Intracranial hypertension has been closely linked to adverse outcomes after traumatic brain injury (TBI); nevertheless there have been no large randomized trials that directly compare intracranial pressure (ICP) treatment thresholds. Data from observational studies and noncontrolled series have suggested thresholds ranging from 15 to 25 mm Hg. The Brain Trauma Foundation’s (BTF’s) latest guideline has identified a lack of Level I evidence and offered, as a Level II, the treatment threshold of 20 mm Hg, mainly based on the largest available prospective observational study, which was published by Marmarou et al. It is also recognized in the BTF guideline that rather than accepting a generic, patient-specific thresholds of intracranial pressure in severe traumatic brain injury

Clinical article

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Object. Based on continuous monitoring of the pressure reactivity index (PRx), the authors defined individualized intracranial pressure (ICP) thresholds by graphing the relationship between ICP and PRx. These investigators hypothesized that an “ICP dose” based on individually assessed ICP thresholds would correlate more closely with the 6-month outcome when compared with ICP doses derived by the recommended universal thresholds of 20 and 25 mm Hg.

Methods. This study was a retrospective analysis of prospectively collected data from 327 patients with severe traumatic brain injury.

Results. Individualized thresholds were visually identified from graphs of PRx versus ICP; PRx > 0.2 was the cutoff. Intracranial pressure doses were then computed as the cumulative area under the curve above the defined thresholds in graphing ICP versus time. The term “Dose 20” (D20) was used to refer to an ICP threshold of 20 mm Hg; the markers D25 and DPRx were calculated similarly. Separate logistic regression models were fit with death as the outcome and each dose as the predictor, both alone and adjusted for covariates. The discriminative ability of each dose for mortality was assessed by receiver operating characteristic AUC analysis in which 5-fold cross-validation was used. A clearly identifiable PRx-based threshold was possible in 224 patients (68%). The DPRx (AUC 0.81, 95% CI 0.74–0.87) was found to have the highest area under the curve (AUC) over both D20 (0.75, 95% CI 0.68–0.81) and D25 (0.77, 95% CI 0.70–0.83); the cross-validation model, DPRx remained the best discriminator of mortality (DPRx: AUC 0.77 [95% CI 0.68–0.89]; D20: 0.72 [95% CI 0.66–0.81]; and D25: 0.65 [95% CI 0.56–0.73]).

Conclusions. The authors explored the importance of different ICP thresholds for outcome by calculating patient-specific ICP doses based on the continuous monitoring of cerebrovascular pressure reactivity. They found that these individualized doses of intracranial hypertension were stronger predictors of death than doses derived from the universal thresholds of 20 and 25 mm Hg. The PRx could offer a method that can be directed toward individualizing the ICP threshold.

(key words • intracranial pressure • cerebrovascular pressure reactivity • neuromonitoring • clinical outcome • traumatic brain injury)

Abbreviations used in this paper: ABP = arterial blood pressure; AUC = area under the curve; BTF = Brain Trauma Foundation; CPP = cerebral perfusion pressure; DECRA = decompressive craniectomy; D20, D25, DPRx = ICP doses based on thresholds of 20 mm Hg, 25 mm Hg, and PRx > 0.2; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; MAP = mean arterial pressure; PRx = pressure reactivity index; ROC = receiver operating characteristic; TBI = traumatic brain injury.
absolute ICP threshold, an attempt should be made to individualize thresholds based on patient characteristics, other critical parameters, and on a risk-benefit consideration of treating ICP values.

Cerebrovascular pressure reactivity is defined as the ability of vascular smooth muscle to respond to changes in transmural pressure, and represents one of the key mechanisms responsible for autoregulation of cerebral blood flow.\textsuperscript{23} Pressure reactivity can be determined by observing the response of ICP to changes in mean arterial pressure (MAP); if intact, a rise in MAP will lead within 5–15 seconds to vasoconstriction with reduction of cerebral blood volume, and ICP will decrease; if defective, cerebral blood volume will increase passively and ICP will rise. The opposite applies to a reduction in MAP.\textsuperscript{24} A computer-aided method has been developed at Cambridge to calculate and monitor the moving coherence/correlation index between spontaneous slow waves (20–200 seconds) of MAP and ICP.\textsuperscript{9,27}

This method derives a pressure reactivity index (PRx) that has values in the range between -1 and +1. A negative or zero value reflects a normally reactive vascular bed, whereas positive values reflect passive, nonreactive vessels. Previous studies have established a significant correlation between PRx and outcome after head injury, including a time-dependent element: if PRx persisted above 0.2 for more than 6 hours, this was usually associated with a fatal outcome.\textsuperscript{9,10,29} We defined patient-specific, pressure reactivity–guided ICP thresholds by graphing the relationship between ICP and PRx over the total monitoring time. We hypothesized that an “ICP dose” based on a disturbed pressure-reactivity ICP threshold would correlate more closely with clinical outcome when compared with an ICP dose calculated using the generic, recommended thresholds of 20 and 25 mm Hg. Our aim was to explore the predictive ability of individualized ICP thresholds based on PRx, compared with ICP insults derived from universal thresholds of 20 and 25 mm Hg.

Methods

Patient Population

Monitoring of arterial blood pressure (ABP) and ICP in patients following TBI has been an integral part of routine clinical management. The computerized data storage protocol was reviewed and approved by the local ethics committee of Addenbrooke’s Hospital, Cambridge University, and the neurocritical care unit user’s group. All data were prospectively collected and stored. With individual consent from patient representatives, we retrospectively analyzed anonymized digital recordings of ABP and ICP waveforms obtained in 327 consecutive patients with severe TBI who were admitted to the neurocritical care unit at Addenbrooke’s Hospital between 2003 and 2009.

All patients were sedated, intubated, and received mechanical ventilation during the recording period. A cerebral perfusion pressure (CPP)- and ICP-oriented protocol for management of head injury was used, with CPP maintained at > 60 mm Hg and ICP < 20–25 mm Hg.\textsuperscript{21} Baseline neurological status of each patient was determined using the Glasgow Coma Scale (GCS) score. The postresuscitation GCS score was used in patients in whom sedation was discontinued immediately following hospital admission. In patients who were deemed too unstable to undergo formal neurological assessment on admission, the GCS score collected on scene was used. The clinical outcome was assessed at 6 months by using the Glasgow Outcome Scale (GOS).\textsuperscript{16} All monitoring modalities recorded in the study were part of standard clinical care.

Data Acquisition and Processing

The ABP was monitored invasively through the radial or femoral artery with the aid of a standard pressure monitoring kit (Baxter Healthcare, CardioVascular Group) and was zeroed at the level of the right atrium. The ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff) inserted into the frontal cortex. All signals were digitized using an analog-to-digital converter (DT9801, Data Translation), sampled at a frequency of 100 Hz, and recorded using a laptop computer with ICM+ software (University of Cambridge, Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus). The same software was later used for the retrospective analysis of all stored signals. Time-averaged values of ICP, ABP, and CPP (CPP = ABP – ICP) were calculated using waveform time integration over 60-second intervals. The PRx was calculated as a short-term moving Pearson correlation coefficient between changes in 30 consecutive 10-second averages of ABP and corresponding ICP signals (with 80% overlap of data). Averaging over 10 seconds was used to suppress the influence of pulse and respiratory waves.

The ICP Thresholds: Definitions and “Dose” Calculations

Based on the continuous measurement and monitoring of PRx, we defined patient-specific, individualized ICP thresholds. These thresholds were visually identified from graphs of PRx versus ICP over the total monitoring time for each patient individually. The cutoff used was PRx > 0.2; this was chosen based on previous work from the group demonstrating that at that level there is significant disturbance of pressure reactivity and an increased mortality rate.\textsuperscript{9,25} The value for the ICP threshold was only accepted if the graph showed a distinct change of PRx values from < 0.2 to consistently > 0.2 (Fig. 1 shows 2 examples of individualized ICP threshold determination). To quantify the physiological insult from intracranial hypertension we used a method that accounts for the cumulative extent and duration of these episodes. The method computes a “dose” of secondary brain injury as the cumulative area under the curve above a defined threshold. The trapezoidal method was used to calculate doses from graphs of ICP versus time; the ICP “dose” is measured in mm Hg\textsuperscript{2}times hour.\textsuperscript{32} For an ICP threshold of 20 mm Hg we named the dose D20. Using the same methodology we calculated D25 and DPRx. For identification of ICP thresholds and calculation of doses the investigators were blinded to clinical outcome.

Statistical Analysis

The data are presented as mean or median values.
Pressure reactivity-based individualized ICP thresholds

Descriptive Statistics

The database population included 327 patients (246 males, 75%), ranging in age from 15 to 87 years (median age 36 years). The median baseline GCS score was 6 and ranged from 3 to 15; 25% of patients had a baseline GCS score > 8, but their condition subsequently deteriorated, requiring critical care and warranting invasive monitoring. The GOS score was missing in 5 patients (1.5%). Outcomes were grouped as follows: good recovery in 51 (16%); moderate disability in 82 (25%); severe disability in 105 (32%); persistent vegetative state in 9 (3%); and death in 75 (23%). Patients in persistent vegetative state were excluded from further outcome analysis because

Results

Fig. 1. Examples of individualized ICP threshold determination based on PRx > 0.2 for 2 patients. A: A distinct change is shown from PRx < 0.2 to PRx > 0.2 at an ICP of 12 mm Hg. B: Tracings from a different patient in whom the ICP threshold is 56 mm Hg (PRx changes from < 0.2 to > 0.2 at a range of 54–58 mm Hg). Both patients subsequently developed refractory intracranial hypertension.

with their standard deviation or range, where appropriate. The nonparametric Wilcoxon rank-sum test was used to compare each measure by GOS status. Nonparametric Spearman correlations and associated p values were used to correlate ICP and PRx. For outcome analysis, 1 mean value of the variables PRx, CPP, and ICP was calculated for each patient. The predictive ability of each marker on death was assessed. Logistic regression was performed for each binary outcome and for each marker in the study. For each analysis, receiver operating characteristic (ROC) curves were calculated and the area under the curve (AUC) was used as a measure of discriminative ability. Because observed AUCs are “over fit” to the data, to determine how well the ICP doses would perform in terms of prediction, 5-fold cross-validation of each covariate-adjusted model was performed. For this procedure, the logistic regression model was iteratively fit to four-fifths of the data, and a predicted AUC was calculated on the remaining one-fifth of the data; the 5 AUCs were then averaged. Cross-validated results are presented as cross-validated AUC and the 5th and 95th percentiles, and provide an estimate of how well the different ICP doses would predict death in a new data set. Statistical analyses were performed using SAS version 9.3 and R 2.14.2 software.
this group is disproportionally smaller than other outcome groups, leaving 313 patients for outcome analysis. Duration of data recording ranged between 1 and 28 days per patient, with a mean of 4 days. Descriptive statistics and p values for GCS score, age, MAP, ICP, CPP, and PRx according to GOS group are reported in Table 1. Age, GCS score, ICP, CPP, and PRx were significantly different based on GOS status (p < 0.05).

The ICP Thresholds and ROC Analysis

Patient-specific ICP thresholds were visually identified from graphs of PRx versus mean ICP. A clearly identifiable threshold based on the set criteria was possible in 224 patients (68%). The mean, median, interquartile range, and SD values for the ICP threshold based on PRx were 25, 24, 20–32, and 10, respectively. Figure 2 depicts the ICP threshold distribution for PRx > 0.2 for the whole cohort. Separate logistic regression models with death as the outcome and dose as the predictor (both alone and adjusted for the covariates GCS score, age, and sex) were fit. To assess the discriminative ability of each dose for mortality, an ROC analysis was performed and the AUC was reported (Table 2).

In the covariate-adjusted logistic regression model, all the doses calculated were significantly associated with death (p < 0.0001 for D20, D25, and DPRx). Furthermore, DPRx (0.81, 95% CI 0.74–0.87) was found to have the highest AUC over both D20 (0.75, 95% CI 0.68–0.81) and D25 (0.77, 95% CI 0.70–0.83), indicating that it has the best discriminative ability. Cross-validation confirmed the results of the observed AUCs; the cross-validated model, DPRx was still the best predictor of death (DPRx AUC 0.77 [95% CI 0.68–0.89], D20 0.72 [95% CI 0.66–0.81], and D25 0.65 [95% CI 0.56–0.73]). Figure 3 depicts the resulting observed ROC curves for DPRx versus D20, both unadjusted and adjusted for covariates. The larger area under the ROC curve indicates that inclusion of these covariates improves the discriminative ability of the marker.

Discussion

Raised ICP is detrimental across different neurological conditions. Different management thresholds apply depending on the clinical scenario. Patients with chronic hydrocephalus withstand, without adverse effects, an ICP rise up to 40 mm Hg during infusion studies.18 In pseudotumor cerebri, patients often have chronically elevated ICP > 30 mm Hg without immediate neurological compromise.4 In contrast, patients with severe TBI are thought to have an increased mortality rate after an ICP threshold that lies between 20 and 25 mm Hg. This can be attributed to an acute, unaccounted for impairment of free CSF communication; a mechanism serving to equilibrate any detrimental pressure gradients within the craniospinal space (Pascal’s law).

We explored the predictive ability of individualized ICP thresholds based on the PRx, as compared with “standard” fixed ICP thresholds. We found that the ICP doses derived from an index describing the status of cerebrovascular pressure reactivity were stronger predictors of the 6-month mortality rate compared with doses calculated based on the “suggested” ICP threshold of 20 mm Hg and also from a second fixed threshold of 25 mm Hg. The most recent version of the BTF guidelines has recognized the lack of Level I evidence as it pertains to ICP thresholds.5 The guidelines concluded with proposals, as key issues for future investigation, to explore methods for identifying critical ICP or “herniation pressure,” and for identifying physiological parameters that would complement measurements of absolute ICP, in an effort to better

### TABLE 1: Patient demographics, clinical variables, and outcome in 322 patients with severe TBI*

<table>
<thead>
<tr>
<th>GOS Group</th>
<th>No. of Pts</th>
<th>Age (yrs)†</th>
<th>M/F</th>
<th>GCS Score†</th>
<th>MAP</th>
<th>ICP</th>
<th>CPP</th>
<th>PRx†</th>
</tr>
</thead>
<tbody>
<tr>
<td>death</td>
<td>75</td>
<td>45 ± 18</td>
<td>60:15</td>
<td>6 ± 3</td>
<td>95 ± 9</td>
<td>22 ± 11</td>
<td>73 ± 12</td>
<td>0.09 ± 0.2</td>
</tr>
<tr>
<td>PVS</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>severe disability</td>
<td>105</td>
<td>38 ± 15</td>
<td>78:27</td>
<td>6 ± 3</td>
<td>94 ± 6</td>
<td>16 ± 4</td>
<td>78 ± 6</td>
<td>0.02 ± 0.16</td>
</tr>
<tr>
<td>moderate disability</td>
<td>82</td>
<td>32 ± 14</td>
<td>67:15</td>
<td>8 ± 4</td>
<td>93 ± 7</td>
<td>16 ± 5</td>
<td>78 ± 7</td>
<td>0.01 ± 0.14</td>
</tr>
<tr>
<td>good recovery</td>
<td>51</td>
<td>34 ± 17</td>
<td>32:19</td>
<td>7 ± 3</td>
<td>94 ± 6</td>
<td>15 ± 4</td>
<td>78 ± 7</td>
<td>−0.01 ± 0.13</td>
</tr>
<tr>
<td>total</td>
<td>322</td>
<td>34 ± 17</td>
<td>237:85</td>
<td>7.5 ± 7</td>
<td>17.5 ± 7</td>
<td>0.03 ± 0.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD. The MAP, ICP, CPP, and PRx values were averaged in each patient over the whole monitoring period. Pts = patients; PVS = persistent vegetative state; — = excluded from further analysis.
† Significant difference (p < 0.05, ANOVA) between GOS groups.
quantify the impact of intracranial hypertension on secondary brain injury and neurological outcome. We found highly significant correlations of increased mean ICP and ICP dose with mortality rates. Intracranial hypertension is commonly encountered in patients with severe TBI and, although not universally, is widely accepted to correlate strongly with neurological outcome. Nevertheless, recent publications have challenged the traditional understanding on monitoring and treatment of high ICP. Shafi et al. analyzed the National Trauma Data Bank for the period 1994–2001, comparing patients who underwent ICP monitoring with those who were not monitored. After adjustment for multiple confounding factors, including admission GCS score, age, blood pressure, and injury severity score, ICP monitoring was associated with a 45% lower rate of survival. The authors interpreted this result as a failure of BTF criteria to identify the patients who were most likely to benefit from ICP monitoring. Further possible explanations include the idea that intracranial hypertension is a surrogate for severity of brain injury, and that treatment interventions are either ineffective or even potentially harmful.

In discussing interventions, the recent decompressive craniectomy (DECRA) trial showed that this intervention, despite effectively reducing ICP, did not translate into improved neurological outcomes. It is of relevance that the issue of an appropriate ICP threshold was highlighted as one of the critiques and main differentiating features of the DECRA trial from the ongoing RESCUEicp (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP) study. Our findings become further pertinent in view of the recent publication of the randomized controlled trial of ICP monitoring in severe TBI by Chesnut et al. This was the first such trial to compare management of intracranial hypertension based on monitoring and treatment of ICP above the fixed threshold of 20 mm Hg, versus a protocol based on clinical examination and neuroimaging. This trial found no benefit of one protocol over the other. It is beyond our scope to discuss this study in detail; nevertheless and in conjunction with the aforementioned DECRA trial, we believe that an important aspect in interpreting the results should be the limitation of using fixed, universal ICP thresholds and thus disregarding patient-specific injury patterns, individual pathophysiology, and response to treatment interventions.

We chose to quantify secondary brain injury caused by intracranial hypertension by using a method that accounts for the cumulative extent and duration of these episodes. This method computes a “dose” of intracranial hypertension as the cumulative area under the curve above a defined threshold. This approach may more accurately reflect the impact of secondary brain insults on outcome than did previous methods (for example, traditionally taking into account only the mean ICP or the time spent above a given threshold), because it accounts for both the degree and the duration of ICP elevation. An additional advantage, as pointed out by Vik et al., is that the predictive power of doses for different thresholds can be explored.

In this study we explored different thresholds by calculating doses based on pressure reactivity and comparing them against doses derived from the conventionally accepted threshold of 20 mm Hg, and from a second fixed threshold of 25 mm Hg, because this is the recommended range in the BTF guidelines. To our knowledge this is the first report attempting the determination of individualized patient-specific ICP thresholds in patients with severe TBI, using these thresholds to quantify ICP dose per patient, and comparing these doses to the ones derived from the currently accepted generic thresholds of 20–25 mm Hg. Although not undertaken in the present work, similar methodology could be applied in the evaluation of different CPP thresholds; furthermore, the relative contribution to secondary brain injury of ICP versus CPP insults could be explored. Cerebrovascular pressure reactivity is an intrinsic underlying mechanism of cerebral blood flow regulation. The status of pressure reactivity has been shown to be important in bridging CPP with ICP-targeted approaches. In the current analysis, as in prior data from our group, the PRx is strongly correlated with death (Table 1).

Steiner et al. and more recently Aries et al. have

### Table 2: Logistic regression for ICP doses and ROC analysis of predictive power for mortality in patients with severe TBI

<table>
<thead>
<tr>
<th>ICP Dose</th>
<th>Univariate p Value</th>
<th>Univariate AUC</th>
<th>95% CI</th>
<th>Covariate-Adjusted p Value*</th>
<th>Covariate-Adjusted AUC</th>
<th>95% CI</th>
<th>Cross-Validated AUC*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D20</td>
<td>&lt;0.0011</td>
<td>0.63</td>
<td>0.55–0.70</td>
<td>&lt;0.0001</td>
<td>0.75</td>
<td>0.68–0.81</td>
<td>0.72</td>
<td>0.66–0.81</td>
</tr>
<tr>
<td>D25</td>
<td>0.0001</td>
<td>0.65</td>
<td>0.57–0.73</td>
<td>&lt;0.0001</td>
<td>0.77</td>
<td>0.70–0.83</td>
<td>0.65</td>
<td>0.56–0.73</td>
</tr>
<tr>
<td>DPRx</td>
<td>&lt;0.0001</td>
<td>0.72</td>
<td>0.63–0.80</td>
<td>&lt;0.0001</td>
<td>0.81</td>
<td>0.74–0.87</td>
<td>0.77</td>
<td>0.68–0.89</td>
</tr>
</tbody>
</table>

* Adjusted for baseline GCS score, age, and sex.

**Fig. 3.** The ROC curves for DPRx versus D20, both unadjusted and adjusted for covariates. The larger area under the ROC curve indicates superiority of DPRx over D20; also, inclusion of covariates improves the discriminative ability of the markers.
demonstrated the value of using the PRx in identifying an optimal CPP, under and above which outcome worsens. In fact, this work has been recognized and incorporated in the BTF guidelines as a method of optimizing cerebral perfusion.\(^6\,\text{19}\) In addition, we have observed that continuous bedside monitoring of PRx in certain circumstances can serve as a physiological alarm before the occurrence of refractory intracranial hypertension (Fig. 4, recording from a patient in our database). Finally, we report here that an ICP dose as calculated by a patient-specific ICP threshold corresponding to PRx > 0.2 was the best discriminator of mortality in our cohort and as compared with doses derived from “fixed” thresholds of 20 and 25 mm Hg.

**Limitations of the Study**

Intracranial pressure thresholds were identified retrospectively from recordings of the whole period of ICP monitoring. The findings, therefore, are not necessarily applicable to real-time data collected in the ICU. Threshold determination was done by visual inspection of ICP versus PRx graphs; the next step to improve this methodology would include an algorithm for objective and automated identification of a patient-specific threshold. To limit bias, both threshold identification and dose calculation were done by investigators who were blinded to clinical outcome.

We were able to identify a PRx-based ICP threshold in two-thirds of our patients; frequent reasons that prevented us from identifying a specific threshold are depicted in Fig. 5. Three patterns emerge: one of disturbed PRx throughout the ICP range; a second reverse pattern where PRx remains consistently preserved; and a third pattern where PRx varies randomly with ICP. In these situations, PRx cannot be used in assessing ICP thresholds with the current methodology. Possible explanations for these patterns relate to an insufficient number of data sets either because of inadequate recording time or, less likely, because of a high rate of artifacts (artifacts were minimized mainly because patients were under heavy sedation and neuromuscular blockade). It should be also kept in mind that the calculation of PRx requires the presence of spontaneous fluctuations in ABP. Although such fluctuations are present in the majority of patients following TBI, the magnitude may be insufficient to produce significant ICP changes. In such cases the value of PRx will be unreliable.

Apart from representing technical limitations, these patterns could be physiologically interpreted as states of dissociation between cerebrovascular pressure reactivity and mean ICP. One should also consider that the influence of treatment targets on the relationship between ICP thresholds and neurological outcomes is unknown. However, this bias is inevitable because this is a retrospective review of patients from 2003 to 2009, who were treated according to best available contemporary evidence, and institutional and international guidelines. Last, in this study we did not investigate markers of brain tissue oxygenation and metabolism that have been used in attempts to characterize the physiological burden of intracranial hypertension and to correlate these markers to neurological outcomes.\(^30\,\text{31}\) The interplay between cerebrovascular pressure reactivity, tissue oxygenation, tissue metabolism, and ICP is complex and not fully understood. It is plausible that information from multimodality monitoring will provide a more complete description of the physiological consequences of ICP insults at the tissue level. In addition, these multimodality data could potentially serve in tailoring treatment thresholds and interventions away

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**Fig. 4.** An episode of refractory intracranial hypertension is depicted. At time point A, PRx is noted to increase progressively; shortly thereafter ICP is noted to rise. Time point B is characterized by a precipitous ICP increase.
from fixed, generic ICP values, and toward dynamic and patient-specific cerebral physiology.

Conclusions

The predictive ability of individualized ICP thresholds based on the continuous monitoring of cerebrovascular pressure reactivity was stronger than fixed thresholds of 20 and 25 mm Hg, in a large single-center database of patients with severe TBI. Monitoring of the PRx could supplement ICP monitoring by offering patient-specific pathophysiological information.

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Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Lazaridis, Czosnyka. Analysis and interpretation of data: Lazaridis, DeSantis, Smielewski, Czosnyka. Drafting the article: Lazaridis, Czosnyka. Critically revising the article: Lazaridis, Smielewski, Menon, Hutchinson, Pickard, Czosnyka. Reviewed submitted version of manuscript: Smielewski, Menon, Hutchinson, Pickard, Czosnyka. Approved the final version of the manuscript on behalf of all authors: Lazaridis. Statistical analysis: DeSantis. Study supervision: Czosnyka.

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