Contribution of CSF and vascular factors to elevation of ICP in severely head-injured patients

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The authors studied the relative contribution of cerebrospinal fluid (CSF) and vascular parameters to the level of intracranial pressure (ICP) in 34 severely head-injured patients with a Glasgow Coma Scale score of less than 8. This was accomplished by first characterizing the temporal course of CSF formation and outflow resistance during the 5-day period postinjury. The CSF formation and outflow resistance were obtained from pressure responses to bolus addition and removal of fluid from an indwelling ventricular catheter. The vascular contribution to the level of ICP was assessed by withdrawing fluid at its rate of formation and observing the resultant change in equilibrium ICP level. It was found that, with the exception of patients with subarachnoid hemorrhage, CSF parameters accounted for approximately one-third of the ICP rise after severe head injury, and that a vascular mechanism may be the predominant factor in elevation of ICP.

KEY WORDS • head injury • intracranial pressure • cerebrospinal fluid outflow resistance • cerebrospinal fluid absorption

Our work and studies by other investigators have shown that the single most frequent cause of death in aggressively managed head-injured patients is uncontrollable intracranial hypertension. Studies in Richmond indicated that high intracranial pressure (ICP) was initially present in two-thirds of patients without intracranial space-occupying lesions who were comatose at admission. Half of the patients who developed intracranial hypertension, or in whom elevated ICP persisted, died despite therapy. Raised ICP continues to be a frequent cause of death in head injury, yet the sequence of events which leads to pressure elevation is poorly understood.

What factors account for sustained pressure elevation? According to theoretical analysis of the ICP, pressure equilibrium is intimately related to cerebrospinal fluid (CSF) volume equilibrium, and efforts to characterize the steady-state relationship of ICP have in part described the steady-state relationship of CSF formation and absorption. More specifically, our studies of ICP dynamics implicate at least three parameters that contribute to the level of pressure: at equilibrium, the rate of fluid formation ($I_f$); the outflow resistance offered to the egress of fluid ($R_o$); and a component ($P_v$) identifying the vascular contribution to ICP. The objective of this present study was to measure the changes in these parameters in head-injured patients and to determine the relative contribution of CSF and vascular components to the level of ICP.

Clinical Material and Methods

Patient Population

This report describes the information gathered thus far in a study population of 42 severely head-injured patients (Glasgow Coma Scale score of less than 8) who were admitted to the intensive care unit within 6 to 18 hours after injury. Among this patient group, access to the CSF compartment via ventricular catheter for volume manipulation and ICP measurement was possible in 34 patients, for whom the primary diagnoses are listed in Table 1. Pressure-volume testing was restricted to this latter group.

All patients underwent continuous monitoring of ICP and pressure dynamics studies as part of a standard clinical protocol. The pressure transducer* for measurement of ICP was referenced to the level of the

* Pressure transducer, Model P23D, manufactured by Gould Electronics, Cleveland, Ohio.
TABLE 1
Primary diagnosis in the 34 head-injured patients in this study

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>closed head injury</td>
<td>13</td>
</tr>
<tr>
<td>epidural hematoma</td>
<td>5</td>
</tr>
<tr>
<td>intracerebral hematoma</td>
<td>8</td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>6</td>
</tr>
<tr>
<td>intraventricular hemorrhage</td>
<td>2</td>
</tr>
</tbody>
</table>

external auditory canal with the patient's bed elevated 20° to the horizontal plane. In general, the techniques used in determining CSF formation rate (If), outflow resistance (Ro), and vascular pressure (Pv) by volume manipulation are those reported previously. Adaptation of these techniques to studies of head-injured patients is described in the following sections.

Measurement of CSF Formation Rate

Following stabilization of the ICP, a small bolus of CSF (0.5 to 1.5 cc) was removed and the pressure-volume index (PVI, which describes the intracranial compliance) was estimated from the equation:

\[ PVI_w = \Delta v / \log(Po/Pm). \]  (1)

The elements of this equation are the PVI computed from withdrawal of CSF (PVI\(_w\)), the volume of the CSF bolus (\(\Delta v\)), the initial pressure prior to removal (Po), and the minimum pressure reached immediately following withdrawal (Pm). The withdrawal maneuver, in addition to providing a measure of the PVI, also permitted the calculation of CSF formation rate (If). For this calculation, a small amount of fluid (2 to 4 cc) was removed, and the initial pressure prior to removal (Po), the minimum pressure that developed immediately upon removal (Pm), and a pressure point P1 on the return trajectory at time t1 was inserted in the equation:

\[ If = [(PVI/t1)(\log P1/Pm)]. \]  (2)

Calculation of Injected CSF Volume Limit and PVI

Next, the volume (V\(_{\text{max}}\)) necessary to limit the pressure rise to that during bolus injection (Pmax, usually 35 mm Hg) was computed using the equation:

\[ V_{\text{max}} = (PVIw)(\log P\text{limit}/Po). \]  (3)

A safe volume margin (V\(_{\text{max}}\)) was calculated in a manner similar to that suggested by Sullivan, et al. 23 Subsequent injections of CSF were kept below this volume limit. Two to three bolus injections were performed, and the initial pressure (Po), peak pressure (Pp), and CSF volume added (\(\Delta v\)) were obtained from the pressure response to calculate the PVI at injection (PVI\(_i\)) using the following equation:

\[ PVI_i = \Delta v / (\log Pp/Po). \]  (4)

Calculation of Outflow Resistance

The resistance to outflow (Ro) was calculated from the same pressure response to bolus addition using the equation:

\[ Ro = t2 \times Po / (PVIi)(P2/Pp)(Pp - Po)/(P2 - Pp), \]  (5)

where pressure P2 refers to a pressure point on the return trajectory at time t2 (usually selected at 2 minutes).

Separation of CSF and Vascular Components of ICP

The product of CSF formation rate and outflow resistance defined the CSF component of ICP (If \(\times\) Ro) as described by the steady-state equation:

\[ ICP = CSF + \text{Vascular} = (If \times Ro) + Pv. \]  (6)

The remaining vascular parameter (Pv) in the steady-state equation was estimated by withdrawing fluid at the calculated formation rate using a motorized syringe pump. This maneuver shunts the newly formed fluid and essentially cancels the gradient of ICP necessary to absorb fluid. Thus, with the CSF component eliminated, the remaining equilibrium pressure was considered the vascular contribution to ICP. 12

The rise in baseline ICP over time was considered to be the difference between the ICP and an accepted norm of 10 mm Hg (or \(\Delta ICP = ICP - 10\)). The percentage rise of ICP caused by the CSF component (%ICP\(_{\text{csf}}\)) given by the product of CSF formation (If) and outflow resistance (Ro) was calculated by Equation 7, in which the quantity (If \(\times\) Ro)\(_{\text{exp}}\) refers to the experimental value of If and Ro measured in each patient:

\[ %ICP_{\text{csf}} = \frac{(If \times Ro)_{\text{exp}} - (If \times Ro)_{\text{norm}}}{ICP} \times 100\%. \]  (7)

According to data reported by Cutler, et al., 3 normal values for CSF formation average 0.35 ml/min ± a standard error of the mean (SEM) of 0.02 ml/min. Data from Shapiro, et al., 24 indicate that the normal value for outflow resistance determined by the bolus technique is about 3.0 mm Hg/ml/min. This value was used to calculate the normal If \(\times\) Ro product (1.05 mm Hg). Similarly, the vascular contribution to the rise in ICP (%ICP\(_{\text{vasc}}\)) was calculated using Equation 8, in which the quantity P\(_{\text{vexp}}\) refers to the experimental value of Pv measured in each patient:

\[ %ICP_{\text{vasc}} = \frac{(Pv_{\text{exp}} - Pv_{\text{norm}})}{ICP} \times 100\%. \]  (8)

The normal value of the vascular component of ICP (Pv) was estimated by inserting the normal values for CSF formation, outflow resistance (Ro), and ICP in the steady-state equation, ICP = (If \(\times\) Ro) + Pv. Inserting
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0.35 ml/min for If, 3.0 for Ro, and 10 mm Hg for Po (the ICP before withdrawal of the CSF bolus) yields an estimated normal Pv of 8.95 mm Hg. This constant was inserted for Pvnorm in Equation 8 for calculation of %ICPvasc.

Results

Comparison of PVI Measured by Bolus Injection or Withdrawal

As described in the Clinical Material and Methods section, the first maneuver was to withdraw a small bolus of CSF in order to estimate the PVI. The PVI on withdrawal was compared to subsequent indices obtained by bolus injection. This was an important consideration, since at high ICP levels it was not always possible to add volume. A total of 68 comparisons were made (Table 2) and were analyzed as a function of steady-state ICP level. It can be seen from Table 2 that the PVI on withdrawal (18.9 ml ± a standard deviation (SD) of 7.7 ml) compares favorably with indices obtained from bolus injection (18.4 ± 6.9 ml). This close agreement was maintained throughout the range of pressure above and below 15 mm Hg, supporting the concept that the pressure data extracted from the withdrawal maneuver can be used as an accurate measure of the PVI.18

Rate of CSF Formation

In patients with steady-state ICP levels less than 15 mm Hg, the rate of CSF formation averaged 0.337 ml/min ± an SD of 0.1 ml/min (Table 3). This is equivalent to 485 cc/day and is very close to the accepted normal value of 500 cc/day.3 As ICP levels increased to more than 25 mm Hg, the mean rate of CSF formation decreased moderately to 0.296 ± 0.06 ml/min. Although this represents a 12% reduction compared to the low-pressure group, these values are still within the normal range. It is important to note the wide variation of fluid formation in the ICP range of 15 to 25 mm Hg (Table 3). In studies of two patients (Cases 4 and 14, Table 5), the rate of fluid formation exceeded 0.74 ml/min, and we believe this represents edema clearance through the CSF system in these cases. This high rate of ventricular clearance was confirmed in both patients by withdrawing fluid at the estimated formation rate for several hours, and by observing that the reduced level of pressure was sustained while CSF was drained at these high rates.

Temporal Course of CSF Formation after Head Injury

It was possible to obtain estimates of CSF formation rate in 21 (62%) of the 34 patients within 24 hours after injury. These data were combined with 34 studies among 26 patients to characterize the temporal course of CSF formation over a 5-day period (Fig. 1). As indicated earlier in this report, a fluid formation rate of 0.74 ml/min was measured in two patients, which is equivalent to 1065 cc/day. However, when evaluated as a group, the average rate of fluid formation measured during the 5-day postinjury period remained within the normal range (0.324 to 0.293 ml/min), with a tendency to decrease over time. This reduction of fluid forma-
Fig. 2. Plot of cerebrospinal fluid (CSF) formation versus equilibrium intracranial pressure (ICP) determined from 55 measurements obtained in 26 patients just prior to removal of fluid. Although the regression line of formation rate tends to decrease with increasing ICP (r = 0.33), the reduction is not statistically significant (Student’s t-test).

Table 4
Cerebrospinal fluid Ro in head-injured patients

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>No. of Studies</th>
<th>Intracranial Pressure (mm Hg)</th>
<th>Ro (mm Hg/ml/min)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>38</td>
<td>&lt; 15</td>
<td>9.0 ± 8.53</td>
</tr>
<tr>
<td>19</td>
<td>40</td>
<td>&gt; 15</td>
<td>11.77 ± 7.14</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations. The median outflow resistance (Ro) value was 7 mm Hg/ml/min.

Fig. 3. Graph showing outflow resistance (Ro) to cerebrospinal fluid (CSF) determined by daily measurements of the intracranial pressure response to bolus addition of fluid (1 to 3 cc) and calculating the Ro according to Equation 5. In all 22 studies conducted in 22 patients evaluated, pressure returned to the predisturbance level within minutes. Normal Ro, as assessed by the bolus injection technique, is approximately 3.0 mm Hg/ml/min.

Resistance to CSF Absorption

Table 4 compares the resistance to CSF absorption measured by the bolus injection technique in two groups of patients with steady-state ICP levels above and below 15 mm Hg. When ICP was below 15 mm Hg, the mean value of resistance equaled 9.0 ± 8.53 mm Hg/ml/min, a threefold increase above normal values for resistance to bolus injection. Absorption resistance varied over a wide range, with the highest values measured in patients with subarachnoid hemorrhage. The resistance value in the high-pressure group averaged 11.77 ± 7.14 mm Hg/ml/min and was also above normal; however, according to Student’s t-test, resistance in this group was not statistically different from that in the low-pressure group.

Temporal Course of CSF Outflow Resistance in Head Injury

The temporal course of CSF outflow resistance was determined from 67 studies conducted during the...
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![Graph showing the rise in intracranial pressure (ICP) due to cerebrospinal fluid (CSF) parameters determined in 19 cases by measurement of CSF formation and outflow resistance and computing the percentage ICP increase using Equation 7. The estimated vascular contribution (vase) was considered equal to the remainder of ICP rise. The component of ICP increase due to CSF parameters averaged 33.1% and the estimated vascular component was 67.7%. The predominant contribution of the vascular component is more evident at higher ICP levels. SD = standard deviation.](image)

The notion that the CSF component of ICP is given by the product of CSF formation and outflow resistance as described by the steady-state equation (Equation 6) allowed the determination of the percentage ICP rise caused by fluid absorption (Table 5). The mean steady-state ICP in this group of 19 patients was 16.80 mm Hg, representing an ICP rise of 6.80 mm Hg above the accepted normal opening pressure of 10 mm Hg. The product of normal formation and resistance (If x Ro) for the bolus techniques was calculated as 0.35 x 3.0, or 1.05 mm Hg. Thus, at a normal opening pressure of 10 mm Hg, the CSF component (1.05 mm Hg) accounts for 10.5% of the steady-state pressure, while the remainder (8.95 mm Hg, or 89.5%) is attributed to the vascular component (Pv). The percentage rise of ICP due to the CSF and vascular components of each patient was calculated by Equations 7 and 8, respectively. After inserting the measured values of If and Ro in Equation 7, it was found that in these patients the component of ICP rise due to CSF absorption accounted for 33.10% ± 34.25% of the ICP elevation (Table 5 and Fig. 4). Although Pv was not measured in this group of patients, the estimated pressure rise due to the vascular component equaled 67.69% ± 32.37%. The vascular contribution was even more predominant in patients with ICP greater than 20 mm Hg (Fig. 4).

Vascular Component of ICP

In nine patients it was possible to obtain measures of the vascular component of ICP (Pv) from withdrawal tests and independent measures of If and Ro using bolus manipulation (Table 6). The mean ICP level of this patient group averaged 20.0 mm Hg ± an SD of 6.89 mm Hg. The rise above accepted normal opening pressure equaled 10.0 mm Hg. By inserting the values for rate of fluid formation (If), outflow resistance (Ro), and measured vascular component (Pv), the rise of ICP due to CSF parameters equaled 26.07% while the measured contribution of the vascular component equaled 66.01%. This difference was statistically significant (p < 0.05). Ideally, the sum of the CSF and vascular components should total 100%. According to these methods, adding the CSF and vascular components of our head-injured patients accounted for 92% of the ICP rise. This is illustrated in Fig. 5.

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FIG. 5. Graphs showing the percentage contribution of cerebrospinal fluid (CSF) and vascular components (Pv) of intracranial pressure (ICP) over the range of pressures observed in these studies. Only the nine patients in whom it was possible to obtain independent measures of CSF and vascular components are included. In the graph at left, note that as ICP rises, the Pv increases linearly and accounts for the greater component of ICP increase (Y = -0.61 + 0.84X, r = 0.97). The difference between the Pv line (unity) and the baseline ICP should be accounted for by the CSF component. In the graph at right, the CSF component in each patient, given by the product of CSF formation and CSF outflow resistance (If × Ro), is shown added to the Pv line of the left graph. The observation that the sum is very close to baseline ICP (regression Y = 0.061 + 0.96, r = 0.98) indicates that the techniques used in assessing the CSF and vascular components are correct within reasonable experimental error and that the component of baseline ICP attributed to CSF parameters remains low in proportion to the ICP level.

Discussion

These data were obtained during the course of treatment, and in the majority of cases represent the combined effect of mannitol administration, hyperventilation, CSF drainage, and barbiturates. Despite aggressive therapy, ICP remained elevated, and 20% of the patients studied went on to develop intractable hypertension and died from progressive neurological deterioration. What is the contribution of outflow resistance to the ICP rise? The moderate increase in outflow resistance observed in these studies does not account for an appreciable elevation of the ICP. Moreover, the CSF fluid formation rate was within the normal range, which limited the challenge to the absorptive mechanism. Thus, the pressure gradient necessary for absorption, defined as the product of CSF formation and outflow resistance, accounted for less than one-third of the ICP rise. High levels of outflow resistance were observed only in patients with evidence of intracranial hemorrhage. Diversion of CSF would be effective in reducing ICP in this subgroup. High outflow resistance values associated with blood in the CSF have been reported by several investigators.6,7,9,12 Kosteljanetz studied CSF dynamics in patients with intracranial hemorrhage using similar bolus techniques and found a linear correlation between outflow resistance and steady-state ICP. Close to 90% of the ICP rise in the study by Kosteljanetz could be attributed to the increase in outflow resistance. Fuhrmeister, et al.,6 found outflow pressure to be elevated by threefold in cases with subarachnoid hemorrhage, with a concomitant reduction in intracranial compliance. The hydrodynamic parameters tended to normalize very slowly, and normal outflow resistance was not achieved until 40 to 50 days following initial assessment. Thus, high outflow resistance values in CSF contaminated with blood are to be expected and would explain the elevated values we observed in some patients. However, despite varying degrees of bleeding, in our head-injured patients, these values were not excessive. Data reported by Kosteljanz confirm this view.9 The median outflow resistance of 15 head-injured patients studied by Kosteljanz approached 9.4 mm Hg/ml/min, which is similar to the 12.13 mm Hg/ml/min mean value reported in this study (see Table 5).

The bolus withdrawal technique estimates total fluid production. This includes newly formed CSF from the choroid plexus and brain tissue and edema draining into the ventricular system. The observation that fluid formation exceeded 50 cc/hr in two of the 34 patients studied provides direct evidence of edema clearance through CSF pathways.11,15,23 This high rate of CSF formation was confirmed by withdrawing fluid at a rate of 55 cc/hr for several hours and observing that ICP was sustained at a reduced level. In these circumstances, particularly when outflow resistance is high, controlled electronic drainage of fluid may be effective in reducing...
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ICP; the application of this technique in selected head-injured patients will be described in greater detail in another report. However, patients with high CSF formation were the exception. In the majority of patients, including those who developed uncontrollable ICP, the CSF formation rate was within the normal range. In many patients with evidence of acute brain swelling, clearance of edema (as assessed by these techniques) was minimal. The greater variability in the clearance rate of extracellular fluid remains unexplained. Experimental work has shown that there is bulk-flow clearance of edema fluid by the ventricular route when a driving force of pressure exists at the site of edema formation. With a reduction of the driving pressure or a reduction of edema formation rate, no edema clearance through the ventricular system occurred despite a wholly edematous brain. Thus, extrapolation of these results to the current patient studies in which there was high ventricular clearance of edema fluid implies that an active edema generator is present. The heterogeneous nature of the lesions, their surgical treatment, their location, and the duration of active edema production in the patient population studied may partially account for the variable rates of edema clearance observed in these studies.

To what degree are vascular mechanisms involved in ICP elevation? The combination of moderately increased outflow resistance and fluid formation according to the steady-state ICP relationship defines the CSF component of ICP. As described earlier, when only CSF formation and outflow resistance were measured, this contribution equaled 33.10%. The contribution of the CSF component to the ICP rise was confirmed by an independent test in which CSF was shunted at its estimated formation rate and steady-state pressure was monitored at pressure equilibrium. Under these conditions, the CSF contribution to ICP (26.07%) was eliminated and the remainder, or 66.01%, must have been due to other factors.

It is generally accepted that intravascular pressure must be slightly greater than brain-tissue pressure or the vessels would collapse. We believe that upon withdrawal of fluid at the estimated formation rate, ICP will gradually fall to a level equivalent to that of the resting intravascular pressure. Our studies show that this pressure is elevated and accounts for the greater percentage of ICP rise.

The well-known steady-state equation, ICP = (If x Ro) + Pv, where If x Ro defines the CSF component and Pv indicates the vascular contribution to ICP, must be placed in proper perspective. This equation arose from the studies of Davson, who proposed that outflow of CSF was proportional to the pressure gradient (ICP - dural sinus pressure) divided by the resistance of the CSF pathway acting to impede egress of fluid. This relationship has been confirmed by many investigators and is regarded as a basic tenet of CSF hydrodynamics. The application of this equation to the head-injured patient requires modification. To be applied in a general sense the equation must be altered to include a volume-induced rise in ICP which is not subject to CSF flow hydrodynamics. If this were not the case, then raised ICP could only be explained by an increase in dural sinus pressure. Martins, et al. explored this possibility and did find elevated dural sinus pressure in three of 12 patients studied. Although this possibility has not been fully explored, it is unlikely that ICP and dural sinus pressure are so closely coupled. It is reasonable to propose that the equation should accommodate intracellular or extracellular volume change that is not subject to normal CSF hydrodynamic relationships. For example, in the acute stage of swelling in which intracranial CSF volume is not depleted, the normal relationships between CSF flow and pressure are valid since the absorbing mechanisms in the early stage cannot distinguish between newly formed fluid and brain tissue which is swelling and displacing existing fluid. If the exchange of swollen brain tissue and CSF takes place at a relatively slow rate, then no pressure rise will occur. The combination of moderately increased outflow resistance and fluid formation according to the steady-state ICP relationship defines the CSF component to the ICP rise. Pressure and volume are tightly "coupled," and bolus addition of fluid in these circumstances results in a pressure response which fails to return to predisturbance levels. We observed this response in two patients who subsequently developed uncontrollable ICP and died. Failure of pressure to return to its predisturbance level may signify a terminal stage of volume compensation.

We interpret the pressure studies of our head-injured population to reflect an intermediate stage of compensation where the effect of brain-volume increase acts primarily to compress the more compliant vessels. Intravascular pressure on the venous side of the circulation increases as a result of this compression and is reflected by the high vascular component measured in these studies.

Conclusions

Our study shows that factors other than CSF parameters account for the greater proportion of ICP rise in head-injured patients. We suspect that the rise of ICP is mediated primarily through the vasculature in response to intracranial swelling, as proposed by Langfitt, et al., and Miller, and more recently by Obrist, et al. The well-known steady-state equation used in CSF hydrodynamics requires modification to include a mass-effect component when applied to the analysis of ICP in cases of head injury.

Considering that CSF parameters evaluated in head-injured patients play a relatively minor role in elevations of ICP, we believe that future research should focus on vascular dynamics for resolving the sequence of events leading to ICP elevation in head injury.
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