Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma

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Object. The aim of this study was to compare the effects of two different treatment protocols on physiological characteristics and outcome in patients with brain trauma. One protocol was primarily oriented toward reducing intracranial pressure (ICP), and the other primarily on maintaining cerebral perfusion pressure (CPP).

Methods. A series of 67 patients in Uppsala were treated according to a protocol aimed at keeping ICP less than 20 mm Hg and, as a secondary target, CPP at approximately 60 mm Hg. Another series of 64 patients in Edinburgh were treated according to a protocol aimed primarily at maintaining CPP greater than 70 mm Hg and, secondarily, ICP less than 25 mm Hg for the first 24 hours and 30 mm Hg subsequently.

The ICP and CPP insults were assessed as the percentage of monitoring time that ICP was greater than or equal to 20 mm Hg and CPP less than 60 mm Hg, respectively. Pressure reactivity in each patient was assessed based on the slope of the regression line relating mean arterial blood pressure (MABP) to ICP. Outcome was analyzed at 6 months according to the Glasgow Outcome Scale (GOS).

The prognostic value of secondary insults and pressure reactivity was determined using linear methods and a neural network. Patients treated according to the CPP-oriented protocol, even short durations of CPP insults were strong predictors of death. In patients treated according to the ICP-oriented protocol, even long durations of CPP insult—mostly in the range of 50 to 60 mm Hg—were significant predictors of favorable outcome (GOS Score 4 or 5). Among those who had undergone ICP-oriented treatment, pressure-passive patients (MABP/ICP slope $< 0.13$) had a better outcome. Among those who had undergone CPP-oriented treatment, the more pressure-active (MABP/ICP slope $> 0.13$) patients had a better outcome.

Conclusions. Based on data from this study, the authors concluded that ICP-oriented therapy should be used in patients whose slope of the MABP/ICP regression line is at least 0.13, that is, in pressure-passive patients. If the slope is less than 0.13, then hypertensive CPP therapy is likely to produce a better outcome.

Key Words: traumatic brain injury • intracranial pressure • cerebral perfusion pressure • pressure reactivity • outcome

One current debate concerning the treatment of TBI centers on which parameter is the most crucial to control during intensive care: ICP or CPP. Different opinions also exist regarding the CPP levels that are dangerous and may cause secondary brain injury. Such factors have led to diverse treatments in patients with brain trauma among even the best academic neurosurgical centers.

The aim of this study was to evaluate the effects of two CPP therapies on physiological features and outcome in patients with TBI. The study was based on admission, outcome, and physiological monitoring data from two neuro-intensive care centers: Uppsala University Hospital, Uppsala, Sweden, which used a primarily ICP-oriented protocol, and Western General Hospital, Edinburgh, United Kingdom, which used a primarily CPP-oriented protocol.

Clinical Material and Methods

Patients and Data Collection

Two series of patients with TBI were compared: one series of 67 patients who had been treated using an ICP-oriented protocol at the Uppsala University Hospital between December 1, 1998 and July 1, 2002, and another series of 64 patients who had been treated with a CPP-oriented protocol at the Western General Hospital in Edinburgh between May 1, 1995 and May 1, 1998. Patients older than 79 or younger than 16 years were excluded. While in intensive care, all patients were monitored using a computer, with physiological data being sampled and recorded once per minute. Each patient was required to have at least 6 hours of ICP, CPP, and MABP data recorded within 96 hours of injury. The mean duration of valid CPP monitoring within the 96-hour window was 54 hours per patient. All of the
valid monitoring data for each patient within the 96-hour window were used in this analysis. The median time between injury and the start of CPP monitoring was 28 hours in patients in Uppsala and 10 hours in those in Edinburgh; the delay in monitoring in the patients in Uppsala is explained by the larger and more sparsely populated catchment area compared with that in Edinburgh. Minute-by-minute monitoring data were manually validated to remove artifacts by using a computer program that enabled automatic outlier detection. The GOS* score was assessed at 6 months. Admission, monitoring, and outcome data in the two patient groups are summarized in Table 1.

**Treatment Protocols**

In the patients in Uppsala, the goal was to keep ICP less than 20 mm Hg and CPP greater than 60 mm Hg. In general, no attempt was made to increase CPP to greater than 60 mm Hg by increasing blood pressure above normal levels. In cases in which patients had an increased ICP with a high CPP, the amount of the sedative was increased followed by the administration of antihypertension therapy if necessary. Vasopressor agents were used to stabilize systemic pressure but not to treat CPP.6 In the patients in Edinburgh, a more CPP-oriented approach was applied, with the primary aim of reaching a CPP of at least 70 mm Hg. Maintaining ICP below 25 mm Hg was a secondary target; after 24 hours, however, the ICP threshold was raised to 30 mm Hg. Vasopressor agents were used to maintain CPP at 70 mm Hg in cases of persistent elevations in ICP.

**Secondary Insults**

In each patient, ICP insults were quantified as the percentage of monitoring time that ICP was at least 20 mm Hg, and CPP insults as the percentage of monitoring time that CPP was less than 60 mm Hg.

**Pressure Reactivity**

An important component of cerebral pressure autoregulation is the ability to maintain a stable ICP for a wide range of MABP levels.17 Patients are described as pressure passive if ICP varies together with MABP, and pressure active if ICP varies inversely with MABP. If ICP was stable over a wide range of MABP levels, then the patient was described as pressure stable. To assess this relationship in each patient for each hour of computer monitoring, mean ICP and MABP values were calculated. Regression lines were fitted to these data points for each patient in the study, and the slope of the regression line was used as a measure of pressure reactivity. For pressure-active patients the slope was negative; for pressure-passive patients it was positive. Intracranial pressure values greater than 40 mm Hg were excluded because the MABP/ICP relationship changes when ICP is that high for sustained periods. If a patient is dying from the effects of very severe ICP, then typically ICP is increasing while MABP is decreasing. Such patients would be classified as pressure active according to our definitions, but it is unlikely that they are in fact pressure active in the sense that pressure autoregulation is partially preserved. Three patients from the Edinburgh group were excluded from the pressure reactivity analysis because all of their ICP values were greater than 40 mm Hg.

**Data Analysis**

Approximately normally distributed data are presented as the means ± SD, and significance was assessed using the Student t-test. Otherwise data are expressed as the median value, and variability is presented graphically in histograms. When data were not normally distributed, significance was assessed based on the Mann–Whitney U-test. Distributions involving proportions of monitoring time (for example, the proportion of monitoring time that ICP ≥ 20 mm Hg) were highly nonnormal. Categorical variables were compared using contingency tables. Subgroup percentages are presented with 95% CIs computed as 1.94 × standard error, calculated with the usual approximation. Linear regression was determined using the singular value decomposition.

Some results were obtained using a bayesian neural network.16 As used here, a neural network is an extension of logistic regression that allows for general, nonlinear classification surfaces. The bayesian system generates a se-
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**TABLE 2**
Median percentages of monitoring time and mean slope on the 1st and subsequent 3 days postinjury

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
<th>2–4</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>median % monitoring time</td>
<td>ICP (\geq 20) mm Hg</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CPP (&lt; 60) mm Hg</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>mean slope (MABP/ICP)†</td>
<td>0.14 ± 0.42</td>
<td>0.07 ± 0.65</td>
<td>0.350</td>
</tr>
</tbody>
</table>

* Comparison of the two time periods for each variable.
† Values represent the means ± SD.

series of models in a Monte Carlo Markov chain guaranteed to converge to the posterior probability distribution on models given the data. A set of models generated after convergence (typically a few hundred) are then used to generate a set of estimates, which represent a sample from the posterior probability of the target value given the data. This sample is then converted into a discrete approximation of the posterior probability distribution by using Parzen window density estimation. The maximum likelihood estimate of the posterior probability is obtained from the mode of this discrete distribution; 90% confidence bounds, from the boundaries of the region of the discrete distribution with the highest probability that contains 90% of the probability density.

We use this technique to show graphically how patient outcome probabilities change as a function of physiological variables, for example, the percentage of monitoring time with a CPP less than 60 mm Hg. The x-axis of the graph represents increasing values of the variable, the y-axis the probability of a certain outcome (for example, death or good outcome). The maximum likelihood estimate of the probability is plotted together with the 90% confidence region. Data are plotted as “rugs” along the bottom and top of the graph. Each tic mark in a rug represents a value for a physiological variable in a given patient. Marks along the top of the graph represent the values for patients who had the designated outcome, whereas those on the bottom are for patients who did not have that outcome.

**Results**

**Secondary Insults**

The median amount of monitoring time that a patient experienced an ICP greater than or equal to 20 mm Hg was 6% in those who had undergone the ICP-oriented therapy (Uppsala) compared with 7% in those who had undergone the CPP-oriented approach (Edinburgh). The median amount of monitoring time that CPP was less than 60 mm Hg was 7% in the ICP therapy group compared with 1% in the CPP therapy group (p < 0.001). The distributions of these features over the two patient groups are shown in Fig. 1.

**First Day Postinjury Data Compared With Subsequent Data**

The patients in Edinburgh tended to arrive at the neurointensive care unit closer to the time of injury than the patients in Uppsala (Table 1); consequently, there are more data from the 1st day following injury for the Edinburgh patients. The ICP and CPP insults were less likely to occur on the 1st day following injury than on the subsequent 3 days—significantly so in the case of ICP insults (Table 2). Note, however, that the results of a comparison of the occurrence of secondary insults between the two centers are identical to the numerical precision reported here when data from the 1st day postinjury are omitted. Therefore, the difference between the two centers in the start of monitoring activity (MABP/ICP slope) between the 1st day and the following days were not significant.

**Secondary Insults and Outcome**

Figure 2 shows the relationship between CPP insult and patient outcome at the two centers. In the CPP-treated (Edinburgh) patients the probabilities of death and severe disability increased rapidly as the duration of CPP insults increased. On the other hand, in ICP-treated (Uppsala) patients, longer durations of CPP insults were associated with a favorable outcome and a reduced probability of death.

To quantify this result more directly, the patients from both centers were divided into two groups based on CPP insult: low insult, CPP less than 60 mm Hg for less than 10% of the monitoring time; and high insult, CPP less than 60 mm Hg for more than or equal to 10% of the monitoring time. The outcome distributions in these four groups are shown in Table 3. In the CPP-treated group, there were only five patients in the high insult group. All five of these patients died, whereas the mortality rate in the remaining CPP-treated patients was only 15% (p < 0.001). In contrast, the 24 ICP-treated patients in the high insult group had significantly more favorable outcomes (GOS Score 4 or 5) compared with those in the low insult group (71 compared with 42% favorable outcome, respectively; p = 0.02), as well as fewer deaths (8 compared with 14%), although this latter result was not statistically significant (p = 0.50).

The association between low CPP and favorable outcome in the ICP-treated patients was also noted in those who had a CPP less than 60 mm Hg for the longest periods of time. The eight patients who suffered the longest durations of CPP insult all had favorable outcomes (GOS Score 4 or 5).
In these eight patients, monitoring time with a CPP less than 60 mm Hg ranged from 28 to 68%.

Histograms of CPP readings in the high insult patient groups—in both Edinburgh and Uppsala—are shown in Fig. 3. In the patients in Edinburgh, CPP readings were dominated by very severe insults (CPP/ICP/H11021 40 mm Hg); however, this did not hold true for patients in Uppsala. Four of the five patients from Edinburgh with a CPP insult more than 10% of the time also had very severe refractory ICP (Table 4). The fifth patient in this group had very severe associated injuries as indicated by an injury severity score of 58. The Uppsala patients with CPP insult more than 10% of the time also had more ICP insult than the remaining Uppsala patients, but this difference was less pronounced than that in the Edinburgh patients (Fig. 4).

Pressure Reactivity

The pressure reactivity data for this study, derived as described in Clinical Material and Methods, is displayed in Fig. 5. At both centers, higher MABP values were generally associated with increased ICP. By calculating the individual slope of the MABP/ICP regression line for each patient, we found that the mean individual slope was 0.096 ± 0.196 in Uppsala and 0.067 ± 0.213 in Edinburgh. The slope was negative for 22% of the ICP-treated patients and 23% of the CPP-treated patients, indicating a pressure-active response, with ICP tending to decrease with increased MABP levels.

Pressure Reactivity and Severity of Injury. Pressure reactivity quantified as the slope of the MABP/ICP regression line did not correlate with GCS motor score in patients on admission in either Uppsala (r = 0.03, p = 0.84) or Edinburgh (r = 0.02, p = 0.86).

Pressure Reactivity and Outcome. In CPP-oriented (Edinburgh) patients, pressure reactivity was negatively correlated with the GOS score; that is, the pressure-active response tended to relate with good outcome and the pressure-passive response with poor outcome (r = -0.36, p < 0.01). In ICP-oriented (Uppsala) patients, the reverse was true; pressure-passive patients tended to do better than pressure-active patients. Pressure reactivity was positively correlated with GOS score (r = 0.22), although this result was only a statistical tendency (p = 0.066).

The probability of a favorable outcome (GOS Score 4 or 5) as a function of the MABP/ICP slope, estimated using a bayesian neural network, is plotted for the Edinburgh and Uppsala patients in Fig. 6. Superimposing the two curves (Fig. 7) shows that they cross over at a pressure reactivity slope of approximately 0.13. Patients whose pressure reactivity slope was less than that fared better when treated according to the CPP-oriented protocol; otherwise, the ICP-oriented approach resulted in a better outcome. Based on this criterion, 61 patients received the better treatment for their condition and 67 received the worse treatment (Table 4). Note that 64% of the better treatment group had favorable outcome compared with 45% of the worse treatment group (p = 0.03).

Discussion

Treatment Protocols

Controversy exists regarding the optimal CPP level. The Brain Trauma Foundation recommends a 70-mm Hg treat-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Low CPP Insult</th>
<th>High CPP Insult</th>
<th>Low CPP Insult</th>
<th>High CPP Insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Uppsala</td>
<td>Edinburgh</td>
<td>Uppsala</td>
<td>Edinburgh</td>
</tr>
<tr>
<td>no. of patients</td>
<td>43</td>
<td>24</td>
<td>59</td>
<td>5</td>
</tr>
<tr>
<td>age (yrs)†</td>
<td>44 ± 17</td>
<td>34 ± 18</td>
<td>38 ± 17</td>
<td>51 ± 17</td>
</tr>
<tr>
<td>GCS motor score†</td>
<td>4.3 ± 1.2</td>
<td>4.8 ± 0.9</td>
<td>3.5 ± 1.6</td>
<td>3.2 ± 1.8</td>
</tr>
<tr>
<td>patients w/ GOS score (%)‡</td>
<td>6 (14 ± 11)</td>
<td>2 (8)</td>
<td>9 (15 ± 9)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>2–3</td>
<td>19 (44 ± 15)</td>
<td>5 (21 ± 17)</td>
<td>16 (27 ± 11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4–5</td>
<td>18 (42 ± 15)</td>
<td>17 (71 ± 19)</td>
<td>34 (58 ± 13)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Low CPP insult = CPP < 60 mm Hg less than 10% of monitoring time; high CPP insult = CPP < 60 mm Hg more than or equal to 10% of monitoring time.
† Values are presented as the means ± SD.
‡ Percentage indicates subgroup with 95% CI.
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TABLE 4
Admission and insult data in five Edinburgh patients in the high CPP insult group

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>GCS Motor Score</th>
<th>No. Fixed Pupils</th>
<th>Injury Severity Score</th>
<th>% Monitoring Time</th>
<th>GOS Score 6 Mos Post-injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27, M</td>
<td>2</td>
<td>0</td>
<td>58</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>55, M</td>
<td>5</td>
<td>0</td>
<td>9</td>
<td>27</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>72, M</td>
<td>5</td>
<td>0</td>
<td>25</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>40, M</td>
<td>3</td>
<td>2</td>
<td>16</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>59, M</td>
<td>1</td>
<td>2</td>
<td>33</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Hg were not only well tolerated but were significant predictors of a favorable outcome. This was true even for sustained insults lasting in the range of 28 to 68% of monitoring time. It seems difficult to interpret this unexpected result as anything other than a strong indication that even a CPP treatment threshold of 60 mm Hg may be too high for many patients.

This result is surprising in light of concerns about ischemia and inadequate cerebral oxygenation following brain trauma. Analysis of study data relating CPP to direct measurements of brain tissue PO2 has shown that there is a relationship. No improvement in brain tissue PO2 has been demonstrated in pushing CPP beyond 60 mm Hg, however, and there is virtually no improvement beyond 50 mm Hg.10,21 These results still do not explain why in the ICP-treated patients, those with the most severe CPP insult had a better outcome than the remainder of the patients. In a prospective study from Edinburgh, researchers found that artificially increasing CPP in patients with impaired autoregulation results in vascular engorgement and hyperemic cerebral metabolism, thus increasing the risk for high ICP and brain edema.12 These data may explain the association of low CPP with favorable outcome in the Uppsala patients.

Pressure Reactivity Methodology

Our approach to evaluating the relationship between MABP and ICP is in line with that used in several other studies that have been focused on this relationship as an indication of the state of cerebral autoregulation.5,11,18 Furthermore, the methodology used in this study to quantify a patient’s pressure-reactivity state is similar to the pressure-reactivity index proposed by Czosnyka and colleagues.5 The pressure-reactivity index is the moving correlation be-

![Image](352x158 to 568x255)

Fig. 4. Bar graphs indicating the nature of the ICP insults in two Uppsala patient groups: those with CPP insult less than 10% of the time (left) and those with CPP insult more than or equal to 10% of the time (right). The patients with more CPP insult had a significantly better outcome than those with less insult, despite the fact that they had also experienced more ICP insult.
between MABP and ICP. Both MABP and ICP are evaluated every 5 seconds, and their correlation is computed based on the last 40 samples. This index has been evaluated in patients treated according to a CPP-oriented strategy similar to the one used in Edinburgh, and it was found to be negatively correlated with GOS.5,20 In other words, consistent with the results from Edinburgh, pressure-active patients generally had a better outcome than pressure-passive patients. Because the pressure-reactivity index is generally computed based on 5-second averages collected during a time window of 200 seconds and our index was based on 1-hour averages collected during a variable time window of at least several hours, it is not clear that the same physiological property is being measured in both cases. This question should be the subject of future investigation.

The measure of pressure reactivity in this study cannot be used directly to guide the choice of treatment in the critical early stages because it is based on data collected over a period of up to a few days. Currently, we are designing a study to identify methods that can be used to gauge quickly a patient’s pressure reactivity in a way that corresponds well to long-term measures. Pressure-reactivity index is one of the alternative methodologies that we will consider.

Pressure Reactivity and Outcome

In CPP-treated (Edinburgh) patients, the pressure-active response was associated with a good outcome. This result is related to the fact that in these patients, pressure reactivity was also highly correlated with the amount of the ICP insult suffered \((r = 0.39, p = 0.002)\). With the CPP-oriented treatment protocol, the greater the tendency for increased ICP as a response to increased MABP, the more prolonged the ICP insult and the worse the outcome. In ICP-treated (Uppsala) patients, pressure reactivity was not correlated with ICP insult but was correlated with CPP insult \((r = 0.32, p = 0.008)\). With this treatment protocol, pressure-passive patients tended to have lower CPP and better outcome compared with pressure-active patients.

The relationship of pressure reactivity to outcome in the two treatment groups is summarized in Fig. 7. It is convenient to divide the patients in this study into two groups based on the critical threshold of a slope of 0.13 for the MABP/ICP regression line. If the slope was less than 0.13, we considered the patient to be pressure active or pressure stable; if it was greater, the patient was categorized as pressure passive (Table 5). In pressure-passive patients the ICP-oriented therapy resulted in a better outcome, whereas in pressure-active and pressure-stable patients the CPP-oriented therapy was more beneficial. Based on this data, 67 (52%) of 128 patients in this study received the wrong treatment for their condition. We estimate that the correct treatment in these patients would on average have increased the probability of a favorable outcome from 45 to 64%. Overall, choosing the correct therapy would increase favorable outcome from 52 (Uppsala) or 53% (Edinburgh) to 64%.

Conclusions

Our results support the view that artificially increasing CPP in many cases has the effect of reducing ICP and that this increase has a positive effect on patient outcome. On the other hand, the results also show that relatively low CPP—between 50 and 60 mm Hg—is not harmful in many cases and in fact is associated with a favorable outcome. The variability of pressure reactivity provides a means of identifying the appropriate treatment strategy for a given patient. Pressure reactivity can be quantified as the slope...
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of the regression line relating MABP to ICP. Patients who are pressure active or pressure stable, with a slope less than 0.13, respond best to hypertensive CPP-oriented therapy. Pressure-passive patients, whose regression lines have slopes greater than 0.13, have a better outcome with hypotensive ICP-oriented therapy. Analysis of our data indicates that this combined approach will result in significantly better overall patient outcome than either protocol separately.

Acknowledgments

We thank our many colleagues in Edinburgh and Uppsala who participated in designing and building these databases. Most especially we acknowledge the contributions of the late Prof. J. Douglas Miller.

References


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**TABLE 5**

<table>
<thead>
<tr>
<th>Pressure Reactivity</th>
<th>Uppsala</th>
<th>Edinburgh</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>active/stable</td>
<td>41 (61 ± 12)</td>
<td>35 (57 ± 13)</td>
<td>76 (59 ± 9)</td>
</tr>
<tr>
<td>passive</td>
<td>26 (39 ± 12)</td>
<td>26 (43 ± 13)</td>
<td>52 (41 ± 9)</td>
</tr>
<tr>
<td>total patients</td>
<td>67</td>
<td>61</td>
<td>128</td>
</tr>
</tbody>
</table>

* Patients were defined as pressure passive if the slope of the regression line relating ICP to MABP was greater than or equal to 0.13, and pressure stable or pressure active otherwise. The pressure-active and pressure-stable patients did better with CPP-oriented therapy.