# Zero-G and ICP: Invasive and Noninvasive ICP Monitoring of Astronauts on the ISS (Williams, Malm) & Multimodal Modeling Towards Noninvasive Assessment of ICP in Weightlessness and Biomarker Identification of Predisposition To VIIP Syndrome (Zanello)

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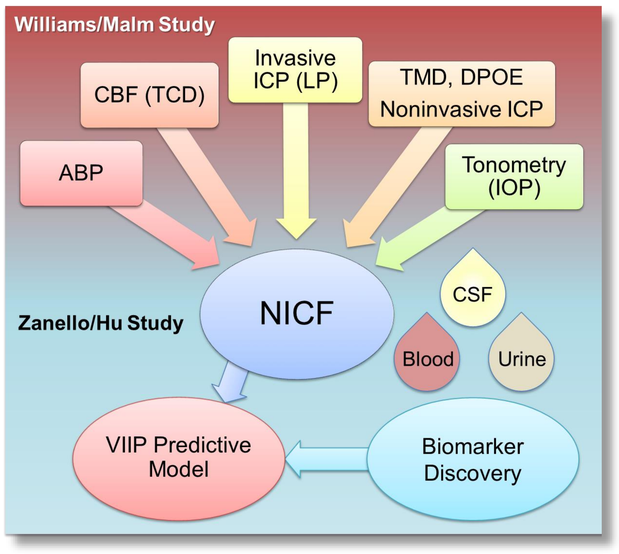
## INTRODUCTION

- This international project, supported by NASA (PIs: Williams and Zanello) and the Swedish National Space Board (PI: Malm), comprises 3 complementary studies addressing the high priority risk of Visual Impairment and Intracranial Pressure (VIIP) in astronauts. The project is under the study integration and flight definition phases.
- This project will investigate the physiological evidence of intracranial pressure (ICP) in long-duration spaceflight, using both invasive and noninvasive methods, and will use noninvasive measures plus biomarkers as input to build a predictive model that will inform the likelihood of a given crew member developing VIIP post flight.




## RELEVANCE

**a) First-ever study of invasive ICP measurement in astronauts, providing direct physiologic evidence to determine whether VIIP is associated with alterations of ICP in long-duration spaceflight.**

**The ICP research goals are:**

**1) To identify whether the pre-flight ICP pattern is normal or abnormal, and whether it predicts the risk for in-flight development of abnormal ICP**

**2) To identify whether and when ICP becomes abnormal during long-duration spaceflight**

**3) To determine whether and when post-flight ICP returns to baseline after return to Earth.**

**b) Evaluate and validate indirect, non-invasive ICP measurement techniques, including the tympanic membrane displacement (TMD) CCFP Analyzer and distortion product otoacoustic emissions (DPOAE).**

**c) Validate and further develop an algorithm for estimation of ICP using multiple modalities of ICP-related noninvasive measurement, the Noninvasive Intracranial Pressure Framework (NICF)**

**d) Measure intraocular pressure (IOP) with an applanation resonance tonometer to test the hypothesis that an imbalance between IOP and ICP contributes to VIIP.**

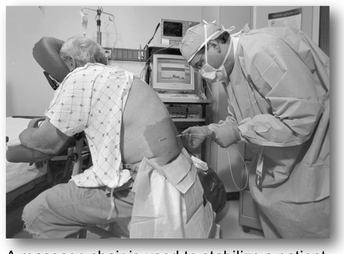
**e) Use molecular biomarker discovery approaches, to investigate biomarker signatures from CSF, blood, and urine indicative of predisposition to VIIP.**

## SELECTION OF INVASIVE ICP METHODS

- The selection of the invasive ICP method reflects a balance of potential risks and expected benefits.
- NASA has not made a final selection for the invasive ICP method. Options include:
- Methods that must be inserted in flight:
  1) Prolonged recording via LP needle
  2) Temporary spinal catheter
  3) Intracranial methods (catheters, parenchymal microtransducers)
- Methods that can be implanted pre-flight
  1) Telemetric ICP sensor (e.g., Raumedic)
- LP is a safe procedure that has a very small risk in comparison to the benefit of obtaining accurate ICP measurement to resolve the role of ICP in VIIP.
- While an implanted telemetric ICP sensor may seem appealing, the implantation procedure requires general anesthesia and a small craniotomy, which carries a small rate of significant risks (e.g., brain hemorrhage, postoperative wound infection, seizures, or delayed infection), and the long-term accuracy of telemetered ICP is uncertain.
- We recommend that the only method that is feasible and safe for short-term or long-term ICP monitoring of astronauts on the ISS is LP.

## Possible LP Procedure on the ISS

- 3 Astronauts to perform the LP
  - 2 Sterile: One to insert the needle and one to assist
  - 1 for situational awareness and oversight
- Method to secure the astronaut having the LP and the astronaut inserting the needle
- Transparent tent-like glovebox to maintain sterile environment and prevent equipment or CSF from floating away



A massage chair is used to stabilize a patient for lumbar puncture for spinal catheter insertion. This method can be adapted to secure an astronaut on the ISS for LP.

**Proposed Study Time Points**

| PRE-FLIGHT | | IN-FLIGHT | | POST-FLIGHT | |
|---|---|---|---|---|---|
| L-270 to L-180 | L-45 | FD 30 | FD 170 to FD 180 | R+14 | R+90 |
| LP Noninvasive ICP Specimen Collection | Noninvasive ICP | LP Noninvasive ICP Specimen Collection | LP Noninvasive ICP Specimen Collection | LP Noninvasive ICP Specimen Collection | Noninvasive ICP |

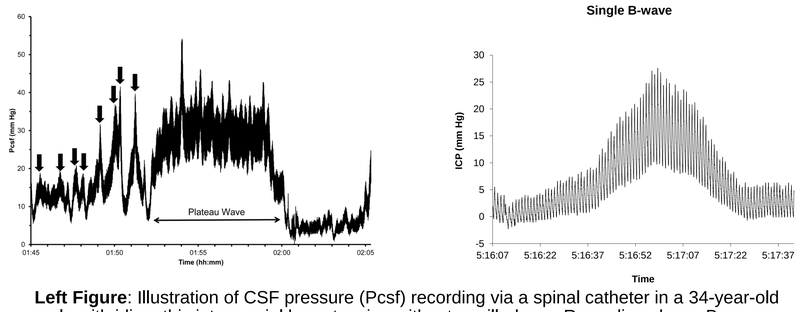
## FLIGHT EXPERIMENT IMPLEMENTATION

**Safely accomplishing invasive ICP monitoring on the ISS requires:**

**1) Selection of ICP monitoring paradigms**
**2) Selection of invasive and noninvasive ICP methods**
**3) Selection of study time points**
**4) Standardization of procedures and measurement methods**
**5) Training of astronauts**
**6) Contingency planning for adverse outcomes on the ISS**
**7) Analysis and interpretation of invasive and noninvasive ICP data.**

## JUSTIFICATION FOR INVASIVE ICP MONITORING

- <u>The pathophysiology of VIIP remains unsolved</u>.
- The long-term risks of VIIP are unknown.
- For exploration spaceflight to be safe, VIIP countermeasures must be in place, but these cannot be developed until the pathophysiology of VIIP is understood.
- Without countermeasures, the worst case scenario is untreatable visual impairment that compromises astronaut health and mission safety
- Astronauts have an important stake because VIIP, if untreated, could prevent them from flying.
- <u>Astronauts will be the first and most direct recipients of any benefits of this research</u>, which also has the potential to help patients with similar disorders on Earth.
- Invasive ICP monitoring is indicated when noninvasive methods do not answer an important and <u>clinically relevant question that, if answered, would change treatment or prognosis</u>.
- <u>VIIP meets this criterion</u>.
- Invasive ICP methods are more accurate and require a sample size (n=7) that is less than half that needed for noninvasive ICP methods (n=17) to confirm whether ICP is abnormal in VIIP.
- After noninvasive ICP methods are validated, invasive ICP methods should no longer be needed.




**Left Figure**: Illustration of CSF pressure (Pcsf) recording via a spinal catheter in a 34-year-old male with idiopathic intracranial hypertension without papilledema. Recording shows B-waves at 30–60 second intervals (arrows) and a plateau wave lasting ~8 min. Note that the B-waves persist atop the plateau wave, which terminates rapidly (<2 min) with a fall in CSF pressure from ~30 mmHg to 5 mmHg accompanied by a reduction in CSF pulse pressure and temporary loss of B-wave activity. From: Qvarlander S, Williams MA. Intracranial pressure physiology and VIIP. In: Vision Impairment: Fluid Shifts in Microgravity, Intracranial Pressure and Its Effect on Vision in Space and on Earth. Editors: Hargens AR, Macias BR, Liu JHK (eds) (In Press)

**Right Figure:** Illustration of a single B-wave rising and falling over ~90 seconds.

In both figures, note the change in the ICP pulse pressure as the ICP rises, a critical feature of ICP hydrodynamics for identifying impaired intracranial compliance, which existing noninvasive ICP methods are incapable of measuring.

## SUMMARY

- Invasive ICP measurements are critical for validating all indirect, non-invasive ICP techniques, as well as the NICF algorithmic estimation.
- We will use simultaneous multiple monitoring modalities to correlate and assess the complex interactions of cerebrovascular, cardiovascular, and ICP physiology, and to refine the NICF tool.
- Blood, urine and CSF specimens will be collected at the same time points as the LP, and novel methods of mRNA and microRNA profiling (RNAseq) and bioinformatics will be applied to identify candidate urinary and plasma biomarkers that align with VIIP-related physiologic variables.