Relative Position of the Third Characteristic Peak of the Intracranial Pressure Pulse Waveform Morphology Differentiates Normal-Pressure Hydrocephalus Shunt Responders and Nonresponders

Robert Hamilton, Jennifer Fuller, Kevin Baldwin, Paul Vespa, Xiao Hu, and Marvin Bergsneider

Abstract *Introduction*: The diversion of cerebrospinal fluid (CSF) remains the principal treatment option for patients with normal-pressure hydrocephalus (NPH). External lumbar drain (ELD) and overnight intracranial pressure (ICP) monitoring are popular prognostic tests for differentiating which patients will benefit from shunting. Using the morphological clustering and analysis of continuous intracranial pulse (MOCAIP) algorithm to extract morphological metrics from the overnight ICP signal, we hypothesize that changes in the third peak of the ICP pulse pressure waveform can be used to differentiate ELD responders and nonresponders. *Materials and Methods*: Our study involved 66 patients (72.2 ± 9.8 years) undergoing evaluation for possible NPH, which included overnight ICP monitoring and ELD. ELD outcome was based on clinical notes and divided into nonresponders and responders. MOCAIP was used to extract mean ICP, ICP wave amplitude (waveAmp), and a metric derived to study P3 elevation (P3ratio). *Results*: Of the 66 patients, 7 were classified as nonresponders and 25 as significant responders. The mean ICP and waveAmp did not vary significantly ($p = 0.19$ and $p = 0.41$) between the outcome groups; however, the P3ratio did show a significant difference ($p = 0.04$). *Conclusion*: Initial results suggest that the P3ratio might be used as a prognostic indicator for ELD outcome.

Keywords Intracranial pressure • Normal-pressure hydrocephalus • Waveform morphology • Shunt response • Pulse pressure waveform • External lumbar drain

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Introduction

Normal-pressure hydrocephalus (NPH) is a particular form of communicating hydrocephalus (CH) initially described by Hakim and Adams [5] over 50 years ago. The traditional clinical triad of dementia, gait disturbance, and urinary incontinence, along with evidence of ventriculomegaly, characterize NPH. The diversion of cerebrospinal fluid (CSF) via a ventricular shunt remains the principal treatment option; however, the differentiation of patients who will benefit from this procedure is still widely debated.

The past several decades have introduced a variety of methods for identifying shunt responders. Recent guidelines on supplementary prognostic tests for NPH reviewed a broad spectrum of these tests and, based on the review, the use of external lumbar drain (ELD; 500 ml/3 days) for differentiating patients who are most likely to respond to a shunt was

B.-T. Ang (ed.), *Intracranial Pressure and Brain Monitoring XV*, Acta Neurochirurgica Supplement, Vol. 122,
DOI 10.1007/978-3-319-22533-3_67, © Springer International Publishing Switzerland 2016

recommended [13]. However, despite the evidence for ELD, the high economic cost (extended hospital stay) and the increased risk to the patient (infection), several institutions have implemented additional prognostic procedures to help to identify shunt responders.

Overnight intracranial pressure (ICP) monitoring is one example of a possible alternative/supplement to ELD. Most of the prognostic literature on overnight ICP monitoring has focused on slow wave activity characterized by Lundberg [11] in the early 1960s. Despite some early positive results that linked increased slow wave activity to positive shunt response [14], others have shown no correlation [19]. In addition to investigations of slow wave activity, recent studies of the cardiac-induced ICP pulse pressure waveform have shown promising results. Eide and Sorteberg [2] compared mean ICP, ICP pulse amplitude (waveAmp), and other ICP metrics from overnight ICP recordings as possible prognostic features for NPH shunt outcome. Their study reported 98 % and 70 % sensitivity and specificity, respectively, based on the average and percentage time values for waveAmp, where mean ICP reported much lower values of sensitivity and specificity [2]. Another example of advanced ICP waveform analysis is the morphological clustering and analysis of intracranial pulse (MOCAIP) algorithm developed by our group [7]. The MOCAIP algorithm allows for the quantification of several morphological ICP features and has been shown to be advantageous over traditional monitoring/diagnostic techniques in several clinical studies [8, 9]. Of particular interest to the present work, Hu et al. [8] used the MOCAIP algorithm to identify subtle changes in the ICP waveform of those patients with severe brain injury that correlated with changes in cerebral blood flow (CBF) measured by ^{133}Xe. Specifically, they reported an elevation in the third characteristic peak (dP3) as an indicator of low CBF (<20 ml/100 g/min).

Based on the aforementioned work by Hu et al. [8] on the detection of ischemia in brain injury patients, this study investigates the ability of a novel ICP metric, the ratio of dP3 and waveAmp (P3ratio) from overnight ICP monitoring, to predict ELD outcome.

Materials and Methods

From July 2007 to November 2011, 167 probable NPH patients were admitted to the UCLA Hydrocephalus Clinic for a 3-day ELD trial. Of the 167 patients, 66 (40 %) received overnight ICP monitoring before the placement of the lumbar drain (LD). This patient cohort consisted of 45 men and 21 women with an average age of 72.2 ± 9.8 years, ranging from 45 to 91 years. The local IRB committee approved all data collection and diagnostic procedures and written consent was obtained from the patient or medical proxy before all procedures. For ICP monitoring, an intraparenchymal ICP microsensor (Codman and Shurtleff, Raynaud, MA, USA) was placed in the right frontal lobe and monitoring started one night before the placement of the LD. Both ECG and ICP were collected continuously, with a sampling rate of 240 Hz using the BedMaster system (Excel Medical Electronics, Jupiter, FL, USA).

ICP Analysis

Following data collection the ICP waveforms were analyzed using the MOCAIP algorithm; a detailed description can be found in our previous publication [7]. MOCAIP utilizes a series of signal processing blocks coupled with a clinical database of validated ICP pulses to quantify the ICP morphology and was developed in MATLAB 7.5 R2007b (MathWorks, Natick, MA, USA). First, ECG is used to segment the individual pulses based on the R-R interval. Following the segmentation, a representative pulse (dominant pulse) is produced from a user-defined time interval (30 s in this study) based on a hierarchical clustering method, where the dominant pulse is defined as the mean of the largest cluster. To ensure that the dominant pulse is not entirely noise, it is compared with a clinical database of over a 1,000 validated ICP pulses. Once the dominant pulse has been verified using the ICP pulse library, the three characteristic peaks and valleys are automatically assigned. Following the identification of the landmarks, 128 MOCAIP metrics are extracted for each dominant pulse. In addition to the MOCAIP metrics, an additional feature was extracted to investigate specific changes in the ratio of the third peak (P3ratio), which is not represented in the original MOCAIP metrics. The P3ratio was defined as the amplitude of the third peak divided by the wave amplitude of the waveAmp shown in Fig. 1. To specifically address our hypothesis that relative elevations in the P3ratio might be a prognostic indicator of ELD outcome, P3ratio was compared with traditional measurements of ICP pulse pressure features, mean ICP, and waveAmp.

Patient Outcome

The patient's response to the ELD was evaluated at the follow-up appointment approximately 2 weeks after discharge, with an emphasis on gait impairment, as this is the most likely symptom to improve. Furthermore, the patients were divided into nonresponders and significant responders based on the clinical observations.

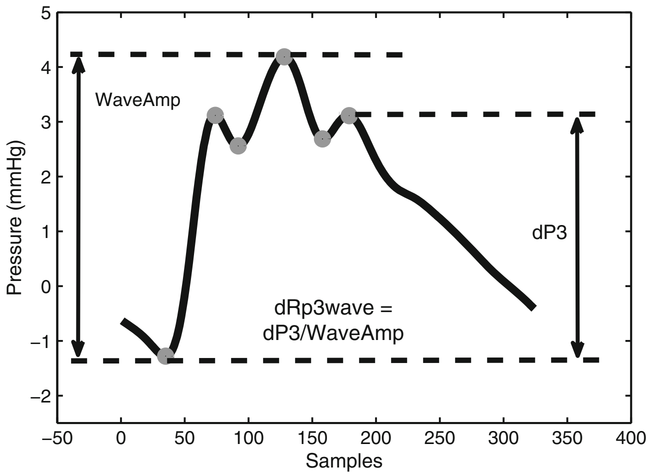

Fig. 1 A representative intracranial pressure (ICP) pulse pressure waveform and illustration of P3ratio, which equals the ratio of dP3 over waveAmp

Statistical Methods

For each of the aforementioned ICP features (mean ICP, waveAmp, and P3ratio), the median overnight values for the nonresponders and significant responders were compared using the Wilcoxon rank-sum test, with a level of significance of 0.05 in MATLAB 7.5 R2007b (MathWorks, Natick, MA, USA).

Results

For the 66 patients there were 75,670 dominant ICP pulses, with an average and standard deviation of 1,146.5 ± 394.9 dominant pulses per patient. Of the 66 patients, 7 were classified as nonresponders and 25 as significant responders based on the follow-up clinical notes; the remaining patients were classified as intermediate ($n = 34$).

The mean ICP and waveAmp did not vary significantly ($p = 0.47$ and $p = 0.19$ respectively) between the outcome groups; however, the measure of P3 elevation (P3ratio) did show a significant difference ($p = 0.04$). The ICP morphological metrics (median and interquartile ranges) and demographic information are shown in Table 1. The violin plots of the three ICP features are shown in Fig. 2.

Discussion

The ability to accurately select NPH patients who will likely benefit from CSF shunting has eluded clinicians and researchers for decades. Although established methods such as ELD, report high prognostic accuracy, most are expensive and put the patient at increased risk of infection. Previous attempts at measuring overnight ICP have focused on the mean ICP, the presence of slow wave activity [14, 15, 19], and more advanced ICP features [2, 9]; however, these results remain controversial. In our retrospective study of the morphological metrics of overnight ICP we introduce novel, physiologically based ICP features that differentiated ELD responders from more traditional measures of ICP pulse pressure waveform.

P3ratio

One common criticism of morphological metrics is the lack of a physiological origin. To address this concern, the P3ratio was derived from the results of a recent study investigating ICP waveform morphology and low CBF [8]. The foundation of this study was data driven; however, through interpretation of the features selected for classification, the elevation of the 3rd peak of the ICP waveform correlated well with a reduction in global blood flow (<20 ml/min/100 g). Selected waveform comparisons for two nonresponders and two significant responders with identical mean ICP values are shown in Fig. 3, which show an increased P3ratio for nonresponders (Fig. 3a, c) vs significant responders (Fig. 3b, d).

Historically, the ICP pulsations have been attributed to both arterial and venous components [1]. Although most reports concluded that CSF pulsations have the arterial system as an origin, there is a venous component. Cardoso et al.

Table 1 Morphological and demographic ICP results for the nonresponders and significant responders

	Morphological ICP metrics			Demographics	
Group (n)	Mean ICP (mmHg)	WaveAmp (mmHg)	P3ratio	Age	Sex M/F
Significant responders (25)	4.7 (3.6)	5.0 (1.5)	0.70 (0.11)	71.7 ± 10.0	16/9
Nonresponders (7)	3.8 (3.9)	5.5 (1.5)	0.80 (0.09)	74.6 ± 7.4	5/2
p value	0.47	0.19	0.04	0.48	N/A

For the ICP morphological metrics the average median value and (interquartile range) are given for the significant responders and nonresponders. The p values reported are between the significant responders and the nonresponders using the Wilcoxon rank-sum test. For the age of the three groups the mean ± standard deviations are given

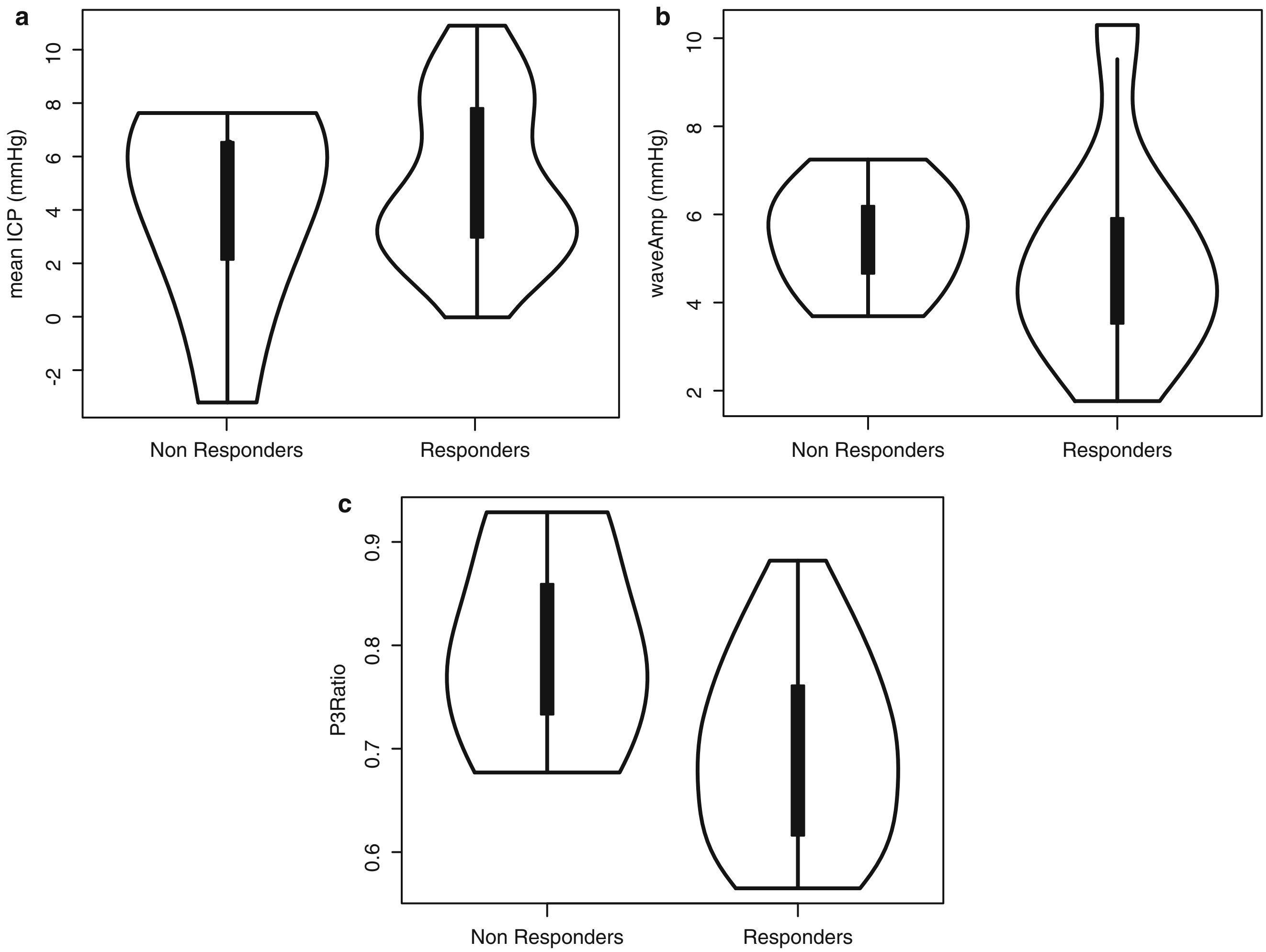

Fig. 2 Violin plots of the ICP pulse pressure variables. Violin plots for nonresponders and significant responders: (**a**) mean ICP; (**b**) waveAmp; (**c**) P3ratio. Only P3ratio was found to be significant when comparing significant responders and nonresponders

attributed the third peak (p3, or dicrotic wave) to changes in venous pressure. This work suggests that the changes we found between significant responders and nonresponders could represent changes in venous pressure, possibly having an impact on cerebral perfusion pressure or inducing some other pathological change in the venous system.

Cerebral Ischemia in Hydrocephalus

Both global and/or regional CBF have been used to both diagnose NPH verse other forms of dementia, and predict shunt outcome using variety of different modalities including ^{133}Xe clearance [4], single photon emission computed tomography (SPECT) [3], Xe contrast CT [12], PET [10]. Although there remain some conflicting results [18], a vast majority concluded there is some degree of ischemia in NPH [3, 4, 12].

Prognostic Value of CBF

In addition to using CBF as a diagnostic indicator of NPH, others have attempted to use CBF as a prognostic indicator for shunt outcome. Hayashi et al. investigated CBF and ICP in patients with secondary hydrocephalus following aneurysm rupture [6]. There were two main findings that are relevant to our study. First, of the 43 patients who underwent shunting to treat the hydrocephalus, none who had a CBF of 25 ml/100 g/min or less responded well. Second, the authors reported a correlation between ICP irregularities (aka B-waves) and CBF. In other words, those patients who had no ICP irregularities (no b-waves) had a lower mean CBF; thus, they were less likely to respond to shunt treatment. This result correlates well with selected studies that suggest that the increased presence of ICP slow waves might predict a positive outcome after shunting [14, 16]. Although we did not measure CBF in our study, the ICP morphological metric P3ratio demonstrated analogous

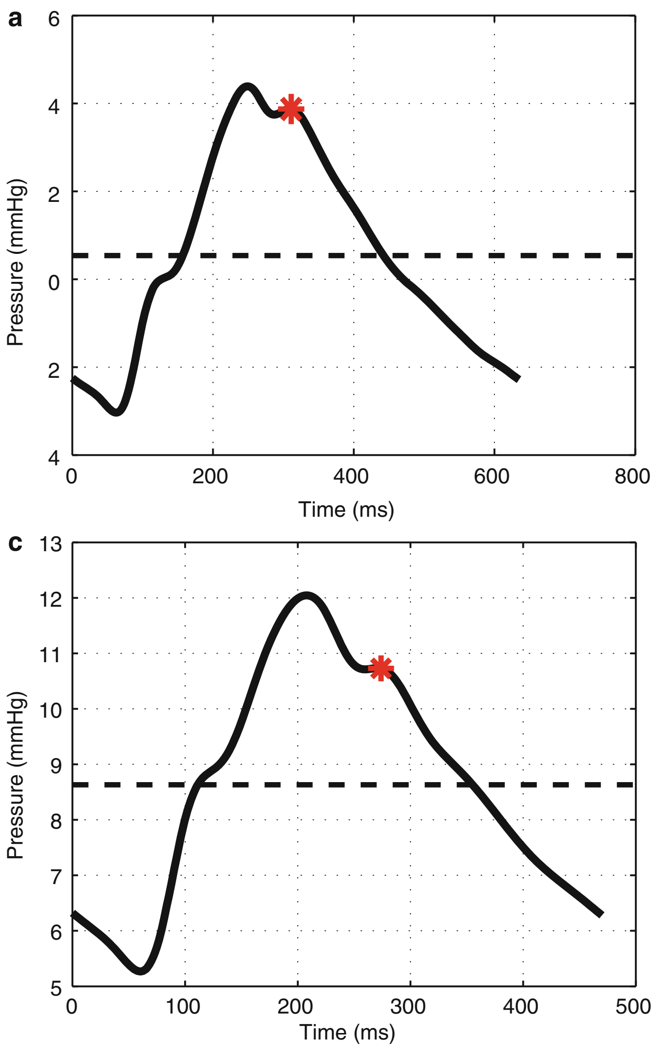

Fig. 3 Comparison of ICP pulse pressure waveform between responders and nonresponders. Examples of dominant pulses from 4 patients, 2 nonresponders, and two significant responders. Each set has equal mean ICP values. (**a**) Nonresponder with a relative high P3ratio (0.93) and mean ICP of 0.54 mmHg (*dotted line*), which is compared with (**b**) a dominant pulse of a significant responder with relatively low P3ratio (0.57) and mean ICP of 0.54 mmHg. (**c**) Nonresponder with P3ratio of (0.80) and a mean ICP of 8.6 mmHg. (**d**) Significant responder with P3ratio (0.60) and mean ICP of 8.6 mmHg. Characteristic third peak determined by MOCAIP is marked by the *asterisk* (*)

results, which suggests that once the elevation reached a certain threshold (or higher in the case of the P3ratio), there might be irreversible damage and the shunting might have little or no impact. These results were echoed in another study by Tanaka et al. investigating the prognostic ability of CBF in 21 NPH patients [17]. The study determined a threshold of 20 ml/100 g/min for improvement, where again, patients with blood flows below the given threshold failed to respond to shunting. Both thresholds for improvement (25 and 20 ml/100 g/min) correlated well with the value of CBF in our previous publication using ICP waveform morphology to differentiate ischemic states in patients with severe brain injury [8]. In a conflicting study, Klinge et al. suggested the opposite trend, that patients with lower CBF (36 ± 7 ml/100 g/min) might be more likely to respond than those with high flow measurements (44 ± 8 ml/100 g/min) [10]. However, upon closer inspection the CBF values reported in this study did not eclipse the aforementioned thresholds and therefore may be difficult to compare. Summarizing the findings of the aforementioned studies, the Hu et al. study suggested that a high P3 elevation might be related to low CBF, whereas in the papers by Tanaka et al. and Hayashi et al., the authors showed that NPH patients are less likely to respond to shunting if they fall below a given CBF threshold. Our study reinforces these findings by suggesting that a high P3ratio (which correlates well with low CBF) might be associated with a lack of response to CSF drainage.

ICP as a Prognostic Indicator of Shunt Outcome

More directly linked to our study are the several attempts to use overnight ICP monitoring as a prognostic indicator of shunt outcome in NPH patients. As mentioned previously, several authors have attempted to use slow waves (Lundberg B-waves [11]) to differentiate shunt responders and nonresponders. A few studies have suggested that increased slow wave activity might correlate with positive outcome [14, 16]; however, others report no correlation [15]. Another popular ICP-derived feature is CSF outflow resistance (R_o); however, it has yet to show sufficient evidence for wide adoption and requires additional procedures [13].

The previously mentioned methods do not utilize ICP waveform morphology specifically, but infer some information about the physiological state from the either the mean ICP or slow wave activity. Recent advances in ICP morphology allow for an entirely new set of variables to be explored. Eide and Sorteberg reported a sensitivity and specificity of 98 % and 70 % respectively for an average waveAmp greater than 4 mmHg combined with 10 % of the recording time greater than 5 mmHg, suggesting a positive outcome following CSF shunting [2]. In a data-driven approach by Hu et al. to differentiate ELD responders using overnight ICP, the percentage of waveAmp and average values were not shown to be predictive of outcome; however, using simple combinations of ICP features the authors were able to obtain an accuracy of 89 % [9]. Unfortunately, the results presented here suggest that waveAmp alone might not be able to differentiate shunt response, with average overnight values both above 5 mmHg and statistically nondifferentiable ($p=0.19$, Table 1). Our data suggest that the advanced ICP morphological feature P3ratio might be able to provide additional evidence to differentiate significant responders from nonresponders. Although the purely data-driven approach obtained a high accuracy (89 %), this study has a physiological foundation (low CBF), which Marmarou et al. recommended in recent NPH guidelines [13].

Limitations of Our Study

Advancing age and co-morbidities contribute to the difficulty in determining a precise outcome for NPH patients. One obvious limitation of this study was the subjective outcome assessment based on a 2-week follow-up examination compared with more quantitative methods including the Mini-Mental State Examination (MMSE), 10-m walk, clinical scale, and a patient questionnaire. However, we attempted to mitigate some of the issues by using clinical follow-ups that were performed by only one clinician (PV). Furthermore, the segmentation of the groups was performed while blinded to the ICP variables reported in this study.

Conclusion

We have shown in our previous work that an elevated third peak of the ICP pulse pressure waveform is associated with ischemia. With this link, the results presented in this study suggest that NPH patients with high P3ratios do not respond to ELD, whereas those with a lower P3ratios are more likely to respond. These findings correlate well with the current literature related to CBF as a prognostic indicator of shunt responsiveness, along with providing additional evidence for the use of advanced ICP morphological metrics. Physiologically, this result can be interrupted, as once a given level of ischemia has been reached, the patient is less likely to respond to the ELD procedure. Finally, this study supports the further study of advanced ICP morphological metrics, specifically the P3ratio, as it would provide an economic alternative to ELD and reduce the complications and increased risks of a full ELD trial.

Acknowledgments The present work was partially supported by the National Institutes of Health (NIH) and the National Institute of Neurological Disorders and Stroke (NINDS) NS059797, NS054881, and NS066008.

Conflict of Interest No conflicts of interest to report for this work.

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