The resistance to CSF outflow in hydrocephalus – what it is and what it isn’t.

Davson et al 1970, The mechanism of drainage of CSF. Brain 93:665-8

1989, Copenhagen, Alfred Benzon Foundation
CSF outflow is linear function of pressure, therefore the resistance to CSF outflow exists!

CSF hydrodynamic studies in man

JAN EKSTEDT

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SUMMARY With the patient in the supine position, the subarachnoidal space was infused with artificial CSF at several constant pressure levels. The resulting flow of liquid was recorded. By draining CSF at a low pressure the CSF production rate was determined. Normal values are given and discussed for (1) the resting pressure, (2) the conductance of the CSF outflow pathways, (3) the formation rate of CSF, (4) the pressure difference across the CSF outflow pathways, and (5) the sagittal sinus pressure. None of the variables showed any age dependence, nor was there any sex difference.

Fig. 1 Example of the relation between pressure and flow obtained in a patient aged 64 years, considered to be “normal”. Abscissa: the CSF pressure obtained when the flow at each level has stabilised after the initially higher flow rate. Ordinate: the corresponding inflow of artificial CSF from the bottle to the patient’s subarachnoidal space. There is obviously a rectilinear relation between pressure and flow which is also true in the majority of all other recordings made. The regression line of flow on pressure, the conductance of the CSF outflow pathways (G_op), has been calculated according to the formula given in the text. The horizontal line below the abscissa represents the CSF formation rate of 4.6 mm^3 s^{-1} obtained in this patient. The intersection of this line with the regression line thus represents the pressure that should have existed if there were no production of CSF and thus no outflow through the arachnoidal villi—that is, the pressure of the CSF recipient, mainly the sagittal sinus. Below this pressure no elimination of CSF can occur. For further information, see Ekstedt (1977).
Model of CSF circulation (A. Marmarou 1973)

\[
\frac{1}{E \cdot (p - p^o)} \cdot \frac{dp}{dt} + \frac{p - p^b}{R_{CSF}} = I(t)
\]


Rout > 13 mm Hg/(ml/min) – Borgesen and Gjerris, Brain 1981
Rout >18 mm Hg/(ml/min) - Boon et al; ‘Dutch study’, J. Neurosurg 1997
Rout >??? – European trial – Klinge et al. 2008?
Cross-validation: Lumbo-Ventricular Perfusion Study (Copenhagen) versus Computerized Infusion Test (Warsaw)

\[ R_{cSF} = \frac{1}{C_{out}} \]

Relationship between clinical status and resistance to CSF outflow (249 with NPH of various etiology; iNPH=90, post SAH= 87; HI NPH =34, post-meningitis NPH=38)

Resistance to CSF outflow versus outcome (164 patients, NPH, N.Keong 2008; Failure= no clinical improvement)
How to establish thresholds for normal and increased resistance?

The best threshold is this which maximizes ‘F’ statistics- 13 mm Hg/(ml/min), but 17 mm Hg/(ml/min) gives also a local maximum.
Aetiology matters!

- Idiopathic versus post-traumatic NPH

![Graph showing resistance to CSF outflow in NPH and HI patients.](image)
Resistance to CSF outflow was significantly greater in post-SAH than in idiopathic NPH
Impact of duration of symptoms on CSF dynamics in idiopathic normal pressure hydrocephalus


Objective: Cerebrospinal fluid (CSF) pressure during compensation.

Resistance to CSF outflow (mm Hg/(ml/min))

- R = -0.048; p = 0.66

Resistance to CSF outflow (mm Hg/(ml/min))

- R = -0.61; p = 0.0018

Duration [months]

Duration of symptoms [months]
Cerebrospinal Fluid (CSF) pressure-volume compensatory parameters change in time in pathological but also under normal circumstances. Normal ageing proved to affect CSF compensation: the resistance to CSF outflow increases and the formation of CSF decreases with age.

Cranioplasty increases Rcsf

Craniotomy. Does it encourage transmantle pressure gradient?
Relationship with Pulse Amplitude and Elasticity in NPH

- Pulse amplitude [mm Hg] with $R=0.25; p=0.0035$
- Elasticity [1/ml] with $R=0.24; p=0.017$
Rcsf increases with hypercapnia (27-48 mm Hg; 18%)

Arterial hypotension decreases RCSF (17% per 50 mm Hg)

Czosnyka M, Richards HK, Czosnyka Z, Piechnik S, Pickard JD.
Autoregulation is worse in patients with lower Rcsf.
Cerebrovascular factors:
Rcsf in patients with ‘pure’ NPH and patients with additional signs of cerebrovascular disease (Owler, Czosnyka&Czosnyka, Pickard 2000)

\[ R_{\text{outflow}} \text{[mmHg/(ml/min)]} \quad p<0.0001 \]
Power of B waves in overnight ICP monitoring

Thanks to Prof. M. Schuhmann
Link between infusion study and overnight monitoring

Rcsf poorly correlates with amplitude (or incidence) of B waves in overnight ICP monitoring.
Mean ICP (overnight) correlates with baseline ICP (infusion study) but the correlation is not very close!

\[
\text{Mean ICP (overnight)} \quad [\text{mm Hg}] \\
\text{Baseline ICP during infusion test} \quad [\text{mm Hg}]
\]

\[R = 0.552; p < 0.003\]
Fig. 12 Three constant pressure method investigations on the same patient: a preoperative, a 3-month postoperative follow-up, with a properly functioning Delta® shunt, and a 36 months test revealing a dysfunctioning shunt. At the baseline investigation there was a typical NPH conductance of \( G_{out} = 6.3 \text{ µl/s/kPa} \) (\( R_{out} = 20 \text{ mm Hg/ml/min} \)). At 3 months postoperative of \( G_{out} = 57 \text{ µl/s/kPa} \) (\( R_{out} = 2.2 \text{ mm Hg/ml/min} \)) which is expected for a patient with a Delta shunt. At 36 months \( G_{out} \) was reduced to 25 µl/s/kPa (\( R_{out} = 5.0 \text{ mm Hg/ml/min} \)) indicating partial block, and there was a tendency to flow a low \( P_{IC} \) suggesting that the valve did not close. (Figure modified from [26])

Technical factors

Linear or Non-linear?
Repeatability
Davson’s equation- does it work?
Assessment of cerebrospinal fluid outflow resistance

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Noam Alperin · Jan Malin · Marek Czosnyka ·
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Abstract The brain and the spinal cord are contained in a cavity and are surrounded by cerebrospinal fluid (CSF), which provides physical support for the brain and a cushion against external pressure. Hydrocephalus is a disease, associated with disturbances in the CSF dynamics, which can be surgically treated by inserting a shunt or third ventriculostomy. This review describes the physiological background, modeling and mathematics, and the investigational methods for determining the CSF dynamic properties, with specific focus on the CSF outflow resistance, $R_{out}$. A model of the cerebrospinal fluid dynamic system, with a pressure-independent $R_{out}$, a pressure-dependent compliance and a constant formation rate of CSF is widely accepted. Using mathematical expressions calculated from the model, along with active infusion of artificial CSF and observation of corresponding change in ICP allows measurements of CSF dynamics. Distinction between normal pressure hydrocephalus and differential diagnoses, prediction of clinical response to shunting and the possibility of assessment of shunt function in vivo are the three most important applications of infusion studies in clinical practice.

Fig. 6 Curves for the intracranial pressure and external flow describing the constant pressure method. The left graph shows typical $P_{IC}$ data and accumulated infused volume versus time. The right graph is calculated from the time series to the left and shows points for mean pressure and flow determined for each steady state level. Outflow resistance is determined with linear regression and interpreted as the inverse of the slope

Linear within limits 0-40 mm Hg!
Repeatability of \( \text{Rcsf} \) measurement

16/01/19xx: (infusion test) 
\[ \text{Rcsf} = 8 \text{ mm Hg} / (\text{ml/min}) \]

21/01/19xx (ICP monitoring)

31/01/19xx (infusion test) 
\[ \text{Rcsf} = 7.8 \text{ mm Hg} / (\text{ml/min}) \]
Site of infusion

Rcsf [mm Hg/(ml/min)]

p=0.015; N=90; iNPH

Ommaya

Lumbar

Site of infusion
<table>
<thead>
<tr>
<th>RECORD OUTPUT</th>
<th>KNOWN INPUT</th>
<th>EXTRACT PARAMETERS</th>
<th>COMPUTE</th>
<th>UNITS</th>
<th>RESTRICTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram I" /></td>
<td>A. ( \Delta V(ML) )</td>
<td>C. ( P_o, P_p )</td>
<td>D. ( PVI = \frac{\Delta V}{\log_{10} \frac{P_p}{P_o}} )</td>
<td>E. ML</td>
<td>F. ( P &gt; P_o )</td>
</tr>
<tr>
<td><img src="image" alt="Diagram II" /></td>
<td>B. (-\Delta V(ML))</td>
<td>C. ( P_o, P_m, P_1, t_1 )</td>
<td>D. ( C = \frac{0.4343 \times PVI}{P} )</td>
<td>E. ML/MMHg</td>
<td>F. ( \frac{\Delta V}{\Delta T} &gt;&gt; I_F )</td>
</tr>
<tr>
<td><img src="image" alt="Diagram III" /></td>
<td>C. ( I_N = \Delta V_N ) ( (ML/\text{MIN}) )</td>
<td>C. ( P_o, P_s_1, \ldots, P_s_n )</td>
<td>D. ( I_F = \frac{P_s_i-P_o}{\Delta t} ) ( (ML/\text{MIN}) )</td>
<td>E. MMHg/ML/\text{MIN}</td>
<td>F. ( \Delta P_o = 0 )</td>
</tr>
<tr>
<td><img src="image" alt="Diagram IV" /></td>
<td>D. ( \Delta V(ML) )</td>
<td>C. ( P_o, P_p, P_2, t_2 )</td>
<td>D. ( PVI = \frac{\Delta V}{\log_{10} \frac{P_p}{P_o}} )</td>
<td>E. ML</td>
<td>F. ( \Delta P_o = 0 )</td>
</tr>
</tbody>
</table>

A. Marmarou, K. Shulman and R. M. Rosende

*J. Neurosurg. / Volume 48 / March, 1978*
Resistance to outflow of cerebrospinal fluid determined by bolus injection technique and constant rate steady state infusion in humans.

Kosteljanetz M.

Abstract
Two methods for the determination of resistance to the outflow of cerebrospinal fluid, the bolus injection technique and the constant rate steady state infusion technique, were compared. Thirty-two patients with a variety of intracranial diseases (usually communicating hydrocephalus) were studied. There was a high degree of correlation between the resistance values obtained with the two methods, but values based on the bolus injection technique were systematically and statistically significantly lower than those obtained with the constant rate infusion test. From a practical point of view, both methods were found to be applicable in a clinical setting.

PMID: 3982612 [PubMed - indexed for MEDLINE]
Davson’s Equation: 
ICP = Rout * CSF production + Pss

Lack of relationship between resistance to cerebrospinal fluid outflow and intracranial pressure in normal pressure hydrocephalus


Objective – To explore whether calculation of resistance to cerebrospinal fluid (CSF) outflow (Rcsf) by the lumbar constant rate infusion test in a reliable way predicts the intracranial pressure (ICP) profile in normal pressure hydrocephalus (NPH). Methods – A prospective study was undertaken including 16 cases with clinical signs of normal pressure hydrocephalus that were investigated with both continuous ICP monitoring and the lumbar constant rate infusion test. Intracranial pressure monitoring was performed for about 24 h, and supplied with a simultaneous lumbar constant rate infusion test at the end of the monitoring period. The pressure recordings were analysed using the Sensomedics® Pressure Analyser. Various characteristics of the pressure curves were compared. Results – The continuous ICP recordings were considered as normal (mean ICP < 11.5 mmHg) in all 16 cases. The lumbar infusion test showed an apparently abnormal resistance to CSF outflow (Rcsf) (>12.0 mmHg/ml/min) in 12 of 16 cases. There was no relationship between lumbar Rcsf and mean ICP during sleep. We could not find any relationship between lumbar Rcsf and number of nightly ICP elevations of 15–25 mmHg lasting 0.5 or 1 min. Neither resistance to CSF outflow (Rcsf) nor mean ICP during sleep was related to the ventricular size. Conclusions – The results of this prospective study revealed no significant relationship between resistance to CSF outflow (Rcsf) and the ICP profile in NPH cases. The results also suggest that caution should be made when predicting the ICP profile on the basis of measuring the lumbar CSF pressure for a few minutes duration.

The way we calculate Rcsf. Is Sagittal Sinus Pressure always constant?
Idiopathic intracranial hypertension

ICP [mmHg]

Rcsf [mm Hg/(ml/min)]

IIH  NPH

IIH  NPH
Rcsf

ICP

NPH

Acute hydrocephalus

Normal CSF dynamics

Idiopathic Intracranial Hypertension

13?

18?
Resistance to CSF outflow

What it is?

Reliable parameter describing circulation of CSF
Predictor of improvement after shunting (although not ideal)
Good in assessment of shunt functioning in-vivo

What it isn’t?

It is not a single parameter which should be taken into account in making decision about shunting. Multivariate methods will be more reliable.

Management thresholds may be affected by vascular factors, age, duration of symptoms, aetiology and co-morbidity
WHO NEEDS A SHUNT?

He needed shunt. But it did not help

Ignoring CSF dynamics. Is it always wise?
Outcomes – internal audit
(Mrs N. Keong)

Cambridge CSF Clinic

n = 140

Shunt responders
69%
n = 97

Shunt non-responders
31%
n = 43

Lasting improvement
47%
n = 66

Late decline
15%
n = 31

Thanks to Ms. N. Keong
### Dichotomization: A&B vs C

<table>
<thead>
<tr>
<th></th>
<th>Outcome A&amp;B</th>
<th>Outcome C</th>
<th>p</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>72 +/- 8.5</td>
<td>71 +/- 9.1</td>
<td>p = 0.31</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;46;85</td>
<td>&lt;46;86</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex (f:m)</strong></td>
<td>37:60</td>
<td>14:29</td>
<td>p = 0.65</td>
<td>Chi Square</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>64:12</td>
<td>30:17</td>
<td>p = 0.018</td>
<td>Chi Square</td>
</tr>
<tr>
<td>(G&amp;D):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(G or D)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Rcsf</strong></td>
<td>19.1 +/- 6.82</td>
<td>15.6 +/- 6.9</td>
<td>p = 0.0012</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;6-46</td>
<td>&lt;3-42</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>E</strong></td>
<td>0.26 +/- 0.17</td>
<td>0.22 +/- 0.15</td>
<td>p = 0.096</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;0.002;0.98</td>
<td>&lt;0.04;0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICPbeg</strong></td>
<td>10.4 +/- 4.6</td>
<td>8.9 +/- 3.99</td>
<td>p = 0.029</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;-1;17.9</td>
<td>&lt;-1;17.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AMPbeg</strong></td>
<td>2.57 +/- 1.65</td>
<td>2.7 +/- 1.81</td>
<td>p = 0.42</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;0.1;7.9</td>
<td>&lt;0.1;7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CSFprod</strong></td>
<td>0.45 +/- 0.23</td>
<td>0.48 +/- 0.24</td>
<td>p = 0.64</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;0.05;0.94</td>
<td>&lt;0.1;0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AMP_p</strong></td>
<td>0.30 +/- 0.13</td>
<td>0.34 +/- 0.20</td>
<td>p = 0.22</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td></td>
<td>&lt;0.043;0.064</td>
<td>&lt;0.02;0.92</td>
<td></td>
<td></td>
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</table>

Thanks to Ms. N. Keong
## Rcsf as a predictor of good outcome

<table>
<thead>
<tr>
<th>Rcsf mmHg/(ml/min)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 17</td>
<td>81 %</td>
<td>38 %</td>
</tr>
<tr>
<td>&gt; 13</td>
<td>75 %</td>
<td>55 %</td>
</tr>
</tbody>
</table>

Thanks to Ms. N.Keong
1982. Threshold 12 mm Hg/(ml/min)
Positive predictive value 100%
Negative predictive value 100%

1997: Rcsf best predictive parameter
Threshold 18 mmHg/(ml/min)
Positive predictive value 92%
Negative predictive value 34%

2009: No correlation between Rcsf and outcome
Dutch Normal-Pressure Hydrocephalus Study: the role of cerebrovascular disease

AGNITA J. W. BOON, M.D., JOSEPH T. J. TANS, PH.D., ERNST J. DELWEL, M.D., SASKIA M. EGELE-PERDEMAN, M.D., PATRICK W. HANLO, M.D., PH.D., HANS A. L. WURZER, M.D., AND JO HERMANS, PH.D.

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Object. This study was conducted to determine the prevalence of cerebrovascular disease and its risk factors among patients with normal-pressure hydrocephalus (NPH) and to assess the influence of these factors on the outcome of shunt placement.

Methods. A cohort of 101 patients with NPH underwent shunt placement and was followed for 1 year. Gait disturbance and dementia were quantified using an NPH scale and handicap was determined using a modified Rankin scale (mRS). Primary outcome measures consisted of the differences between preoperative and last NPH scale and mRS scores. The presence of risk factors such as hypertension, diabetes mellitus, cardiac disease, peripheral vascular disease, male gender, and advancing age was recorded. Cerebrovascular disease was defined as a history of stroke or a computerized tomography (CT) scan revealing infarcts or moderate-to-severe white matter hypodense lesions.

The prevalence of risk factors for cerebrovascular disease was higher in the 45 patients with cerebrovascular disease than the 56 without it. Risk factors did not influence outcome after shunt placement. Intent-to-treat analysis revealed that the mean improvement in the various scales was significantly less for patients with a history of stroke (14 patients), CT scans revealing infarctions (13), or white matter hypodense lesions (32 patients) than for those without cerebrovascular disease. The proportion of patients who responded to shunt placement was also significantly lower among patients with than those without cerebrovascular disease (p = 0.02).

Conclusions. The authors identified a subgroup of patients with NPH and cerebrovascular disease who showed disappointing results after shunt placement. Cerebrovascular disease was an important predictor of poor outcome.

KEY WORDS • normal-pressure hydrocephalus • ventriculoperitoneal shunt • outcome • vascular risk factors • white matter hypodense lesion • cerebrovascular disease
Not everyone who needs a shunt is going to improve!

Many thanks to Mr Brian Owler for this illustration!
Testing vascular factors in clinical practice: CO2 reactivity in patients suffering from NPH
Who needs a shunt?

He needs!

She needs!!!

She does not!!!

He does not need, observation!
Message to take home:

• Resistance to CSF outflow is increased in hydrocephalus
• Thresholds: 13 mmHg/(ml/min) or 18 mm Hg/(ml/min)
• Normal resistance < 10 mm Hg/(ml/min)
• Increased resistance is not 100% reliable predictor of improvement
• Vascular comorbidity is a factor worth consideration