Is There a Link Between ICP-Derived Infusion Test Parameters and Outcome After Shunting in Normal Pressure Hydrocephalus?

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Abstract *Objective*: The term "hydrocephalus" encompasses a range of disorders characterised by clinical symptoms, abnormal brain imaging and derangement of cerebrospinal fluid (CSF) dynamics. The ability to elucidate which patients would benefit from CSF diversion (a shunt or third ventriculostomy) is often unclear. Similar difficulties are encountered in shunted patients to predict the scope for improvement by shunt re-adjustment or revision.

Materials and methods: We compared retrospective pre-shunting infusion test results performed in 310 adult patients diagnosed with normal pressure hydrocephalus (NPH) and their improvement after shunting.

Results: Resistance to CSF outflow correlated significantly with improvement ($p < 0.05$). Other markers known from the literature, such as amplitude in CSF pulse pressure, the slope of the amplitude–pressure regression line, or elasticity did not show any correlation with outcome.

Conclusion: Outcome following shunting in adult NPH is associated with resistance to CSF outflow; however, the latter cannot be taken as an absolute predictor of shunt response.

Keywords Hydrocephalus · Infusion test · CSF outflow · Resistance

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Introduction

The strict relationship between shunt responsiveness and increased resistance to cerebrospinal fluid outflow (Rout) was reported in 1981 by Børgesen and Gjerris [1]. Rout was measured using a lumbo-ventricular perfusion study, a method that potentially ensured a high level of accuracy, but is no longer in use because of its invasiveness. Predictive powers of 100% was observed for a threshold of 12 mmHg/(ml/min). Nearly 15 years later, the relationship between Rout and the results of shunting was investigated in the so-called Dutch Normal Pressure Hydrocephalus (NPH) trial [2]. The threshold for successful shunting was found to be at a higher level (17 mmHg/(ml/min)). The positive predictive power was 92%, but the negative predictive power was only 34%. Rout was measured using Katzman's lumbar infusion study [3]. Finally, quite recently, the "European NPH study" [4] reported no correlation between Rout (again, assessed using a lumbar test) and outcome following shunt surgery.

Is the result of shunting really dependent on cerebrospinal pressure volume compensation and CSF circulation? What happened between the timing of the three studies listed above, that the results changed so dramatically?

Is this a way that Rout is measured? Original lumbo-ventricular perfusion was compared with the "computerised constant rate lumbar study" and agreement between the two methods was found to be very satisfactory [5]. The "computerised infusion test" was a computer-supported single-rate Katzman's lumbar study and it is rather unlikely that such computer support was so decisive in the calculation of a relatively simple parameter such as Rout.

Perhaps the initial selection of the patients has changed. In 1981 more "pure hydrocephalus" was selected for a relatively invasive technique, whereas later, less invasive lumbar infusion study permitted patients with overlapping brain problems, such as small vessels disease, parkinsonism, Alzheimer's, etc., to be accepted.

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We started our comprehensive program of CSF dynamics study in patients diagnosed with NPH in 1992. Recently, we reviewed our ongoing database to study patients with an initial diagnosis of NPH to compare the parameters describing CSF circulation and pressure–volume compensation and clinical improvement after shunting.

Materials and Methods

A total of 310 adult patients (aged 40–86) were eligible for retrospective analysis. All patients had probable NPH following clinical assessment and brain imaging. Patients underwent infusion tests and were available for follow-up via the multidisciplinary CSF clinic. Outcomes were assessed using the in-house pragmatic categorisation of patient cohorts into three groupings – sustained improvement, short-term improvement and no improvement.

The infusion test requires fluid infusion to be made into any accessible CSF compartment and monitoring of CSF pressure at the same time. Lumbar infusion, even if it has understandable limitations, is less invasive and therefore, more frequently performed. The second most frequent approach is an intraventricular infusion into a subcutaneously positioned reservoir, connected to an intraventricular catheter or shunt antechamber. In such cases, two hypodermic needles (gauge 25) are used: one for the pressure measurement and the second for the infusion.

During the infusion, the computer calculates and presents the mean pressure and pulse amplitude (with time along the *X* axis, Fig. 1). The resistance to CSF outflow can be calculated using simple arithmetic as the difference between the value of the plateau pressure during infusion and the resting pressure divided by the infusion rate. However, in many cases strong vasogenic waves or excessive elevation of the pressure above the safe limit of 40 mmHg do not allow the precise measurement of the final pressure plateau. Computerised analysis produces results, even in difficult cases when the infusion is terminated prematurely (i.e., without reaching the end-plateau). The algorithm utilizes a time series analysis for volume–pressure curve retrieval, the least-mean-squares model fitting and an examination of the relationship between the pulse amplitude and the mean CSF pressure. Apart from resting CSF pressure and the resistance to CSF outflow, the elastance coefficient or pressure–volume index, cerebrospinal compliance, CSF formation rate and the pulse wave amplitude of CSF pressure are calculated. All data recordings and calculations are performed using software ICM+ (https://icmplus.neurosurg.cam.ac.uk/).

Pulse amplitude increases proportionally to mean CSF pressure during the infusion study. The slope of the amplitude–pressure line (AMP/p) has been implicated as having a strong association with outcome following shunting [6]. Similarly,

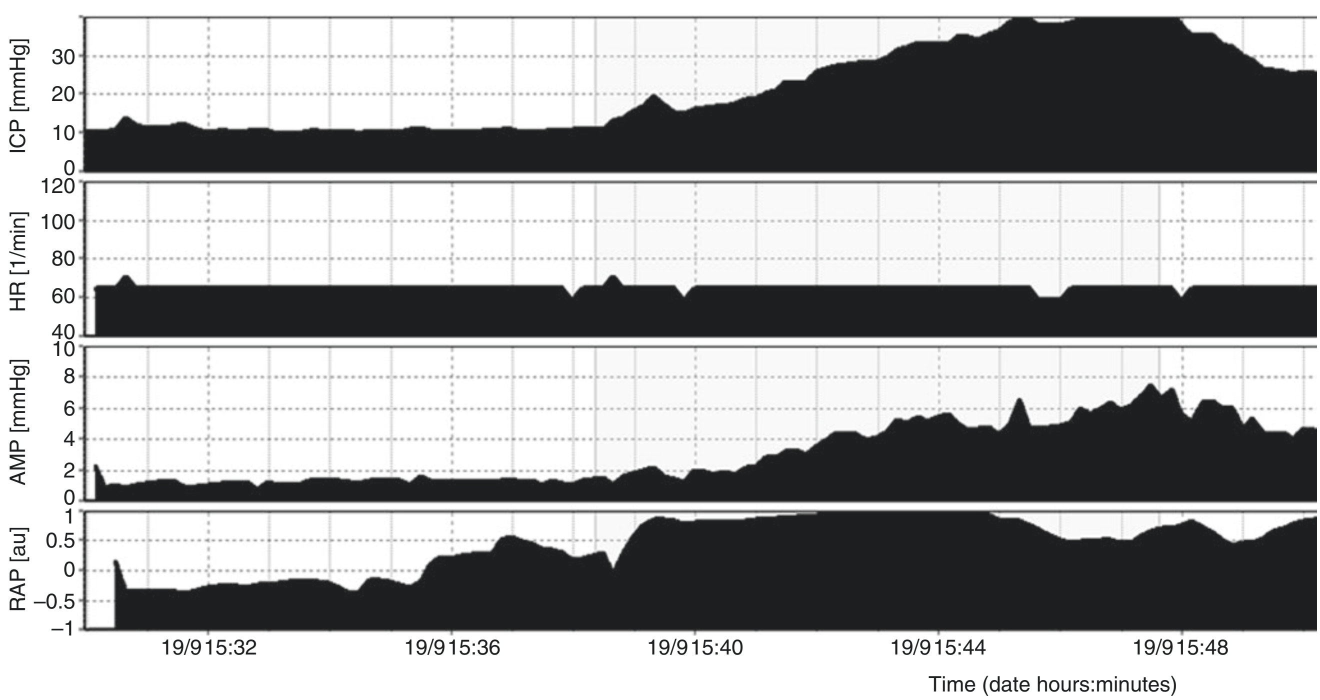

Fig. 1 Typical infusion study. Recording of mean cerebrospinal fluid (CSF) intracranial pressure (ICP). Heart rate, pulse amplitude of ICP (AMP) and index characterizing pressure volume compensatory reserve (RAP – correlation coefficient between slow changes in pulse amplitude and mean ICP). Infusion started at 15:37 with a rate of 1.5 ml/min and after 10 min, plateau pressure at 39 mmHg was reached. Elevated resistance to CSF outflow was demonstrated (21 mmHg/(ml/min)). The patient improved after shunting

pulse amplitude has been reported to be a strong predictor of outcome after surgery [7]. Consultants deciding on shunting were not blinded to the results of the infusion study.

Results

Baseline ICP was lower than 18 mmHg, median 9 mmHg. Median amplitude was 3 mmHg, median Rout 16 mmHg/(ml/min) and elasticity 0.3 (1/ml).

Seventy-nine percent of patients showed improvement after shunt insertion (60% sustainable, 19% temporary). Improvement rate increased from 1992 (60%) to 2013 (86%); $p = 0.0003$. Of all calculated CSF compensatory parameters, only Rout was associated with outcome ($p = 0.014$). Patients with Rout >13 mmHg/(ml/min) had an improvement rate of 79%, compared with 63% ($p = 0.011$) with Rout <13. Notably, none of the patients with low Rout (lower than 6 mmHg/(ml/min); $n = 7$) improved after shunting. Neither age nor sex correlated with outcome.

We investigated the best threshold value of Rout to differentiate between good and poor outcome.

On the *X* axis is a threshold value of Rout and on the *y* axis an *F* value of statistics for improvement.

This distribution presents two maxima (Fig. 2):

– at 13 mmHg/(ml/min)—close to the value as proposed by Børgesen and Gjerris [1]
– at 18 mmHg/(ml/min)—which was suggested in a Dutch study [3].

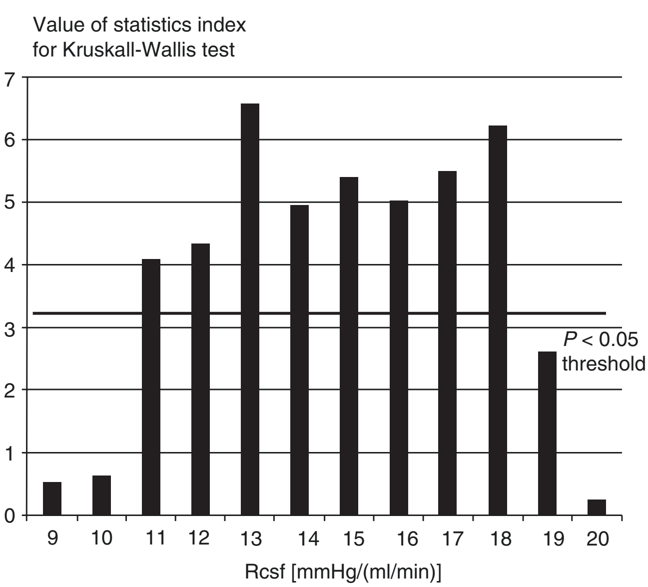

Fig. 2 Value of Kruskal–Wallis test statistics in testing the difference between improvement and no improvement after shunting as a function of estimated resistance to CSF outflow. Two maxima of distribution show the best thresholds for estimation of Rout

Discussion

Rout is related to outcome, but cannot be taken as a single discriminatory parameter in the making decision to shunt. If Rout was very low, lower than 6, we did not observe any improvement. However, between 6 and 13, the improvement rate was considerably higher. Other compensatory parameters are poorly related to outcome in our material. We need to search for better predictors for improvement after shunting in NPH. Rout was the only CSF compensatory parameter correlating with outcome following shunting. The relationship was weak but significant. Infusion studies appeared to be helpful in the assessment of the compensatory parameters both for diagnosing and yielding baseline values as a benchmark for further investigations in cases of suspected shunt malfunctions and complications.

Conclusion

- Rout is related to outcome, but cannot be taken as a yes/no parameter in decision-making about shunting.
- If Rout was very low, lower than 6, we did not observe any improvement.
- Other compensatory parameters are poorly related to outcome in our material.
- We need to continue searching for better predictors for improvement after shunting in NPH.

Conflicts of interest statement We declare that MC has a financial interest in a fraction of ICM+ software licensing fee (licensed by Cambridge Enterprise Ltd, UK).

References

1. Børgesen SE, Gjerris F. The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. Brain. 1982;105:65–86.
2. Katzman R, Hussey F. A simple constant infusion manometric test for measurement of CSF absorption. Neurology (Minneap). 1970;20:534–44.
3. Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, Avezaat CJ, de Jong DA, Gooskens RH, Hermans J. Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. J Neurosurg. 1997;87(5):687–93.
4. Wikkelsø C, Hellström P, Klinge PM, Tans JT. European iNPH Multicentre Study Group. The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF Tap Test in patients with idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 2013;84(5):562–8.
5. Børgesen 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. 1992;119(1–4):12–6.
6. Anile C, De Bonis P, Albanese A, Di Chirico A, Mangiola A, Petrella G, Santini P. Selection of patients with idiopathic normal-pressure hydrocephalus for shunt placement: a single-institution experience. J Neurosurg. 2010;113(1):64–73.
7. Eide PK, Brean A. Intracranial pulse pressure amplitude levels determined during preoperative assessment of subjects with possible idiopathic normal pressure hydrocephalus. Acta Neurochir. 2006;148(11):1151–6.