SIH: CSF outflow resistance and other objective measurements

Prof. Dr. J. Beck
Chairman, Dept. of Neurosurgery
Medical Center – University of Freiburg, Germany
 Neuere Anschauungen zur Pathophysiologie der Liquorzirkulation

Von G. Schaltenbrand

Zentralblatt für Neurochirurgie 1938 Nr. 5

Aliquorrhoe: (traumatisch, toxisch, Plexusatrophie)

«Aliquorrhoe»
Spontaneous Idiopathic Hypotension

- (orthostatic) headache
  +
- Low CSF pressure < 6 cm H₂O
  - Evidence of CSF leaking on imaging

International Classification of Headache Disorders, 2018
Spontaneous Idiopathic Hypotension

- (orthostatic) headache
- Low CSF pressure < 6 cm H$_2$O
- Evidence of CSF leaking on imaging
Spontaneous Idiopathic Hypotension

\[ \text{modified:} \quad \bullet \text{(orthostatic) symptoms} \]

\[ + \]

\[ \bullet \text{Low CSF pressure} < 6 \text{ cm H}_2\text{O} \]

\[ \bullet \text{Evidence of CSF leaking on imaging} \]
$P_{CSF} = 6.29 + 1.16 \times \log(\text{duration})$

$p$-value $= 0.002$
Spontaneous Intracranial Hypotension
Spontaneous Intracranial Hypotension
Lumbar infusion test

Rationale

• A CSF leak should alter normal CSF parameters

• A CSF leak implies a low resistance to CSF outflow
A computer system for the identification of the cerebrospinal compensatory model.  
Czosnyka M¹, Batorski L, Laniewski P, Maksymowicz W, Koszewski W, Zaworski W.


Assessment of cerebrospinal fluid outflow resistance

Anders Eklund · Peter Smielewski · Iain Chambers · Noam Alperin · Jan Malm · Marek Czosnyka · Anthony Marmarou
Assessment of cerebrospinal fluid outflow resistance

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Anthony Marmarou
Lumbar infusion test

Beck et al.  J Neurosurg Spine 2017
Lumbar infusion test – computerized ICM+®
Cerebrospinal fluid outflow resistance as a diagnostic marker of spontaneous cerebrospinal fluid leakage


**FIG. 4.** Graph showing the pressure response of a computerized lumbar infusion test in a patient without a spinal CSF leak. Note the high opening pressure (about 14 mm Hg) with a steep incline of pressure, which corresponds to the resistance of the needle after the start of the infusion. Thereafter, the graph shows a rather quick increase in pressure up to a plateau at about 36 mm Hg.

**FIG. 5.** Graph showing a pressure response of a computerized lumbar infusion test in a patient with a spinal CSF leak. Note the low opening pressure (about 4 mm Hg), with a steep incline of pressure, which corresponds to the resistance of the needle after start of the infusion. Thereafter, the graph shows a slow increase in pressure, without reaching a plateau. The maximum pressure is about 22 mm Hg.
The gold standard for a CSF leak

- extrathecal contrast after intrathecal application or
- visualization during microsurgery
Lumbar infusion test – ICM+

- 31 patients
- 17 females
- median 55 years
- 14 had proven spinal CSF leak
Lumbar pressure at baseline – ICM+®

57 % > 6 cm H$_2$O

4.4 mmHg ≈ 6 cm H$_2$O

proven spinal CSF leak
LP-baseline-P

R-CSF_{out}

57 %

14 %

Beck et al.  J Neurosurg Spine 2017
Lumbar pressure at baseline

No spinal CSF leak: \textbf{11.77mmHg}

Proven spinal CSF leak: \textbf{5.26mmHg}

P<0.001
Lumbar pressure at plateau

No spinal CSF leak: 32.06 mmHg

Proven spinal CSF leak: 16.11 mmHg

P<0.001
Pulse amplitude at baseline

Pulse amplitude (mmHg):

- The pulse amplitude is a pressure response ($\Delta P$) to the transient increase in intracranial blood volume during a cardiac cycle ($\Delta V$).

- Due to the exponential shape of the pressure–volume curve, pulse amplitude increases with increasing pressure.
Pulse amplitude at baseline

No spinal CSF leak: 0.38mmHg

Proven spinal CSF leak: 0.18mmHg

P<0.017
Pulse amplitude at plateau

No spinal CSF leak: 2.80 mmHg

Proven spinal CSF leak: 1.03 mmHg

P < 0.001
Resistance to CSF outflow (mmHg/(ml/min)):

- The resistance to outflow measures the impedance to CSF drainage.

- It is equal to the effective pressure increase (ICP plateau - ICP baseline) divided by the rate of infusion.
Resistance to CSF outflow computerized

No spinal CSF leak: 11.78mmHg/ml/min

Proven spinal CSF leak: 1.97mmHg/ml/min

P<0.001
Resistance to CSF outflow (Rcsf)

AUC 0.958
Elastance:

The elastance coefficient describes the **stiffness** of the cerebrospinal system, e.g. the ability to compensate for a cerebrospinal volume increase.
Elastance

No spinal CSF leak: 0.11mmHg

Proven spinal CSF leak: 0.09mmHg

P<0.237
Pressure volume index

Pressure volume index (ml):

• The pressure volume index is the volume that has to be added to raise the pressure 10-fold.
Pressure volume index

No spinal CSF leak: 20.93ml
Proven spinal CSF leak: 26.43ml

P=0.003
Results

<table>
<thead>
<tr>
<th></th>
<th>No leak</th>
<th>Proven leak</th>
<th>P-value</th>
<th>ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_{\text{CSF}} ) computerized</td>
<td>Median 11·78</td>
<td>Median 1·97</td>
<td>&lt;0·001</td>
<td>0·958</td>
</tr>
<tr>
<td>Lumbar pressure plateau</td>
<td>Median 32·06</td>
<td>Median 16·11</td>
<td>&lt;0·001</td>
<td>0·942</td>
</tr>
<tr>
<td>AMP plateau</td>
<td>Median 2·80</td>
<td>Median 1·03</td>
<td>&lt;0·001</td>
<td>0·893</td>
</tr>
<tr>
<td>Pressure volume index</td>
<td>Median 20·93</td>
<td>Median 26·43</td>
<td>0·003</td>
<td>0·888</td>
</tr>
<tr>
<td>Lumbar pressure baseline</td>
<td>Median 11·77</td>
<td>Median 5·26</td>
<td>&lt;0·001</td>
<td>0·866</td>
</tr>
<tr>
<td>AMP baseline</td>
<td>Median 0·38</td>
<td>Median 0·18</td>
<td>0·017</td>
<td>0·752</td>
</tr>
</tbody>
</table>
Lumbar infusion test – ICM+®

- Specific pattern of CSF dynamics
- Investigator independent
- Rcsf out may be the best CSK leak specific diagnostic parameter

Beck et al. J Neurosurg Spine 2017
Anatomy of the Optic Nerve Sheath

- Lüdemann W, Berens von Rautenfeld D, Samii M, Brinker T: Ultrastructure of the cerebrospinal fluid outflow along the optic nerve into the lymphatic system. Child Nerv. Syst. 21, 96-103: 2005
- www.glaucoma.org
Results – Diameter

No statistically significant difference of ONSD

0.538 cm ± 0.091 vs. 0.539 cm ± 0.090; \( p=0.957 \)
Diagnostic work-up  CSF-leak-protocol

➢ First in supine position -> secondary in upright position
Patients with newly suspected SIH  
\( n = 44 \)

Patients without active/current (or history) of orthostatic headaches  
\( n = 26 \)

Patients with active/current orthostatic headaches  
\( n = 18 \)
Results – Diameter

Significant difference between supine and upright position in patients with orthostatic headaches

ONSD Supine = \(0.549 \text{cm} \pm 0.097\) vs. Upright = \(0.484 \text{cm} \pm 0.095\); \(p=0.036\)
Ultrasound of the optic nerve sheath
Management of spontaneous intracranial hypotension – Transorbital ultrasound as discriminator
Before and After Microsurgical Closure of a CSF leak

- assessment of the ONSD in Patients with spontaneous intracranial hypotension two times

- 14 Patients with proven fistula in myelography and surgery

- compared ONSD before and after surgery
Before and After Microsurgical Closure of a CSF leak

- Significantly different between supine and upright position **before surgery**
  - 5.1mm vs. 4.7mm; $p=0.002$

- No significant different between supine and upright position **after surgery**
  - 5.3mm vs. 5.3mm; $p=0.940$
Transorbital ultrasound – before and after closure of the CSF leak

Δ = -0.5mm vs. 0.01mm; p=0.004
Ultrasound of the optic nerve sheath

Fichtner et al. J Neurol Neurosurg Psychiatry August 2015
Table 3  Magnetic resonance imaging findings

S  Subdural fluid collection
E  Enhancement of meninges
E  Engorgement of veins
P  Pituitary hyperaemia
S  Sagging of brain

Schievink W, Cephalgia, Dez 2008
Predicting spinal CSF leaks in intracranial hypotension: a scoring system based on brain MRI findings

Tomas Dobrocky,1 Lorenz Grunder,1 Philine S Breiding,1 Mattia Branca,2 Andreas Limacher,2 Pascal J Mosimann,1 Pasquale Mordasini,1 Felix Zibold,1 Levin Haeni,3 Christopher M Jesse,3 Christian Fung,3,4 Andreas Raabe,3 Christian T Ulrich,3 Jan Gralla,1 Jürgen Beck,3,4* Eike I Piechowiak1*

(1) University Institute of Diagnostic and Interventional Neuroradiology, University of Bern, Inselspital, Bern, Switzerland
(2) CTU Bern, and Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland
(3) Department of Neurosurgery, University of Bern, Inselspital, Bern, Switzerland
(4) Department of Neurosurgery, Medical Center — University of Freiburg, Germany
Orthostatic headache

Diagnostic work-up

1. Cranial MRI
2. Transorbital optic nerve sheath ultrasound
3. MRI thin slice fluid sensitive spinal axis
4. Lumbar puncture, infusion test and application of 0.5 ml Lithium Gadolinium
5. MRI spinal axis intrathecal Gadolinium
6. Dynamic myelography (repeated)
7. Post-myelo spinal CT
   Dynamic Myelo-CT (repeated)
8. Microsurgical exploration

Bern-Freiburg CSF-leak-protocol

non-invasive diagnostic

invasive diagnostic
Predicting spinal CSF leaks based on brain MRI findings

Patients evaluated for SIH
n=118

Prooven CSF leak
n=73

Study population
n=56

Myelography

No extrathecal contrast
n=45

Brain MRI

No or inadequate brain MRI
n=17

+ 60 healthy controls
+ 20 prosp. validation

Dobrocky... Piechowiak et al. submitted
The gold standard for a CSF leak

- extrathecal contrast after intrathecal application or
- visualization during microsurgery
<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Quantitative</th>
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</thead>
<tbody>
<tr>
<td>Engorgement of venous sinus</td>
<td>Pontomesencephalic angle</td>
</tr>
<tr>
<td>Distended inferior intercavernous sinus</td>
<td>Suprasellar cistern</td>
</tr>
<tr>
<td>Pachymeningeal enhancement (smooth and diffuse)</td>
<td>Prepontine cistern</td>
</tr>
<tr>
<td>Midbrain descent (subjective)</td>
<td>Midbrain descent (iter to incisural line)</td>
</tr>
<tr>
<td>Superficial siderosis</td>
<td>Venous-hinge angle</td>
</tr>
<tr>
<td>Subdural fluid collection</td>
<td>Mamillopontine distance</td>
</tr>
<tr>
<td>Superior surface of pituitary (concave, flat, convex)</td>
<td>Pituitary height</td>
</tr>
<tr>
<td></td>
<td>Tonsillar herniation (relating to McRae line)</td>
</tr>
<tr>
<td></td>
<td>Area cavum veli interpositi</td>
</tr>
<tr>
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<td><strong>Suprasellar cistern</strong></td>
<td>2</td>
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<tr>
<td><strong>Pachymeningeal enhancement (smooth and diffuse)</strong></td>
<td>Prepontine cistern</td>
</tr>
<tr>
<td>Midbrain descent (subjective)</td>
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<td></td>
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</tbody>
</table>
• 4 mm  Suprasellar cistern
• 5 mm  Prepontine cistern
• 6.5 mm  Mamillo-pontine distance
<table>
<thead>
<tr>
<th>Condition</th>
<th>Coefficient (95%-CI)</th>
<th>OR (95%-CI)</th>
<th>p-value</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Engorgement venous sinus</td>
<td>2.95 (1.18 to 4.72)</td>
<td>19.12 (3.26 to 112.30)</td>
<td>0.001</td>
<td>2</td>
</tr>
<tr>
<td>Pachymeningeal enhancement</td>
<td>4.04 (2.50 to 5.59)</td>
<td>57.01 (12.18 to 266.78)</td>
<td>&lt;0.001</td>
<td>2</td>
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<tr>
<td>Subdural fluid collection</td>
<td>1.54 (-0.10 to 3.17)</td>
<td>4.65 (0.90 to 23.92)</td>
<td>0.066</td>
<td>1</td>
</tr>
<tr>
<td>Suprasellar cistern (≤4 mm)</td>
<td>3.48 (2.36 to 4.60)</td>
<td>32.32 (10.55 to 99.02)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Prepontine cistern (≤5 mm)</td>
<td>1.47 (0.41 to 2.52)</td>
<td>4.34 (1.51 to 12.47)</td>
<td>0.007</td>
<td>1</td>
</tr>
<tr>
<td>Mamillopontine distance (≤6.5 mm)</td>
<td>1.13 (0.07 to 2.19)</td>
<td>3.08 (1.07 to 8.90)</td>
<td>0.037</td>
<td>1</td>
</tr>
<tr>
<td>Patients</td>
<td>Dural enhancement</td>
<td>Subdural collection</td>
<td>Venous engorgement</td>
<td>Tonsillar ectopia (&gt;5 mm)</td>
</tr>
<tr>
<td>----------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Alcaide</td>
<td>26</td>
<td>100%</td>
<td>50%</td>
<td>77%</td>
</tr>
<tr>
<td>Aslan</td>
<td>34</td>
<td>68%</td>
<td>41%</td>
<td>62%</td>
</tr>
<tr>
<td>Tian</td>
<td>26</td>
<td>88%</td>
<td>38%</td>
<td>28%</td>
</tr>
<tr>
<td>Shankar</td>
<td>17</td>
<td>71%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Watanabe</td>
<td>18</td>
<td>83%</td>
<td>72%</td>
<td>72%</td>
</tr>
<tr>
<td>Farb</td>
<td>15</td>
<td>95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranz</td>
<td>99, 53% with leak</td>
<td>83%</td>
<td></td>
<td>75%</td>
</tr>
<tr>
<td>Our study</td>
<td>56</td>
<td>83%</td>
<td>54%</td>
<td>65%</td>
</tr>
</tbody>
</table>
Predicting spinal CSF leaks based on brain MRI findings

![Bar chart showing frequency of SIH with CSF leak and Controls in different score categories](chart.png)
Predicting spinal CSF leaks based on brain MRI findings

![Bar chart showing frequency of SIH with and without CSF leak](image-url)
### Derivation cohort

<table>
<thead>
<tr>
<th>Cutpoint</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>100.0%</td>
<td>40.0%</td>
<td>1.7</td>
<td>0.0</td>
</tr>
<tr>
<td>≥2</td>
<td>100.0%</td>
<td>73.3%</td>
<td>3.8</td>
<td>0.0</td>
</tr>
<tr>
<td>≥3</td>
<td>92.9%</td>
<td>93.3%</td>
<td>13.9</td>
<td>0.1</td>
</tr>
<tr>
<td>≥4</td>
<td>91.1%</td>
<td>98.3%</td>
<td>54.7</td>
<td>0.1</td>
</tr>
<tr>
<td>≥5</td>
<td>78.6%</td>
<td>98.3%</td>
<td>47.1</td>
<td>0.2</td>
</tr>
<tr>
<td>≥6</td>
<td>66.1%</td>
<td>100.0%</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>
### Validation cohort

<table>
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<tr>
<td>( \geq 1 )</td>
<td>100.0%</td>
<td>33.3%</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>( \geq 2 )</td>
<td>100.0%</td>
<td>66.7%</td>
<td>3.0</td>
<td>0.0</td>
</tr>
<tr>
<td>( \geq 3 )</td>
<td>100.0%</td>
<td>77.8%</td>
<td>4.5</td>
<td>0.0</td>
</tr>
<tr>
<td>( \geq 4 )</td>
<td>100.0%</td>
<td>88.9%</td>
<td>9.0</td>
<td>0.0</td>
</tr>
<tr>
<td>( \geq 5 )</td>
<td>81.8%</td>
<td>88.9%</td>
<td>7.4</td>
<td>0.2</td>
</tr>
<tr>
<td>( \geq 6 )</td>
<td>63.6%</td>
<td>88.9%</td>
<td>5.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>
No patient with a proven spinal CSF leak had a normal brain MR score of 0 or 1
Timing
• **Diagnostic criteria: Low CSF pressure (<60 mmCSF)**  
  (ICHD 3rd Version, Cephalgia 2018)

• **Normal CSF pressure is common in up to 2/3 of patients**  
  (Kranz, Cephalgia 2015; Beck J Neurosurg Spine 2017)

• **Lumbar infusion testing has proven to be a useful tool**  
  (Beck, J Neurosurg Spine 2017)
• Symptoms most severe initially

• The orthostatic nature of the headache may become less obvious over time
(IHHD 3rd Version, Cephalgia 2018; Ducros, Lancet 2015; Tyagi, Pract Neurol 2016;
Lobo, BMJ Case Rep 2013; Mokri, Headache 2013; Schievink, Headache 2011)

• Opening pressure increases slowly with increasing symptom duration
(Kranz, Cephalgia 2015)
<table>
<thead>
<tr>
<th>Natural history of SIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
</tr>
<tr>
<td>( \leq 10 ) weeks</td>
</tr>
<tr>
<td>Subacute</td>
</tr>
<tr>
<td>11-52 weeks</td>
</tr>
<tr>
<td>Chronic</td>
</tr>
<tr>
<td>&gt;52 weeks</td>
</tr>
</tbody>
</table>
Update - lumbar infusion test – $ICM^+$

- 137 lumbar infusion tests
- 53.3% female
- Mean age 49 years
- 69 had proven spinal CSF leak
Admitted for investigation of possible SIH  
\( n = 137 \)

- Proven CSF Leak  
  \( n = 69 \)
  - Acute symptoms  
    \( n = 29 \)
  - Subacute symptoms  
    \( n = 21 \)
  - Chronic symptoms  
    \( n = 19 \)

- No proven CSF Leak  
  \( n = 68 \)
  - SIH without CSF Leak  
    \( n = 12 \)
  - No SIH / other Diagnosis  
    \( n = 56 \)
Proven CSF Leak

Correlation coefficient = 0.457    p < 0.001
Update - lumbar infusion test – ICM+

Symptom duration

Lumbar Baseline Pressure (mmHg)

Acute: 5.02
Subacute: 7.21
Chronic: 8.52

ns

*
Update - lumbar infusion test – ICM+

![Graph showing CSF outflow resistance (mmHg/ml/min) across symptom duration: Acute (2.95), Subacute (7.85), Chronic (14.15).]
same patients over time

![Graph showing two lines representing Patient 1 and Patient 2 over time.](image-url)
Type of headache acute vs. subacute and chronic
Type of headache and CSF parameter
Update - lumbar infusion test – *ICM+*
Lumbar infusion testing over the course of SIH

- Patients with different symptom duration show clearly different profiles of CSF fluid dynamics
- Longer symptom duration is associated with an altered CSF fluid dynamics (normalization?) and with atypical symptoms
- Natural history: what is the compensatory mechanism?
Spontaneous Intracranial Hypotension
Thank you!

Freiburg im Breisgau