Cerebrospinal compensation of pulsating cerebral blood volume in hydrocephalus

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Objective: The aim of the study was to develop a computational method for the assessment of brain pressure compensation of cerebrospinal arterial blood inflow. The method was verified using clinical recordings performed during infusion studies in a group of patients diagnosed with hydrocephalus.

Materials and methods: We studied 27 patients suspected of having normal pressure hydrocephalus. The infusion test was used to measure the resistance to cerebrospinal fluid outflow, and the elastance coefficient was performed together with recording of the blood flow velocity in the middle cerebral artery. From the blood flow velocity waveform, the pulsatile pattern of increasing cerebral blood volume during one heart cycle was evaluated as a time integral of the arterial blood flow velocity minus the mean arterial blood flow. Cerebrospinal ‘compliance index’ ($C_i$) was calculated as the amplitude of change in blood volume divided by the amplitude of intracranial pressure pulse waveform.

Results: Compliance index $C_i$ decreased during the infusion test, proportionally inverse to the rise in intracranial pressure controlled by the external infusion of saline ($R = -0.76; p = 0.005$). A relative change in compliance (from baseline to the plateau phase of the study) was positively associated with greater brain elasticity ($R = 0.61; p < 0.005$) and poorer compensatory reserve at the phase of infusion ($R = 0.51; p = 0.009$).

Conclusion: $C_i$ decreases during the infusion study and seems to well replicate the relative changes in cerebrospinal compensatory reserve in hydrocephalus.

Keywords: Brain, cerebrospinal compliance index, intracranial pressure, cerebral blood flow, TCD monitoring

Introduction

The intracranial space can be modeled by accounting for the volumes of three interacting compartments: brain, cerebral blood and cerebrospinal fluid (CSF). The Monro–Kelly doctrine implies that the mechanical and physiological changes of any compartment affect other compartments. According to various models, this ‘global’ compliance represents the cumulative effect of the compliance of the arterial and the venous blood bed and of the CSF space and brain tissue. Out of these four components, the compliance of two compartments predominate, that of the venous bed and the CSF space (its compliance is associated with the distensible lumbar sac).

Net cerebrospinal compliance is inversely proportional to intracranial pressure (ICP) with a proportionality coefficient equal to the elastance coefficient ($E^c$). $E$ is an inverse of the so-called pressure–volume index (PVI) measured in clinical practice using rapid (bolus) CSF volume injection. Assuming that $E$ (or PVI) remains constant, monitoring of ICP would be equivalent to monitoring compliance. This hypothesis has been confirmed by the experience of many independent centers using the Spiegelberg brain compliance monitor, where compliance was measured as the pressure response to the known intracerebral volume increase, provoked by the inflation of an intraventricular balloon.

Magnetic resonance imaging (MRI) physicists have suggested that intracerebral compliance can be measured by accounting for the change of the net cerebral volume (arterial blood inflow, venous outflow and outflow of CSF from the cerebral subarachnoid space and the ventricles towards the lumbar space) and the pulse amplitude of the intraventricular pressure. This produced a promising technique that made it possible to get a snapshot measurement of compliance, although continuous monitoring has proven unrealistic thus far. In 2003, Lang and colleagues attempted to validate the compliance monitor using cardiac waveform analysis of tympanic membrane movements. Although this seemed to be an interesting approach, its clinical usefulness has yet to be demonstrated.
The technique utilized in this work derives from the measurement of magnetometric blood flow in the isolated common carotid artery in dogs for calculating the stroke volume of arterial blood inflow, as first used by Avezaat and van Eijndhoven. We used transcranial Doppler (TCD) ultrasonography to record the profile of the blood flow velocity in the middle cerebral artery (MCA) and subjected it to a mathematical transformation similar to that of Avezaat and van Eijndhoven.

Using this approach, we presume that the pulse of intracranial pressure is first of all the response to the cerebral arterial inflow that, with a certain delay, is accommodated by the venous outflow and the outflow of CSF through the foramen magna towards the distensible lumbar subarachnoid space.

Therefore, dividing the inflow of the pulsatile arterial blood volume by the pulse amplitude of ICP can approximate the combined compliance of the cerebrospinal space. Such a procedure can be repeated from one heartbeat to another, which makes the continuous monitoring of the ‘compliance index’ possible. The term ‘compliance index’, instead of ‘compliance’, is used deliberately, as a lot of simplifying assumptions (discussed in detail later) might make it different from the results of direct methods for evaluation of cerebrospinal compliance.

We validated this novel technique during CSF infusion studies in hydrocephalic patients, where it was possible to evaluate cerebrospinal compliance directly and to estimate the elastance coefficient \( E \).

Materials and Methods

Twenty-seven symptomatic patients with hydrocephalus presenting via the multidisciplinary CSF clinic were studied. The degree of ventriculomegaly in this group was calculated using the Bicaudate index (BCI). The mean BCI is 0.31 and ranged from 0.11 to 0.62; the mean width of the third ventricle is 13 mm and ranged from 7 to 27 m. They all presented with clinical symptoms, including gait difficulty, cognitive problems, memory loss and difficulty in doing things normally.

The real change in cerebral blood volume over one cardiac cycle can be calculated as an integral of the difference between arterial inflow and venous outflow.

\[
CBV(t) = \int_{t_0}^{t}[CBFa(t) - CBFv(t)]dt
\]
where CBV(t) is the change in cerebral blood volume, CBFa(t) is the cerebral arterial blood flow and CBFv(t) is the cerebral venous blood outflow, and all are expressed as functions of time. At the beginning and the end of each cardiac cycle, CBV(t) equals 0, as all arterial inflow is equilibrated by venous outflow, but during the cycle, changes in blood volume take place, and they are responsible for changes in the pulse amplitude of the CSF pressure (Figure 1).

The pulsatile flow of the arterial region (e.g. MCA) can be captured by TCD. The sampled data can be used to analyse changes in CBV over a series of consecutive intervals (e.g. over a series of cardiac cycles). However, TCD measures the flow velocity rather than the flow and thus, the cross-sectional area of the insonated vessel (Sv), the value of C1 cannot be calibrated. However, C1 can be monitored by taking baseline values as 100% and evaluated as the relative change when an increase in ICP is recorded during infusion study.

Statistical analysis

Paired statistical tests were used to compare the mean values of two different phases of ICP waves (baseline and plateau). All values are given as mean ± SD. The Wilcoxon signed-rank method was applied due to the skewed distribution of the variables. Two-tailed p values are reported for all comparisons. All statistical analyses were performed using the SPSS statistical software (SPSS Inc, Chicago, IL, USA), and statistical significance was inferred at p<0.05.

Results

Median values and 25th and 75th percentiles of the physiological and analytical parameters calculated from the 27 ICP and the cerebral blood flow velocity recorded in the patients are given in Table 1. Each section of the infusion test that was used for these calculations was at least 10 minutes long.

During the infusion study, ICP increased almost four-fold. The flow velocity of blood decreased (by ~10%). The amplitudes of ICP, CBFVa and CaBV all increased. The calculated compliance index of the cerebrospinal space (C1) decreased (Figure 2).

The relative change in the compliance index C1 during the infusion study correlated positively with the elastance coefficient (Figure 3A). This relationship indicates that greater changes in compliance were associated with the greater elastance coefficient (i.e. ‘stiffer’ intracranial space). There was no correlation between the relative changes in C1 and resistance to CSF outflow and the size of the ventricles.
The relative changes in $C_i$ also correlated with the lower compensatory reserve during the plateau phase of infusion (measured with RAP index) (Figure 3B).

Finally, the model showing the inverse relationship between the compliance index $C_i$ and mean ICP was verified in individual cases. In all but three of the 27 cases, $C_i$ indicated a good fit to the inverse proportional model with increasing ICP (Figure 4). The mean correlation coefficient was $0.78$ with a standard deviation of $0.18$ (the $p$ value for the zero coefficient was less than $0.005$).

**Discussion**

Intracranial compliance can be divided into three different compartmental compliances: parenchymal, vascular and CSF. According to the Monro–Kellie doctrine, volumetric changes of these compartments compensate in a reciprocal fashion. Analysis of the non-invasive TCD ultrasound blood flow velocity waveform and the recording of the invasive ICP pulse waveform may enable a continuous heartbeat to heartbeat analysis of relative changes in the cerebrospinal compliance index. However, this method has a number of limitations, which can potentially increase the error of estimation in a non-quantified manner.

The first limitation comes from the assumption that the venous blood outflow is steady, without any

Table 1 Median values with 25th and 75th percentiles of the variables and calculated indices (i.e. $t$) before and during the infusion of the Hartmann solution

<table>
<thead>
<tr>
<th>Status</th>
<th>Baseline</th>
<th>Plateau</th>
<th>$p$ (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP (mmHg)</td>
<td>5.785 (2.33 ; 10.75)</td>
<td>20.28 (17.7 ; 26.46)</td>
<td>0.000</td>
</tr>
<tr>
<td>CBFVa (cm/s)</td>
<td>49.8075 (34.75 ; 61.21)</td>
<td>44.665 (31.39 ; 61.19)</td>
<td>0.000</td>
</tr>
<tr>
<td>AMPICP (mmHg)</td>
<td>0.741 (0.23 ; 1.00)</td>
<td>1.695 (0.63 ; 2.82)</td>
<td>0.000</td>
</tr>
<tr>
<td>AMP_CarbV (cm/s)</td>
<td>12.77 (7.99 ; 16.15)</td>
<td>13.097 (8.095 ; 17.64)</td>
<td>0.016</td>
</tr>
<tr>
<td>AMP_CarbV (%)</td>
<td>100 (100 ; 100)</td>
<td>104.366 (94.16 ; 114.66)</td>
<td>0.219</td>
</tr>
<tr>
<td>$C_i$ (%)</td>
<td>100 (100 ; 100)</td>
<td>46.02 (35.23 ; 53.34)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Median (25th and 75th percentile). Significance ($p$) is calculated between baseline and plateau. ABP: arterial pressure; ICP: intracranial pressure; CBFVa: blood velocity in the MCA (middle cerebro-artery); AMPICP: pulse amplitude of intracranial pressure; AMP_CarbV: percentage change of pulse amplitude of volume parameter; $C_i$: percentage change in cerebrospinal compliance index.

$$AMP_{CarbV}(\%) = \frac{AMP_{CarbV}(\text{plateau})}{AMP_{CarbV}(\text{baseline})} \times 100 \quad \text{and} \quad C_i(\%) = \frac{C_i(\text{plateau})}{C_i(\text{baseline})} \times 100$$
pulsations, and always matches the mean arterial blood inflow, which is not true. In fact, if a mismatch between inflow and outflow of blood takes place, it is temporary in nature and leads to vasogenic waves of ICP. Inflow and outflow integrated over a longer time must be equilibrated (with the exception of cases of deep ischemic brain insults, which lead to dramatic decreases in cerebral blood flow). On the other hand, during each heartbeat, the mismatch between the time profile of inflow occurs naturally, but during a very short time (brain equilibrium time point), which corresponds to the end of the net cervical cerebrospinal ‘flushing’, and the temporal values of the arterial inflow equals venous outflow.

A recent study shows that, where extracranial jugular and epidural veins present large oscillations, intracranial sinus flows were less pulsating. Therefore, the venous outflow blood velocity in equation (2), which is not directly measured in our methodology, can be substituted by the averaged arterial inflow as presented in equation (4). Formally, presuming a constant venous blood outflow, we presume that the compliance of distal (extracranial) veins is very large in comparison to the compliance of cerebrospinal system.

A further limitation of this work is that CSF movements from the cranial to lumbar spaces are not taken into account in our methodology. In fact, the arterial systolic peak inflow first provokes CSF ‘flushing’ into the spinal canal (first from the cranial subarachnoid space and then from the ventricles) before it ‘mobilizes’ the venous blood outflow. Our model presumes that both cranial and lumbar spaces behave as a single cerebrospinal space with a common pressure–volume system.

The next limitation comes from the assumption that change in the cross-sectional area of the insonated large cerebral vessel (e.g. MCA), during one heart pulse, is negligible. Cadaver studies suggest that this change is less than 5%. Active arterial wall tension probably further decreases this distensibility. In a previous study using MRI at the limit of the spatial resolution, no significant cross-sectional differences were found during the cardiac cycle.

Our previous studies indicated that, during an infusion study, the change in cerebral perfusion pressure is less than the increase in ICP, due to the usual rise in arterial pressure. Therefore, it can be argued that the possible effect of vasodilation influencing the calculated compliance index may be neglected. Finally, MCA delivers only ~50% of the total blood flow to the brain. Unequal distribution and changes over time might limit the accuracy of our methodology.

Despite these limitations, this study has demonstrated that the change in the cerebrospinal compliance index \(C_i\) correlates with the indirect measurement of the elastence coefficient \(E\). This coefficient has previously been validated in numerous studies and described as being sensitive to the development of brain edema, acute hydrocephalus and brain or subdural hematoma. Changes in the compliance index observed during the study are proportional to the compensatory reserve (RAP index) recorded in the course of infusion. In this period, the compensatory reserve was reduced, as the cerebrospinal ‘working point’ shifted form a horizontal to a steep (exponential) part of the pressure–volume curve. A more advanced shift (a higher RAP index) proved to be correlated with a greater decrease in the compliance index during the study.

Finally, we demonstrated that the decrease in \(C_i\) followed the increase in ICP recorded during the test. Our findings have suggested that the relationship between \(C_i\) and ICP follows an inverse proportional model as previously hypothesized.

**Conclusion**

Visualization of relative changes in the compliances of the cerebral arteries and the CSF space is possible using the transformed blood flow velocity signal and pulsatile components of intracranial pressure. The ability to continuously monitor this compliance might facilitate brain monitoring in many clinical scenarios.

**Acknowledgement**

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References

1. Kelly G. An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3rd, and whose bodies were discovered in the vicinity of the Leith on the morning of the 4th of November 1821, with some reflections on the pathology of the brain. Trans Med Chir Sci Edinburgh 1824; 1: 84–169


