An index of cerebrospinal compensatory reserve (RAP) has been introduced as a potential descriptor of neurological deterioration after head trauma. It is numerically computed as a linear correlation coefficient between the mean intracranial pressure and the pulse amplitude of the pressure waveform. We explore how RAP varies with different forms of physiological or nonphysiological intracranial volume loads in adult hydrocephalus, with and without a functioning cerebrospinal fluid (CSF) shunt.

### Methods

A database of intracranial pressure recordings during CSF infusion studies and overnight monitoring in hydrocephalic patients was reviewed for clinical comparison of homogeneous subgroups of patients with hypothetical differences of pressure-volume compensatory reserve. The database includes 980 patients of mixed etiology: idiopathic normal pressure hydrocephalus (NPH), 47%; postsubarachnoid hemorrhage NPH, 12%; noncommunicating hydrocephalus, 22%; others, 19%. All CSF compensatory parameters were calculated by using intracranial pressure waveforms.

### Results

In NPH, RAP correlated strongly with the resistance to CSF outflow ($r_s = 0.35$; $P = 0.045$), but weakly correlated with ventriculomegaly ($r_s = 0.13$; $P = 0.41$). In idiopathic nonshunted NPH patients, RAP did not correlate significantly with elasticity calculated from the CSF infusion test ($r_s = 0.11$; $P = 0.21$). During infusion studies, RAP increased in comparison to values recorded at baseline (from a median of $0.45–0.86$, $P = 0.14\times10^{-8}$), indicating a narrowing of the volume-pressure compensatory reserve. During B-waves associated with the REM (rapid eye movement) phase of sleep, RAP increased from a median of 0.53 to 0.89; $P = 1.2\times10^{-5}$. After shunting, RAP decreased (median before shunting, 0.59; median after shunting, 0.34; $P = 0.0001$). RAP also showed the ability to reflect the functional state of the shunt (patent shunt median, 0.36; blocked shunt median, 0.84; $P = 0.0002$).

### Conclusion

RAP appears to characterize pressure-volume compensatory reserve in patients with hydrocephalus.

**Key Words:** Hydrocephalus, Pressure-volume compensation, Shunting, Waveform analysis

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**Index of Cerebrospinal Compensatory Reserve in Hydrocephalus**

**Objective:** An index of cerebrospinal compensatory reserve (RAP) has been introduced as a potential descriptor of neurological deterioration after head trauma. It is numerically computed as a linear correlation coefficient between the mean intracranial pressure and the pulse amplitude of the pressure waveform. We explore how RAP varies with different forms of physiological or nonphysiological intracranial volume loads in adult hydrocephalus, with and without a functioning cerebrospinal fluid (CSF) shunt.

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**Abbreviations:** AMP, pulse amplitude; CSF, cerebrospinal fluid; E, elasticity; ICP, intracranial pressure; NPH, normal pressure hydrocephalus; RAP, pressure-volume compensation index; $r_s$, Spearman’s correlation coefficient

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**Hydrocephalus** is a neurological disorder that can result in significant disability or even death, regardless of age, sex, or any other individual characteristic. Because of the complex interaction between intracranial pressure (ICP) and hydrocephalus, no clear conclusions can be drawn from the magnitude of ICP alone. Uncontrolled and increased ICP is one of the most common causes of neurological death, whereas patients with large space-occupying lesions may have clinical signs of neurological distortion (e.g., brainstem) without significant elevation of ICP (17, 23). The phenomena of local or global effects such as ventricular dilation, raised ICP, and a depleted pressure-volume relationship are textbook concepts (5, 33). These may be regarded as symptoms that reflect the presence of a space-occupying process, which can no longer be compensated for. Consequently, subsidiary
parameters are required to produce a better clinical judgment that may indicate when the equilibrium of the cerebrospinal fluid (CSF) system is disturbed or pressure-volume compensation is poor. Pressure-volume compensation index (RAP), used for head-injured patients (6, 9) may be an adequate indication of these conditions in hydrocephalus. Although the abbreviation is not intuitive, it is historically justified and derives from R (correlation coefficient), A (pulse amplitude), and P (mean intracranial pressure) (9, 11, 13, 14).

To interpret RAP, it is critical to understand the pressure-volume curve, which is derived from the hypothetical relationship between the change in volume of the CSF compartment and the ICP, and is mainly divided into 3 regions, as shown in Figure 1 (5, 23–26). The curve in Region I shows a linear increase of pressure, with volume indicating good compensatory reserve (13). In this state, compliance of the system is independent of mean ICP. Further increase in the intracerebral volume produces an exponential rise in pressure, which indicates a decrease in compliance inversely proportional to the rising pressure (18). This is defined as Region II in Figure 1. The transition point from the linear to the exponential part of the pressure-volume curve is attributable to exhaustion of spatial compensatory capacity. In traumatic brain injury, Region III in Figure 1 can also be observed at very high values of ICP. It is characterized by a decrease of slope of the pressure-volume curve, and denotes impairment of active cerebrovascular regulatory mechanisms and subsequent ischemia. Such dramatic intracranial hypertension is seldom seen in hydrocephalus, particularly in normal pressure hydrocephalus (NPH) (2, 25).

The concept of a moving correlation coefficient between mean ICP and associated changes in pulse amplitude (AMP) of ICP was introduced as a measure of compensatory reserve in head-injured patients (2, 9, 12, 14). It is related to the shape of the ICP-volume curve, which has 2 different trends depending on the region (Region III is not considered for hydrocephalus). In Region I (initial horizontal curve), AMP does not vary with the mean ICP. In Region II, when ICP increases more than proportionally to changes in intracranial volume, the amplitude increases in parallel with mean ICP. The transition point in the pressure-volume curve defines the threshold of a change in status in the compensatory reserve. Below this point, the relationship between CSF pressure and volume is linear, and the whole system is considered stable. However, this transition point is difficult to determine clinically without performing an infusion study; i.e., plotting a full pressure-volume curve (24–26). An easier way of using this information to make a clinical judgment for the status of compensatory reserve in the CSF system is to calculate the correlation coefficient RAP (between ICP and AMP). RAP close to 0 signifies good compensatory reserve, while RAP approaching 1 indicates a poor compensatory reserve (6, 13).

CSF pressure-volume compensation is described by a relatively simple model, represented by a differential equation. The appendix contains a detailed mathematical description of the pressure-volume curve and the relationship between mean ICP and AMP. Although the interpretation of RAP has been extensively discussed in relation to head injuries, a number of issues associated with hydrocephalus remain unclear (2, 9, 12, 14). Very recently, Schuhmann et al. (29) published the first account of use of RAP in diagnosing hydrocephalus in children.

The objective of this article is to validate RAP as a parameter upon which clinical judgments can be made for hydrocephalus. Our analysis includes the following specific studies: 1) the correlation of RAP with elasticity (E) of the craniospinal system, resistance to CSF outflow, and dilation of the lateral ventricle; 2) the behavior of RAP during an external CSF volume load in

**FIGURE 1.** Schematic depiction of the pressure-volume compensation index (RAP) theory. A, pressure-volume curve with 3 distinct regions defined. In Region I, there is a linear relationship between volume and pressure; therefore, the intracranial pressure (ICP) amplitude remains constant (assuming constant pulse volume) (B). Thus, RAP (correlation between mean ICP and ICP pulse amplitude [AMP]) is 0, and that implies good compensatory reserve of the intracranial system (C). In Region II, the shape of the pressure-volume curve changes from linear to nonlinear (i.e., exponential). The curve's first derivative is also exponential; thus, the AMP increases proportionally to mean ICP. Consequently, RAP becomes +1, indicating the state of poor compensatory reserve. Region III of critically elevated ICP with deranged vascular reactivity is not relevant to normal pressure hydrocephalus (NPH) and, therefore, only transitions between Regions I and II are considered in this study. In this region, AMP decreases, with ICP rising further. This is caused by “deflection” of the pressure-volume curve to the right, as the arterial bed starts to collapse (cerebral blood volume decreases). As a consequence, RAP reaches a value close to -1.
an infusion test; 3) the changes of RAP with the effect of B-waves of ICP, which are associated with an increase of cerebral blood volume as a result of vasodilatation; 4) the response of RAP to body posture; 5) the effect of shunting on pressure-volume compensatory reserve; and 6) confirmation by RAP of the performance of the shunt (shunt blockage). The intention was to check whether RAP can be used as an index of compensatory reserve for hydrocephalus in a similar way as it is currently used for head injuries. It will require prospective clinical studies to determine the further usefulness of this index for predicting the outcome after shunting, or to differentiate between active hydrocephalus and atrophy.

**PATIENTS AND METHODS**

**Background of Clinical Data**

Material was acquired from a database of infusion studies conducted as part of routine clinical practice. This study is an audit of data from between 1992 and 2005 at the Academic Neurosurgical Unit, Addenbrooke’s Hospital, Cambridge, England. In total, over 2000 studies were performed of 980 patients with hydrocephalus of various types and etiology (idiopathic NPH, 47%; post-subarachnoid hemorrhage NPH, 12%; noncommunicating hydrocephalus, 22%; others, 19%). The mean age was 65 years (range, 24–94 years) and the male-to-female ratio was 2:1. All patients exhibited ventricular dilatation on the brain scan (computed tomographic or magnetic resonance imaging) and clinical symptoms belonging to Hakim’s triad (83% had gait disturbance, 65% memory problems, and 31% urinary incontinence). Because of the nature of the selection, many patients had complex clinical problems. As part of standard clinical practice, the patients were investigated by using a constant rate infusion study (either via lumbar puncture, 20%; preimplanted Ommaya reservoir, 38%; shunt prechamber, 40%; or open external ventricular drain, 2%), and/or by overnight ICP monitoring of 111 patients in addition to routine clinical and imaging assessment. In 44% of patients with a shunt in situ, tests were performed to check the performance of the shunt.

**Patient Population**

To study the RAP coefficient, the database was examined and homogeneous subgroups of patients were formed, predominantly with neuroimaging/clinical symptoms of NPH in states where poor or good compensatory reserve may be clearly identified on the basis of simple physiological models; Groups 1 and 2, 3 and 4, and 5 and 6 partially overlapped:

1) The group of idiopathic NPH patients (n = 59) were studied, where there were infusion studies as well as precise (magnetic resonance imaging) measures of width of lateral ventricles (bicaudate index).

2) For comparison of RAP index before and during the CSF infusion intraventricular study, all nonsutured patients with clinical symptoms of NPH as well as readily available digital raw signal recordings (2003–2005) were studied (n = 74).

3) For comparison of changes of RAP index during and between B-waves associated with the rapid eye movement phase of sleep, 21 recordings in which such phases can be clearly identified were chosen to analyze the amplitude of slow waves of ICP. In this group, 15 patients had clinical symptoms of NPH, and 6 had bad brain cysts.

4) A further 20 patients with symptoms of NPH displaying a clear difference in ICP with posture (lying in bed with head up [semi-sitting] and lying flat during sleep) were identified by examining mean ICP, and were analyzed to assess the influence of a change in body position on RAP index. Twelve patients in this group were shunted.

5) In 25 NPH patients, the test was repeated before shunting and again after insertion of the shunt. In all of these patients, a post-shunt test did not indicate shunt malfunction (the criterion used was lowering of the resistance to CSF outflow from above 13 mm Hg/[mL/min] to below 8 mm Hg/[mL/min]).

6) In 229 patients (151 with NPH; 78 with noncommunicating hydrocephalus) with the shunt in situ, RAP was compared by studying the tests with patent shunts and shunts underdraining (presumed to be blocked).

**Infusion Study—ICP Recording**

The infusion test was used to investigate CSF dynamics. Typically, 2 needles were inserted into a lumbar space (Whitacre 21-gauge) or a shunt prechamber (25-gauge butterfly). One needle was connected via a stiff saline-filled tube to a pressure transducer, and the other to an infusion pump mounted on a purpose-built trolley containing a pressure amplifier (Simonsen & Will, Sidcup, England) and connected to a computer running ICM + software (University of Cambridge, Cambridge, England) (31). In some cases, because of difficulties with the positioning of the needle in a lumbar subarachnoid space, only 1 needle was used for both infusion and pressure measurements.

A strict aseptic technique was used to keep all the prefilled tubing and the transducer sterile. The skin was carefully prepared with antiseptic solution. After 10 minutes of baseline measurement of ICP, the infusion of normal saline or Hartmann’s solution was started at a rate of 1.5 mL/min (or 1 mL/min if the baseline pressure was higher than 15 mm Hg) and continued until a steady-state ICP plateau was achieved. If the mean ICP increased above 40 mm Hg, the infusion was stopped immediately.

In patients with overnight ICP monitoring, intraparenchymal fiberoptic transducers (Micro Venticular Bolt Pressure Monitoring Kit; Integra NeuroSciences Camino, Plainsboro, NJ) were used.

**Data Acquisition and Analysis**

AMP was calculated as the amplitude of the fundamental harmonic of the Fourier decomposition of the pulse waveform from consecutive, 6-second time periods. Measuring the fundamental harmonics instead of the full shape of the AMP implies some loss of information. However, similar techniques proved to be useful in waveform analysis of ICP or transcranial Doppler for assessing critical closing pressure (1, 32). Generally, good correlation between the AMP first harmonic and the peak-to-peak amplitude is reported within or between patients (19). RAP index was calculated as a Pearson correlation coefficient between mean ICP and AMP from a 4-minute period (amounting to 40 data points). The mean of RAP describes the mean value of RAP during a 10-minute time period. Once a reliable mean is established, the calculation window can be shifted along the time axis with much shorter intervals, usually around 10 seconds. To reduce the effects of noise, reasonable time averaging is necessary to obtain a reliable measure; 10 minutes was deemed sufficient for the system to stabilize the ICP waveform that was recorded continuously, and time trends of mean ICP, AMP, and RAP were calculated.

Computer-aided optimization methods were used to identify parameters of a simple physiological model of CSF circulation (31). Among those parameters, the baseline ICP and resistance to CSF outflow characterizes the static conditions of the CSF circulation. The elastance coefficient E (also termed elasticity) characterizes the ability of the system to store an extra volume of fluid (7, 10). Greater E indicates that smaller volumes may be stored under the same incremental pressure conditions.
Behavior of RAP during the B-waves

In a similar manner to that observed during external volume loading in the infusion studies, the B-waves are caused by cerebral blood volume increase as a result of spontaneous vasodilatation of vessels, which hypothetically diminishes cerebrospinal compensatory reserve (27). In 21 patients, where it was clear that B-waves were associated with the rapid eye movement phase of sleep, RAP increased from a median of 0.53 (range, 0.54–0.83) to 0.89 (range, 0.23–0.97), P < 1.23*10⁻⁵, Wilcoxon signed-rank test, n = 21 (Fig. 4).

RESULTS

Results are described in detail below and summarized in Table 1.

Correlation between RAP, Compensatory Parameters, and Ventricular Dilation

In a group of 59 patients with an initial diagnosis of idiopathic NPH (based on clinical symptoms and neuroimaging), baseline RAP showed no correlation with E (rₛ = 0.11; P = 0.21) as shown in Figure 2. RAP did not significantly correlate with the width of the ventricles (bicaudate ratio, rₛ = 0.13; P = 0.41); however, it correlated positively with resistance to CSF outflow and the correlation coefficient was statistically significant (rₛ = 0.35; P = 0.045).

Change of RAP during the Infusion Study

During the infusion phase of the test, the compensatory reserve diminishes as additional CSF volume is stored in the craniospinal space. Based on the Wilcoxon signed-rank test, the analysis showed a statistically significant increase in RAP (from a median of 0.45 [range, −0.65–0.86] to 0.86 [range, 0.21–0.99], P < 1.48*10⁻⁸, n = 74) (Fig. 3).
Change of RAP with Body Position

With a vertical body position, a certain amount of intracranial CSF volume shifts to the lumbar space. In shunted patients, the effect of this extra intracranial compensatory reserve is magnified, possibly because of accelerated CSF drainage. RAP increases after a change in body position from sitting up to horizontal (during sleep) \( n/20 \) patients; RAP increased from a median of 0.36 (range, 0.71–0.45) to 0.57 (range, 0.12–0.86), \( P < 0.0001 \), Wilcoxon signed-rank test (Fig. 5).

Compensatory Reserve Improvement after Shunt Surgery

In patients in whom the test was repeated before and after shunting (with the shunt functioning well), baseline RAP was found to be significantly decreased after shunting \( n/25 \); median before shunting, 0.59 [range, 0.64–0.91]; median after shunting, 0.34 [range, 0.55–0.84]; \( P = 0.005 \); Wilcoxon signed-rank test).

Change in RAP as a Result of Shunt Blockage

RAP recorded during the infusion study was lower in the case of a functioning shunt, as compared with blocked shunts \( n/239 \), patent shunt; blocked shunt, 0.84 [range, −0.21–0.99]; \( P = 0.0002 \), Mann-Whitney \( U \) test).

DISCUSSION

In the present study we have demonstrated that in hydrocephalus, RAP may reflect loss of compensatory reserve in clearly defined clinical scenarios: during external and internal volume load (infusion test, CSF; B-waves, cerebral blood volume; and shifts of CSF from spinal to cranial space after a change in body position from vertical to horizontal). RAP may also be indicative of improvement in CSF compensation after shunting or CSF drainage. Conversely, an increase in RAP signifies a worsening of the CSF circulation, and may be an indicator of shunt blockage for shunted patients.

Why Are \( E \) and RAP Not Correlated?

RAP correlates with the resistance to CSF outflow. This can be interpreted as impairment in the CSF circulation, leading to a reduction of CSF compensatory reserve. However, the lack of correlation between RAP and \( E \) requires explanation. \( E \) is a descriptor of the hypothetical lumped compliance of the CSF space, independent of mean ICP. Values greater than 0.18 mL/1 are regarded as elevated (11). According to the Monro-Kelly doctrine, the net volume of the craniospinal system in adults remains constant (8). Therefore, an increase in the volume of CSF (during the infusion study) should provoke displacement of blood, most probably from the low-pressure venous pool. \( E \) does not describe how brain tissue is being compressed, but it can describe how readily an amount of blood can be displaced outside the cranium through the venous system. According to a theoretical analysis of the pressure-volume

### TABLE 1. Summary of index of compensatory reserve in different subgroups\(^a\)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of cases</th>
<th>Median (range) and description</th>
<th>Median (range) and description</th>
<th>( P ) value</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes of RAP before and during infusion</td>
<td>74</td>
<td>0.45 (−0.65–0.86) Before infusion</td>
<td>0.86 (0.21–0.99) During infusion</td>
<td>&lt; 1.48(10^{-8})</td>
<td>Paired signed-rank test</td>
</tr>
<tr>
<td>Changes in RAP during B-waves recorded overnight</td>
<td>21</td>
<td>0.53 (0.54–0.83) Without B-waves</td>
<td>0.89 (0.23–0.97) During B-waves</td>
<td>&lt; 1.23(10^{-5})</td>
<td>Paired signed-rank test</td>
</tr>
<tr>
<td>Changes in RAP with body position during ICP monitoring</td>
<td>20</td>
<td>0.36 (0.71–0.45) Upright in bed</td>
<td>0.57 (0.12–0.86) Horizontal, during sleep</td>
<td>&lt; 0.0001</td>
<td>Paired signed-rank test</td>
</tr>
<tr>
<td>Changes in RAP before and after shunting</td>
<td>25</td>
<td>0.59 (0.64–0.91) Before shunting</td>
<td>0.34 (0.55–0.84) After shunting</td>
<td>&lt; 0.0001</td>
<td>Paired signed-rank test</td>
</tr>
<tr>
<td>Comparison of RAP between patients with patent and blocked shunt</td>
<td>239</td>
<td>0.36 (0.67–0.72) Patent shunt</td>
<td>0.84 (0.21–0.99) Blocked shunt</td>
<td>0.0002</td>
<td>Unpaired Mann-Whitney ( U ) test</td>
</tr>
</tbody>
</table>

\( \text{RAP, pressure-volume compensative index; ICP, intracranial pressure.} \)
Pressure-volume curve showing that elasticity (E), the slope to the mechanisms that determine E.

to the state of compensatory reserve, but is not strongly related point, 0 (Fig. 6). This suggests that RAP is an indicator related transition point, RAP is theoretically 1, below the transition part of the curve (no matter what the value of E is). Above the iospinal system is, extrinsic to the steepness of the exponential shape of the pressure-volume curve. RAP has a differ-
equation (see appendix), E reflects the steepness of the exponential shape of the pressure-volume curve. RAP has a different meaning; it shows, relative to the transition point of the pressure-volume curve, where the “working point” of the craniospinal system is, extrinsic to the steepness of the exponential part of the curve (no matter what the value of E is). Above the transition point, RAP is theoretically 1, below the transition point, 0 (Fig. 6). This suggests that RAP is an indicator related to the state of compensatory reserve, but is not strongly related to the mechanisms that determine E.

Clinical Situations in Which RAP is Useful

There are many kinds of intracranial disorders that lead to space-occupying effects (6, 33). The effects of an enlarging mass on the brain are well described clinically in terms of symptoms, signs, and the visualization in brain imaging. The phenomenology of local or global effects of tumors, hematomas, hydrocephalus, or brain swelling leads to the development of intracranial hypertension as a result of exhaustion of the spatial compensatory mechanism. Computerized bedside monitoring technology (e.g., ICP monitoring) has been used to analyze the ICP waveform in patients. However, although measuring ICP gives the pressure level, more information is required for diagnosis and prognosis of individual patients.

RAP is a straightforward method for assessing the compensatory reserve of the CSF system. It requires the invasive monitoring of a single modality (ICP), and continuously traces any transient impairment of compensatory reserve. Its value in head injuries and other acute states has been demonstrated previously (2, 9, 12, 14). In hydrocephalus, it is useful in the detection of events that lead to the exhaustion of cerebrospinal compensatory reserve. For example, typical patterns emerge during B-waves (increase in cerebral blood volume), after a change in body posture (shift of certain fluid volume accumulated previously to the lumbar CSF and venous blood volume), and during blockage of a shunt. Furthermore, the patency of a shunt is visualized by the decrease of RAP. Although the threshold generally registers up to 0.6 in RAP (as determined in our unit), the difference of the threshold for individual patients depends on age and disease. Therefore, the true transition point of RAP for hydrocephalic patients is difficult to estimate. However, RAP is a correlation and is normalized (i.e., −1 ≤ RAP ≤ 1). Hence, comparison between patients is straightforward; it may be used in clinical scenarios where poor compensatory reserve may be attributed to certain types of clinical complications, but this needs to be confirmed by prospective clinical studies. Perhaps the most important advantage of RAP is the ability to demonstrate how the CSF compensatory reserve changes over time, both in overnight ICP monitoring and during infusion studies.

Limitations

The pressure of some of the patients with overnight ICP monitoring was recorded by using an intraparenchymal fiberoptic transducer, while in the infusion study intraventricular and lumbar CSF pressure was analyzed. In light of current literature, differences between slow changes in AMP and mean pressures from both transducers should stay negligible (34). A good correlation was observed in a few patients with head injuries, where both pressures were recorded simultaneously (13).

Marmarou et al.’s (26) model does not take into account any long-term modifications of cerebral blood volume or cerebral tissue. However, in hydrocephalus, which is by its nature more chronic than acute brain trauma, such an assumption should not affect interpretation of the coefficient of cerebrospinal compensatory reserve.

The findings that retrospectively classified hydrocephalus patients can show statistical variance with the RAP are interesting, but they do not precisely prove that a specific RAP value is useful in clinical decision-making. A prospective study correlating RAP with improvements after shunting is necessary to verify this point.

The observation of differences in RAP really suggests differences in the characteristics of intracranial systems. In this way, other methods such as measurements of the ICP amplitude by itself, or the implications of phase shifts or time-varying transfer functions, may also be useful, and RAP should be compared with such techniques (15, 16, 20).

The major criticism of this study may be the definition of NPH. Basically, we defined it as the presence of the clinical triad in association with ventriculomegaly, but this is notoriously inaccurate and, therefore, patients with brain atrophy could well have been included. We would like to emphasize that in this work, RAP was discussed as an index of cerebrospinal compensatory reserve in hydrocephalus.
ness of this index for differentiating between different brain pathologies needs to be further investigated.

CONCLUSION

RAP is an index of the CSF compensatory reserve based on the pressure-volume characteristic of the cerebrospinal space, and is numerically computed using the linear correlation coefficient between AMP and the mean ICP. RAP monitors spontaneous waveforms and the correlation between them, and allows continuous identification of CSF compensatory reserve.

Disclosure

ICM+ is software licensed by University of Cambridge, Cambridge Enterprise Ltd.; Peter Smielewski, Ph.D., and Marek Czosnyka, Ph.D., have a financial interest in a part of the licensing fee. The other authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES


APPENDIX

To create an identifiable model, one has to make simplifying approximations. In the case of the CSF circulation system, there are 3 main approximations that have to be made. First, the fluid must be regarded as incompressible; second, the system must be confined to a single compartment of fixed volume; and third, the production and absorption of CSF must vary with time (2, 12, 30).

Based on the principle of mass conservation without long-term fluctuations of the cerebral blood volume, storage of CSF derives from the difference between its production and absorption rates:

\[ \text{Storage of CSF} = \frac{\text{rate of CSF production} - \text{rate of CSF absorption}}{\text{rate of CSF production}} \]

\[ \left( \frac{dV}{dt} = I_p(t) - \text{rate of CSF absorption} \right) \]
Where \( I_a \) is the rate of total production (CSF, internal; saline compound, external), \( I_r \) is the rate of absorption, and \( t \) is time.

According to the pressure-volume relationship, the storage of CSF varies in time and is proportional to the cerebrospinal compliance \([C(P)]\) (units, mm Hg/ml):

\[
\frac{dV}{dt} = \frac{dV}{dP} \frac{dP}{dt} = C(P) \frac{dP}{dt}
\]

Where \([V(t)] = V(p(t))\) is the function of volume (CSF system), \([P(t)]\) is the function of pressure (CSF system), and \([C(P)]\) is the cerebrospinal compliance.

The compliance of the cerebrospinal space can be defined such that it is inversely proportional to the difference between the CSF pressure \([P]\) and the reference pressure \([p_0]\), when the pressure is greater than the hypothetical transition point \([P_{z,V_z}\)] (Fig. 1) (21, 22):

\[
[C(P)] = \frac{1}{E(P(t)-P_0)}
\]

Where the coefficient \( E \) is defined as the cerebral elasticity (or elastance coefficient) (units, mL-1).

For pressures below the hypothetical transition point \([P_{z,V_z}\)] and the pressure in the sagittal sinuses \([P_{ss}\)] (Fig. 1) (21, 22):

\[
[C(P)] = C_0 \quad (NB: [C_0] = \text{constant})
\]

The rate of CSF production can be defined as the sum of the equilibrium component \([I_a]\) and the external saline compound addition \([I_{inf}(t)]\). Hence, the rate of production is denoted as follows:

\[
[I_p] = I_a + I_{inf}(t)
\]

Reabsorption of CSF is proportional to the difference between the CSF pressure \([P]\) and the pressure in the sagittal sinuses \([P_{ss}]\):

\[
\text{Reabsorption} = [I_a] = (P(t)-P_{ss})/R
\]

The coefficient \( R \) (symbol \( [R_{eq}] \) is also used) is defined as the resistance to CSF reabsorption of outflow (units, mm Hg/ml/min). This equation implies that all CSF absorption takes place in the sagittal sinus. If there is any alternative route for CSF absorption in addition to absorption into the sagittal sinus, 2 resistances should be used in parallel; i.e., \([R_{eq}]\) and a resistance to alternative CSF outflow. Such a complex model would, however, be very difficult to identify in clinical conditions.

Therefore, the equilibrium value of ICP \([P_{eq}]\) depends on sagittal sinus pressure \([P_{ss}]\), CSF formation rate, and resistance to CSF outflow \( R \) (3, 4, 24, 26).

\[
P_{eq} = P_{ss} + I_{eq}R
\]

Based on the relationship of the initial formula, the CSF model can be divided into 2 types of models, linear and nonlinear, depending on where the pressure is either before or after the transition point of the curve, resulting in two subsequent equations:

\[
\begin{align*}
\frac{dV}{dt} &= C_0 \frac{dP}{dt} = I_a(t) - I_r(t) \\
\frac{dV}{dt} &= C(t) \frac{dP}{dt} = I_a(t) - I_r(t)
\end{align*}
\]

\([C]\) can be solved analytically for \([V > V_z]\) and \([V < V_z]\).

For a rapid addition of volume \([V-V_z]\) at time \( t = 0 \), \([V-V_z]\) may be possible (for non-linear part of the model) or negative (for linear part of the model). Therefore, the relationship between pressure and volume for both parts are:

\[
\begin{align*}
[V \leq V_z] P &= P_z + (P_z-P_0)e^{(V_z-V)/\Delta CBV} \\
[V > V_z] P &= P_z + (P_z-P_0)e^{(V_z-V)/\Delta CBV}
\end{align*}
\]

Below the transition point, pressure is a linear function of \([V-V_z]\) and above that point it is an exponential function. The AMP, assuming that it is provoked by a sudden addition of blood ACBV, is independent of pressure for \([P-P_z]\) and is a linear function of mean ICP above \([P_z]\):

\[
\begin{align*}
[P \leq P_z] \text{AMP} &= (P_z-P_0)e^{(E\Delta CBV)} \\
[P > P_z] \text{AMP} &= (P_z-P_0)e^{(E\Delta CBV)-1}
\end{align*}
\]

Therefore, the linear correlation between AMP and \( P \) above the transition point \([P_{z,V_z}]\) results in a value of AMP index 1, and below a value of 0.

**COMMENTS**

The search for the perfect index for evaluating cerebrospinal compliance or cerebrospinal compensatory reserve (RAP), which would allow the neurosurgeon to formulate the most adequate surgical indication in cases of hydrocephalus and to predict the surgical prognosis, reminds me of the medieval search for the philosophers’ stone. Unfortunately, at least for the moment, this kind of philosophers’ stone has been not found yet, essentially because of the difficulties in applying a mathematical model to a living subject, and because the disease of such a living subject, namely a patient with normotensive hydrocephalus, is multifactorial in nature and evolving in time, and therefore it defies understanding by the neurosurgeon. Thus, Kim et al. should certainly be admired for their continuing efforts to investigate the fine aspects of cerebrospinal fluid (CSF) dynamics. This article is another example of their tireless search, but it also shows the limits that are still encountered in this field. Indeed, in spite of the attempts of the authors to evaluate for comparison “homogeneous subgroups of patients with hypothetical differences of pressure-volume compensatory reserve,” the pathological substratum is likely to be different in each individual subject, owing to age, sex, nature of the pathological process, duration of the disease, response of the brain to the insult, degree of ventricular dilatation, etc., consequently preventing the definition of an index suitable for prognostic evaluation for all patients. On the other hand, should the conclusions provided by the authors concerning the value of the RAP index in assessing the functional state of an inserted CSF shunt device be confirmed by other studies, then the authors could have found an indicator useful to at least understand the real role of CSF shunting in many patients whose clinical response does not apparently correspond to the patency or occlusion of their CSF shunt apparatus.

Concezio Di Rocco
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This is a technical article that evaluates the use of RAP in hydrocephalus. As I understand it, RAP is a mathematical reflection of the well-known phenomenon seen in head injury, in which the amplitude of the intracranial pressure (ICP) trace increases as the ICP increases. The authors used an infusion of artificial CSF in adults with ventriculomegaly, and noted that, with increasing CSF volume, the compensatory reserve decreased, as expected. There was no correlation of reserve with ventricle size, again as expected, since there is a well-known disconnect between compliance and ventricular size. There was no correlation of compensatory reserve with elastance, which the authors attempt to explain, but which I honestly did not understand.

The major criticism of this work is the definition of normal pressure hydrocephalus (NPH) in their patients. They defined it basically as the presence of the clinical triad in association with ventriculomegaly, but this is notoriously inaccurate, and patients with brain atrophy could well have been included. Did they use the results of their infusion data
to retrospectively define the patients as having NPH? Would the results have been the same in a population of Alzheimer’s disease patients? The implication of this article is that the use of the RAP could be used to determine whether a patient with possible NPH might benefit from a shunt, although this is never stated. Since this is not demonstrated in any way, the clinical value of the findings is unclear.

Leslie N. Sutton
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As the authors note, the pressure-volume compensation index has been used with some benefit in treating head-injured patients. In this article, they apply similar techniques to measure the RAP in a group of hydrocephalic patients. They found that RAP positively correlated with outflow resistance but not with elastance or ventricular volume. When a CSF-diverting shunt was occluded, the RAP was increased. As the authors point out, the RAP breakpoint varies with elastance, and one does not know the elastance for a given patient without undertaking an infusion study or calculating the correlation coefficient between ICP and pulse amplitude. Another variable is that the elastance in any given patient is subject to change.

The authors acknowledge that there are a number of limitations to this study; however, with further investigation, the measurement of RAP may be useful in differentiating NPH from other abnormalities that bear a close resemblance.

J. Gordon McComb
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This article demonstrates a potentially interesting analysis of a large dataset of patients with hydrocephalus. The technique of determining the RAP regression coefficient has been used by the authors many times in other studies. In this study, the goal is to link the calculated RAP to a clinically interesting concept, an “index of compensatory reserve.” It is important for the reader to bear in mind that this is an interpretation that may be substantiated—or not—by further clinical and mathematical analysis, and it is not a definition. The finding that retrospectively classified hydrocephalus cases can show statistical variance with the RAP is interesting, but it does not yet prove that the RAP has predictive value in clinical decision-making. The observation of differences in RAP really supports growing literature suggesting that the response of the ICP to the pulsatile cardiac input tells something about what engineers would call the “systems characteristics” of the intracranial contents. As such, other indicators of systems change, such as measurement of the ICP amplitude by itself (1), or the implications of phase shifts (2) or time-varying transfer functions (3) may all be ways of attempting to observe differences between 1 patient and another. It will clearly be of value to consider these and other mathematical approaches when searching for a clinically useful test. Such a synthesis of these new mathematical techniques will be an important challenge to those who would work in this area in the future.

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