Impaired pulsation absorber mechanism in idiopathic normal pressure hydrocephalus

Laboratory investigation

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Object. The pathophysiology of normal pressure hydrocephalus (NPH), and the related problem of patient selection for treatment of this condition, have been of great interest since the description of this seemingly paradoxical condition nearly 50 years ago. Recently, Eide has reported that measurements of the amplitude of the intracranial pressure (ICP) can both positively and negatively predict response to CSF shunting. Specifically, the fraction of time spent in a “high amplitude” (>4 mm Hg) state predicted response to shunting, which may represent a marker for hydrocephalic pathophysiology. Increased ICP amplitude might suggest decreased brain compliance, meaning a static measure of a pressure-volume ratio. Recent studies of canine data have shown that the brain compliance can be described as a frequency-dependent function. The normal canine brain seems to show enhanced ability to absorb the pulsations around the heart rate, quantified as a cardiac pulsation absorbance (CPA), with properties like a notch filter in engineering. This frequency dependence of the function is diminished with development of hydrocephalus in dogs. In this pilot study, the authors sought to determine whether frequency dependence could be observed in humans, and whether the frequency dependence would be any different in epochs with high ICP amplitude compared with epochs of low ICP amplitude.

Methods. Systems analysis was applied to arterial blood pressure (ABP) and ICP waveforms recorded from 10 patients undergoing evaluations of idiopathic NPH to calculate a time-varying transfer function that reveals frequency dependence and CPA, the measure of frequency-dependent compliance previously used in animal experiments. The ICP amplitude was also calculated in the same samples, so that epochs with high (>4 mm Hg) versus low (≤ 4 mm Hg) amplitude could be compared in CPA and transfer functions.

Results. Transfer function analysis for the more “normal” epochs with low amplitude exhibits a dip or notch in the physiological frequency range of the heart rate, confirming in humans the pulsation absorber phenomenon previously observed in canine studies. Under high amplitude, however, the dip in the transfer function is absent. An inverse relationship between CPA index and ICP amplitude is evident and statistically significant. Thus, elevated ICP amplitude indicates decreased performance of the human pulsation absorber.

Conclusions. The results suggest that the human intracranial system shows frequency dependence as seen in animal experiments. There is an inverse relationship between CPA index and ICP amplitude, indicating that higher amplitudes may occur with a reduced performance of the pulsation absorber. Our findings show that frequency dependence can be observed in humans and imply that reduced frequency-dependent compliance may be responsible for elevated ICP amplitude observed in patients who respond to CSF shunting.

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Key Words • pulsation absorber • notch filter • transfer function analysis • intracranial pulsations • idiopathic normal pressure hydrocephalus

The pulsatile waveform of ICP comes from the beating heart, conveyed in pressure waves through the arteries into the head. Normal mean and pulsatile ICP, however, represent only a fraction of mean and pulsatile arterial pressure. Some physiological mechanism that is not completely understood “absorbs” these pressures. The mechanism of this autoregulatory process possibly arises within the intracranial vascular tree, or possibly with the movement of CSF, or both, and it represents a particular kind of intracranial compliance. It is commonly observed in critical care that, as ICP rises, the resulting ICP wave becomes taller and more rounded and eventually strongly resembles the arterial pressure. A manner in which to study this is to break down the complex arterial and ICP waves into component frequencies and determine how each frequency is adjusted in amplitude (called “gain”) and timing (called “phase”)

Abbreviations used in this paper: ABP = arterial blood pressure; CPA = cardiac pulsation absorbance; GEE = generalized estimating equations; ICP = intracranial pressure; ICPa = ICP amplitude; NPH = normal pressure hydrocephalus; VP = ventriculoperitoneal.
for a system that translates one waveform signal into another. This analytical technique is called transfer function analysis. The greatest power of the arterial pulse lies in the fundamental frequency, which is essentially the heart rate. The normal ICP pulse waveform is the result of a markedly suppressed fundamental frequency (a notch filter in engineering terms) and the degree of suppression is quantified in this paper as cardiac pulsation absorbance (CPA). When absorbance falters, the fundamental frequency progressively becomes more prominent in the ICP leading to the higher and more rounded ICP pulse wave. This analysis has been previously carried out in dogs. In this paper, a similar analysis has been carried out in human patients with idiopathic NPH and the result of this study may give some insight into the pathophysiology of this condition.

The pathophysiology of idiopathic NPH has elicited immense speculation since 1965 when this seemingly paradoxical condition was first described. Similarly, identifying which patients are likely to benefit from CSF shunting has proven controversial for years. Recently, Eide and his colleagues have reported that the amplitude of ICP pulse waves, or more specifically, measurement of the fraction of time spent by an individual patient with elevated ICP amplitude (≥ 4 mm Hg) can predict response to CSF shunting. This approach is based on earlier experimental and clinical observations of elevated pulsatility of the hydrocephalic condition. It is generally understood that increased ICP pulse amplitude indicates decreased brain compliance, which might play an important role in the pathophysiology of idiopathic NPH. However, in the strictest sense, the connection is not straightforward, since the conventional concept of brain compliance is based on a static measure of a pressure-volume ratio.

Recent transfer function analysis using arterial and intracranial pressure waveforms recorded from canine experiments has suggested that compliance can be understood as a dynamic process involving increased or decreased dependence on frequency. Under the assumption that an arbitrary waveform can be broken down to sinusoidal waves with various amplitudes and frequencies, transfer function analysis has revealed that the intracranial system acts differently in response to arterial pulsatile inputs coming at different frequencies. The normal canine brain seems able to absorb strong arterial pulsations around the cardiac frequency with characteristics of a “notch filter” (in engineering terms) or a “pulsation absorber” (in our terms), whereas the hydrocephalic canine brain is less able to absorb pulsations, indicating decreased frequency dependence. These observations suggest that brain compliance can be “frequency dependent” in nature. However, no studies have investigated whether the frequency dependence can be observed in humans.

In this study, we retrospectively analyze data obtained in a small cohort of patients who underwent ICP monitoring and ABP monitoring synchronously. This uncommon and unique data set allows calculation of both the transfer function and CPA index, which quantifies frequency-dependent compliance. Since this is the first opportunity to use the techniques developed for canine experiments on human data, we sought to determine whether a frequency dependence could be observed and whether it was different in epochs with high ICP amplitude (more characteristic of hydrocephalic pathophysiology), compared with epochs of low ICP amplitude. Our hypothesis was that frequency dependence would be shown in humans. Furthermore, we hypothesized that epochs with lower amplitude would occur in conjunction with a better performance of the pulsation absorber (or better frequency-dependent compliance) and that higher amplitudes may occur with a diminished performance of the pulsation absorber. To test our hypotheses, the same transfer function method used in the previous studies was applied to ABP and ICP waveforms recorded from 10 patients undergoing evaluations of presumed idiopathic NPH. The ICP pulse amplitude was also calculated in the same data set to examine its relation to frequency-dependent compliance.

Our findings may illuminate the theoretical rationale for explaining why ICP amplitudes might increase in patients who respond to shunt surgery.

**Methods**

**Patient Population**

Simultaneous ICP and ABP data were collected from 13 patients evaluated for CSF shunting at the Department of Neurosurgery, Rikshospitalet, Oslo, from 2002 to 2005. The patients in this study had consented to invasive ABP monitoring in addition to ICP monitoring on a research protocol approved by the hospital authority of Rikshospitalet University Hospital, Oslo, and this analysis was retrospectively performed later. Analysis was technically feasible in 10 of the 13 sets of recordings; 3 showed synchronization problems and as a result were excluded (see Table 1 for details). The age range of the 10 patients was 67–82 years (median age 76 years).

The diagnostic workup of patients with the symptoms of gait disturbance, incontinence, and dementia, combined with radiological ventriculomegaly, was performed during a 3-day hospitalization. Following clinical and radiological assessment on the day of admission, pressure monitoring was done. The patients returned 1–3 weeks later for surgical treatment if it was indicated.

**Clinical and Radiological Assessment**

The severity of clinical idiopathic NPH was graded using our NPH grading scale (15 scores ranging from 7 to 13, assessing the combined severity of gait disturbance, urinary incontinence, and dementia). Patients underwent CT or MRI on the day of admission if neither of these diagnostic studies had been recently performed. The Evans index and ventricular score were also estimated following the same method as previously described.

**Monitoring of ICP and ABP**

Intracranial pressure was monitored by means of a Codman ICP MicroSensor (Johnson & Johnson). The sensor was placed 1–2 cm into the brain parenchyma via
Pulsation absorber in human hydrocephalus

**TABLE 1: Demographic, clinical, and radiological data for 10 patients with idiopathic NPH**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Preop Data</th>
<th>Surgical Tx Data</th>
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<tbody>
<tr>
<td></td>
<td>NPH Score†</td>
<td>Evans Ratio‡</td>
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<td>0.4</td>
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<tr>
<td>2</td>
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<td>5</td>
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<td>10</td>
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</table>

* CodVP = indicates Codman VP shunt (Hakim programmable valve shunt system); NA = not applicable; P = Pressure; proGAV = proGAV shunt system; Sx = Symptoms; Tx = Treatment; Vent = Ventricular.† Total of triad symptoms. ‡ Estimated from radiological assessment. § Opening pressure of 6 cm H2O in the horizontal position and 25 cm H2O in the vertical position.

a small straight skin incision, frontal bur hole, and minimal opening in the dura mater. Placement was performed using local anesthesia in the operating room. The ICP MicroSensor was zeroed against atmospheric pressure.

Arterial blood pressure was measured continuously in the right radial artery using the Truwave PX-600F Pressure Monitoring Set (Edwards Lifesciences LLC). The ABP sensor was placed at the level of the heart. Patients were kept in their bed during the entire pressure recording period, which ranged from 7 to 20 hours.

**Surgical Treatment**

The criteria for surgical treatment were determined by a combination of a triad of symptoms of NPH (gait disturbance, incontinence, and dementia), increased ventricular size (Evans index > 0.3), and findings from the diagnostic ICP monitoring (focusing on the static ICP such as mean ICP and B-wave activity; mean ICP wave amplitude did not influence the process of selecting patients for surgical treatment).

Seven of 8 shunt-treated patients received a Codman VP shunt (Hakim Programmable Valve Shunt System, Codman & Shurtleff, Inc., Medos S.A.). The median opening pressure at shunt implantation was 12 cm H2O (range 10–20 cm H2O). One patient received a programmable gravitational shunt (proGAV shunt system, Aesculap and Miethke) positioned at 6/25 (opening pressure of 6 cm H2O in the horizontal position and of 25 cm H2O in the vertical position).

**Follow-Up and Outcome Assessment**

The observation period for patients’ post–shunt placement outcome ranged from 1 to 5 years. During follow-up, all patients were examined clinically. If a patient was unable to attend the clinic for one of the follow-up examinations, he or she was interviewed by phone. As a signature of clinical improvement that normally correlates with patient and families’ perception, we have defined an increase of 2 points or more on the NPH scale used in Rikshospitalet University Hospital, Oslo. The shunt-treated patients were classified either as responders (change in NPH score ≥ 2) or nonresponders (change in NPH score < 2).

**Data Analysis**

**Pulsation Dynamics Metrics.** The ICP and ABP signals were sampled at either 100 or 200 Hz and recorded continuously for periods ranging from several hours to approximately 20 hours. The time-varying transfer function method applied to ICP and ABP to calculate a CPA index requires a relatively longer data segment than the 6-second window used in several earlier studies.5–13 Thus, in the present study, hours of recording were divided into segments of 5 minutes (see Fig. 1A) and the number of the 5-minute segments varied among the individual patients. Evaluating changes in CPA with respect to changes in ICP amplitude requires minimal fluctuations from mean values of ICP as well as ICP amplitude within each 5-minute window and yet, at the same time, requires having a variety of amplitudes across 5-minute windows. Some of the representative examples of 5-minute windows are shown in Fig. 1A. A total of 242 five-minute segments obtained in 10 patients were analyzed, and both CPA and ICP amplitude were calculated for each segment. Since synchronously recorded ICP and ABP data are required for CPA index calculations using systems analysis, only a relatively small number of patients were available for this study.

For CPA shown in Fig. 1B, the same data preprocessing and the same technical processes described in our previous study were also applied to the present analysis.25
In an effort to avoid redundancy, we refer the reader to previous publications for more details about the techniques. Particularly in Park et al., the concept of transfer function was also graphically summarized with nontechnical terms for readers unfamiliar with the systems approach. For mean ICPa shown in Fig. IC, no data pre-processing was performed before the calculation, and the calculation was done following principles of the method described in earlier studies.

**Statistical Methods.** A repeated-measures ANOVA, using a generalized estimating equations (GEE) approach to handle serial measurements from the same patient, was applied to compare changes in frequency dependence exhibited by shape of gain of transfer function, throughout a range of frequency for data segments with low ICPa of ≤ 4 mm Hg and with high ICPa of > 4 mm Hg (see Fig. 2). The time-varying transfer function analysis was initially performed without prior knowledge of which of the 10 patients actually underwent shunt placement and which of the shunt-treated patients were actually responders. Our hypothesis is that CPA is inversely
related to ICPa, meaning higher amplitude is related to a lower performance of the pulsation absorber (that is, lower CPA). Nonlinear regression was applied to evaluate the relationship between CPA and ICPa, and logistic regression modeling was used to determine whether lower CPA is predictive of higher ICPa (>4 mm Hg) with the likelihood ratio test used as the statistic for assessing significance. Two-tailed values of \( p < 0.05 \) were considered statistically significant.

**Results**

To determine whether frequency dependence could be observed in humans, and whether the frequency dependence would differ in high-ICPa and low-ICPa epochs, we applied the same technique—time varying transfer function method—used for canine experimental data to ICP and ABP recorded from 10 patients with idiopathic NPH.

Figure 2 shows the difference of the shape of gain curves between high and low ICPa. The individual gain curves were calculated from all 5-minute segments associated with mean ICPa with a mean ICPa greater than 4 mm Hg or a mean ICPa of 4 mm Hg or less (Fig. 2A and B) and averaged over the number of segments for each group (the high and low ICPa segments groups) (Fig. 2C). The GEE model revealed a between-groups difference in slopes that nearly reached statistical significance (\( p = 0.07 \), slope F test). The difference is that for the low ICPa segments group, there is a breakpoint in gain function for a certain range of frequency close to the heart rate, identified as 1.77 Hz. In contrast, for the high ICPa segments group, such a breakpoint is absent. The presence or absence of breakpoint suggests alterations in the characteristics of frequency dependence. Such a distinction depends on the change in ICPa associated with patients’ response to shunting, indicating that there is frequency dependence of compliance in human hydrocephalus.

We further examined a relationship between pulsation absorber function and mean ICPa. Logistic regression analysis suggests that lower CPA is a significant predictor of high ICPa (likelihood ratio statistic = 82.9, 1 d.f., \( p < 0.0001 \)), confirming that a measure of pulsation absorber performance is inversely related to ICPa (Fig. 3 upper panel). Taking a closer look at specific details regarding surgical outcome of individual patients (Fig. 3 lower panel), we can observe the following: Eight patients were treated with CSF shunting. Seven were classified as good responders and they showed a relatively lower CPA index and higher ICPa than the 1 patient who was classified as a nonresponder. Two patients did not undergo shunt placement. One of them was recommended for CSF shunting but did not consent to the procedure, and this patient showed a lower CPA index and higher ICPa.
than the single patient for whom shunt placement was not recommended. The results show that elevated ICP pulse amplitude may happen with a diminished function of the pulsation absorber.

**Discussion**

Epochs with high ICP pulse amplitude in patients with idiopathic NPH mimic alterations of the pulsation absorber characteristics seen in acute CSF infusion or onset of chronic hydrocephalus in canine models, whereas epochs with low amplitude mimic those seen in canines under normal condition (see Fig. 2). This observation indicates that frequency dependence of brain compliance would also be seen in humans.

In capturing frequency dependence, the time-varying transfer function method was applied to ICP and ABP waveforms to assess how the intracranial system responds to the arterial input. This method was used for 2 earlier canine studies and the present human study. The transfer function of the brain system translates the contribution of each frequency component of the input (ABP) waveform to the output (ICP) waveform, and this contribution is evaluated by gain in the transfer function. In the previous and present studies, we have shown that there is a dip or notch that appears centered around a frequency close to the heart rate in the graph of gain versus frequency.

The change in the pulsation absorber as observed by changes in the transfer function may represent altered capacity of the intracranial vascular system to buffer the pulsatile component of flow, which occurs at the frequency of the heart rate. As argued in previous papers, this change in brain compliance could be an effect of the vascular alterations (such as diminished vessel wall elastance or restriction to free flow of CSF) and would be a potential cause of symptoms in hydrocephalus by virtue

**Fig. 3. Upper:** Plot of the CPA and mean ICPa values calculated using 10 patients’ ICP and ABP recordings. The *horizontal black line* indicates a threshold amplitude (4 mm Hg), which is used to predict good outcome from CSF shunting. The estimated probability of ICP amplitude greater than 4 mm Hg as a function of CPA values is indicated by the *purple line.* **Lower:** Details of outcome of shunt treatment for individual patients.
of changing the pattern of blood flow in the microvasculature. This may be the reason that the change in pulse wave amplitudes, as opposed to mean pressure, is such a strong predictor of response or lack of response to CSF shunting.

The results suggest that there is an inverse relationship between changes in frequency-dependent compliance and changes in intracranial pulsatility: higher amplitude may occur with a diminished performance of the pulsation absorber and lower amplitude would occur in conjunction with a better performance of the pulsation absorber. Failure of a pulsation absorber could explain why higher amplitudes of CSF pressure waves are seen more frequently in patients with idiopathic NPH who respond to shunting.\textsuperscript{7,10,28} If the pulsation absorber is not in failure, the pulsation amplitudes would remain low, and the pathophysiological state is not as likely to respond to CSF diversion. Perhaps there will soon be methods that allow us to visualize the mechanisms of the pulsation absorber directly, or visualize microvascular flow dynamics dependent on the absorber mechanism. Until such methods appear, there will be some degree of speculation in determining the causal connection between these correlated variables.

Limitations of the Study

An obvious limitation to this study is that few patients evaluated invasively turned out to not qualify for shunting. However, from prior larger series of clinical studies, we know that individuals without hydrocephalus tend to have amplitudes lower than 4 mm Hg for the vast majority of the time. It would seem likely that if sufficient ICP and ABP data were collected from controls (in epochs of low amplitude), and if the transfer function resembled either control laboratory animals or the NPH patients during “low-amplitude” epochs, the net result would confirm a more robust pulsation absorber.

This study encompasses a small set of patients because the transfer function analysis requires simultaneous recordings of ICP and ABP. Such simultaneous data collections are rare, and we used data that happened to be available. For statistical analysis, logistic regression was used to determine the relationship between CPA and ICP amplitude to discern if lower CPA was associated with a greater probability of higher amplitude ( > 4 mm Hg). We used an appropriate generalized estimating equations approach with a binomial distribution and logit link function to handle the repeated segments (every 5 minutes) over time within the same patient (correlated data). Although the present analysis is based on 10 patients and therefore limited due to small sample size, the recordings from each patient yielded a large amount of CPA data, providing good statistical power in predicting high ICP amplitude from CPA. For generalization of study findings, more comprehensive studies using a larger set of data will be needed in the future.

Conclusions

This study shows that the pulsation absorber phenomenon can be observed in humans, just as previously seen in animal studies, and that an impairment of the pulsation absorber function (or diminished frequency-dependent compliance) may be responsible for the elevated ICP pulse amplitudes in shunt responders. Our findings may help in the understanding the pathophysiology of idiopathic NPH and introduce new ways to study the pathogenesis of hydrocephalus in general as well as other ICP-related conditions. Slit ventricle syndrome, pseudotumor cerebri, and compensated hydrocephalus, for example, might be better understood in the future by analysis of the pulsation absorber.

Disclosure

Drs. Park, Zurakowski, and Madsen report no conflict of interest concerning the materials or methods used in this study or findings specified in this paper. Professor Eide discloses financial interest in the company (dPCom AS) manufacturing the Sensometrics software used for ICP analysis published in several of his papers (cited in the present paper), which were used as the basis of the clinical component of the present analytical studies. Financial support for the development of analytical methods was provided by The Webster Family Fund (E.-H.P. and J.R.M.).

Author contributions to the study and manuscript preparation include the following. Conception and design: Madsen, Park, Eide. Acquisition of data: Eide. Analysis and interpretation of data: all authors. Drafting the article: Park. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Madsen. Statistical analysis: Park, Zurakowski.

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References


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