Alterations of pulsation absorber characteristics in experimental hydrocephalus

Laboratory investigation

EUN-HYOUNG PARK, PH.D.,1 STEPHEN DOMBROWSKI, PH.D.,2 MARK LUCIANO, M.D., PH.D.,2 DAVID ZURAKOWSKI, PH.D.,3 AND JOSEPH R. MADSEN, M.D.1

Departments of 1Neurosurgery and 2Anesthesiology, Children’s Hospital Boston, Harvard Medical School, Boston, Massachusetts; and 3Department of Neurological Surgery, Section of Pediatric and Congenital Neurosurgery, Cleveland Clinic, Cleveland, Ohio

Object. Analysis of waveform data in previous studies suggests that the pulsatile movement of CSF may play a role in attenuating strong arterial pulsations entering the cranium, and its effectiveness in attenuating these pulsations may be altered by changes in intracranial pressure (ICP). These findings were obtained in studies performed in canines with normal anatomy of the CSF spaces. How then would pulsation absorbance respond to changes in CSF movement under obstructive conditions such as the development of hydrocephalus? In the present study, chronic obstructive hydrocephalus was induced by the injection of cyanoacrylate gel into the fourth ventricle of canines, and pulsation absorbance was compared before and after hydrocephalus induction.

Methods. Five animals were evaluated with simultaneous recordings of ICP and arterial blood pressure (ABP) before and at 4 and 12 weeks after fourth ventricle obstruction by cyanoacrylate. To assess how the intracranial system responds to the arterial pulsatile component, ABP and ICP waveforms recorded in a time domain had to be analyzed in a frequency domain. In an earlier study the authors introduced a particular technique that allows characterization of the intracranial system in the frequency domain with sufficient accuracy and efficiency. This same method was used to analyze the relationship between ABP and ICP waveforms recorded during several acute states including hyperventilation as well as CSF withdrawal and infusion under conditions before and after inducing chronic obstructive hydrocephalus. Such a relationship is reflected in terms of a gain, which is a function of frequency. The cardiac pulsation absorbance (CPA) index, which is simply derived from a gain evaluated at the cardiac frequency, was used to quantitatively evaluate the changes in pulsation absorber function associated with the development of hydrocephalus within each of the animals, which did become hydrocephalic. To account for normal and hydrocephalic conditions within the same animal and at multiple time points, statistical analysis was performed by repeated-measures ANOVA.

Results. The performance of the pulsation absorber as assessed by CPA significantly deteriorated after the development of chronic hydrocephalus. In these animals the decrement in CPA was far more significant than other anticipated changes including those in ICP, compliance, or ICP pulse amplitude.

Conclusions. To the extent that the free CSF movement acts as a buffer of arterial pulsation input to flow in microvessels, alterations in the pulsation absorber may play a pathophysiological role. One measure of alterations in the way the brain deals with pulsatile input—the CPA measurement—changes dramatically with the imposition of hydrocephalus. Results in the present study suggest that CPA may serve as a complementary metric to the conventional static measure of intracranial compliance in other experimental and clinical studies. (DOI: 10.3171/2010.5.PEDS09142)

Key Words • pulsation absorber • notch filter • hydrocephalus • transfer function analysis • intracranial pulsation

In our previous studies,44 a mathematical technique called “TVTF” was applied to pressure data from physiologically normal canines. This technique revealed that pulsatile CSF movement may play a role in attenuating strong arterial pulsations entering the cranium. This attenuation mechanism was termed “pulsation absorber,” or “notch filter.” One interpretation of this systems analysis was that the intracranial system behaves differently in response to inputs coming at different frequencies.44 The computational aspects of TVTF are graphically summarized in Figs. 1 and 2. Figure 1 serves as an explanation of the concept of a transfer function: an arbitrary waveform composed of sine waves is...
translated into another waveform by a transfer function (representing for example, the intracranial system). This translates the contribution of each frequency component of the input waveform to the output waveform. Figure 2 features the same kind of principles using experimental data from the present study.

To evaluate performance of the pulsation absorber in different conditions and states, which typically include a notch at the heart rate, we developed a more general approach than comparing notch shapes. We call this metric the “cardiac pulsation absorbance” (CPA), defined as a negative gain evaluated at the heart rate. A higher CPA indicates better pulsation absorbance.

**Fig. 1.** Schematic demonstrating the transfer function concept. An arbitrary input waveform has been composed of 3 sine waves with different amplitudes, frequencies, and phases. This waveform (a) is a “signal,” which is a series of numbers representing quantities that vary in time. A “system” is a process translating 1 signal to another or generating a signal in response to an input. Transfer function representing a system describes how the contribution at specific frequency components of the input signal is translated to the output signal. The input signal can be translated into attenuation or amplification depending on the gain evaluated at a particular frequency. In this example, a notch filter was chosen as a system. A notch filter is a filter that attenuates frequencies in a particular narrow range of frequencies centered at a specific frequency but passes all other frequencies. The center frequency of Transfer Function A is 2 Hz and that of Transfer Function B is 13 Hz. Magnitude response (or gain) of those transfer functions are shown in panels (b) and (d), respectively. When these 2 transfer functions are applied to the same input signal, 2 different output signals are calculated (c and e, respectively).

**Fig. 2.** Schematic showing the translation of 1 experimental waveform using a transfer function representing the intracranial system. A: The system considered in the present paper is the intracranial system, and the input and output waveforms are ABP and ICP recordings. B: The TVTF can be calculated using experimental input (ABP) and output (ICP) signals. C: Conversely, using the same input signal and transfer function, the output signal can be calculated. Parentheses indicate calculated results.
Alterations of the pulsation absorber mechanism CPA value indicates better performance of the notch filter, or pulsation absorber. The goal of this paper is to use this technique to see how the intracranial system changed in relation to obstructive hydrocephalus. We hypothesized that CSF pulsation absorber performance evaluated by a gain at the cardiac frequency, or simply the CPA, can be an alternative discriminator of the hydrocephalic from the normal canine brain. To test this hypothesis, the TVTF method was applied to femoral ABP input and ICP output data recorded from 5 dogs in different acute states (that is, hyperventilation, CSF removal, and CSF infusion) and chronic conditions (that is, normal and hydrocephalic). Our findings may provide a complementary method of evaluating intracranial compliance based on the frequency dependence of pulsatile dynamics and its relation to pathological conditions involving cerebral blood flow dynamics such as hydrocephalus.

Methods

Throughout this study, we arbitrarily use the term “condition” to indicate “normal” or “induced hydrocephalus,” and “state” to refer to manipulations during testing such as “baseline,” “hyperventilation,” “infusion,” or “removal.”

Animal Population

All experimental procedures in 5 male adult mongrel dogs (25–30 kg) were performed in accordance with the Cleveland Clinic fully accredited animal care facility under the guidelines of the Guide for the Care and Use of Laboratory Animals. Beagles and greyhounds were excluded given a high incidence of spontaneous hydrocephalus in those breeds. All animals underwent MRI imaging and neurological evaluation prior to and at 4 and 12 weeks of hydrocephalus induction. Animals with ventricular enlargement or abnormal neurological findings at baseline were excluded from the study.

Surgical Procedure

Animals were prepared for a sterile surgical procedure using sodium pentothal (20 mg/kg intravenously), intubated, and connected to a ventilator. General anesthesia (1.0% isoflurane gas) was maintained throughout the operative procedure. Presurgical medications included phentoin (5 mg/kg intravenously) to prevent postoperative seizures, dexamethasone (0.25–1.0 mg/kg intravenously) to reduce inflammation, glycopyrrolate (0.01 mg/kg intravenously), to reduce respiratory secretions, and gentamicin (3 mg/kg intravenously) and cefazolin (1 mg subcutaneously) to prevent infection. Nasal temperature, heart rate, and arterial pressure were monitored throughout the surgical procedure. Arterial blood pressure was obtained via the femoral artery, from which blood samples could be obtained for blood gas analysis and subsequent ventilation control.

Surgical Induction of CH

The procedure for inducing chronic obstructive hydrocephalus in this study has been established in the Cleveland Clinic laboratory. Animals were placed prone in a stereotactic head frame (Kopf, Inc.) with the head slightly elevated. A suboccipital craniectomy was performed to allow visualization of the dorsal cerebellar vermis and brainstem. Using bipolar cautery, suction, and retraction, a small opening was made in the arachnoid membrane to permit visualization of the floor of the fourth ventricle, through which flexible silicon catheter tubing (1.5 mm outer diameter) was inserted. Approximately 0.4 ml of cyanoacrylate gel (Loctite Corp.) was injected into the fourth ventricle (Fig. 3). The catheter was cut and left in position, dorsal to the spinal cord. The dura mater was closed, and all muscle layers were closed in a layered fashion with interrupted sutures.

Methods for Confirming the Severity of Obstructive Hydrocephalus

To confirm the severity of obstructive hydrocephalus, 3D volumetric MRI imaging was performed. Before inducing hydrocephalus and 4–12 weeks postinduction, MR imaging was undertaken in all animals while sedated (Domitor, 0.02 ml/kg intravenously or intramuscularly). Routine spin echo MR images were acquired using a 1.5-T Siemens Magnetom Vision unit and archived on optical disk for subsequent volumetric analyses. Ventricle size was measured in the coronal plane. Magnetic resonance imaging 3D volumetric measures and Evans ratios (ventricular width/brain width), standard measures of ventricle size, were calculated. Intracranial pressure monitoring was also performed in each animal at baseline during surgery and at either 4 or 12 weeks post–CH induction. In brief, animals were placed prone and secured in a stereotactic head frame as described above. A single midline sagittal incision was made, and skin, fascia, and temporalis muscle were retracted. A small bur hole (5 mm) was manually drilled in the skull overlying the dorsolateral parietal cortex. The dura was opened, and an ICP probe (Camino, #110–4BT, Integra Neurosciences) was placed directly into the brain parenchyma at least 2 cm below the cortical surface. Intracranial pressure probe placement was performed using magnification loupes to aid visualization.

Experimental Sequence

The experimental procedures and sequence are shown in Fig. 4. Intracranial pressure, ABP, and electrical activity of the heart were intraoperatively recorded online and in real time in all dogs by using an analog/digital data acquisition system (PowerLab, version 5.2, AD Instruments). Data were collected during 2 surgical sessions (that is, before and after obstruction was created) and across several acute states within those sessions: initial baseline, hyperventilation, baseline 2, CSF removal, baseline 3, CSF infusion, and final baseline. These sequential recordings were performed for a minimum duration of 3 hours and a maximum of 5 hours. In all 5 dogs, ABP was measured from the femoral artery, and ICP was recorded via probes placed in the brain parenchyma.

Brief Update on the Signal Processing Performed

Because the same method of analysis used previously, the TVTF technique, was also applied in the present
study, a detailed description of data preprocessing and analysis can be referred to in the previous paper. The only differences are as follows: the data sampling rate is higher in the current data set, and the parameter values for a band-stop filter used to suppress the respiration effect have been adjusted. The signal initially sampled at either 100 or 200 Hz was down-sampled to a lower frequency (25 Hz); this was done because our main focus was around the cardiac frequency (around 2 Hz), which is much lower than the original sampling rate. To down-sample, we used a Matlab “resample” function, which applies an anti-aliasing low-pass finite impulse response filter to the input signal during the down-sampling process. As for the parameter value used for the band-stop filter, stop band attenuation was set as 5 dB in the present study. Other relevant technical details are provided in Appendices A through F in our previous study.

Cardiac Pulsation Absorbance

A relationship between ABP input and ICP output
Alterations of the pulsation absorber mechanism

waveforms was evaluated using the TVTF technique introduced in our earlier paper. For this evaluation, a magnitude of the calculated transfer function, which is a gain, was used to represent the response of the intracranial system to arterial pulsations at varying frequencies.

In our previous study, significant attenuation of a gain close to the cardiac frequency was observed in physiologically normal dogs with normal ICP. This attenuation was revealed as a “sharp notch” in the gain curve as a function of frequency. However, data in the present study revealed that the gain estimated in normal dogs in a resting state could show an arbitrary shape (that is, a shape without a clear “notch”) with the center frequency exhibiting a measurable difference from the cardiac frequency. Therefore, an alternative method was required to compare alterations in the pulsation absorber in physiological or pathological conditions. Such an assessment was made using a simple new metric, the CPA.

Figure 5 shows how the CPA was obtained using a gain of transfer function estimated from the initial baselines before and after the manipulation causing the development of hydrocephalus. The CPA is a negative gain evaluated at the heart rate; therefore, a higher CPA value indicates better performance of the pulsation absorber.

Conventional Discriminators Used to Estimate Altered Brain Characteristics: ICP, Amplitude, and Compliance

Other conventional methods, including ICP, brain compliance, and IPA, were also used to assess alterations in brain characteristics and to differentiate between a normal and a hydrocephalic brain. Thus, the mean ICP was calculated by averaging ICP recordings over the segmented period within each acute state such as baselines, hyperventilation, CSF removal, and CSF infusion. Brain compliance, defined as a pressure change in response to a CSF volume change, was estimated for both the removal and infusion of CSF. Intracranial pulse amplitude was calculated following the method described in earlier studies in which the mean IPA was used as an alternate indicator of shunt response in normal pressure hydrocephalus.

Further details on the calculations of compliance and pulse amplitude are shown in Fig. 6. The ABP and ICP data segment used for the TVTF calculation for each epoch and the compliance estimation for the epochs of removal and infusion of CSF ranges from 100 to 300 seconds. The transitions from baseline 2 to the removal of CSF under normal and hydrocephalic conditions are shown in Fig. 6. For the estimation of compliance derived from the pressure-volume relation, the difference in the absolute ICP between resting state and CSF withdrawal (or infusion) was evaluated. The segment for the compliance estimation was selected close to the onset of the decrease (or increase) in ICP, whereas the segment for the transfer function analysis was chosen to be a bit longer and more stable. Pulse amplitude, which is the difference between a peak and a trough associated with each single wave, is also featured in Fig. 6.
Five dogs underwent surgery intended to obstruct the normal circulation of CSF and had pressure measurements through the various acute states described above. Time-varying transfer function analysis was performed in a blinded manner, without knowledge of which of the 5 dogs actually had obstructive ventriculomegaly as a result of surgery. Because of the obstruction, 4 of the 5 animals actually demonstrated hydrocephalus associated with the relative increase in CSF ventricular volume measured in the lateral, third, and fourth ventricles is shown (A). Since the size of the brain, which consists of the brainstem, cerebellum, and cerebrum, varies among dogs, the ratio of CSF volume relative to the brain provides an estimate indicative of the development of hydrocephalus. The averaged ratio (over all 5 dogs) for preinduction and that for postinduction is shown (B), as is the postinduction ratio for each individual dog (C). Specifically, the ratio for the fifth dog (D94) is about 40% below the mean value, suggesting that hydrocephalus did not develop in this particular dog.

**Statistical Methods**

Five dogs underwent surgery intended to obstruct the normal circulation of CSF and had pressure measurements through the various acute states described above. Time-varying transfer function analysis was performed in a blinded manner, without knowledge of which of the
Alterations of the pulsation absorber mechanism

tion structure and robust standard errors to compare the normal versus hydrocephalic conditions. In this statistical approach, measurements at the 7 epochs are treated as “repeated measures” (or equivalently, a within-subjects factor), and physiological condition (either normal or hydrocephalus) is considered a within-subject factor, which defines the 2 conditions within each animal. Repeated-measures ANOVA and the Wald chi-square test for post hoc testing were applied using the SPSS software package (version 16.0, SPSS, Inc.) to compare normal versus hydrocephalus paired measurements for ICP, IPA, and CPA and to evaluate each measurement in differentiating the hydrocephalus from the normal non-hydrocephalic condition. In summary, the repeated-measures ANOVA was based on a mixed-model approach using generalized estimating equations to account for measurements within the same animal at 7 different time points and in the normal versus hydrocephalic condition within the same animal. All statistical results are expressed as the means ± SEs and are summarized in Table 1. Two-tailed values of p < 0.05 were regarded as statistically significant.

TABLE 1: Intracranial pressure, pulse amplitude, and CPA for normal and hydrocephalic conditions

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal</th>
<th>Hydrocephalus</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL1</td>
<td>13.9 ± 4.8</td>
<td>5.8 ± 1.4</td>
<td>0.03†</td>
</tr>
<tr>
<td>BL2</td>
<td>15.6 ± 5.5</td>
<td>12.0 ± 2.0</td>
<td>0.37</td>
</tr>
<tr>
<td>BL3</td>
<td>15.4 ± 5.4</td>
<td>13.9 ± 2.0</td>
<td>0.74</td>
</tr>
<tr>
<td>BL4</td>
<td>16.3 ± 6.4</td>
<td>13.6 ± 3.6</td>
<td>0.66</td>
</tr>
<tr>
<td>HV</td>
<td>10.9 ± 4.2</td>
<td>4.2 ± 1.5</td>
<td>0.05†</td>
</tr>
<tr>
<td>REM</td>
<td>13.4 ± 5.5</td>
<td>11.2 ± 2.1</td>
<td>0.58</td>
</tr>
<tr>
<td>INF</td>
<td>17.2 ± 5.6</td>
<td>15.8 ± 2.3</td>
<td>0.77</td>
</tr>
<tr>
<td>pulse amplitude (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL1</td>
<td>2.0 ± 0.6</td>
<td>2.2 ± 0.8</td>
<td>0.59</td>
</tr>
<tr>
<td>BL2</td>
<td>2.3 ± 0.7</td>
<td>3.6 ± 1.4</td>
<td>0.32</td>
</tr>
<tr>
<td>BL3</td>
<td>2.3 ± 0.7</td>
<td>4.2 ± 1.4</td>
<td>0.18</td>
</tr>
<tr>
<td>BL4</td>
<td>2.4 ± 0.9</td>
<td>4.3 ± 1.6</td>
<td>0.26</td>
</tr>
<tr>
<td>HV</td>
<td>1.5 ± 0.4</td>
<td>1.9 ± 0.7</td>
<td>0.45</td>
</tr>
<tr>
<td>REM</td>
<td>2.0 ± 0.6</td>
<td>3.5 ± 1.4</td>
<td>0.23</td>
</tr>
<tr>
<td>INF</td>
<td>2.7 ± 0.7</td>
<td>4.6 ± 1.5</td>
<td>0.22</td>
</tr>
<tr>
<td>CPA (dB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL1</td>
<td>3.1 ± 1.1</td>
<td>1.9 ± 1.2</td>
<td>0.002†</td>
</tr>
<tr>
<td>BL2</td>
<td>2.1 ± 0.8</td>
<td>2.2 ± 1.2</td>
<td>0.08</td>
</tr>
<tr>
<td>BL3</td>
<td>2.3 ± 1.2</td>
<td>1.0 ± 0.6</td>
<td>0.02†</td>
</tr>
<tr>
<td>BL4</td>
<td>2.1 ± 1.1</td>
<td>0.5 ± 1.0</td>
<td>0.03†</td>
</tr>
<tr>
<td>HV</td>
<td>5.1 ± 1.9</td>
<td>3.2 ± 2.5</td>
<td>0.10</td>
</tr>
<tr>
<td>REM</td>
<td>3.8 ± 2.0</td>
<td>1.3 ± 1.4</td>
<td>0.009†</td>
</tr>
<tr>
<td>INF</td>
<td>1.2 ± 0.4</td>
<td>0.1 ± 0.7</td>
<td>0.04†</td>
</tr>
</tbody>
</table>

* Data are expressed as the means ± SE. Analysis was performed by repeated-measures ANOVA to account for normal and hydrocephalic conditions within the same animal and multiple time points. Abbreviations: BL1, . . . BL4 = baseline 1, . . . baseline 4; HV = hyperventilation; INF = CSF infusion; REM = CSF removal.
† Statistically significant, with mean values lower for hydrocephalus.

Results

The CPA estimation at the initial baselines revealed that the pulsation absorber in normal canines performs more effectively than in hydrocephalic ones. Under the influence of dynamic variation in ICP such as hyperventilation, CSF withdrawal, and CSF infusion, the CPA index consistently exhibits higher levels in the normal physiological condition than in the hydrocephalic condition. Statistical analysis confirmed the significance of the CPA index in differentiating normal and hydrocephalic dogs.

Overall Clinical Conditions of the Animals Following Surgery

No deaths or significant morbidity occurred in any hydrocephalic animal in this study, which is consistent with earlier reports on this technique. Animals recovered from anesthesia without complication and began eating and drinking within 36 hours. Compatible with earlier observations reported in Bayston et al., several transient clinical signs were exhibited in the first 7 days immediately after surgery and were resolved within the first 1–2 days.

Experimental Observation: Hydrocephalus Associated With Obstructive Ventriculomegaly

A direct comparison between pre– and post–CH induction CSF ventricular volume was used to confirm the degree of CH (Fig. 7). Among 5 dogs that underwent a surgical procedure for obstruction of CSF circulation, 4 of them in post–CH induction conditions showed consistent increase in CSF ventricular volume compared with that under pre–CH induction conditions.

Based on the results of MR imaging and ICP monitoring, the severity of obstructive hydrocephalus manifested in the 4 dogs was moderate or mild. These 4 dogs were evaluated and included for analysis to determine the statistical significance of the ability of each metric (such as ICP, IPA, and CPA) to differentiate obstructive ventriculomegaly from the normal condition.

Estimation of Altered Characteristics of the Brain in Response to Pressure Changes

Altered characteristics of the brain before and after the induction of hydrocephalus were assessed using measurements derived from a steady, or “frequency-independent,” component of CSF flow and from a pulsatile, or “frequency-dependent,” component of CSF flow. The former group includes IPA and CPA. The estimated values of absolute ICP, IPA, and CPA index as well as statistical analysis performed for the measurements are noted in the following sections.

Alterations Assessed by the Absolute Mean Value of ICP During all Epochs

To determine whether the absolute ICP value could reliably reflect differences between normal and hydro-
cephalic conditions in this particular experiment, the absolute ICP value was calculated for all epochs. Figure 8A shows the values of ICP estimated during initial baseline, CSF removal, and CSF infusion. In this particular experiment, most of the absolute ICP data were lower in the hydrocephalic condition than in the normal condition, which has been seen variably in this model. Statistical analysis performed using repeated-measures ANOVA indicated that there were no significant differences between the normal and hydrocephalic conditions except at baseline and the hyperventilation period. However, this is statistically significant, with mean values surprisingly higher in the normal condition and lower in the hydrocephalic condition (Table 1).

**Alterations Assessed by the Mean IPA During all Epochs**

To determine whether ICP pulse amplitude could differentiate between the normal and hydrocephalic condition, the amplitude was calculated for all epochs. Figure 8B shows the averaged pulse amplitudes, which were estimated from each single pulse waveform at the initial baseline, CSF removal, and CSF infusion. While no statistically significant differences between the normal and hydrocephalic conditions were detected, the values of IPA show consistently higher values in the hydrocephalic than in the normal condition (Table 1).

**Alterations Assessed by the CPA Index During all Epochs**

The CPA index was estimated at all epochs, including hyperventilation as well as CSF withdrawal and infusion, to examine the response of the pulsation absorber mechanism to dynamic ICP changes in the normal and hydrocephalic conditions. Figure 8C shows CPA values examined at the cardiac frequency for initial baseline, CSF withdrawal, and CSF infusion. In almost all epochs, the CPA index was statistically significantly lower in the hydrocephalic condition than in the normal condition. By ANOVA we were able to confirm significant differences between the normal and hydrocephalic conditions for all epochs except the hyperventilation and hyperventilation-recovery periods (that is, baseline 2). A summary of the mean values and SEs are listed in Table 1. Based on the mean values for all epochs shown in the table, on average, the CPA value in normal canines is a little more than 1 dB higher than that for the hydrocephalic group, meaning that the pulsation absorber in normal canines is able to reduce the output power by 20%. The results suggest that the pulsation absorber performs better in normal physiological conditions under the influence of either elevated or decreased ICP.

**Conventional Estimator of Intracranial Compliance: an Estimation of Pressure Changes in Response to CSF Volume Changes**

Decreased brain compliance can be used as an indication of hydrocephalus. Intracranial compliance (C) is estimated by the relationship between ICP change (ΔP) and CSF volume change (ΔV; that is, C = ΔV/ΔP). Better compliance can be indicated by an increase in volume with a small change in pressure. Figure 9 shows estimated
intracranial compliance based on the pressure-volume relation before and after CSF was withdrawn and before and after it was infused. In the present study, compliance estimated before and after the withdrawal of CSF did not show a clear difference between the normal and hydrocephalic conditions. Moreover, the result is seemingly counterintuitive, suggesting that brain compliance may be higher in hydrocephalus.

**Discussion**

Systems analysis was applied to ABP and ICP data recorded from 5 dogs, which initially were normal and later became affected by surgically induced hydrocephalus. For both normal and hydrocephalic dogs the CPA index is relatively low in ICP increased by CSF infusion compared with ICP decreased by hyperventilation or the withdrawal of CSF. Regardless of the level of ICP, the CPA index is noticeably higher in normal than in hydrocephalic dogs. This pulsation absorbance index shows more consistency and significance in discriminating hydrocephalic dogs from normal dogs compared with the absolute mean value of ICP and conventional compliance estimation based on the pressure-volume relationship.

The dog that underwent surgery but did not exhibit hydrocephalus showed no changes in CPA such as those in dogs demonstrating hydrocephalus. In the 1 dog without hydrocephalus, the CPA at baseline increased on average from 1.9 dB at preinduction to 4.5 dB at postinduction. Because of the consistently lower values in the dogs with hydrocephalus, the dog without hydrocephalus was blindly identified as an outlier based on its high CPA index.

**Common Variability in CSF Volume and Pressure Changes in an Experimental CH Model**

The experimental model of chronic obstructive hydrocephalus in the current investigation has been studied extensively including the documentation and characterization of specific changes relating to CSF volume and pressure.9–11,22,27,32 In particular, this model mimics the clinical condition referred to as "chronic (adult) hydrocephalus" that can show variable and unpredictable changes in CSF volume and pressure, including few or no changes after obstruction of the CSF fourth ventricle. For example, earlier reports from the Cleveland Clinic laboratory documented a significant (2- to 6-fold) increase in CSF volume at 2 weeks post–CH induction surgery that remained for as long as 16+ weeks.11,22,27,32 By contrast, ICP findings for this experimental model showed a gradual and variable increase over the same investigative period. Overall changes in CSF volume and pressure that have been described using this experimental model of CH may differ widely between individual cases.

**Physiological Implication of CPA: Frequency-Dependent Compliance**

How does pulsation absorbance relate to cerebral physiology? In our previous paper, we proposed that an anatomical origin for the pulsation absorber or notch filter might be derived from the structural relationship of the cerebral vasculature to the CSF spaces. Based on the relationship between elastic arteries and the venous system in a closed cranial vault, it is possible to view CSF movement as a mass that links expansion of the elastic arterial vessels during diastole to the compression of veins separated by a measurable distance and the rebound narrowing of arterial vessels during systole. Characteristics of the free movement of CSF may be affected by perturbation from pathological entities, which may result in its inability to absorb strong arterial pulsations, eventually causing an increase in pulsatility in capillary beds. In the literature, an increase in capillary pulsations has been associated with reduced intracranial compliance.24,25 As presented in this study, obstructing CSF flow to cause hydrocephalus can be one such pathological entity that perturbs the pulsation absorber and alters intracranial compliance. Conventionally, intracranial compliance reflects how well ICP responds to increases in CSF volume or overall stiffness of the tissue.25,28,30,31,34 but our earlier work called attention to frequency-dependent responses in the intracranial system (Fig. 10). In the latter view, intracranial compliance reflects how the system responds to different input frequencies; such a system response can be measured by the performance of a pulsation absorber or notch filter (that is, CPA index). A higher CPA value indicates better performance of the pulsation absorber, which also means higher frequency-dependent compliance.

In the past 2 decades there has been growing interest...
in the intracranial pulsatile phenomena. This approach suggests that some characteristics of intracranial compliance may be frequency dependent in nature.

**Clinical Implications**

To what extent do pulsatile phenomena contribute to the clinical problem of hydrocephalus? Previously, we
Alteredes the pulsation absorber mechanism

outlined the rationale and its advantage of time-frequency analysis, including the TVTF technique.\textsuperscript{44} We also revealed our major motivation for this type of research, which was to gain insight into the disordered intracranial system resulting from altered fluid volume and pressures. Some recent theoretical views suggest a major role of pulsatility,\textsuperscript{2,4,13,23–25} whereas others indicate that almost all clinically important questions can be explained by measuring the quantity of bulk flow and mean pressure.\textsuperscript{8,29,31,36,39,40} To resolve the importance of pulsatile and steady (bulk) flow in hydrocephalus, it is essential to study pathophysiological phenomena in settings in which both pulsatile flow characterized by frequency dependence and bulk flow identified by zero frequency can be modulated. Therefore, our analysis was performed with ABP and ICP signals recorded from normal and hydrocephalic dogs under several epochs, such as hyperventilation as well as the removal and infusion of CSF, during which both the absolute mean value of ICP and pulsatile waveform were subject to vary.

The TVTF approach revealed a pulsation absorber mechanism (or notch filter) in which pulsatile CSF movement plays a critical role in attenuating arterial pulsations transmitted into the microvascular bed. When this mechanism works under normal physiological conditions, a “notch” around the heart rate can be observed.\textsuperscript{44} The earlier study\textsuperscript{44} demonstrated that acute increases in ICP through the addition of fluid obliterated this physiological notch, suggesting that decreased intracranial compliance resulted in increased capillary pulsations. It is generally accepted that intracranial compliance (C) is a change in ventricular volume (∆V) in response to a change in pressure (AP) resulting from the addition or the removal of CSF (C = ∆V/AP or C = dV/dP in the infinitesimal case). This definition does not account for the frequency of the input volume or pressure. The implication of frequency dependence is that frequency affects intracranial compliance and must be considered. A further technical implication of our previous study is that frequencies of input signal near the heart rate may be absorbed or handled within the cranium in a manner different from other frequencies.

How do compliance changes correlate with the development of hydrocephalus using the concept of pulsatility? For example, it has been proposed that larger variations in pulsatile flow in the aqueduct of Sylvius predict a better response to shunting in normal pressure hydrocephalus\textsuperscript{45} and that larger pulsation amplitudes of ICP predict shunt response more reliably in the same condition than the absolute mean value of ICP.\textsuperscript{46} Changes of compliance near the heart rate can be diagnosed using Doppler ultrasonography and flow-sensitive MR imaging. Our management options measure potential frequency sensitivity, but require further development. For example, shunts are intrinsically nonlinear response devices\textsuperscript{26,25} and have frequency dependent properties. Shunts that respond to the unique clinical situation could improve outcomes or explain the observation that some patients fare better than others with certain shunts. It is possible that the frequency dynamics of these devices play a role in this otherwise obscure phenomenon.

Data in the present study suggest that changes in the pulsatile dynamics in a particular canine model indicate changes of hydrocephalus better than the hydrostatic compliance change. However, there are myriad other factors to consider including growth factors, changes in mechanical properties of cells, and so forth. A full appreciation of the phenomena in clinical hydrocephalus will require integration of the hydrostatic, hemodynamic, and perhaps biomechanical aspects of the brain.

Conclusions

The pulsation absorber mechanism changes significantly with the development of hydrocephalus. This is possibly a more robust change than with other alterations. Whether the change in the pulsation absorber function and hydrocephalus has a causative relationship or a simple association will be addressed in future studies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or findings specified in this paper. Financial support for these experiments was provided by National Institutes of Health Grant No. R01 NS041553-04 (S.D. and M.L.). Additional support for the development of analytical methods was provided by The Webster Family (E.H.P. and J.R.M.).

Author contributions to the study and manuscript preparation include the following. Conception and design: Park, Dombrowski, Luciano, Madsen. Acquisition of data: Dombrowski, Luciano. Computational analysis: Park. Interpretation of analysis: all authors. Drafting the article: Park. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Park, Zarakowski.

Acknowledgments

The authors thank Anna Leichliter, B.S., Natalie Krajcic, B.S., Zack Leibson, B.S., and April Carter, B.S., CSF Physiology Lab, Cleveland Clinic, for their technical assistance during surgery, and the Ohio Supercomputer Center for providing their computer facilities. The authors also thank Laurel Fleming and Paul Pikitis for copyediting the manuscript.

References

8. Czosnyka M, Pickard JD: Monitoring and interpretation of in-

Accepted May 3, 2010.
A portion of this work was presented in poster form at the Society for Neuroscience 38th Annual Meeting held in Washington, DC, on November 15–19, 2008.
Address correspondence to: Joseph R. Madsen, M.D., Department of Neurosurgery, Children’s Hospital Boston, Harvard Medical School, Hunnewell 244, 300 Longwood Avenue, Boston, Massachusetts 02115. email: joseph.madsen@childrens.harvard.edu.