Analysis of Normal High-Frequency Intracranial Pressure Values and Treatment Threshold in Neurocritical Care Patients
Insights into Normal Values and a Potential Treatment Threshold
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IMPORTANCE Intracranial pressure (ICP) elevation is a compartment syndrome that impairs blood flow to the brain. Despite the importance of ICP values in neurocritical care, normal ICP values and the precise ICP threshold at which treatment should be initiated remain uncertain.

OBJECTIVE To refine our understanding of normal ICP values and determine the ICP threshold most strongly associated with outcome.

DESIGN, SETTING, AND PARTICIPANTS Prospective observational study (2004-2010), with outcomes determined at hospital discharge. The study included neurocritical care patients from a single level I trauma center, San Francisco General Hospital. Three hundred eighty-three patients had a traumatic brain injury with or without craniectomy; 140 patients had another indication for ICP monitoring. Consecutive patients were studied. Data analyses were completed between March 2015 and December 2019.

EXPOSURES Five hundred twenty-three ICP-monitored patients.

MAIN OUTCOMES AND MEASURES A computer system prospectively and automatically collected 1-minute physiologic data from patients in the intensive care unit during a 6-year period. Mean ICP was calculated, as was the proportion of ICP values greater than thresholds from 1 to 80 mm Hg in 1-mm Hg increments. The association between these measures and outcome was explored for various epochs up to 30 days from the time of injury. A principal component analysis was used to explore physiologic changes at various ICP thresholds, and elastic net regression was used to identify ICP thresholds most strongly associated with Glasgow Outcome Scale score at discharge.

RESULTS Of the 523 studied patients, 70.7% of studied patients were men (n = 370) and 72.1% had a traumatic brain injury (n = 377). A total of 4 090 964 1-minute ICP measurements were recorded for the included patients (7.78 years of recordings). Intracranial pressure values of 8 to 9 mm Hg were most commonly recorded and could possibly reflect normal values. The principal component analysis suggested state shifts in the physiome occurred at ICPs greater than 19 mm Hg and 24 mm Hg. Elastic net regression identified an ICP threshold of 19 mm Hg as most robustly associated with outcome when considering all neurocritical care patients, patients with TBI, and patients with TBI who underwent craniectomy. Intracranial pressure values greater than 19 mm Hg were associated with mortality, while lower values were associated with outcome in surviving patients.

CONCLUSIONS AND RELEVANCE This study provides insight into what normal ICP values could be. An ICP threshold of 19 mm Hg was robustly associated with outcome in studied patients, although lower ICP values were associated with outcome in surviving patients.

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Although outcome following traumatic brain injury (TBI) has been correlated with the magnitude and duration of intracranial pressure (ICP) elevation, the threshold at which ICP begins to exhibit detrimental effects is not known with certainty. Likewise, it remains unclear what the ideal treatment threshold for ICP is and whether a common threshold should be used for all patients and pathologies. Since their inception, the Guidelines for the Management of Severe Traumatic Brain Injury have advocated for ICP monitoring, and a treatment threshold has been recommended. This threshold has changed from 25 mm Hg to 20 mm Hg to 19 mm Hg in the last 2 decades, and while the precision of this recommendation is believed to be improving, the optimal value at which treatment should be initiated is not yet known with certainty.

In this study, our group has endeavored to better define the association between ICP and outcome using a large database of high-frequency physiologic data. Scientific mathematics software allowed us to explore how mean ICP and time greater than highly resolved ICP thresholds are associated with outcome, similar to our 2018 work exploring the association between focal brain oxygen measurements and outcome in this same population of patients with TBI.

Methods

Patient Demographics and Management

This study was approved by the University of California at San Francisco Committee on Human Research. A waiver of informed consent was granted because the study was judged to constitute minimal risk, and collected physiologic data were deidentified. All patients included in our study were admitted to San Francisco General Hospital (SFGH). The Brain Trauma Foundation’s Guidelines for the Management of Severe TBI are central to the care of patients with TBI at SFGH, and they are rigorously followed. Patients were selected for ICP monitoring based on the recommendations in these guidelines. The duration of ICP monitoring was based solely on medical necessity as judged by the treating neurosurgeon. An ICP treatment threshold of 20 mm Hg was used for all studied patients. Importantly, external ventricular drains used for ICP measurements were kept clamped to accurately measure ICP. When ICP values exceeded 20 mm Hg for 5 minutes, the drain was opened at 10 cm above the ear for 10 minutes.

Although physiologic data were collected prospectively, demographic data were collected retrospectively. The patients’ level of neurological disability at the time of discharge from SFGH was scored based on the Glasgow Outcome Scale (GOS). To facilitate a pooled analysis of all patients, all were scored with this general scale irrespective of brain pathology.

Data Collection

In conjunction with Aristein Bioinformatics LLC, our group developed a system that continuously and automatically recorded physiologic data from every bedside monitor in the SFGH neurosurgical intensive care unit (ICU) between 2004 and 2010. The time of the first recorded observation in the collection system was thus denoted as time “1,” distinct from the time of injury.

Variables displayed on the bedside monitor were collected at 1-minute intervals for the entirety of the patients’ ICU stay. In rare instances where 2 ICP monitors were used, the average was analyzed. Data on heart rate, peripheral oxygen saturation, brain oxygenation, and mean arterial pressure were also collected and analyzed.

Data Analysis

Intracranial pressure values were analyzed with the assistance of MATLAB software (MathWorks). We calculated mean ICP values and counted the number of 1-minute epochs with ICP values greater than specific thresholds between periods specified by the investigator. We analyzed ICPs greater than 79 different thresholds from 1 to 80 mm Hg in 1-mm Hg increments. The proportion of values greater than thresholds were analyzed to account for different numbers of observations between patients. Microsoft Excel, SPSS (IBM), and GraphPad were used to graph data, and figures were tiled using either PowerPoint (Microsoft) or Photoshop CC (Adobe). Error bars represent standard error of the mean (SEM).

Statistical Analysis

SPSS software, version 25, was used for statistical analyses. Analysis of variance (ANOVA) was used as a first step in the analysis of mean values from normally distributed continuous data. Post hoc tests for group differences were determined by Tukey and Bonferroni tests to adjust for multiple comparisons. Binomial logistic regression was used to analyze dichotomous categorical data. To test outcome group differences across ICP proportions, a generalized estimating equation was used; a repeated-measure model with a γ distribution. For mean values of continuous data, the “n” was considered to be the total number of observations. Where proportions greater than the threshold were analyzed, a single proportion was calculated for each patient, and the “n” in those cases was the number of patients in each group. A 2-sided P value less than .05 was set as the threshold for significance.

Principal components analyses (PCA; eMethods in the Supplement) were used to assess the association between physiologic measures (heart rate, mean arterial blood pressure, peripheral oxygen saturation, brain oxygenation [P_{tcO_2}])
Table. Characteristics of Included Patients in Association With Neurological Outcome at Time of Discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>No outcome data</th>
<th>Death</th>
<th>Vegetative</th>
<th>Severe disability</th>
<th>Moderate disability</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.9 (22.8)</td>
<td>57.0 (19.1)</td>
<td>47.1 (22.3)</td>
<td>42.5 (17.5)</td>
<td>35.9 (16.7)</td>
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<tr>
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<tr>
<td>Male</td>
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<td>22</td>
<td>192</td>
<td>42</td>
<td>.57</td>
<td></td>
</tr>
<tr>
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<td>48</td>
<td>13</td>
<td>76</td>
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<tr>
<td>Cranietomy, No.</td>
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<tr>
<td>Yes</td>
<td>6</td>
<td>68</td>
<td>16</td>
<td>139</td>
<td>33</td>
<td>.32</td>
<td></td>
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<tr>
<td>No</td>
<td>7</td>
<td>83</td>
<td>19</td>
<td>131</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hospital stay, d</td>
<td>35.3 (30.8)</td>
<td>15.1 (26.7)</td>
<td>57.2 (50.8)</td>
<td>46.3 (44.6)</td>
<td>15.6 (17.0)</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Total measurements</td>
<td>5178.4 (1151.4)</td>
<td>7068.2 (506.2)</td>
<td>11434.0 (1246.9)</td>
<td>9143.1 (439.6)</td>
<td>4187.2 (557.8)</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Postresuscitation GCS</td>
<td>7.5 (3.5)</td>
<td>7.2 (4.1)</td>
<td>6.5 (4.3)</td>
<td>8.5 (3.9)</td>
<td>9.3 (4.2)</td>
<td>&lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: GCS, Glasgow Coma Scale score.

*Continuous data were analyzed by analysis of variance, with outcome group as the independent variable. Dichotomous data were analyzed with binomial logistic regression, with outcome group as the independent variable. P less than .05 was considered statistically significant.

and 15 binary ICP threshold categories. This physiome analysis was necessarily restricted to 229 patients who underwent both ICP and PbtO2 monitoring and was used to partition the variance in physiologic parameters across patients into orthogonal PCs. Principal component loading values reflect the unique association between each parameter and the variance explained within a particular PC. Thus, a higher loading for a particular measure indicates that measure contributes more to the variance explained by that PC.

Elastic net regression (with 10-fold cross-validation) was used to assess the relative contribution of each putative ICP threshold (between 15-30 mm Hg) in predicting GOS score at discharge. The threshold identified by this method was then included in an optimal scaling regression model along with other known factors associated without coming to determine the strength of the threshold in predicting outcome as compared with other key factors. The elastic net optimal scaling regression workflow was repeated and performed separately for all patients, only patients with TBI, and patients with TBI who underwent a craniectomy.

Results

Patient Characteristics

Our data collection system recorded physiologic data for a total of 523 patients who underwent ICP monitoring, 383 of whom had a TBI. Of patients without TBI, 74 (52.9%) had hemorrhagic stroke, 27 (19.3%) had nontraumatic subarachnoid hemorrhage, 8 (5.7%) were being treated for a brain tumor, 6 (4.3%) had acute ischemic stroke, 6 (4.3%) had anoxic brain injury, and 19 (13.6%) were classified as other. Outcome data (GOS) were available for all but 14 patients. A total of 4 090 964 one-minute ICP measurements were recorded for the included patients (7.78 years of recordings).

Patient demographics are presented in the Table and eTable in the Supplement. Patients with poorer outcomes tended to be older (mean [SD] age at death, 57.0 [19.1] years; vegetative, 47.1 [22.3] years; severe disability, 42.5 [17.5] years; and moderate disability, 35.9 [16.7] years; P < .001; ANOVA) with longer hospital stays (mean [SD] stays for death, 15.1 [26.7] days; vegetative, 57.2 [50.8] days; severe disability, 46.3 [44.6] days; and moderate disability, 15.6 [17.0] days; P < .001; ANOVA) and a greater number of physiological measurements (death, 5178.4 [1151.4]; vegetative, 11 434.0 [1246.9]; severe disability, 9143.1 [439.6]; and moderate disability, 4187.2 [557.8]; P < .001; ANOVA), except for patients who died. Similarly, patients with poorer outcomes tended to have lower postresuscitation Glasgow Coma Scale (GCS) scores (mean [SD] score for death, 7.2 [4.1]; vegetative, 6.5 [4.3]; severe disability, 8.5 [3.9]; and moderate disability, 9.3 [4.2]; P < .001; ANOVA), except for patients who died. Patients with TBI were more likely to be younger (mean [SD] age, 43.9 [20.3] years vs 53.3 [16.0] years; P = .04; ANOVA) and men (292 patients [76.2%] vs 78 patients [55.7%]; P < .001; binomial logistic regression) and also more likely to undergo craniectomy (175 patients [45.6%] vs 37 patients [27.4%]; P = .04; binomial logistic regression).

Among patients with TBI, Rotterdam scores are available for 345, and of these, 11 had a score of 1 (3.2%), 55 had a score of 2 (15.9%), 126 had a score of 4 (36.5%), 87 had a score of 4 (25.2%), 60 had a score of 5 (17.4%), and 6 had a score of 6 (1.7%). Traumatic subarachnoid hemorrhage was present in 239 of the patients with TBI (69.3%), and their mean postresuscitation GCS score was 8.1 (mode, 3). The mean amount of midline shift noted on cranial imaging of the patients with TBI was 9.64 mm. A total of 54.3% of patients with TBI required a craniotomy or craniectomy. Basal cistern status was assessed in 346 of these patients, and they had a normal appearance in 179 (51.7%). In 137 patients (39.6%), they were compressed, and they were absent in 30 (8.7%). In the heterogeneous patients who did not sustain a TBI, the mean age was 53.2 years, and 52 (37.4%) required a craniotomy or craniectomy.

Association Between Intracranial Pressure and Outcome

We thoroughly analyzed ICP values in different epochs from all patients and TBI-only patients (eFigure 1 in the Supplement). Salient data for days 3 to 5 and days 1 to 30 are shown in Figure 1. A discrete peak in ICP values (consistent with the mode) was consistently seen at approximately 8 to 9 mm Hg, a possible indi-
The distribution of intracranial pressure (ICP) measures is plotted for all patients (dark blue solid line) and for patients with traumatic brain injury (TBI) only (orange dotted line). A, Values obtained between 3 and 5 days following admission to the neurocritical care unit are reported while those in B represent all values obtained within 30 days of admission. The most common ICP (nearest integer) measured in all patients from day 3 to 5 was 8 mm Hg (6.19% of all measures), while in patients with TBI, it was 9 mm Hg (6.23%). The most common ICP (nearest integer) measured in all patients from day 1 to 30 was 8 (6.24% of measures), while in patients with TBI it was 9 (6.17%). Given the robust mode demonstrated by these distributions, it is possible that ICP values of 8 to 9 mm Hg may be normal. C, Mean ICP values are shown for noncumulative epochs from time of intensive care unit admission, demonstrating that all mean values are less than present and past recommended ICP treatment thresholds. Patients with TBI had higher mean values than those with other conditions. For all patients, n = 523; for patients with TBI only, n = 383.

* Denotes a statistically significant difference on analysis of variance ($P < .05$).

**Physiologic Changes as ICP Increases**

An initial linear PC analysis (PCA) was run to assess the association between numerous physiologic parameters along with each of the 15 binary ICP threshold categories (yes = 1; no = 0; eFigure 3 in the Supplement). Plotting PC loadings across ICP thresholds for 5 orthogonal principal components demonstrates 2 changes in the association between physiologic variables as ICP increases. These transitions are seen at ICP threshold of approximately 19 and 24 mm Hg (Figure 3); a plot of the PC loadings clearly shows these transitions.

To further assess the unique association between physiologic measures and ICP thresholds, a second set of analyses were then run that included heart rate, mean arterial pressure, peripheral oxygen saturation, and $P_aO_2$ as before, but with a single ICP threshold (between 15-30 mm Hg) included for each PCA iteration. At the bottom of Figure 3, mean loadings for PCAs that included ICP threshold ranges 15 to 19 mm Hg, 20 to 23 mm Hg, and 24 to 30 mm Hg are shown. Heat maps for PC loadings demonstrate the distinct interrelations of physiologic variables seen, when ICPs are 15-19 mm Hg, 20-23 mm Hg, and 24-30 mm Hg. Of course, 19 mm Hg and 24 mm Hg are very close to the historic ICP thresholds recommendations of 20 mm Hg and 25 mm Hg.

**Identifying an Optimal ICP Threshold for Outcome Prediction**

The PCA results identified 2 nodes along the spectrum of ICP threshold values at which multivariate physiologic shifts appear to occur. To further explore the association between ICP...
Figure 2. Association of Intracranial Pressure (ICP) Values With Outcome

A, Data from all studied patients. B, Data only from patients with traumatic brain injury (TBI). In A and B, mean ICP values are plotted for noncumulative epochs following intensive care unit (ICU) admission in patients grouped by their level of disability (Glasgow Outcome Scale score at the time of discharge). Higher mean ICP values were associated with worse outcome. C-F, Plots of the time patients spent with ICP values at greater than 79 different ICP thresholds (1 to 80 mm Hg in 1–mm Hg increments) are shown. In the insets, the region of each graph is replotted for the range of ICP values between 15 and 30 mm Hg to improve visualization. Intracranial pressure values greater than approximately 10 mm Hg are associated with outcome, especially during the period of maximal brain swelling between days 3 and 5 following admission. A significant effect of outcome group across thresholds was seen for all patients at days 3 to 5 and 1 to 30. Patients with TBI only (D and F) showed only a significant difference between death and other groups at days 3 to 5, and main effect of outcome group for days 1 to 30. Thus, higher values seem to discriminate mortality while lower values are associated with outcome in surviving patients.

* Denotes a statistically significant difference on analysis of variance (P < .05).
Figure 3. Principal Component Analysis (PCA) Suggests Physiome Pattern Changes at Intracranial Pressure Thresholds of 19 and 24 mm Hg

Principal component analysis was applied to the physiome (heart rate, peripheral oxygen saturation, intracranial pressure [ICP], focal brain oxygen measurements, and mean arterial blood pressure) based on a dichotomy of ICP values at 15 different ICP thresholds between 15 and 30 mm Hg. An initial PCA was run that revealed 5 unique PC patterns of loadings across thresholds. On the top, loading values for each of 5 identified principal components at each of the 15 ICP thresholds are plotted. This analysis suggests distinct physiologic associations between variables for ICP values less than 19 mm Hg, those between 19 and 24 mm Hg, and those greater than 24 mm Hg, with principal components 2, 3, and 1 dominant in each state, respectively. A second series of PCAs were then run that included each threshold (from 15-30 mm Hg) separately, along with other physiome measures. Mean loadings for 3 ranges of thresholds are shown on the bottom, depicting distinct patterns of associations between ICP threshold and other physiome measures. Blue represents negative loadings and red represents positive loadings. Principal component loadings indicate the extent to which a particular measure contributes to the variance explained within a PC, and the sign of loadings (positive or negative) indicates whether the measures correlate with the PC in the same or opposite directions.

Discussion

A study completed in 2015 has called the value of ICP monitoring into question, as well as the significance of ICP elevation. However, there is no question that ICP elevation is harmful when it impedes delivery of adequate nutrients to the brain. In the extreme circumstance, ICP elevation exceeds arterial pressure and prevents intracranial blood flow, as is seen with brain death. The precise thresholds of ICP and blood flow at which harm begins to occur to the brain are not known with certainty. Studies to date have tended to report ICP thresholds at which the strongest statistical association with outcome is seen; the lowest value at which harm occurs has not been well delineated to date. Our analysis provides new insights into the association between ICP and outcome following brain injury.

Possibly Normal ICP Values

Normal ICP is difficult to define, and numerous normal ranges have been suggested. Because monitoring ICP in healthy patients is unethical, normal ICP is not known with certainty nor with precision. Miller argued for an ICP of less than 10 mm Hg as being normal. Marshall et al instead defined a normal...
ICP elevation following TBI was not firmly established until monitoring in the ICU.

Nevertheless, these data raise the possibility that 8 to 9 mm Hg was consistently seen across distinct epochs and body position. In our study, a discrete mode of 8 to 9 mm Hg was consistently seen across distinct epochs whether all patients or just those with TBI were studied (Figure 1). It is not possible to infer normal ICP values from patients being treated for significant brain pathology. Nonetheless, these data raise the possibility that 8 to 9 mm Hg could reflect normal ICP values, at least in those undergoing monitoring in the ICU.

**Literature to Date Informing the Intracranial Pressure Treatment Threshold**

Although Lundberg first performed detailed study of ventricular fluid pressure recordings in the 1960s and associated ICP elevation with neurological decline, the importance of ICP elevation following TBI was not firmly established until 1977, when Miller et al. demonstrated its correlation with outcome and its role in precipitating death. Widespread clinical application of ICP monitoring followed in the 1980s and it is now viewed as important in the management of most patients with severe TBI treated in North America. Despite more than 3 decades of use and study, "the critical value of ICP... is still a major unanswered question." 

Over the course of the 4 editions of the BTF Guidelines for the Management of Severe TBI, the recommended ICP treatment threshold has changed from 25 mm Hg to 20 to 25 mm Hg to 20 mm Hg to 22 mm Hg. The current guidelines recognize a total of 12 studies that inform the ICP treatment threshold. Unfortunately, strong conclusions cannot be drawn from these studies; most tended to report the ICP value most strongly associated with outcome and do not consider a broad range of possible thresholds. Additionally, few used unbiased and automated computer collection of high-frequency patient measurements, as we have done, which overcomes problems with threshold compliance.

It is important to consider that numerous publications have suggested an ICP treatment threshold less than 20 mm Hg may be appropriate. Analysis of our data suggests that an ICP threshold of 19 mm Hg is most strongly associated with patient outcome and that this threshold is robust across patient subgroups. However, our data suggest that ICP values as low as 10 mm Hg may be associated with harm. Our findings are also consistent with evidence for a higher ICP threshold for mortality than for good outcome.

**Are Normal ICP Values and the ICP Treatment Threshold the Same for All Patients and Conditions?**

Several investigators have argued for distinct normal values or treatment thresholds with specific disease states or patient characteristics. For instance, in hydrocephalus, pressure elevations greater than 15 mm Hg are considered abnormal. Some have argued that a normal ICP value should be defined as less than 11 mm Hg in patients with pseudotumor cerebri, while others argue that the optimal treatment threshold in patients with TBI may vary with computed tomographic head findings, age, or sex. A key finding of our study is that the results of our analyses are consistent across all neurocritical care unit patients (Figure 3).

**Limitations**

Our study has a number of important limitations. The results of this study only pertain to patients in whom ICP monitoring...
was judged appropriate. Our study does not provide insight into causation. Our work describes patients from a single institution and does not capture physiologic events prior to the initiation of ICU monitoring nor the time from injury to initiation of monitoring. We used the COS as the outcome measure for all patients, as has been permissible in other studies.2-9 The use of discharge neurological status was suboptimal but necessary because of a high rate of loss to follow-up. The thresholds that we identified may be confounded by ICP-directed treatments used in an effort to maintain ICP less than 20 mm Hg as well as toxicities of these treatments. However, we note that ICP-directed treatment at SFPGH is not initiated until the 20 mm Hg threshold has been exceeded for 5 minutes. On this basis, we believe that such a confounding effect, if present, would likely occur at greater than the 19 mm Hg treatment threshold we identified.

Conclusions

We have performed a detailed exploration of the association between ICP and outcome using a large database of high-frequency physiologic measurements. Our study suggests that ICPs of 8 to 9 mm Hg could possibly constitute normal values and that 19 mm Hg is the ICP threshold most strongly associated with outcome in all patient groups. Intracranial pressure values at greater than this threshold are associated with mortality, while lower values are associated with outcome in surviving patients. The association between ICP and outcome was remarkably consistent among the heterogeneous pathologies studied. Our findings are consistent with those of Miller et al in suggesting that ICP values lower than 20 mm Hg may be harmful and that a lower ICP threshold may ultimately be judged optimal.

REFERENCES


