The Prediction of Shunt Response in Idiopathic Normal-Pressure Hydrocephalus Based on Intracranial Pressure Monitoring and Lumbar Infusion

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Abstract *Background*: Intracranial pressure (ICP) monitoring and infusion studies have long been used in the preoperative workup of patients with suspected idiopathic normal-pressure hydrocephalus (iNPH). We have analysed the predictive values of different measures derived from both investigations, emphasising the differences between responders and nonresponders. *Materials and methods*: ICP monitoring and lumbar infusion studies were routinely performed during a 6-year period. Shunting was proposed when the resistance to cerebrospinal fluid outflow (R_{OUT}) >12 mmHg/ml/min and/or a minimum 15 % of slow waves were detected. The outcome was evaluated 6 months after surgery. Recorded data from ICP monitoring were mean pressure and pulse amplitude, the total percentage of slow waves and the presence of different types of slow waves following the classification proposed by Raftopoulos et al. Recorded data from lumbar infusion studies were mean values of pressure and pulse amplitude during three epochs (basal, early infusion and plateau), R_{OUT} and the pulsatility response to the increase in mean pressure during the infusion. This response was quantified by two pulse amplitude indexes: the pulse amplitude index during the early infusion stage (A1) and the pulse amplitude index during the plateau stage (A2). *Results*: Thirty shunted patients were evaluated at the end of the follow-up and 23 (76.7 %) of them improved. Differences in the percentage of slow waves, R_{OUT} and both pulsatility indexes were not statistically significant. The proportion of patients with great symmetrical waves and pulse amplitude during the early infusion stage were higher in responders ($p<0.05$). The predictive analysis yielded the highest accuracy, with R_{OUT} and A1 as a logical "OR" combination. *Conclusion*: The combined use of ICP monitoring and lumbar infusion to forecast the response to shunting in patients with suspected iNPH did not improve the accuracy provided by any of them alone.

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Introduction

The way patients with suspected idiopathic normal-pressure hydrocephalus (iNPH) are selected for shunt surgery varies widely [21]. A common policy nowadays is to anchor the decision on the clinical picture, verified ventriculomegaly and most often the results of different supplementary cerebrospinal fluid (CSF) dynamics tests. The improvement rate, however, varies widely and spans from roughly 60 % up to 90 % [1, 8, 9, 11]. This generous gap illustrates the hurdles encountered when dealing with this condition, one of which is selection criteria for shunt surgery.

Intracranial pressure (ICP) monitoring and lumbar infusion studies have long been used in the preoperative workup of patients with suspected iNPH. The rationale for using infusion studies is partly based on the assumption that a defective capacity to reabsorb CSF is a component of the pathophysiology in the NPH syndrome [6, 17]. Infusion studies indirectly evaluate CSF absorption through the measurement of the resistance to CSF outflow (R_{OUT}). However, the utility of R_{OUT} in selecting patients with iNPH for shunt surgery is controversial, with some studies supporting R_{OUT} [5, 6, 18] and others finding it less useful in the selection process [7, 9, 25].

Other theories of the evolving pathophysiology in this condition favour a decrease in intracranial compliance as an important underlying principle. The vinculum between the compliance of the brain and intracranial pulsatility is firmly established. The primary measure of intracranial pulsatility is the pulse amplitude, that is, the variation in pressure from peak to trough in the waveform. In 1962, Bering [4] linked pulsatility, which he erroneously thought came from the

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choroid plexus, with the development of hydrocephalus. Later, Di Rocco et al. [10] reinforced the role of pulsations, demonstrating experimentally how increased CSF pulsatility can lead to the development of ventricular dilation. Over the past decades, clinical studies have shown that the pulse amplitude of ICP and other quantitative measures extracted from the pulse pressure waveform can be valuable tools in hydrocephalus assessment [1, 2, 11, 14]. In particular, the pulse amplitude of ICP recorded during infusion studies was recently suggested as a useful parameter for predicting response in iNPH [1, 12].

The main goal of ICP monitoring is to assess the slow wave activity. Historically, these slowly varying waves were identified by Janny [16] and Lundberg [24] from visual analysis of pressure recordings. They appeared as spontaneous rhythmic oscillations of ICP, ranging from 0.5 to 2 cycles per minute, with variable amplitude. A high relative frequency of slow waves is indicative of reduced craniospinal compliance and it has been shown to be a good predictive factor for shunt responsiveness [33]. However, the cutoffs for the frequency during the recording time and the amplitude of slow waves vary widely [21].

During a 6-year period (2006–2012) our department has used ICP monitoring and lumbar infusion studies in all patients with suspected iNPH. In this study, we have retrospectively analysed the predictive values of three parameters extracted from these supplementary tests, emphasising the differences between responders and nonresponders. Two of them are classical parameters. The slow wave activity (also known as Lundberg's B waves) was measured during ICP monitoring, and the value of R_{OUT} was obtained during a lumbar infusion test. The third parameter aims to summarise the pulsatility response to an increase in mean pressure during lumbar infusion studies. We postulated that, in accordance with theories on the role of pulsations in iNPH, a ratio between the pulse amplitude during volume loading and at baseline could improve the predictive values provided by classical parameters.

Materials and Methods

Management Protocol in Patients with Suspected iNPH

Intraparenchymal ICP monitoring and lumbar infusion studies were routinely performed in our institution between June 2006 and May 2012 in patients with suspected iNPH. All patients had an increase in ventricular size (Evans index > 0.30) and, clinically, different combinations of the classic triad [15]: slowly progressive impairment of gait and balance, cognitive deterioration and sphincter dysfunction. In all patients the three main symptoms of the disease were evaluated according to the NPH scale [33]. This scale has been adopted by other groups because of its simplicity [11]. It assesses the severity of gait, cognitive and sphincter disturbances. The minimum score is 3 points, which indicates that the patient is bedridden or unable to walk, has no contact with the environment and has urinary and faecal incontinence. The maximum score of 15 points reflects highly performing patients with early presentation of iNPH and only subjective complaints difficult to measure other than after neuropsychological tests.

Once the attending neurosurgeon considered that the patient could be eligible for surgical treatment, he or she was subjected to ICP monitoring, usually for two consecutive nights, and an infusion test was performed on the third day after admission. A ventriculo-peritoneal shunt with a gravitational low-pressure valve (GAV shunt system, Aesculap Miethke, Tuttlingen, Germany) was proposed when R_{OUT} was higher than 12 mmHg/ml/min and/or a minimum 15 % of slow waves were detected in the overnight ICP recording file. Informed consent for all aspects of the study was obtained from either the patient or a close relative. The local ethics committee approved the management routine of the department and this retrospective study.

ICP Monitoring

Intracranial pressure monitoring involves drilling a burr hole with a bit measuring 2.7 mm in diameter through the skull in the precoronal area of the non-dominant side under local anaesthesia, screwing in a fixation bolt and introducing the transducer-tipped catheter (MicroSensor™ ICP transducer; Codman/Johnson & Johnson, Raynham, MA, USA) so that its distal tip lies within the parenchyma. Sensors were zeroed against atmospheric pressure (in 10 ml of sterile normal saline measured in a standard container at a depth of 1 cm) before their insertion into the parenchyma. ICP monitoring was performed during the whole night and data from at least 8 h (11 pm to 7 am) were analysed. The arithmetic mean pressure and pulse amplitude were calculated from each night in every patient (mmHg). The presence of slow waves (0.5–2 ICP waves/min with amplitude >5 mmHg, lasting for at least 10 min) was evaluated and expressed as a percentage of the total monitoring time. In those cases in which two nights were recorded, we chose the overnight recording file with a higher percentage of slow waves.

For the purposes of this study, we have determined retrospectively the presence or absence of four types of slow waves proposed by Raftopoulos et al. [31]:

1. Small symmetrical waves (SSW), corresponding to pressure waves of 0.5–2 cycles per minute with an amplitude of less than 10 mmHg
2. Great symmetrical waves (GSW), corresponding to symmetrical slow waves with an amplitude of 10 mmHg or more
3. Intermediate waves (IW), corresponding to asymmetrical slow waves without plateau and an amplitude >10 mmHg
4. Plateau waves, asymmetrical waves with a plateau phase and an amplitude >10 mmHg.

Lumbar Infusion Study

Infusion studies were performed using a variant of the method described by Katzman and Hussey [19]. Under local anaesthesia, patients were positioned in the lateral recumbent position and two needles were inserted in their lower lumbar region (19-gauge). The caudal needle was connected to an infusion pump. For pressure measurement, a three-way stopcock equipped with a short extension line was connected to the rostral needle. Then, a pressure microtransducer (MicroSensorTM ICP transducer) was introduced through the hole of a fenestrated male Luer lock connected to the three-way stopcock. The tip of the pressure microtransducer was pushed inside the extension line towards the rostral lumbar needle. Finally, the transducer was secured in its position, rotating the male Luer lock and tightening the fenestrated cap to avoid CSF leakage.

The examination included a registration of baseline pressure at rest (approximately 5 min). Through the caudal needle, Ringer solution was infused at a constant rate of 1.5 ml/min. The infusion was stopped when a plateau pressure level was achieved, usually after 20 min. Two phases were distinguished during the infusion stage: the early infusion phase, corresponding to the slope stage, and the plateau phase itself (Fig. 1).

For every infusion study, we carefully selected three artefact-free epochs during the baseline, early infusion and the plateau stage of each examination (Fig. 1). The arithmetic means of pressure and pulse amplitude during the three epochs were determined in all studies. R_{OUT} was calculated as the plateau minus baseline pressure, divided by the infusion rate. Amplitude was defined as the peak-to-trough value of the pulse wave, during both ICP monitoring and the infusion test. The pulsatility response during the infusion study was quantified by calculating two pulse amplitude indexes: the pulse amplitude index during the early infusion stage, or ascending slope (A1), and the pulse amplitude index during the plateau stage (A2): A1 = mean pulse amplitude during the early infusion epoch/mean pulse amplitude during the basal epoch; A2 = mean pulse amplitude during the plateau epoch/mean pulse amplitude during the basal epoch.

Data Acquisition

The pressure signal from the analogue output of the microtransducer monitor was displayed on a computer using a commercially available analogue-to-digital signal converter and software (PowerLab, AD Instruments, Colorado Springs, CO, USA). Pressure data from both examinations, ICP monitoring and lumbar infusion studies, were sampled with a rate of 100 Hz.

Outcome Assessment

The follow-up was carried out in our outpatient clinic at regular intervals, the first one, a month after discharge. The response to shunt surgery was determined after 6 months using the NPH scale [33]. Because a small change in the NPH scale score represents a substantial change in the patient's functional status, particularly in the gait domain, we defined a one-point increase in the global score as being indicative of clinical improvement [29]. This change is generally appreciated by the patients and their families or caregivers. Surgically treated patients were categorised as either responders or nonresponders. The neurosurgical attending, the patient and/or his or her relatives confirmed this categorisation on the basis of an obvious and lasting amelioration of at least one feature of the clinical triad.

Statistics

Statistical analyses were performed using PASW Statistics, version 18.0 (SPSS, Chicago, IL, USA). The mean differences between the two groups (responders and nonresponders) were determined using Student's t test. Normality and equality of variances are required to apply this parametric statistical test. Proportions were compared using the Chi-squared test. A p value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were analysed to summarise the performance of a two-class classifier across the range of possible thresholds. This is a graphical representation of the trade-offs between sensitivity and specificity. The area under the ROC curve (AUC) is a single number summary of performance. The ideal value is 1 and the worst-case value is 0.5. A rough guide to classifying the AUC is the traditional academic points system: (A) excellent, if AUC values are between 0.9 and 1; (B) good, when the values range between 0.8 and 0.89; (C) fair, for values between 0.7 and 0.79; (D) poor, for results between 0.6 and 0.69; and (E) bad, if the AUC is within the range 0.5–0.59.

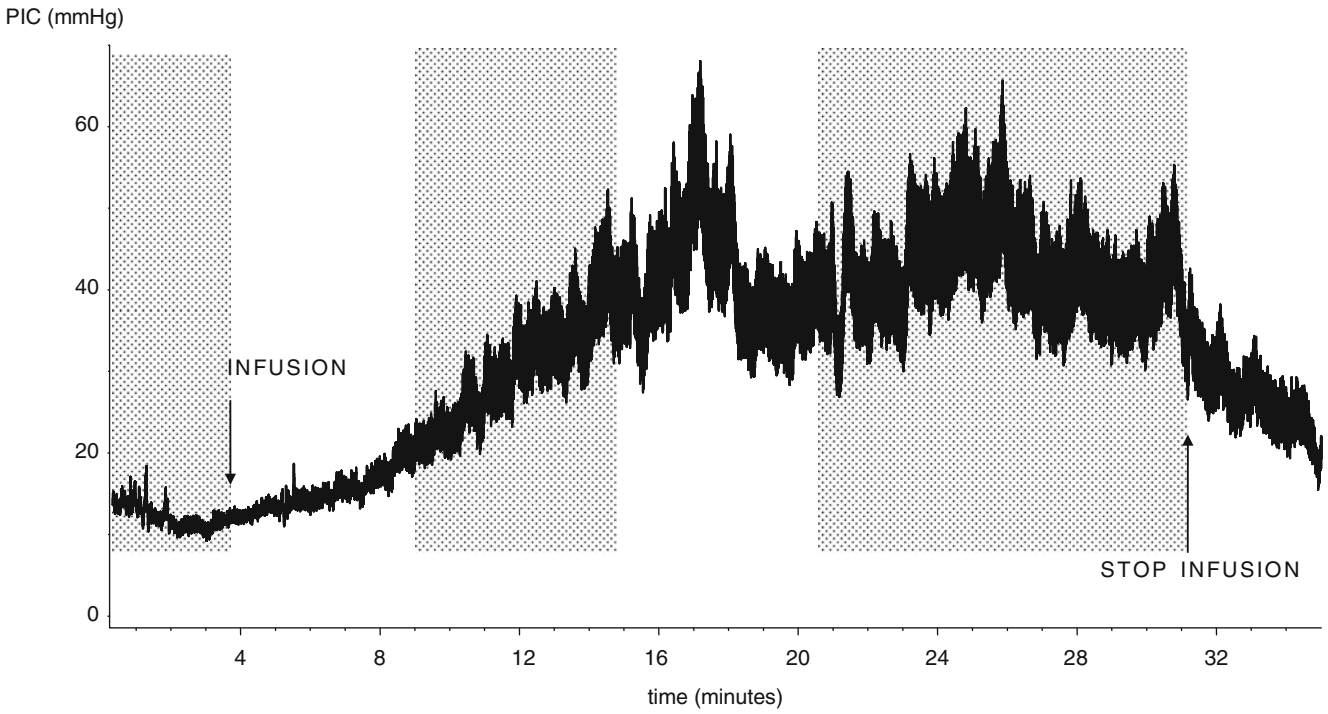

Fig. 1 Example tracing obtained during an infusion study showing the three stages analysed in this study (*shaded areas*). Average values of pressure and pulse amplitude during the baseline, early infusion and plateau stages were determined in all studies

Results

Forty-two consecutive patients with suspected iNPH were evaluated during the study period with ICP monitoring and the lumbar infusion test. Ten patients were not surgically treated and 2 patients died less than 6 months after surgery from causes unrelated to shunting (oncological disease and myocardial infarction). The final sample consisted of 30 patients (20 men [67 %]) with a mean age of 77 years (range 61–88 years). Twenty-three patients had improved by the 6-months follow-up (76.7 %). Postoperative shunt patency was tested in patients who had not improved, performing a new infusion test 3–6 months after surgery. During the follow-up period, 2 responder patients presented shunt-related complications: a shunt infection, which required removal of the shunt and replacement with a new device after a course of antibiotics, and 1 case of symptomatic bilateral subdural haematoma due to overdrainage that was treated by burr holes and replacement of the valve unit, upgrading the antigravity device.

ICP Monitoring

The mean overnight pressure was similar in the two groups (Table 1). Pulse amplitude was higher in responders than in nonresponders, although differences did not reach statistical significance (6.2 vs 4.5 mmHg respectively; $p=0.07$). Two patients had no slow waves and 4 patients had slow waves less than 15 % of the total recording time. The remaining 24 patients (80 %) had slow waves for more than 15 % of the total recording time. The percentage of slow waves during the total recording time was similar in the two groups (40 % in responders vs 45 % in nonresponders; $p=0.68$). We detected sequences of SSW in 26 patients (80 %), GSW in 20 (67 %) and IW in 7 (23 %). Plateau waves were seen only in 1 nonresponder patient. GSW were more common in responders than in nonresponders (78 % vs 29 %; $p=0.015$). The proportions of SSW and IW were similar in the two groups.

Lumbar Infusion Study

During the lumbar infusion test, mean baseline lumbar pressure was higher in nonresponders than in responders, although differences did not reach statistical significance (10.1 mmHg vs 7.3 mmHg respectively; $p=0.07$). R_{OUT} was slightly higher in responders (13.1 vs. 11.6 mmHg/ml/min; $p=0.47$). Pulse amplitude during the early infusion stage was the only pressure parameter with statistically significant differences between the two groups (8 mmHg in responders vs 5.6 mmHg in nonresponders; $p=0.01$). Both pulsatility

indexes, A1 and A2, were higher in responders. However, neither of them reached statistical significance (Table 1).

Receiver operating characteristic curve analysis was used to select the optimal thresholds for sensitivity and specificity. This threshold is the cutoff point in which the highest accuracy is obtained. In our series, the optimal R_{OUT} was 11.8 mmHg/ml/min. However, the AUC value associated with this threshold is poor (0.67). The same analysis was performed with both pulsatility indexes. Optimal A1 was 2 and the AUC associated with this threshold was 0.81. Optimal A2 was 3.1 and the AUC associated with this threshold was 0.68. The accuracy, sensitivity, specificity and positive and negative predictive values of these thresholds are summarised in Table 2. Finally, we performed logical combinations (and/or) with the most important parameters. The highest accuracy was obtained with R_{OUT} and A1 as a logical "OR" combination (Table 2).

Discussion

We have been using intraparenchymal ICP monitoring and lumbar infusion studies to select patients with suspected iNPH for shunt surgery over a 6-year period. This study is retrospective and analyses a small sample of patients. There is also an imbalance between responders and nonresponders, and preselection criteria based on R_{OUT} and the percentage of slow waves. These shortcomings notwithstanding, we considered it to be of interest to report our experience, as the results obtained have led us to reassess the appropriateness of that policy. The percentage of slow waves was similar in responders and nonresponders, in accordance with previous studies [29, 35]. The proportion of patients with GSW was the main distinctive feature in responders and nonresponders derived from ICP monitoring. R_{OUT} was similar in both groups, performing poorly as a predictive parameter of improvement. The pulsatility response, mainly during the early stage of infusion, had higher predictive values than R_{OUT}. Inclusion of ICP monitoring in the preoperative workup of patients with suspected iNPH did not improve the predictive values provided by the lumbar infusion test alone (i.e. the resistance to CSF outflow and pulsatility response to infusion).

It is claimed that disturbed CSF dynamics are involved in the pathophysiology of iNPH [26]. This disturbance within the craniospinal system brings to the fore a mechanical paradigm as the driving force in iNPH, leading ultimately to neuronal damage during its evolving pathophysiology. Data coming from other fields, such as genetics or humoural damage mediated by different biomarkers, are currently scarce and impractical from a clinical standpoint.

Slow Waves

In a past comprehensive survey on the management of NPH in Germany, ICP monitoring was the third priority after clinical presentation (which was considered to be of the highest priority) and CSF removal through a *tap test* [21]. It is noteworthy that the morbidity related to parenchymal or ventricular monitoring of ICP in this fragile population has not been thoroughly reviewed. Even more importantly, it is still

Table 1 Parameters describing the overnight intracranial pressure (ICP) monitoring and the infusion study (mean [standard deviation])

	Responder ($n=23$)	Nonresponder ($n=7$)	p value
ICP monitoring			
Overnight ICP (mmHg)	7.3 (3)	6.8 (3.2)	0.65
Amp (mmHg)	6.2 (2.3)	4.5 (1.2)	0.07
Slow waves (% recording time)	40 (27)	45 (25)	0.68
Great symmetrical waves (% patients)	78	29	**0.02**
Infusion study			
Opening pressure (mmHg)	7.3 (3.8)	10.1 (3.6)	0.07
R_{OUT} (mmHg/ml/min)	13.1 (5)	11.6 (5.3)	0.47
Opening Amp (mmHg)	3 (1.4)	3 (1.1)	0.99
Amp 1 (mmHg)	8 (3.4)	5.6 (1.7)	**0.01**
Amp 2 (mmHg)	13 (6.8)	9.6 (3.1)	0.23
A1	2.9 (1.5)	1.9 (0.5)	0.07
A2	5 (3.9)	3.3 (1.3)	0.25

Amp pulse amplitude, *Amp 1* pulse amplitude during early infusion, *Amp 2* pulse amplitude during plateau, *A1* pulse amplitude index during the early infusion stage, *A2* pulse amplitude index during the plateau stage
Entries in bold highlight p values <0.05

Table 2 Predictive values of R_{OUT}, both pulsatility indexes and great symmetrical waves according to cutoffs as individual or combined parameters

	$R_{OUT}>11.8$	A1>2	A2>3.1	GSW	$R_{OUT}>11.8$ or A1>2	$R_{OUT}>11.8$ and A1>2	$R_{OUT}>11.8$ or GSW
Sensitivity	71	89	75	78	96	64	91
Specificity	75	75	62	71	62	87	71
Positive pv	91	93	87	90	90	95	91
Negative pv	43	67	42	50	83	41	71
Accuracy	72	86	72	77	89	69	87

A1 pulse amplitude index during early infusion stage, *A2* pulse amplitude index during plateau stage, *GSW* great symmetrical waves, *pv* predictive value

unclear when ICP monitoring should be considered pathological. The cutoffs for the frequency during the recording time and the amplitude of slow waves are not uniformly defined [21].

Interpretation of the recorded pressure oscillations is problematic and to our knowledge no standardised criteria for the assessment of ICP recordings have been established. Despite current advances in computerised data analysis, visual screening of the ICP signal to detect slow waves still remains the most common method of analysis. It is not accurate and is further complicated by the findings that the frequency, amplitude and morphology of slow waves are related to different sleep stages and to episodes of oxygen desaturation [20, 32]. These issues may explain the discrepancies of the predictive value of slow waves. Some studies have shown that the frequent presence of ICP slow waves predicts a positive outcome after shunt implant in NPH patients in general, without independent iNPH analyses [28, 31, 34]. In our study, the only distinctive feature derived from ICP monitoring was a higher proportion of patients with GSW in the responder group. This finding is in agreement with theories of compliance being a component of the pathophysiology of iNPH, as a decrease in craniospinal compliance increases the frequency and, in particular, the amplitude of slow waves [23].

Resistance to CSF Outflow

One of the most concordant findings in iNPH patients is high resistance to CSF outflow [5, 25, 27]. It has been stated that if the outflow resistance exceeds a certain threshold, this is an excellent predictor of surgical outcome [6]. The lack of consensus concerning the usefulness of this measure can be explained by several reasons: infusion studies are not standardised and, hence, *how to do it* is a main concern; it has also been argued that iNPH patients can reach an irreversible stage in the disease process, which is accompanied by an increased resistance to CSF outflow [26]; and, finally, there is the possibility of underestimating R_{OUT} in cases of accidental and hidden CSF leakage due to needle laceration of the spinal meninges [13]. In our series, the most efficient value for R_{OUT} was 11.8 mmHg/ml/min. This parameter has shown good positive predictive value, but low negative predictive value and confirms the statement that iNPH patients should not be excluded from shunt surgery on the basis of a negative infusion test alone [25, 29].

Intracranial Pulsatility

The primary measure of intracranial pulsatility is the cardiac-related pulse amplitude, i.e. the variation in pressure from peak to trough in the waveform. The clinical value of this variable, however, is yet to be determined. The first attempts to analyse pulse amplitude failed to identify patients with NPH syndrome who were prone to improvement with CSF shunting [2, 14, 22]. Later on, the shunting of patients with iNPH has been associated with a very good outcome when the selection criterion is based on pulse amplitude parameters [1, 11].

In this series, the pulsatility response to volume loading during the early stage of infusion predicted the shunt response with higher accuracy than R_{OUT}. A theoretical advantage of the pulse amplitude index described in this article over other pulsatility-related measures [1, 30] is that it is a ratio that is straightforward to understand and easily calculated. There is no need to enhance the clinician's background in physics and mathematics.

Likewise, for pulse amplitude at baseline in other studies [8, 11], both pulse amplitude indexes have shown good positive predictive power, but lower negative predictive values for shunt response in iNPH. It is noteworthy that the pulse amplitude index during the early stage of infusion performed better than the pulse amplitude index measured during the steady state or plateau of the infusion test. A similar ratio derived from the pulse amplitude was proposed by Belloni et al., who considered a CSF waveform amplitude increase of more than three times from resting conditions to the rapid

eye movement phase of sleep during ICP monitoring the most reliable indicator in predicting surgical outcome in patients with NPH [3].

Conclusion

The prediction of response to shunting did not improve when combining the pressure parameters derived from ICP monitoring and infusion studies. It still remains unclear when ICP monitoring should be considered pathological and data concerning the morbidity related to this invasive procedure are scarce. Moreover, the analysis of an overnight ICP file involves the interpretation of an irregular time series, and one source of continuing frustration, even if highly experienced in this field, is the ability to visually recognise patterns within these irregular time series. This approach appears to be rather subjective and time consuming with the potential of biased results. The data provided by infusion studies are more objective and a lower workload is associated with this investigation. In our opinion, these arguments favour lumbar infusion studies over ICP monitoring during the demanding task of identifying appropriate candidates for surgery in patients with suspected iNPH.

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Conflict of Interest Statement We declare that we have no conflict of interest.

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