Spaceflight Associated Neuro-ocular Syndrome and Countermeasures

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UCSD
● What is SANS?
● (Patho-) Physiology behind SANS:
  ● Fluid and pressure regulation relative to
    ● gravity
    ● weightlessness
    ● simulated gravity
● Countermeasures
What is SANS?

- Spaceflight Associated Neuro-Ocular Syndrome
- Subset of long-duration crewmembers develop neuro-ocular structural and functional changes
- Can resolve or persist post flight (+7 years)
What is SANS?

- In- and post-flight changes in visual acuity and structural changes of the eye
- Cardinal symptom: Disc edema
- Direct communication with the CSF
- Balance between IOP and ICP
- Diagnose: Uni- or bilateral optic disc edema Frisen grade ≥1
- 10/68 crewmembers (Stenger et al, HRP Evidence Report, 2017)
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SANS – more ocular findings

- Ultra Sound: Optic disc and nerve swelling
- Optical Coherence Tomography: Choroidal and retinal thickening

Preflight, supine

Kramer et al 2012; Mader et al 2011, Stenger et al 2017
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Preflight, supine  Inflight D150

*Kramer et al 2012; Mader et al 2011, Stenger et al 2017*
SANS – more ocular findings

- Globe flattening
- Choroidal and retinal folds
- Nerve fiber infarcts (cotton wool spots)
- Hyperopic refractive error shift (near vision) (correctable to 20/20)

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Kramer et al 2012; Mader et al 2011, Stenger et al 2017
Fluid Shift - initiating and driving factor?

Stasis? Flow and drainage (blood and CSF)
Pressure difference across back of eye
Some resemblance to known clinical syndromes (IIH, NPH, etc)

Mader et al. 2011; Lee et al. 2017

Venous pressure (mmHg)
Arterial pressure (mmHg)

-3.5
0
100
155

Petersen 2016
Gravitational stress (background for countermeasures)

- Hydrostatic pressure gradients
- 75-80% of blood volume below the heart
- Sympathetic activation to maintain central blood-filling and ultimately cerebral blood flow

Petersen 2016; Rowel 1993
Gravitational stress

- Supine; attenuates gravitational stress ($G_z$)
- Head down tilt: Reintroducing and reversing the gradient
- Eccentric brain – large daily pressure variation
- What is the normal ICP? What is the pressure range?
- Very invasive measurement

Gauer and Thorn 1965; Petersen et al. 2011 and 2015
Gravitational stress

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Gauer and Thorn 1965; Petersen et al. 2011 and 2015
Intracranial Pressure
ICP and gravitational stress

CPP = MAP_{Brain} - ICP_{Brain}

Petersen et al. 2016

N=9
ICP and weightlessness

Eight (5/3) former cancer patients:
ICP (omnaya)
Central venous pressure
Arterial blood pressure
Cross-sec area of internal jugular vein
Short term weightlessness (parabolic flight)

PI: Benjamin Levine
ICP and weightlessness

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PL: Benjamin Levine
ICP in relation to weightlessness

- Posture; ICP increased by some 11±2.5 mmHg
- 0G; Reduced ICP (Δ-3.8±2.9mmHg) compared to supine along with a similar decrease in CVP
- No pathological elevation of ICP; reduced compared to supine, but persistently higher than upright *Supine > 0G > upright*

Lawley et al. 2017
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Supine > 0G > upright

Lawley et al. 2017
ICP in relation to simulated weightlessness

Lawley et al. 2016
Update Hypothesis?

supine > weightlessness > upright

Chronic overload?

Lawley et al 2017; Petersen et al 2016; Roberts and Petersen 2019
Brain

- Before (A) and after (B) 6-months ISS mission
- Before (C) and after (D) 2-week shuttle mission
- Increasing mission length leads to new challenges

Roberts et al NEJM 2017
CSF spaces and circulation

Subject 26
ISS Astronaut
Preflight

Roberts et al NEJM 2017; Roberts and Petersen 2019
Updated fluid shift hypothesis

• Astronauts cannot “stand up”
• Daily habitual ICP variability is lost in space
• Chronic cerebral overload and stasis may disrupt microcirculation and pressure regulation
Countermeasures - LBNP

<table>
<thead>
<tr>
<th>Venous pressure (mmHg)</th>
<th>Arterial pressure (mmHg)</th>
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</thead>
<tbody>
<tr>
<td>-3.5</td>
<td>75</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>55</td>
<td>155</td>
</tr>
<tr>
<td>110</td>
<td>210</td>
</tr>
</tbody>
</table>

versus
ICP in relation to simulated gravity
Dose-response (N=10)

A

Intracranial pressure (mmHg)

Supine 0 -15° HDT LBNP -10 LBNP -20 LBNP -30 LBNP -40 LBNP -50

0 5 10 15 20 25 30 35 40

B

Cerebral perfusion pressure (mmHg)

Supine 0 -15° HDT LBNP -10 LBNP -20 LBNP -30 LBNP -40 LBNP -50

0 25 50 75 100 125

C

Intracranial compliance curve

-15° HDT

ΔP ΔV ΔV

LBNP lowers intracranial volume

Petersen et al. 2019
Extended LBNP

Compelling, but does LBNP prevent early signs of SANS?

In strict 3-day bedrest we applied LBNP for 8 hours/24 hours to re-introduce diurnal pressure/volume variability and prevent neuro-ocular remodeling.
8hrs 20 mmHg LBNP during 6° HDT bedrest persistently reduces ICP

PI: Benjamin Levine
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