Cerebrospinal fluid outflow resistance as a diagnostic marker of spontaneous cerebrospinal fluid leakage

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OBJECTIVE Spinal CSF leakage causes spontaneous intracranial hypotension (SIH). The aim of this study was to characterize CSF dynamics via lumbar infusion testing in patients with and without proven spinal CSF leakage in order to explore possible discriminators for the presence of an open CSF leak.

METHODS This analysis included all patients with suspected SIH who were treated at the authors' institution between January 2012 and February 2015. The gold standard for "proven" CSF leakage is considered to be extrathecal contrast accumulation after intrathecal contrast injection. To characterize CSF dynamics, the authors performed computerized lumbar infusion testing to measure lumbar pressure at baseline (opening pressure) and at plateau, as well as pulse amplitude, CSF outflow resistance (R_{CSF}), craniospinal elastance, and pressure-volume index.

RESULTS Thirty-one patients underwent clinical imaging and lumbar infusion testing and were included in the final analysis. A comparison of the 14 patients with proven CSF leakage with the 17 patients without leakage showed a statistically significantly lower lumbar opening pressure ($p < 0.001$), plateau pressure ($p < 0.001$), and R_{CSF} ($p < 0.001$) in the group with leakage. Sensitivity, specificity, and positive and negative predictive values for an R_{CSF} cutoff of ≤ 5 mm Hg/(ml/min) were 0.86, 1.0, 1.0, and 0.89 (area under the curve of 0.96), respectively. The median pressure-volume index was higher ($p = 0.003$), and baseline ($p = 0.017$) and plateau ($p < 0.001$) pulse amplitudes were lower in patients with a proven leak.

CONCLUSIONS Lumbar infusion testing captures a distinct pattern of CSF dynamics associated with spinal CSF leakage. R_{CSF} assessed by computerized lumbar infusion testing has an excellent diagnostic accuracy and is more accurate than evaluating the lumbar opening pressure. The authors suggest inclusion of R_{CSF} in the diagnostic criteria for SIH.

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KEY WORDS CSF outflow resistance; lumbar infusion test; spinal cerebrospinal fluid leak; spontaneous intracranial hypotension; headache; surgical technique

SPONTANEOUS intracranial hypotension (SIH) is an underestimated disease. Rarely diagnosed in the past, it is now recognized as an important cause of headache.^{12,22,24} SIH is caused by spontaneous spinal CSF leakage. Its main symptoms include orthostatic headache, nausea, blurred vision, diplopia, and vestibulocochlear manifestations.^{22,24} The clinical spectrum and radiological manifestations are broad, and diagnostic criteria are hard to establish.^{12,22,23} This is reflected in the evolution of the criteria of the International Classification of Headache Disorders (ICHD) for headache attributed to SIH.^{15,16,21}

Schievink et al. proposed a set of diagnostic criteria for spontaneous spinal CSF leaks and intracranial hypotension that aimed to encompass its varied clinical and radiographic manifestations.²⁵ However, the key criterion remains the direct proof of a spinal CSF leak.^{16,25}

Pathophysiologically, a CSF leak should alter normal CSF parameters.³⁰ Decreased craniospinal pressure causes pathologically low resistance to CSF outflow if sagittal sinus pressure and CSF formation are normal and constant.²⁷ The existence of a CSF leak by definition implies a low CSF outflow resistance (R_{CSF}), which may occur con-

ABBREVIATIONS AUC = area under the curve; ICHD = International Classification of Headache Disorders; ICP = intracranial pressure; IQR = interquartile range; PVI = pressure-volume index; R_{CSF} = CSF outflow resistance; ROC = receiver operating characteristic; SIH = spontaneous intracranial hypotension.

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tinuously or intermittently. Lumbar infusion testing qualifies CSF dynamics and quantifies R_{CSF} . Here, we describe the results of a computerized constant-rate lumbar infusion test in patients with suspected SIH who underwent a standardized diagnostic protocol that included spinal MRI without or with intrathecal contrast, myelography, and postmyelography CT.

Methods

The Bern University Hospital Ethics Committee granted approval for this study. We included all consecutive patients admitted to the Departments of Neurosurgery and Neurology, Bern University Hospital, with suspected SIH according to ICHD criteria. The criteria are as follows: A) any headache fulfilling criterion C; B) low CSF pressure (< 60 mm H₂O) and/or evidence of CSF leakage on imaging; C) development of headache in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery; and D) headache not better accounted for by another ICHD 3rd edition (ICHD-3) diagnosis.¹⁶

In addition, all included patients underwent spinal imaging (myelography and/or spinal MRI) after intrathecal contrast (either iodine or gadolinium) administration.^{15,16} Demographic and clinical data were assessed. Our standardized diagnostic workup was performed as described previously.³ We used our current Bern imaging protocol for detection of CSF leakage. The protocol defines Categories 4 and 5 as a proven CSF leak, in contrast to Categories 0–3 for which there is no proven CSF leak (Table 1).³ Spinal imaging consisted of a stepwise protocol using more invasive imaging techniques with increasing suspicion of a spinal leak. First, 1.5-T MR images of the spine, including T2-weighted images in the sagittal orientation (space 0.9 isovoxel, TR 1500 msec, TE 119 msec) with 3D reformats and T1-weighted images in sagittal orientation (TR 670 msec, TE 9.2 msec), were acquired to detect meningeal cysts or extrathecal fluid collection (Categories 1–3). Then, the computerized lumbar infusion test was performed. At the end of the infusion test, intrathecal gadolinium was administered and another spinal MRI study was performed. Postcontrast MRI included T1 fat saturation acquisition in sagittal and axial orientations (3 mm, TR 520 msec, TE 11 msec). In patients with proven extrathecal contrast media (Category 4) without precise

localization of the leak, fluoroscopy was performed. Contrast flow from intra- to extrathecal space observed during fluoroscopy was defined as a Category 5 CSF leak.

Control Group

The control group comprised the patients who did not exhibit a spinal CSF leak. These patients had undergone lumbar infusion testing in order to confirm that they did not have a spinal CSF leak. Because of its invasiveness, lumbar infusion testing was not performed in a control group of healthy volunteers.

Lumbar Infusion Testing

We used a computerized constant infusion test developed by Czosnyka and colleagues based on the infusion test described by Katzman and Hussey.^{7,10,17,27,28} A lumbar puncture was performed with the patient in the lateral recumbent position with a 20-gauge (0.9-mm outer diameter) needle (Fig. 1). The needle was connected via a 3-way tap to the pressure transducer and the infusion pump. CSF pressure was constantly monitored through the same needle and recorded using ICM+ software (version 7.3, <http://www.neurosurg.cam.ac.uk/icmplus>). After baseline recording of lumbar CSF pressure, infusion was started at a constant rate of 2 ml/min using Ringer solution (50 ml). The infusion test was terminated prematurely if the patient developed symptoms of increased intracranial pressure (ICP) or if CSF pressure exceeded 50 mm Hg. Computerized analysis was done using the tool provided by the ICM+ software for analyzing lumbar infusion tests. The software recorded and computed lumbar pressure and pulse amplitude (at baseline and plateau, R_{CSF} , elastance coefficient, and pressure-volume index (PVI). If a normalized error $> 2\%$ for the R_{CSF} was recorded, we recalculated it manually by calculating the difference between the plateau and the baseline pressures divided by the infusion rate. The lumbar baseline pressure equals the opening pressure.

Parameters of the Lumbar Infusion Test

Baseline pressure (in mm Hg) is the mean pressure over a period of 3–5 minutes before the start of the infusion, with the patient relaxed and in the lateral recumbent position. Baseline pressure equals the lumbar opening

TABLE 1. Categories of spinal imaging findings

Category	Imaging Finding	Imaging Modality	Intrathecal Contrast Material	Interpretation
0	No suggestion of CSF loss	MRI, myelography, CT, cisternography	Gd, iodine, radionuclide	No CSF leak
1	Spinal meningeal cyst, sacral region	MRI, myelography, CT	Gd, iodine	CSF leak unlikely
2	Spinal meningeal cyst, cervicothoracic region	MRI, myelography, CT	Gd, iodine	CSF leak likely
3	Extrathecal fluid detection w/o intrathecal contrast	MRI (T2 SPACE)		CSF leak very likely
4	Extrathecal contrast accumulation after intrathecal contrast application	CT/MRI	Gd, iodine	CSF leak proven
5	Direct visualization of contrast passage from intrathecal to extrathecal space	Fluoroscopy (myelography)	Iodine	CSF leak proven

SPACE = sampling perfection with application of optimized contrasts using different flip angle evolutions.

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FIG. 1. Schematic drawing of the performance of a lumbar infusion test. The patient is in the lateral recumbent position and lumbar puncture is made using a 20-gauge needle. The needle is connected via a 3-way tap to the pressure transducer/computer and the infusion pump. Copyright Inselspital Bern. Published with permission.

pressure. Plateau pressure (in mm Hg) is the mean pressure over the period of time in which the lumbar pressure reached a steady plateau during infusion. Pulse amplitude (in mm Hg) is a pressure response (ΔP) to the transient increase in intracranial blood volume during a cardiac cycle (ΔV).² Because of the exponential shape of the pressure-volume curve, pulse amplitude increases with increasing pressure.² Resistance to CSF outflow (in mm Hg/[ml/min]) measures the impedance to CSF drainage.¹⁹ It is equal to the effective pressure increase (ICP plateau – ICP baseline) divided by the rate of infusion. The elastance coefficient (in ml^{-1}) describes the stiffness of the cerebrospinal system, i.e., the ability to compensate for a cerebrospinal volume increase.³⁰ It reflects the pressure-volume response ($\Delta P/\Delta V$) at a certain level, and it shows how fast compliance of the cerebrospinal space decreases when the mean ICP increases.^{13,29} The PVI (in ml) is the volume that has to be added to raise the pressure 10-fold.^{20,26}

Statistical Analysis

Data from the computerized lumbar infusion test were analyzed using descriptive statistics and compared between patients with proven CSF leak and those in whom a leak was not found by using statistical software (SPSS, version 21, IBM). A 2-sided t-test for unpaired variables was performed, with the presence of a CSF leak (Categories 4 and 5) as the dependent variable. A p value < 0.05 was regarded as significant. Discrimination between the occurrence of a leak or no leak was measured by the area under the curve (AUC) of receiver operating characteristic (ROC) curves, which were compared nonparametrically. An AUC of 1 indicates perfect discrimination, and an AUC of 0.5 indicates no better discrimination than would occur by chance.

Results

Between January 2012 and February 2015, 44 patients

with suspected SIH in whom spinal imaging had been performed were treated at the Departments of Neurosurgery and Neurology, Bern University Hospital. Thirteen patients were excluded because the myelography study had been performed at an outside institution ($n = 2$); absence of the investigator who performed all lumbar infusion tests ($n = 2$); technical problems with data registration ($n = 2$); missing lumbar infusion test data ($n = 2$); and previous spinal surgery, clinically unstable patient, previous lumbar puncture, claustrophobia, and symptom resolution after epidural blood patch ($n = 1$ each) (Fig. 2).

Data from lumbar infusion tests in 31 patients (17 females) were suitable for analysis. The median age was 55 years (interquartile range [IQR] 44–69 years). According to spinal imaging findings and our recently established criteria, 14 of the 31 patients had a proven spinal CSF leak.³ Of these 14 patients, 9 were graded as Category 4 and 5 as Category 5; all displayed extrathecal contrast after intrathecal contrast application for spinal MRI, myelography, or CT myelography. In the remaining 17 patients a spinal CSF leak could not be proven; 5 patients were graded as Category 0, 2 as Category 1, 6 as Category 2, and 4 as Category 3 (Table 1).

Clinical Findings at Presentation

In the 14 patients with proven CSF leakage, clinical symptoms at presentation consisted of headache ($n = 13$, of whom 12 presented with orthostatic headache), nausea ($n = 5$), cochleovestibular manifestations ($n = 5$), photophobia/visual blurring ($n = 3$), altered level of consciousness ($n = 2$), back pain ($n = 2$), limb numbness/paresthesias ($n = 1$), and sweating ($n = 1$).

Patients without a proven CSF leak presented with headache ($n = 15$, of whom 6 presented with orthostatic headache); cochleovestibular manifestations ($n = 5$); paresis ($n = 3$); limb numbness/paresthesias ($n = 2$); and nausea, altered level of consciousness, facial numbness, per-

FIG. 2. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flowchart listing reasons for not continuing with the lumbar infusion test. EBP = epidural blood patch.

sonality change, gait unsteadiness, and speech disturbance (n = 1 each).

CSF Dynamics Measured by Constant-Rate Lumbar Infusion Test

Lumbar CSF pressure and pulse amplitude at baseline and plateau were significantly lower in patients with a proven spinal CSF leak (Table 2 and Fig. 3). In addition, R_{CSF} was significantly lower in patients with proven leaks than in those without (Table 2 and Fig. 3). PVI was higher in patients with proven CSF leak (Table 2 and Fig. 3). Elastance was not related to a proven spinal CSF leak. One lumbar infusion test had to be terminated prematurely due to headache. For this patient, we only included the lumbar baseline pressure and R_{CSF} (calculated as [highest pressure – baseline pressure]/2 [ml/min]) in the analysis. The R_{CSF} was 19.5 mm Hg/(ml/min) in this patient.

Lumbar Baseline Pressure (Opening Pressure)

The median pressure in patients with spinal CSF leakage was 5.26 mm Hg, compared with 11.77 mm Hg in patients without proven CSF leakage ($p < 0.001$). Eight (57.1%) of 14 patients with proven leakage had a baseline pressure above 4.4 mm Hg (60 mm H₂O) (Fig. 3A). IQRs and 95% CIs are provided in Table 2.

Lumbar Plateau Pressure

Patients with spinal CSF leakage had significantly lower median plateau pressures than those without leakage (16.11 mm Hg vs 32.06 mm Hg; $p < 0.001$).

Resistance to CSF Outflow

The median computerized R_{CSF} in patients with spinal CSF leakage was 1.97 mm Hg/(ml/min) versus 11.78 mm Hg/(ml/min) ($p < 0.001$) in the cohort without leakage. Patients without a spinal CSF leak all had an $R_{CSF} > 5$ mm Hg/(ml/min). In contrast, 2 patients with a proven spinal CSF leak had an $R_{CSF} > 5$ mm Hg/(ml/min) (5.15 and 12.45 mm Hg/(ml/min)). Manual recalculation of the R_{CSF} due to a higher normalized error ($> 2\%$) yielded a median R_{CSF} of 4.5 mm Hg/(ml/min) ($p < 0.001$) (Fig. 3C and D).

Amplitude at Baseline

In patients with CSF leakage, the median pulse amplitude at baseline was 0.18 mm Hg versus 0.38 mm Hg in patients without leakage ($p = 0.017$) (Fig. 3E).

Pulse Amplitude at Plateau

In patients with CSF leakage, the median pulse amplitude at plateau was 1.03 mm Hg versus 2.80 mm Hg in patients without leakage ($p < 0.001$) (Fig. 3F).

Pressure Volume Index

In patients with spinal CSF leakage, the median PVI was 26.43 ml versus 20.93 ml in patients without leakage ($p = 0.003$) (Fig. 3G).

Elastance Coefficient

The elastance coefficient in patients with a spinal CSF leak was not significantly different from that in patients

TABLE 2. Results of the computerized lumbar infusion test

Variation	No Proven Leak			Proven Leak			95% CI of Difference*	p Value	ROC	
	Median	IQR	Min/Max	Median	IQR	Min/Max			AUC	95% CI
Lumbar pressure baseline (mm Hg)	11.77	9.04–15.10	4.11/21.02	5.26	2.75–8.37	–0.91/12.80	3.68 to 10.19	<0.001	0.866	0.739–0.992
Lumbar pressure plateau (mm Hg)	32.06	27.71–41.15	19.43/51.02	16.11	15.08–18.91	10.54/37.60	10.17 to 21.76	<0.001	0.942	0.845–1.0
AMP baseline (mm Hg)	0.38	0.17–0.88	0.03/2.30	0.18	0.09–0.26	0.01/0.63	0.08 to 0.72	0.017	0.752	0.557–0.928
AMP plateau (mm Hg)	2.80	1.89–4.40	0.99/7.08	1.03	0.81–1.59	0.36/3.0	0.96 to 2.90	<0.001	0.893	0.78–1.0
R _{CSF} computerized (mm Hg/[ml/min])	11.78	7.22–15.20	5.28/20.34	1.97	1.53–2.62	0.39/12.45	6.09 to 11.95	<0.001	0.958	0.875–1.0
R _{CSF} manually (mm Hg/[ml/min])	11.78	7.22–15.20	5.28/20.34	4.5	4.0–6.0	3.5/11.0	3.83 to 9.26	<0.001	0.933	0.844–1.0
Elastance coefficient (ml)	0.11	0.1–0.18	0.1/0.42	0.09	0.07–0.1	0.04/0.47	–0.03 to 0.11	0.237	0.857	0.7–1.0
PVI (ml)	20.93	12.90–23.04	5.46/23.04	26.43	24.18–34.93	4.94/51.39	–16.64 to –3.70	0.003	0.888	0.737–1.0

AMP = pulse amplitude.

* Difference between the median values in the no proven leak and proven leak groups.

without a CSF leak (0.09 ml⁻¹ vs 0.11 ml⁻¹; $p = 0.237$) (Fig. 3H).

The ROC analysis yielded an AUC of 0.958 for computerized R_{CSF}, 0.933 for manually calculated R_{CSF}, 0.942

for lumbar plateau pressure, 0.893 for pulse amplitude plateau, 0.888 for PVI, 0.866 for lumbar baseline pressure, 0.857 for elastance, and 0.752 for pulse amplitude baseline.

FIG. 3. Scatterplots displaying the lumbar pressure (A and B), R_{CSF} (C and D), pulse amplitude (AMP) (E and F), PVI (G), and elastance (H) of the lumbar infusion test. Results are dichotomized into patients with or without a proven CSF leak.

Discussion

Lumbar infusion testing is a tool for quantifying CSF dynamics. When applying computerized lumbar infusion tests to patients with suspected SIH, we found a distinct pattern of CSF dynamics associated with spinal CSF leakage. In our patients, an $R_{CSF} \leq 5$ was predictive of a spinal CSF leak that was later proven by imaging, whereas an $R_{CSF} > 5$ predicted a low chance of finding leakage on imaging studies.

A diagnosis of SIH is usually difficult to establish.³ Particularly in patients with chronic SIH, the clinical presentation might not match the stereotypical description, and orthostatic headache may be variable or even nonexistent. Obtaining proof of a spinal CSF leak and its precise localization is cumbersome and often requires multiple and invasive diagnostic procedures.³ Many patients with SIH show only subtle signs of extrathecal fluid accumulation on spinal MRI. Depending on the patient's symptoms, imaging often needs to be repeated and other modalities such as intrathecal contrast media must be used. The recently revised guidelines of the ICHD reflect these diagnostic issues.¹⁶ As a result, the diagnostic criteria are rather unspecific, and an additional diagnostic technique to corroborate the diagnosis of SIH would be helpful. A test that can differentiate patients with a CSF leak from patients without one is crucial.

From the pathophysiological point of view, if a leak leads to high outflow of CSF, i.e., low resistance to outflow, it should be possible to diagnose its existence with a lumbar infusion test.

Typical Pattern of CSF Dynamics for Patients With a Spinal CSF Leak

We observed all features of CSF dynamics that were derived theoretically from the assumption of a dural defect. Mathematically, such pathology would represent a very low CSF outflow resistance. The reduced CSF volume would lead to reduced pressure, increased craniospinal compliance, and reduced pulse pressure amplitude. When loaded with a constant rate of volume, patients with leakage, i.e., reduced R_{CSF} , would show less pressure in-

crease, less pulse pressure increase, and greater compliance (Figs. 4 and 5).

The key parameter, however, is the pathologically decreased R_{CSF} , on which the other parameters are dependent. Unfortunately, few studies in the literature have measured R_{CSF} in healthy individuals.^{1,4,9,11,14} Most studies of R_{CSF} were performed to establish the upper threshold of normal R_{CSF} for diagnosing malfunction of CSF shunts or normal pressure hydrocephalus.

Resistance to CSF outflow in young, healthy patients ranges from 5 to 10 mm Hg/(ml/min) and increases with age.^{1,4,9,11,14,18} R_{CSF} values are well studied in hydrocephalus, and R_{CSF} above 13 to 18 mm Hg/(ml/min)—depending on the age of the patient—is used as definition of a disturbed CSF circulation.^{4,6} Due to the SIH pathophysiology resulting from a spinal CSF leak, R_{CSF} values should be lower than normal, but no studies in the literature have investigated the lower limit of the normal value of outflow resistance, and we are not aware of any study reporting R_{CSF} outflow in patients with SIH. In our cohort, the existence of a spinal CSF leak was associated with lower R_{CSF} values. When using 5 mm Hg/(ml/min) as the cutoff, our results yield a sensitivity of 86% and a specificity of 100% for the computerized R_{CSF} for the presence of a spinal CSF leak. Because of the small patient numbers, these results have to be interpreted with caution. The fact that R_{CSF} can also be calculated from a noncomputerized lumbar infusion test (difference between the plateau and the baseline pressure divided by the infusion rate) makes it an easy-to-measure additional parameter in the evaluation of SIH. However, the use of a computerized test enables a quick and reliable assessment of CSF dynamics, eliminates unwanted pressure fluctuations and artifacts, and permits calculation of R_{CSF} even if no steady pressure level is obtained.⁵

A classic diagnostic criterion attributed to SIH is low opening pressure,^{16,25} although it is reported that up to 25% of patients may exhibit a normal opening pressure.²² The suggested cutoff for SIH diagnosis is 60 mm H₂O (4.4 mm Hg).^{16,25} In our cohort of patients with a proven spinal CSF leak, the median opening pressure was 5.26 mm Hg and was therefore higher than the cutoff for diagnosis of SIH according to the ICHD-3.¹⁶ A higher opening pressure

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 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 38 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.

than the suggested cutoff was measured in 8 of 14 patients (57.1%). Therefore, opening pressure by itself might not suffice as the sole parameter of CSF dynamics for confirming the diagnosis of SIH.

In the current series, the plateau pressure was also a specific parameter indicating a spinal CSF leak. However, plateau pressure is not an accurate physiological parameter and does not represent a measure of outflow resistance.⁸ Baseline and plateau pulse amplitudes were also associated with the existence of a spinal CSF leak, probably because these parameters are well correlated with the pressure.³⁰

Unlike elastance or its inverse, compliance, the PVI describes pressure-independent steepness of the entire craniospinal pressure-volume relationship. It is measured as the volume that has to be added to raise the pressure 10-fold.^{20,26} In normal pressure hydrocephalus, PVI is > 20 ml.¹⁰ In occlusive hydrocephalus assessed using ventricular infusion, the PVI is low (< 13 ml), indicating poor compensatory reserve.¹⁰ In our study, the median PVI in patients without proven CSF leakage was 20.93 ml, compared with 26.43 ml in patients with proven spinal CSF leakage. The higher PVI is in line with the pathophysiological concept of SIH. Because of the spinal CSF leak, there is a relative volume depletion, and compliance is greater than in patients without a proven spinal CSF leak.

The lumbar infusion test has the potential to guide management of patients suspected of having a spinal CSF leak. Lumbar infusion testing is superior to opening pressure and can prevent unnecessary imaging studies.

Limitations of the Study

From a pathophysiological point of view, the diagnostic accuracy of lumbar infusion testing hinges on the assumption of open leakage rather than a valve-like intermittent opening of the dural defect. If such a valve mechanism or position-dependent mechanism exists, lumbar infusion testing might still be negative. Despite the sound pathophysiological concept of diagnosing a CSF leak by measuring the resistance to CSF outflow, a defect in the dura mater can be small and covered by the arachnoid or spinal venous plexus, as often observed during surgery. There-

fore, some CSF leaks may open only intermittently and may be position dependent, like a valve mechanism. Further limitations of the study are the single-center setting, the limited number of patients, and that lumbar infusion tests were not performed in healthy volunteers. Yet these preliminary results are promising, and large multicenter studies are warranted.

Conclusions

Lumbar infusion testing seems to capture a specific pattern of CSF dynamics associated with spinal CSF leaks in patients with SIH. Lumbar infusion tests are useful tools in the diagnostic workup of SIH. The key parameter is a pathologically reduced CSF outflow resistance.

References

1. Albeck MJ, Skak C, Nielsen PR, Olsen KS, Børgeesen SE, Gjerris F: Age dependency of resistance to cerebrospinal fluid outflow. *J Neurosurg* **89**:275–278, 1998
2. Avezaat CJ, van Eijndhoven JH, Wyper DJ: Cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. *J Neurol Neurosurg Psychiatry* **42**:687–700, 1979
3. Beck J, Gralla J, Fung C, Ulrich CT, Schucht P, Fichtner J, et al: Spinal cerebrospinal fluid leak as the cause of chronic subdural hematomas in nongeriatric patients. *J Neurosurg* **121**:1380–1387, 2014
4. Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, et al: Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *J Neurosurg* **87**:687–693, 1997
5. Børgeesen SE, Albeck MJ, Gjerris F, Czosnyka M, Laniewski P: Computerized infusion test compared to steady pressure constant infusion test in measurement of resistance to CSF outflow. *Acta Neurochir (Wien)* **119**:12–16, 1992
6. Børgeesen SE, Gjerris F: The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. *Brain* **105**:65–86, 1982
7. Czosnyka M, Batorski L, Laniewski P, Maksymowicz W, Koszewski W, Zaworski W: A computer system for the identification of the cerebrospinal compensatory model. *Acta Neurochir (Wien)* **105**:112–116, 1990

8. Czosnyka M, Czosnyka Z, Momjian S, Schmidt E: Calculation of the resistance to CSF outflow. **J Neurol Neurosurg Psychiatry** **74**:1354–1355, 2003
9. Czosnyka M, Czosnyka ZH, Whitfield PC, Donovan T, Pickard JD: Age dependence of cerebrospinal pressure-volume compensation in patients with hydrocephalus. **J Neurosurg** **94**:482–486, 2001
10. Czosnyka M, Whitehouse H, Smielewski P, Simac S, Pickard JD: Testing of cerebrospinal compensatory reserve in shunted and non-shunted patients: a guide to interpretation based on an observational study. **J Neurol Neurosurg Psychiatry** **60**:549–558, 1996
11. Czosnyka Z, Czosnyka M, Owler B, Momjian S, Kasprówicz M, Schmidt EA, et al: Clinical testing of CSF circulation in hydrocephalus. **Acta Neurochir Suppl** **95**:247–251, 2005
12. Ducros A, Biousse V: Headache arising from idiopathic changes in CSF pressure. **Lancet Neurol** **14**:655–668, 2015
13. Eklund A, Smielewski P, Chambers I, Alperin N, Malm J, Czosnyka M, et al: Assessment of cerebrospinal fluid outflow resistance. **Med Biol Eng Comput** **45**:719–735, 2007
14. Ekstedt J: CSF hydrodynamic studies in man. 2. Normal hydrodynamic variables related to CSF pressure and flow. **J Neurol Neurosurg Psychiatry** **41**:345–353, 1978
15. Headache Classification Committee of the International Headache Society: The International Classification of Headache Disorders: 2nd edition. **Cephalalgia** **24 Suppl 1**:9–160, 2004
16. Headache Classification Committee of the International Headache Society: The International Classification of Headache Disorders, 3rd edition (beta version). **Cephalalgia** **33**:629–808, 2013
17. Katzman R, Hussey F: A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. **Neurology** **20**:534–544, 1970
18. Malm J, Jacobsson J, Birgander R, Eklund A: Reference values for CSF outflow resistance and intracranial pressure in healthy elderly. **Neurology** **76**:903–909, 2011
19. Marmarou A, Shulman K, LaMorgese J: Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. **J Neurosurg** **43**:523–534, 1975
20. Marmarou A, Shulman K, Rosende RM: A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. **J Neurosurg** **48**:332–344, 1978
21. Mea E, Chiapparini L, Savoiardo M, Franzini A, Grimaldi D, Bussone G, et al: Application of IHS criteria to headache attributed to spontaneous intracranial hypotension in a large population. **Cephalalgia** **29**:418–422, 2009
22. Mokri B: Spontaneous low pressure, low CSF volume headaches: spontaneous CSF leaks. **Headache** **53**:1034–1053, 2013
23. Mokri B, Posner JB: Spontaneous intracranial hypotension: the broadening clinical and imaging spectrum of CSF leaks. **Neurology** **55**:1771–1772, 2000
24. Schievink WI: Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. **JAMA** **295**:2286–2296, 2006
25. Schievink WI, Maya MM, Louy C, Moser FG, Tourje J: Diagnostic criteria for spontaneous spinal CSF leaks and intracranial hypotension. **AJNR Am J Neuroradiol** **29**:853–856, 2008
26. Shapiro K, Marmarou A, Shulman K: Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. **Ann Neurol** **7**:508–514, 1980
27. Smielewski P, Czosnyka Z, Kasprówicz M, Pickard JD, Czosnyka M: ICM+: a versatile software for assessment of CSF dynamics. **Acta Neurochir Suppl** **114**:75–79, 2012
28. Smielewski P, Lavinio A, Timofeev I, Radolovich D, Perkes I, Pickard JD, et al: ICM+, a flexible platform for investigations of cerebrospinal dynamics in clinical practice. **Acta Neurochir Suppl** **102**:145–151, 2008
29. Szewczykowski J, Sliwka S, Kunicki A, Dytko P, Korsak-Sliwka J: A fast method of estimating the elastance of the intracranial system. **J Neurosurg** **47**:19–26, 1977
30. Weerakkody RA, Czosnyka M, Schuhmann MU, Schmidt E, Keong N, Santarius T, et al: Clinical assessment of cerebrospinal fluid dynamics in hydrocephalus. Guide to interpretation based on observational study. **Acta Neurol Scand** **124**:85–98, 2011

Disclosures

Dr. Fiechter states that he is a consultant for Brainlab AG.

Author Contributions

Conception and design: Beck, Fung, Ulrich, Raabe. Acquisition of data: Fung, Fiechter, Mordasini, Gralla. Analysis and interpretation of data: Beck, Fung, Ulrich, Fichtner, Z'Graggen. Drafting the article: Beck, Fung. Critically revising the article: Beck, Fung, Ulrich, Raabe. Reviewed submitted version of manuscript: Beck, Fung, Mattle, Mono, Meier, Mordasini, Z'Graggen, Gralla, Raabe. Approved the final version of the manuscript on behalf of all authors: Beck. Statistical analysis: Fung. Administrative/technical/material support: Fung, Raabe. Study supervision: Beck, Raabe.

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