid plexus
  - Arachnoid Granulation function & resporbtion of CSF

# VIIP13: Preventative and Treatment Countermeasures

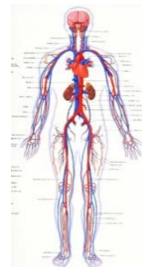
- ❑ Aerobic Exercise

Mechanical:

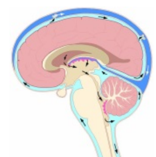
- ❑ Braslet
- ❑ Abdominal LBNP

Drug:

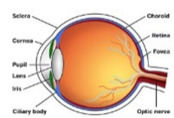
- ❑ Venous Capacitance Augmentation
- ❑ Afterload reduction (ACEI)



- ❑ ICP Drug Countermeasure (Acetazolamide, ANP, AQP1/4 antagonist)



- ❑ Raise IOP (Ibopamine)



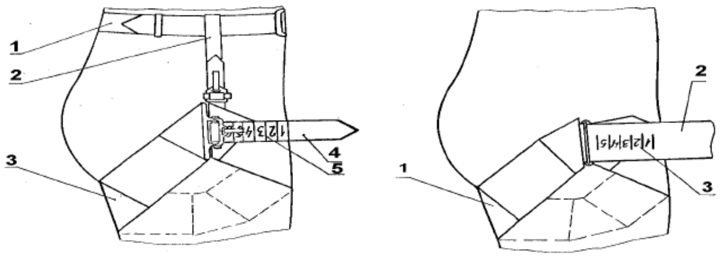

- ➢ Fluid Shifts
- ❑ CM Flight Validation (combination CM)
- ❑ Fluid Shifts "2"
- ❑ NSBRI/Envihab Bedrest VIIP CM

- ✓ Inflight CO2 Reduction

| | |
|---|---|
| HHC | ✓ Completed |
| NSBRI | ➢ Ongoing |
| SD | ❑ To start |

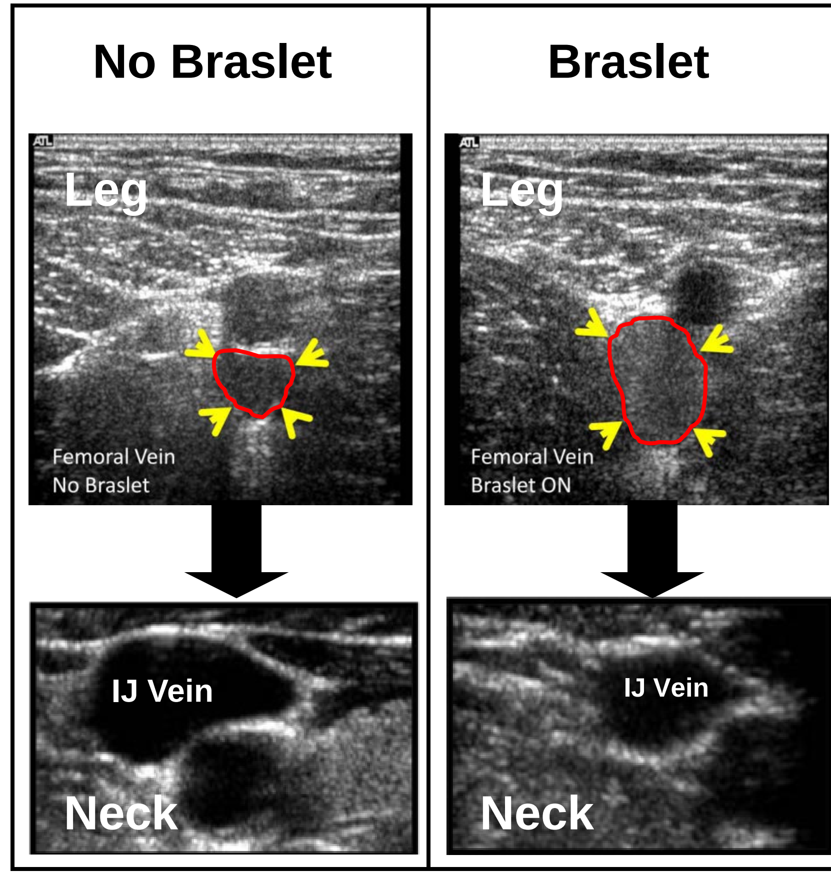
# U.S. - Russian ISS In-flight Braslet Occlusion Cuff Study

Hamilton et al. *Cardiac and vascular responses to thigh cuffs and respiratory maneuvers on crewmembers of the International Space Station.* *J Appl Physiol* 112: 454–462, 2012



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

Sequesters venous blood in the legs




Duncan et al. NASA SDTO 17011

# U.S. - Russian ISS In-flight Braslet Occlusion Cuff Study

- 14 sessions on 9 ISS crew members
- Average exposure to uG at time of measurements=122 days

| uG Measures % 1G Baseline | Braslet Off | Braslet On |
|---|---|---|
| Femoral Vein X-section | 0.58 $cm^2$ | 1.02 $cm^2$ * |
| Internal Jugular Vein X-section | 1.23 $cm^2$ | 0.95 $cm^2$ |
| Left Ventricular Stroke Volume | 69.3 $cm^3$ | 60.7 $cm^3$* |
| Cardiac Output | 4.18 L/min | 3.37 L/min* |

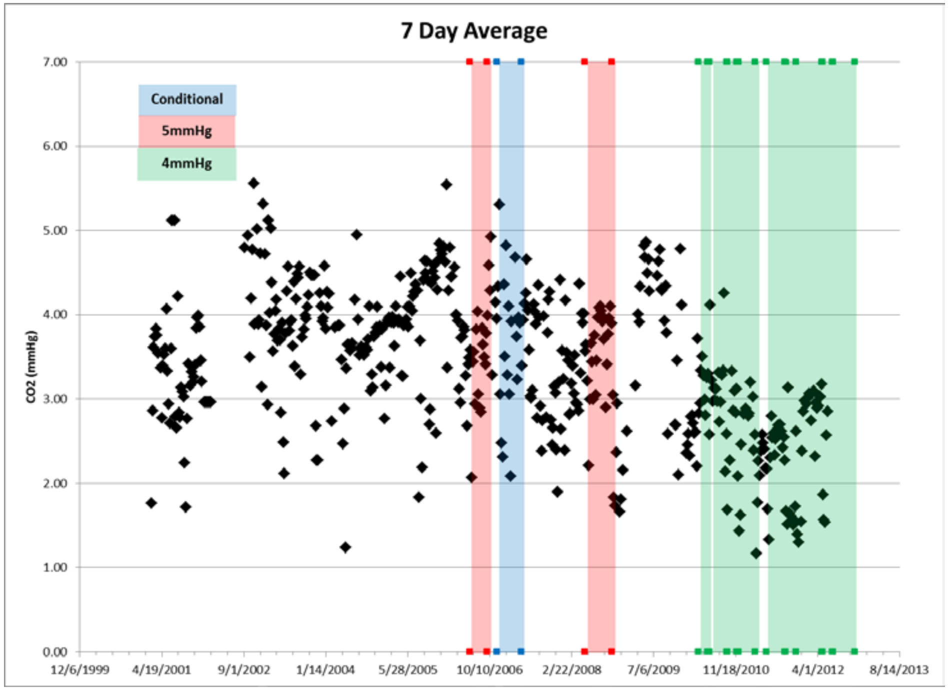
* Significant Difference

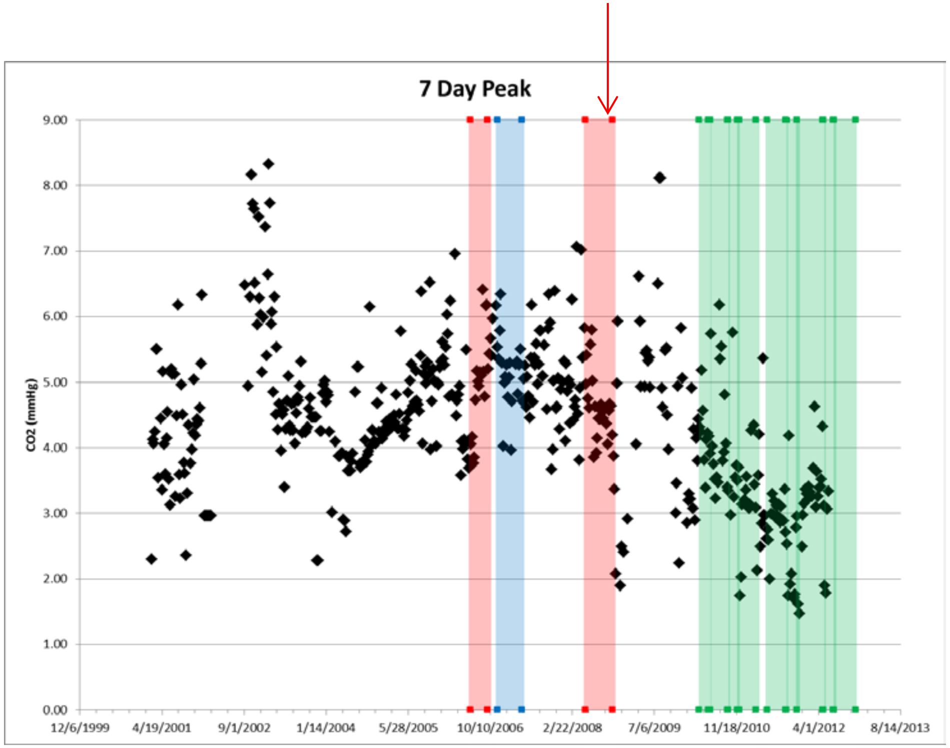
➢Once Braslet is applied responses trend more similarly to terrestrial values
➢Braslet and impact on ICP? (Likely lowers)



Duncan et al. NASA SDTO 17011

# $CO_2$ Levels on ISS: 7-Day

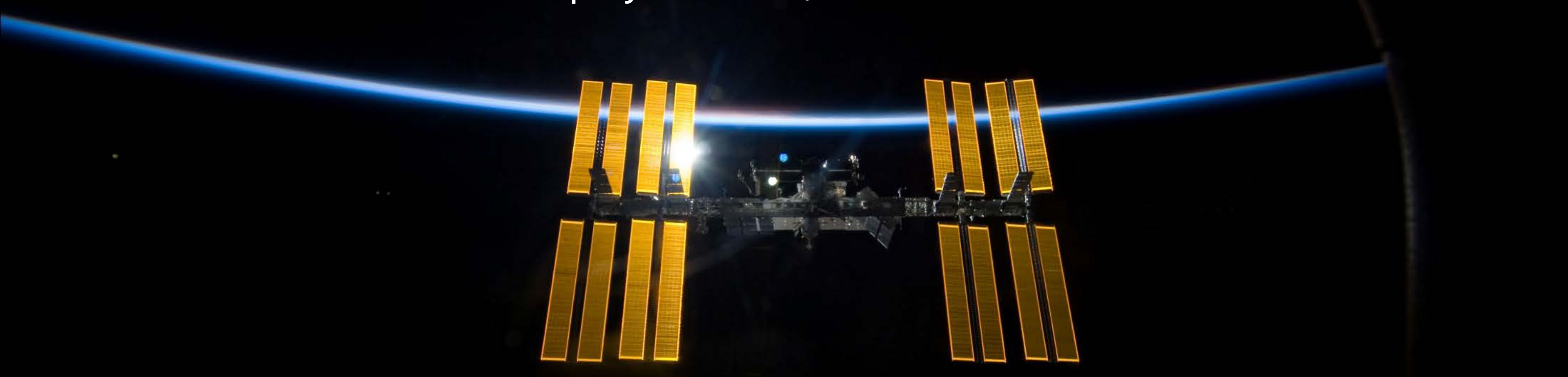



- Note: CO2 level for time period of SMOT Notes
- Since CO2 Reduction CHIT instituted, incidence of papilledema among ISS crew has dropped from 25% to 18%
- *<u>Is CO2 a significant contributor to VIIP?</u>*

# THE VISUAL IMPAIRMENT INTRACRANIAL PRESSURE RISK IN LONG DURATION U.S. ASTRONAUTS: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Christian Otto, M.D., M.MSc.
Lead Scientist, NASA VIIP Risk
Yael Barr, M.D., MPH
Deputy Scientist, NASA VIIP Risk

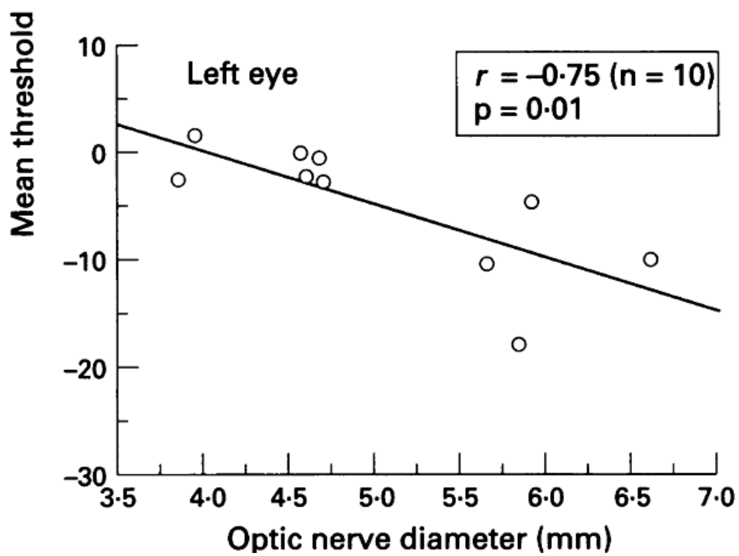


NSBRI Headquarters, Biosciences Collaborative
Houston, TX
Monday February 10, 2014.

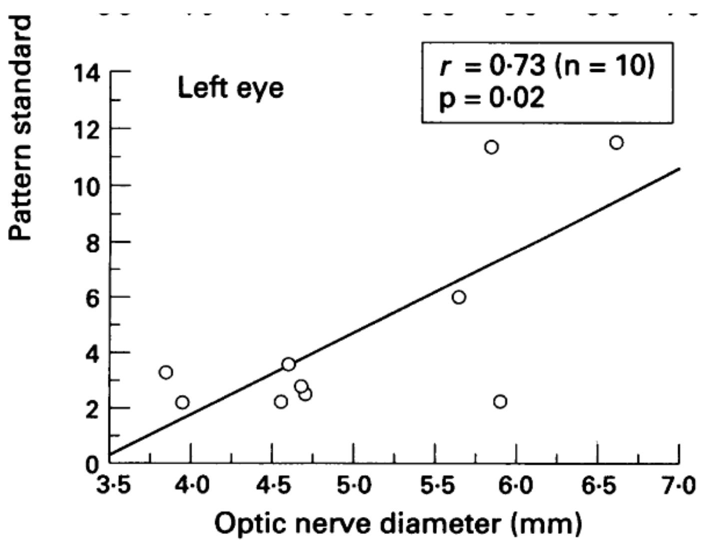
# Correlation of ONSD & Visual Field Deficit

- T. Salgarello et al. ***Optic nerve diameters and perimetric thresholds in idiopathic intracranial hypertension.*** British Journal of Ophthalmology 1996;80:509-514
- 20 patients with IIH (mean age=47) papilledema grade 1.1(range 0-4), 20 controls
- CSF pressure=260-320mmH2O, Mean duration disease=7.65 years
- Perimetric defects in 70% of eyes (28/40)
- Deficit associated with papilledema grade

MD: Average deviation from age matched controls

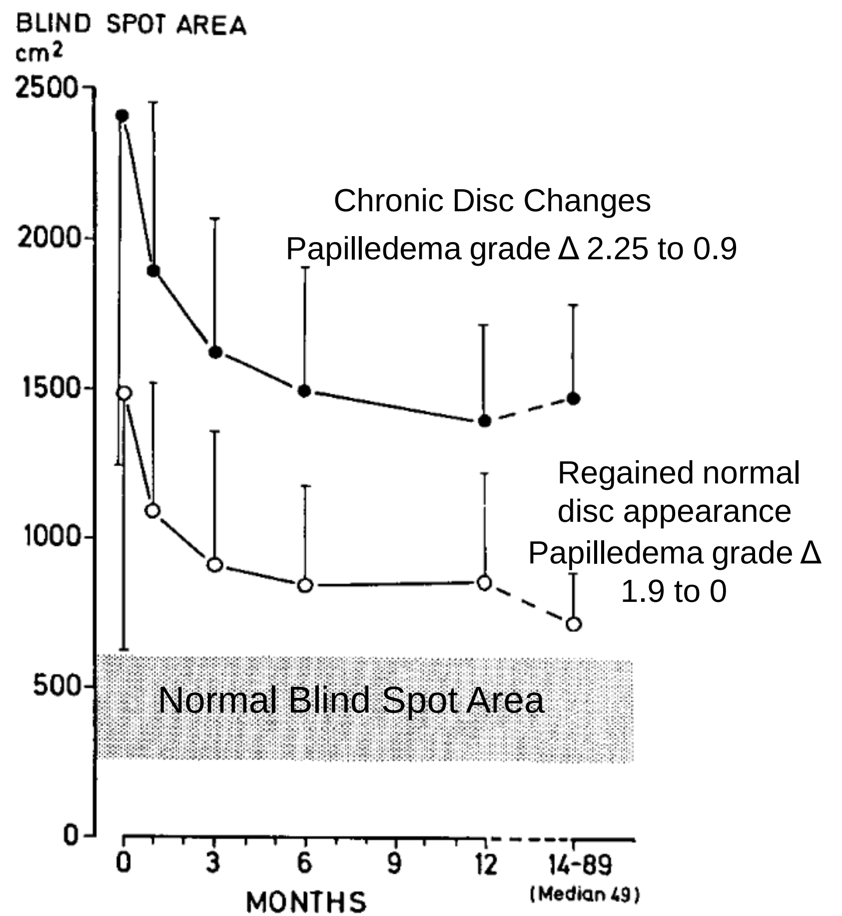



PSD: Measure of visual field irregularities



# Blind Spot Enlargement Following Papilledema

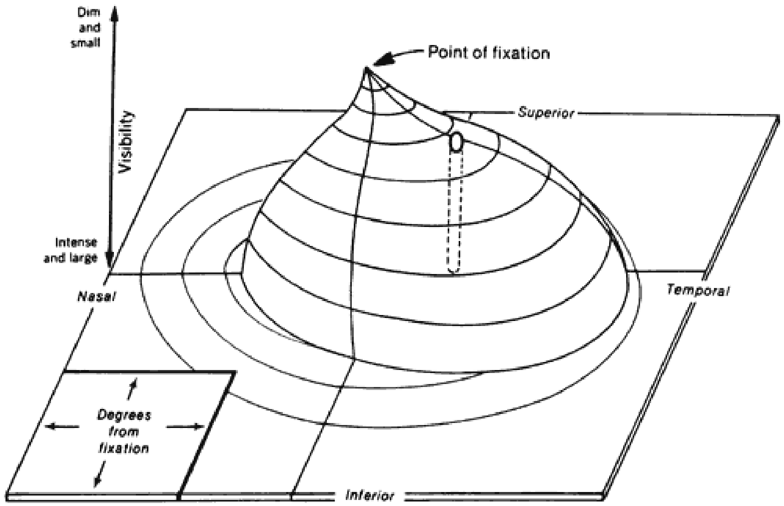
- Sorenson et al. **Clinical course and prognosis of pseudotumor cerebri. A prospective study of 24 patients.** Acto Neurol Scand., 1988:77:164-172
- 24 IIH patients, symptoms present 1-30 months
- Median CSFp=25mm Hg (range 8-45), all had papiledema initially
- Followed for 49 months, treated with Diamox and diuretics 6-18 months
- Patients who regained normal disc (50%) had shorter duration of disease (median=4 months) vs those who developed chronic changes (median=12months)
- Visual field testing not conducted



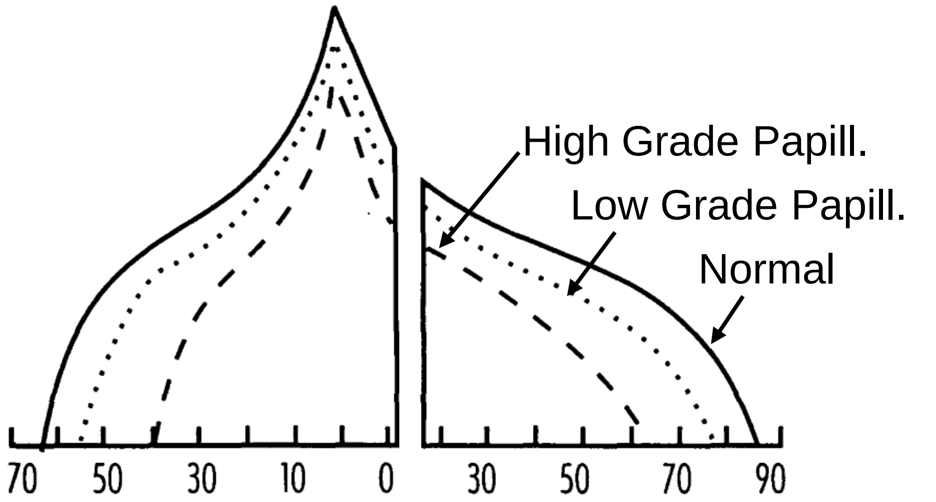
# Visual Loss Associated with Papilledema Grade

- *M.Wall.* **Asymmetric Papilledema in Idiopathic Intracranial Hypertension: Prospective Interocular Comparison of Sensory Visual Function.** IOVS, Jan.1998, Vol. 39, No. 1
- 9 IIH patients (mean age=31.8) with asymmetric papilledema 2+ grade diff.
  - High grade=3 (2-5) vs Low grade=1 (0-2)
- Mean CSFp=347.2 mm $H_2O$
- Visual loss most prominent in eye with higher grade papilledema
- High grade papilledema should be regarded as a risk factor for visual loss

**The Visual Island**



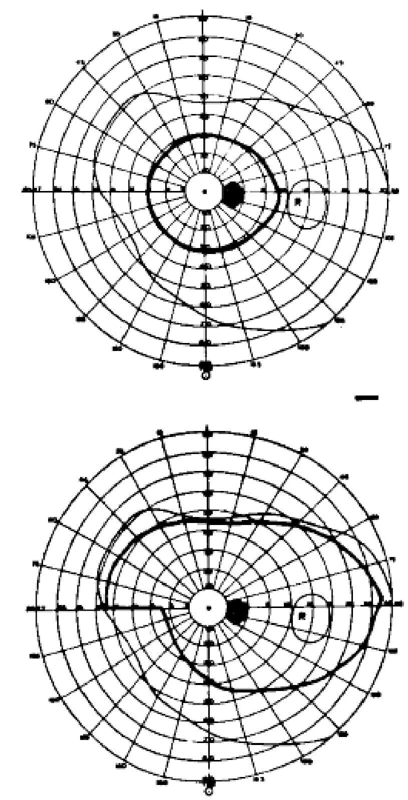

**Depression of the visual island with increasing papilledema grade**



# Mild Papilledema and Visual Field Loss

- *G. Rebolleda* et al. ***Follow-up of Mild Papilledema in Idiopathic Intracranial Hypertension with Optical Coherence Tomography.*** IOVS. 2009 Vol 50, No 11
- N=22, mean age=40, recent diagnosis of IIH
- Mild papilledema, mean= Frisen 2 (range 1-3)
- Mean CSFp=35cmH2O (range 25.5-45)
- 1 Year follow-up:
    - Perimetry: 66% normal VF, 18% enlargement blind spot, 16% irreversible field loss
    - OCT: 10 RNFL thinner than normal (3 visual field constriction, 3 inferonasal defects, 1 had a scotoma)
- RNFL swelling and attrition may occur simultaneously
- Perimetry needed with OCT, since OCT cannot distinguish between decreased swelling vs axonal loss
- *Both OCT and perimetry required for F/U*

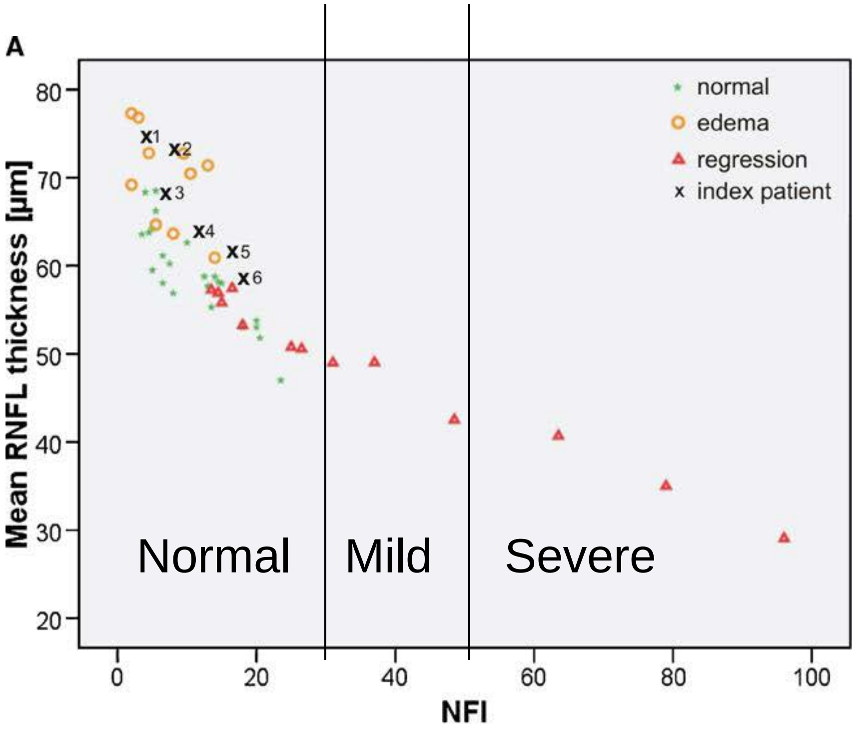
PERIPHERAL CONSTRICTION



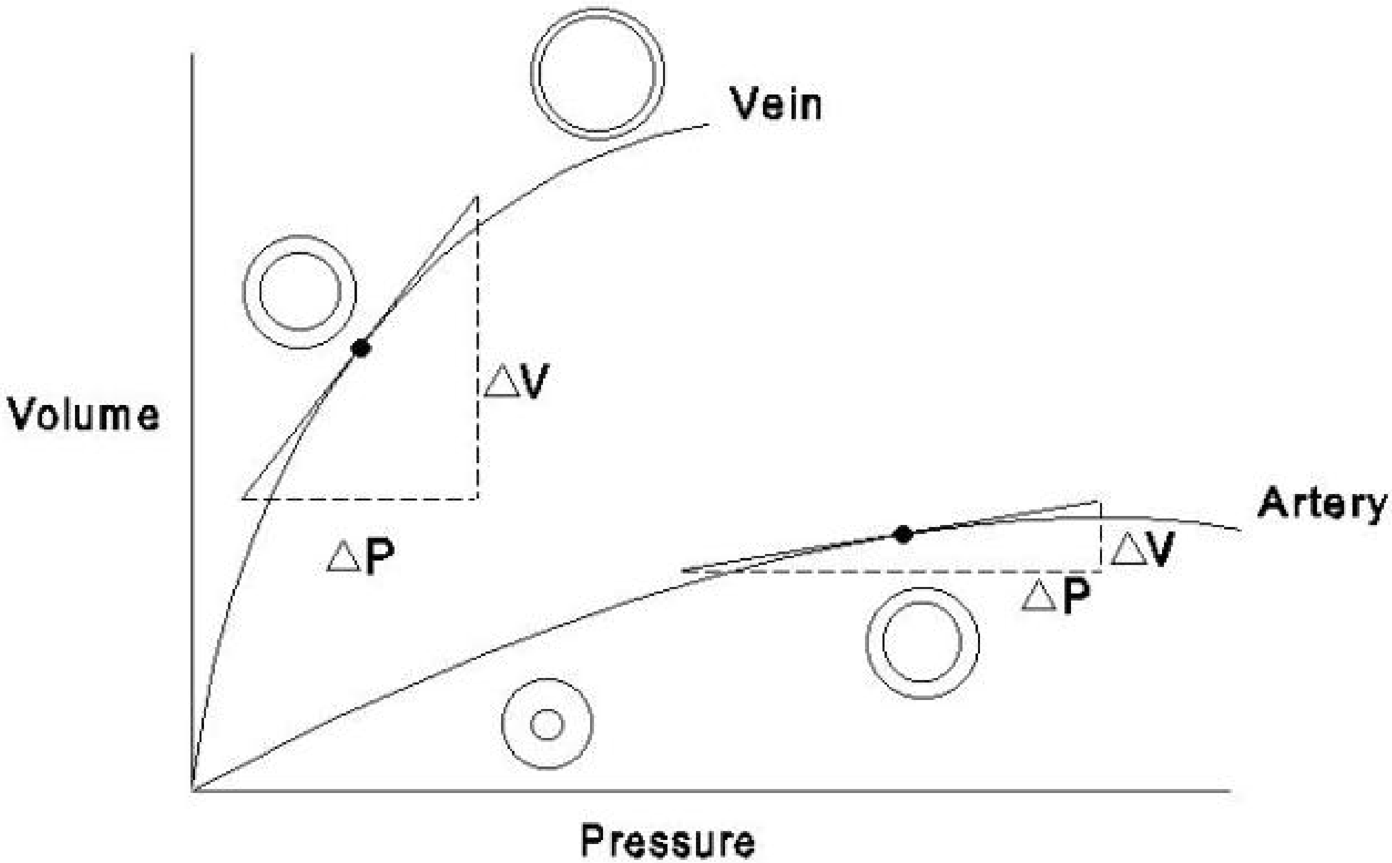
INFERO-NASAL STEP

# Visual Field Damage Following Regression of Papilledema

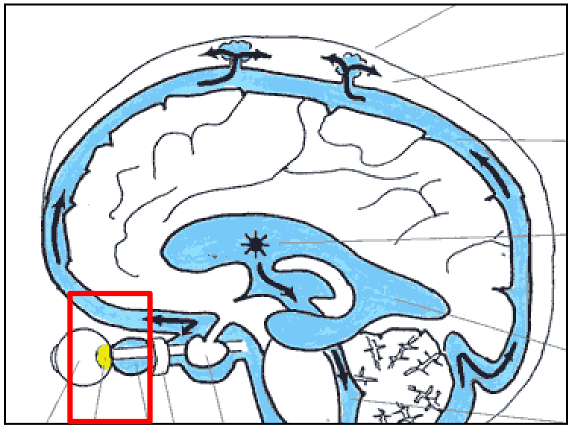
- R. Laemmer. ***Detection of nerve fiber atrophy in apparently effectively treated papilledema in idiopathic intracranial hypertension.*** Graefes Arch Clin Exp Ophthalmol (2010) 248:1787-1793
- 23 IIH patients, mean age 33.8, 23 controls
- Mean follow-up in patients with regression of papilledema=27 months
- 8/13 (63%) regressive papilledema group had mild-moderate concentric visual field damage-superior and inferior regions
- Patients with papilledema, only 1/10 detectable visual field loss
- Data show significant reduction RNFL as a sign of axon loss in patients with apparently treated papilledema
- Minor loss of axons will be masked by structure of retina, with overlapping receptive fields. Thus, 40% of RNFL may be lost before occurrence of visual field damage



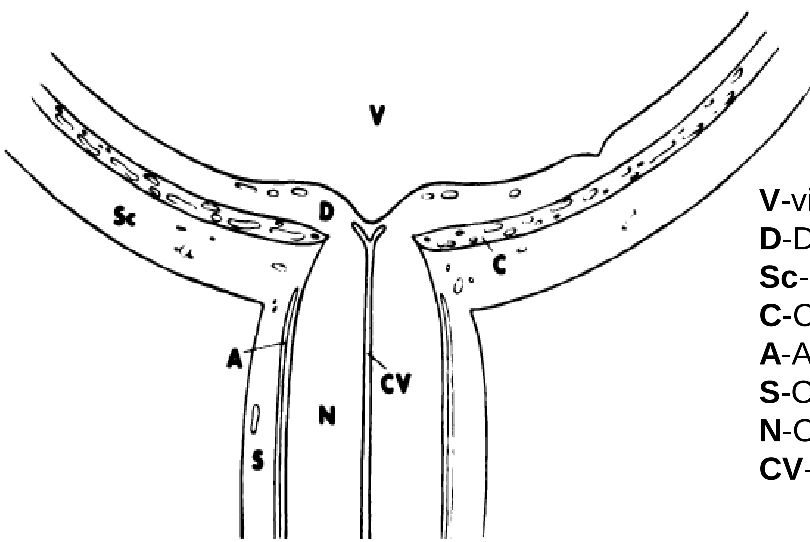
# Increased Volume=Increased Pressure



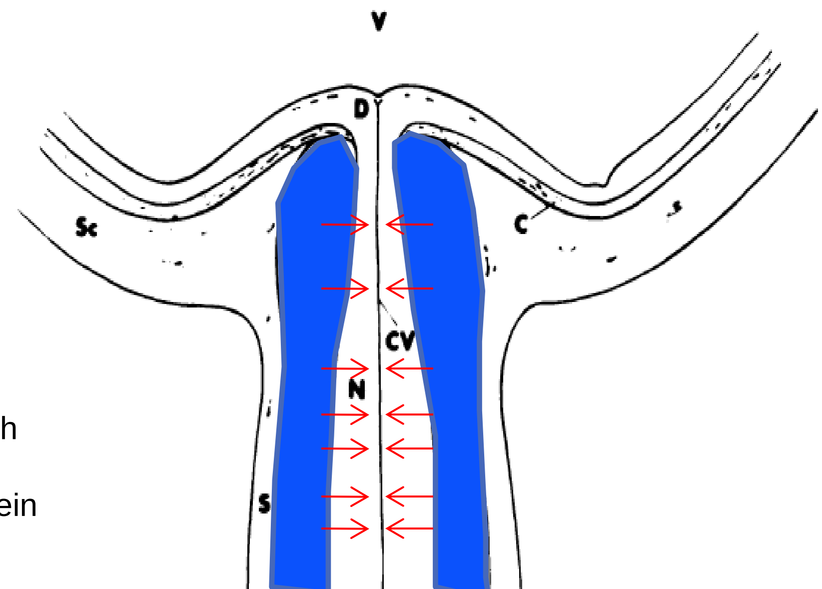
# Ocular Venous Hypertension via Optic Nerve Compression



- Increasing ICP transmitted to optic nerve via CSF space causes compression of optic nerve
- Axoplasmic flow inhibited resulting in papilledema-swelling and protrusion of the optic nerve head



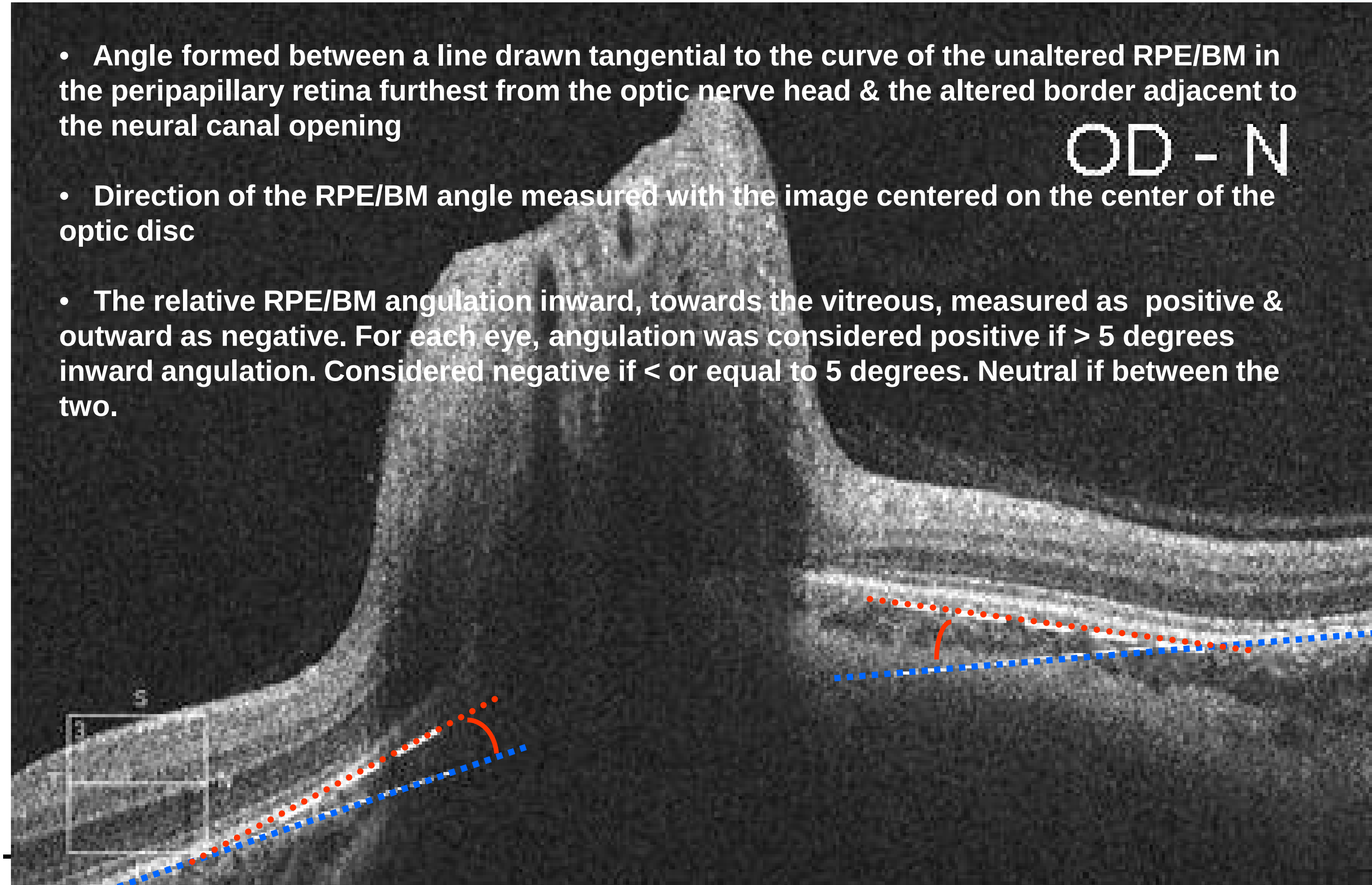

**V**-vitreous
**D**-Disc
**Sc**-sclera
**C**-Choroid
**A**-Arachnoid space
**S**-Optic nerve sheath
**N**-Optic Nerve
**CV**-Central retinal vein




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

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

# Measurement of the RPE Angle



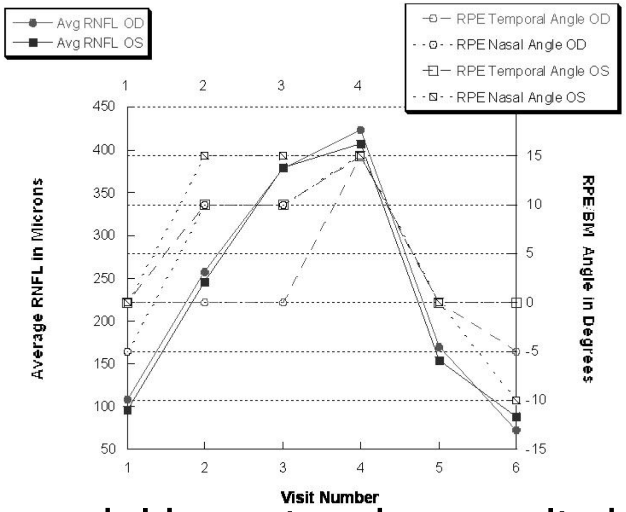

- Angle formed between a line drawn tangential to the curve of the unaltered RPE/BM in the peripapillary retina furthest from the optic nerve head & the altered border adjacent to the neural canal opening

- Direction of the RPE/BM angle measured with the image centered on the center of the optic disc

- The relative RPE/BM angulation inward, towards the vitreous, measured as positive & outward as negative. For each eye, angulation was considered positive if > 5 degrees inward angulation. Considered negative if < or equal to 5 degrees. Neutral if between the two.

# RPE Angle Results

- Positive angulation of the RPE/BM borders 20/30 eyes (67%) Mean inward RPE/BM angle was +1.5 degrees temporally and +2.5 degrees nasally.
- Patients with papilledema: angulation changed with alterations in the RNFL thickness. For all 30 papilledema eyes, the amount of change in the nasal RPE/BM angle (Spearman r = 0.63, p = 0.01) correlated with the change in average RNFL




- Papilledema with intracranial hypertension results in an inward bowing of the RPE/BM layer at the NCO
- Reflects deformation of the underlying peripapillary sclera and lamina cribosa in response to an elevated pressure gradient [globe flattening]
- The degree of structural stiffness can vary among patients, & influences the deformation of the optic nerve. Thus, two patients may respond differently to same CSPp