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Analysis of high-frequency $P_{bt}O_2$ measures in traumatic brain injury: insights into the treatment threshold

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Abstract

OBJECTIVE—Brain tissue hypoxia is common after traumatic brain injury (TBI). Technology now exists that can detect brain hypoxia and guide corrective therapy. Current guidelines for the management of severe TBI recommend maintaining partial pressure of brain tissue oxygen ($P_{bt}O_2$) > 15–20 mm Hg; however, uncertainty persists as to the optimal treatment threshold. The object of this study was to better inform the relationship between $P_{bt}O_2$ values and outcome for patients with TBI.

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Author Contributions

Conception and design: Hawryluk, Hirschi, Zimmermann, Manley. Acquisition of data: Hawryluk, Zimmermann, Manley. Analysis and interpretation of data: Hawryluk, Hirschi, Nielson, Huie, Saigal, Ding, Ferguson, Manley. Drafting the article: Hawryluk, Hirschi, Nielson, Huie. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hawryluk. Statistical analysis: Hawryluk, Hirschi, Nielson, Huie, Ding, Ferguson. Administrative/technical/material support: Hawryluk. Study supervision: Hawryluk, Manley.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Supplemental Information

Previous Presentations

Portions of this work were presented in abstract/oral presentation form at the 2017 AANS Annual Scientific Meeting, Los Angeles, California, April 24, 2017. Portions of this work were also presented in poster form as a finalist for the Trainee Poster Competition at the National Neurotrauma Society annual meeting, Snowbird, Utah, July 10, 2017.

METHODS—$P_{bt}O_2$ measurements were prospectively and automatically collected every minute from consecutive patients admitted to the San Francisco General Hospital neurological ICU during a 6-year period. Mean $P_{bt}O_2$ values in TBI patients as well as the proportion of $P_{bt}O_2$ values below each of 75 thresholds between 0 mm Hg and 75 mm Hg over various epochs up to 30 days from the time of admission were analyzed. Patient outcomes were determined using the Glasgow Outcome Scale. The authors explored putative treatment thresholds by generating 675 separate receiver operating characteristic curves and 675 generalized linear models to examine each 1–mm Hg threshold for various epochs.

RESULTS—A total of 1,380,841 $P_{bt}O_2$ values were recorded in 190 TBI patients. A high proportion of $P_{bt}O_2$ measures were below 20 mm Hg irrespective of the examined epoch. Time below treatment thresholds was more strongly associated with outcome than mean $P_{bt}O_2$. A treatment window was suggested: a threshold of 19 mm Hg most robustly distinguished patients by outcome, especially from days 3–5; however, benefit was suggested from maintaining values at least as high as 33 mm Hg.

CONCLUSIONS—This analysis of high-frequency physiological data substantially informs the relationship between $P_{bt}O_2$ values and outcome. The results suggest a therapeutic window for $P_{bt}O_2$ in TBI patients along with minimum and preferred $P_{bt}O_2$ treatment thresholds, which may be examined in future studies. Traditional treatment thresholds that have the strongest association with outcome may not be optimal.

Keywords

brain tissue oxygenation; $P_{bt}O_2$; outcome; threshold; treatment window; traumatic brain injury; head injury; Licox; trauma

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BRAIN hypoxia is a frequent and important consequence of traumatic brain injury (TBI).[1,7,36] Monitoring of brain hypoxia allows corrective intervention and ongoing titration of therapy. $S_{jv}O_2$ (jugular venous oxygen saturation) monitoring is an established monitoring technique that can intermittently assess the oxygen content of venous blood returning from the brain to provide insights into oxygen utilization in large portions of the cerebrum.[26] Approximately 2 decades ago, new technology emerged that allowed the invasive and continuous monitoring of smaller brain regions of interest.[18,33,35] The recently published BOOST II (Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase II) randomized controlled trial of Licox technology (Integra) suggests that therapy guided by focal, continuous measurements of the partial pressure of oxygen in the brain ($P_{bt}O_2$) significantly reduces brain hypoxia and also reduces mortality by approximately 10%.[24]

Unfortunately, the treatment threshold for $P_{bt}O_2$ has not been established with certainty. Although the third edition of the Brain Trauma Foundation's (BTF's) *Guidelines for the Management of Severe Traumatic Brain Injury* provided a Level III recommendation that $P_{bt}O_2$ be maintained greater than 15 mm Hg, the fourth edition deemed that there is insufficient evidence meeting current standards to recommend a $P_{bt}O_2$ threshold.[3,5] Many currently adhere to the Neurocritical Care Society's consensus statement, which recommends maintenance of $P_{bt}O_2 > 20$ mm Hg.[15] Both of these sources acknowledge the weak nature of the evidence currently informing the treatment threshold.

Important advancement in the TBI field has come from analysis of large data sets, likely because these data sets help overcome the tremendous heterogeneity inherent to TBI patients.[11,20,25,29] Our group has a large, prospectively collected database of physiological measures from all patients admitted to the neurological ICU at San Francisco General Hospital during a 6-year period. This database also contains 1,380,841 $P_{bt}O_2$ values recorded during every minute of the ICU stay of 190 consecutively treated patients with TBI. This large quantity of high-frequency data allows us to study the relationship between specific $P_{bt}O_2$ values and outcome with high resolution and thus provide insight into what the optimal treatment threshold may be.

Methods

Patient Characteristics and Management

We studied a consecutive series of brain-injured patients who were admitted to the neurological ICU between 2005 and 2011 and underwent $P_{bt}O_2$ monitoring. Patients were managed with a standardized treatment protocol strongly adherent to the BTF's *Guidelines for the Management of Severe Traumatic Brain Injury*.[4,10] $P_{bt}O_2$ monitoring over this time period was performed exclusively using Licox monitors (Integra). Over the duration of this study, most patients who had an external ventricular drain placed per BTF guideline recommendations also had a Licox monitor placed for $P_{bt}O_2$ monitoring, although the decision to place a $P_{bt}O_2$ monitor was based solely on the attending neurosurgeon's judgment of medical need. These monitors were placed through a distinct burr hole ipsilateral to the external ventricular drain in a standardized location 2 cm lateral and 2 cm anterior to Kocher's point. In most instances, the monitors were placed on the right side of the brain. The $P_{bt}O_2$ threshold used in all studied patients was the contemporaneous 15–mm Hg threshold recommended by the third edition of the BTF guidelines.[2] Low $P_{bt}O_2$ values were treated by means such as optimizing ventilator settings, investigating and treating pulmonary pathology, increasing the F_iO_2 (fraction of inspired oxygen), augmenting blood pressure, and optimizing intracranial pressure.

Data Collection

Using a computerized data acquisition system developed by our group in conjunction with Aristein Bioinformatics LLC, data were collected and stored automatically from patients' bedside monitors in the ICU. Prospective data collection with this system adhered to patient privacy regulations and was approved by our institutional review board. Patient consent was not required due to the minimal risk to patients and lack of patient contact. The system recorded values at 1-minute intervals and initiated automatically once patient data appeared on a bedside monitor and continued for the duration of the ICU stay.

Data Curation

Data for each patient was extracted to separate Microsoft Excel (Microsoft Corp.) files maintained on an encrypted computer and analyzed using Matlab (Math-Works) computing software. Our group designed a program that calculated average $P_{bt}O_2$ values between time periods specified by the analyst. The program also counted the number of epochs with $P_{bt}O_2$ values below specified thresholds between specified periods. We chose to analyze brain

tissue oxygenation values below 75 different thresholds from 0 mm Hg to 75 mm Hg in 1–mm Hg increments for various epochs post-injury. The proportion of $P_{bt}O_2$ values that fell below each of the 1–mm Hg increment thresholds relative to the total recordings in the epoch was quantitated to account for variation in the number of observations between patients. This analysis is similar to one we recently performed to examine the relationship between mean arterial blood pressure values and outcome from spinal cord injury.[6,12]

Data Analysis

Statistical analyses were performed using IBM SPSS (version 24, IBM Corp.) software. $P_{bt}O_2$ data for proportions below each 1–mm Hg threshold increment were analyzed for each of the first 7 days post-TBI and for other epochs of interest. Data from patients with confirmed TBI, Glasgow Outcome Scale (GOS) score at discharge, and daily $P_{bt}O_2$ data were included in the analyses. Receiver operating characteristic (ROC) curves were used to calculate the area under the curve (AUC) to test whether the number of recordings below each 1–mm Hg threshold could significantly predict mortality, represented as a binary outcome of GOS score 1 (dead) versus any of the higher GOS scores (alive) at discharge. Since we analyzed 75 separate AUCs for each of the 7 days, plus combined data for days 3–5 and days 1–7 post-TBI, a total of 675 separate AUCs were generated. In order to visualize a potential threshold, the p values from each of these AUCs for each threshold were plotted for each day post-TBI to determine at which threshold the prediction of mortality was nearing significance.

ROC curves tend to be a very conservative predictive statistic; therefore, a second wave of more liberal data-driven analyses was performed with the same criteria listed above using a generalized linear model (GLM). The GLM was used that was fit to a gamma distribution in order to best model the proportional data. The main effect of GOS score was tested for the proportion of $P_{bt}O_2$ values below each of the 75 thresholds in 1–mm Hg increments for each day post-TBI, plus days 3–5 combined and 1–7 combined.

To assess for possible confounding in the univariate relationship between $P_{bt}O_2$ values and outcome, we performed a multivariable analysis. We developed an optimal regression model that allowed us to benchmark the predictive validity of the 19–mm Hg $P_{bt}O_2$ threshold from days 3 to 5 on GOS score at discharge against other putative predictors of outcome, including age, type of injury (focal or diffuse), and injury severity (Glasgow Coma Scale [GCS] scores from the field and emergency department).

Data Visualization

GraphPad Prism (GraphPad) and Microsoft Excel were used to plot graphs of the results, and multipanel figures were organized using Microsoft PowerPoint (Microsoft Corp.), Adobe Photoshop (Adobe Systems), and Illustrator CC 2017 (Adobe Systems). In all cases, error bars represent standard error of the mean.

Results

In our database, 190 patients were identified with TBI and recorded $P_{bt}O_2$ values. A total of 1,380,841 $P_{bt}O_2$ values obtained every minute were recorded and analyzed for these

patients. For analyses stratified by outcome, our analysis was necessarily restricted to those patients with GOS scores available, which included 185 patients. This analysis was also restricted to values recorded in the first 30 days after ICU admission. Figure 1 demonstrates the inclusion criteria for this study.

The GOS scores used to stratify patients based on outcome reflect those that were available or could be calculated at the time of discharge. Because of low rates of follow-up inherent to trauma patients at our county hospital, a meaningful analysis stratified by outcomes at a later time post-discharge was not possible. Of the analyzed patients, 51 (27.6%) died (GOS score 1). Fifteen (8.1%) were in a persistent vegetative state (GOS score 2); 110 patients (59.4%) had a GOS score of 3 (severe disability), and 9 patients (4.9%) achieved moderate disability (GOS score 4).

Patient Demographics

Characteristics of studied patients stratified by outcome are presented in Table 1. TBI patients were most often male in all outcome groups. There was a significant difference in the age of patients in each outcome group ($p < 0.0001$). Those achieving the best outcome (GOS score 4) were also the youngest (31.7 years), while those who died (GOS score 1) had the oldest average age (56.4 years). Additionally, Table 1 shows that the average total hours monitored between outcome groups were significantly different ($p < 0.0001$). Those who remained in a persistent vegetative state had the highest average number of hours monitored (520.3 hours), followed by GOS score 3 (347.2 hours), GOS score 1 (236.3 hours), and GOS score 4 (127.0 hours).

Distribution of $P_{bt}O_2$ Values

The distribution of $P_{bt}O_2$ values at various time points for the 190 TBI patients can be seen in Fig. 2. The proportion of counts in 1–mm Hg $P_{bt}O_2$ bins between 1 and 75 mm Hg are shown and demonstrate that although most values were above 15 mm Hg, a high proportion fell below this value. Of all recorded $P_{bt}O_2$ values from TBI patients from days 1 to 30, 19.0% were below 15 mm Hg. In the first 7 days following ICU admission, 19.7% of values were below 15 mm Hg. From days 3 to 5, an epoch with prevalent brain swelling and secondary brain insults,[31] 12.4% of TBI patient values were below 15 mm Hg.

Relationship Between Average $P_{bt}O_2$, Proportion of Measures Below $P_{bt}O_2$ Thresholds, and Outcome

Figure 3A displays average $P_{bt}O_2$ values subsequent to admission. Mean $P_{bt}O_2$ values were above the current threshold of 20 mm Hg at every time point and in every patient group. Moreover, while each outcome group exhibited significantly different mean $P_{bt}O_2$ values ($p < 0.001$), mean $P_{bt}O_2$ values did not correlate well with outcome. The proportion of values below thresholds demonstrated a stronger correlation with outcome. A detailed analysis of different $P_{bt}O_2$ thresholds found that 19 mm Hg most robustly discriminated patients by outcome, especially for the combined period of days 3–5 (and in particular for days 3 and 4). This is illustrated in Fig. 3B, where we plotted the proportion of $P_{bt}O_2$ values below 19 mm Hg for groups stratified by GOS score at the time of discharge for various noncumulative epochs relative to ICU admission. This finding is important, as it

suggests that the proportion of brain oxygenation below thresholds have a more important relationship with outcome than average $P_{bt}O_2$ values.

$P_{bt}O_2$ Thresholds and Neurological Recovery After Head Injury

To further explore possible treatment thresholds for $P_{bt}O_2$ management, we plotted the proportion of values below 75 different potential $P_{bt}O_2$ thresholds for analysis in 1–mm Hg increments between 1 and 75 mm Hg (Fig. 4). When lines on the plot cross, diverge, or differ among GOS groups, a relationship between $P_{bt}O_2$ and neurological outcome is suggested. Our identified threshold of 19 mm Hg is denoted by vertical red lines and tends to fall where values for the outcome groups are highly separated. Of interest, separation of outcome lines up to $P_{bt}O_2$ values of approximately 45 mm Hg suggests that values up to 45 mm Hg are associated with outcome, particularly in moderate and severe disability outcome groups. This raises the possibility that there may be an outcome benefit to maintaining $P_{bt}O_2$ values up to that threshold if they can be achieved.

Data-Driven Discovery of a Candidate Therapeutic Tissue Oxygenation Window After TBI

Supplementing our qualitative analysis of the data, we deployed quantitative methodologies to hone in on $P_{bt}O_2$ values that most strongly predict clinical outcome. The p values from predictive statistical models were plotted by the threshold being tested for predicting the GOS score at discharge to reveal any asymptotes or spikes in the predictive patterns that can help identify the most robust $P_{bt}O_2$ threshold. Both the ROC curve (Fig. 5) and the GLM graphs (Fig. 6) revealed consistently low p values between 15 and 35 mm Hg. Post hoc testing for days on which significant results were identified (days 3–7) using least-significant-difference tests revealed the specific relationship between $P_{bt}O_2$ thresholds at the peak of the p value dip for the GLM and GOS score at discharge, suggesting that 19 mm Hg may be a robust minimum threshold to maintain to prevent lower GOS scores at discharge. A value of 33 mm Hg emerged as a higher threshold that may afford greater safety and might be conceptualized as an ideal threshold.

Multivariable Analysis to Benchmark the Predictive Value of a $P_{bt}O_2$ Threshold Against Other Variables

Our multivariable analysis served to benchmark the predictive validity of the suggested $P_{bt}O_2$ threshold of 19 mm Hg from days 3 to 5 against possible confounding variables. In this model, age was the strongest predictor of outcome; the $P_{bt}O_2$ threshold of 19 mm Hg was the only other significant predictor (Table 2). TBI type—defined as focal or diffuse—was not a statistically significant predictor of outcome in this model and neither was TBI severity as assessed by the GCS in both the field and in the emergency department.

Discussion

Literature to date has demonstrated that low $P_{bt}O_2$ values correlate with outcome and that correcting low values improves outcome.[1,16,22,23,28,30] Much about brain oxygen monitoring remains to be refined, however. It is particularly important to define the optimal treatment threshold, and a very large data set of high-frequency $P_{bt}O_2$ values from nearly 200 patients

represents a unique opportunity to explore the relationship between highly resolved $P_{bt}O_2$ values and outcome.

The Literature Basis for Existing $P_{bt}O_2$ Treatment Thresholds

Several publications have outlined the relationship between $P_{bt}O_2$ values and neurological outcome after head injury.[1,32,34] In 1998, Bardt et al. reported that patients spending > 30 minutes with $P_{bt}O_2$ < 10 mm Hg had a significantly greater chance of unfavorable outcome and death than those spending < 30 minutes with $P_{bt}O_2$ < 10 mm Hg. They concluded that low $P_{bt}O_2$ values and duration of time spent at low $P_{bt}O_2$ are associated with mortality; however, the study provided limited information regarding potential treatment thresholds.[1] Valadka et al. published a similar study in 1998 and also concluded that low $P_{bt}O_2$ values and duration of time spent at low $P_{bt}O_2$ are associated with mortality.[32] More specifically, Valadka and associates concluded that the likelihood of death increased with an increasing duration of time below a $P_{bt}O_2$ of 15 mm Hg or with any occurrence of values below 6 mm Hg. Van den Brink and colleagues also concluded in 2000 that low $P_{bt}O_2$ values and the duration of time spent with low $P_{bt}O_2$ are associated with mortality. They found that a 50% risk of death was associated with a $P_{bt}O_2$ < 15 mm Hg lasting > 4 hours.[34] These past studies are in agreement in suggesting that lower $P_{bt}O_2$ values and prolonged periods of hypoxia are associated with higher mortality rates. Together, the papers of Valadka and Van den Brink and their colleagues served as important evidence leading to the BTF's published treatment threshold of 15 mm Hg in the third edition of the guidelines.[3]

Several works published more recently have also explored the effect of $P_{bt}O_2$ values on outcome after head injury.[10,17,19] Maloney-Wilensky published a systematic review in 2009 of 3 studies including 150 patients recovering from severe TBI.[19] It was concluded that brain hypoxia ($P_{bt}O_2$ < 10 mm Hg) is associated with worse outcome after TBI and that treating patients to increase $P_{bt}O_2$ may improve neurological outcome. In 2009 Chang et al. performed a retrospective analysis of hourly $P_{bt}O_2$ measures in 27 patients who sustained severe TBI.[7] They explored $P_{bt}O_2$ cutoffs at 10 mm Hg, 15 mm Hg, 20 mm Hg, 25 mm Hg, and 30 mm Hg and found that the 20–mm Hg cutoff was most strongly associated with poor functional outcome. In 2010, Spiotta et al. reported improved outcomes in 70 patients in whom a $P_{bt}O_2$ target > 20 mm Hg was maintained compared with historical controls.[28] In 2015 Lin et al. published a prospective randomized study to compare the effect of $P_{bt}O_2$-guided therapy with traditional intracranial pressure–guided treatment on outcome in moderate and severe TBI patients.[17] They employed a $P_{bt}O_2$ threshold of 20 mm Hg and concluded that the survival rate in the $P_{bt}O_2$-guided group was significantly increased at 3 and 6 months after injury, indicating that therapy directed by $P_{bt}O_2$ monitoring is valuable for treatment in these patients. Eriksson et al. published a study in 2012 and concluded that the first 72 hours of $P_{bt}O_2$ monitoring predicts mortality similar to the analysis we present in this study.[10] They proposed that mortality is increased when the $P_{bt}O_2$ monitor remains below 29 mm Hg in the first 72 hours of monitoring, raising the possibility that a higher threshold for brain oxygen monitoring should be considered.

The Neurocritical Care Society consensus statements on advanced neuromonitoring cited several lines of evidence in their recommendation to maintain $P_{bt}O_2$ values above 20 mm

Hg.[15] They argue that the higher threshold provides a buffer that helps prevent critically low $P_{bt}O_2$ values (< 10–15 mm Hg).[28] They also cited evidence that neuronal mitochondria have been found to require an intracellular pO_2 that corresponds to a $P_{bt}O_2$ of about 20 mm Hg to maintain aerobic metabolism.[27,28] Additionally, $P_{bt}O_2$ decreases below 20 mm Hg have been associated with other markers of cerebral ischemia or cellular dysfunction.[15] We view our study as being largely confirmatory of the Neurocritical Care Society recommendations.

The recently published BOOST II randomized controlled trial employed the 20–mm Hg treatment threshold and was stopped early after meeting its predetermined endpoint, demonstrating that $P_{bt}O_2$-guided therapy is not futile.[24] $P_{bt}O_2$-directed therapy also demonstrated a 9% reduction in mortality in this study. Given this result, there is strong reason to further optimize brain oxygen–directed therapy and in particular the treatment threshold. The work we present here contains important, high-resolution insights into the relationship between specific $P_{bt}O_2$ values, as we have analyzed—to our knowledge—the largest number of severe TBI patients with $P_{bt}O_2$ values to date and over 3 times the number of $P_{bt}O_2$ measures found in the next largest study.[28] Our analyses suggest that 19 mm Hg deserves consideration and further study as the minimum $P_{bt}O_2$ treatment threshold. It additionally demonstrated that values at least as high as 33 mm Hg correlate with outcome, suggesting that there might be benefit to maintaining higher $P_{bt}O_2$ values when they can be achieved.

Average $P_{bt}O_2$ Values Correlate Poorly With Outcome

Remarkably, the results shown in Fig. 3A demonstrate that all average $P_{bt}O_2$ values were above both published treatment thresholds.[3,15] In contrast, our analysis of the proportion of measures below thresholds demonstrated that a large proportion of values fell below the recommended thresholds. Simply looking at average values can thus be deceiving. Patient outcome correlated much more strongly with time spent below thresholds—in particular, 19 mm Hg—than with average values. Importantly, this suggests that efforts to avoid low $P_{bt}O_2$ values are more important than those to augment them above threshold and that even brief periods of time spent below threshold may be harmful.

$P_{bt}O_2$ Values Above 19 mm Hg and as High as 45 mm Hg May Be Beneficial

Our data suggest that a minimum $P_{bt}O_2$ threshold of 19 mm Hg should be considered after head injury; this suggested threshold was derived in a traditional fashion based on the strongest statistical association with outcome. The importance of this $P_{bt}O_2$ threshold is supported by our multivariable regression model, which served to control for putative variables confounding the relationship between $P_{bt}O_2$ and outcome. In this multivariable analysis, the only other significant predictor of outcome besides age was the $P_{bt}O_2$ threshold of 19 mm Hg from days 3 to 5.[21]

Importantly, our analysis also suggests that there may be therapeutic benefit to maintaining higher $P_{bt}O_2$ values, as an association with outcome was robust up to 33 or 45 mm Hg, depending on the analysis performed (Figs. 4 and 6). Moreover, Fig. 4 demonstrates that higher $P_{bt}O_2$ values seem more important for discriminating better outcomes while lower $P_{bt}O_2$ values were more strongly associated with discriminating poorer outcomes.

This indicates that patients might benefit from maintenance of $P_{bt}O_2$ values above current thresholds.

With this in mind, our article is remarkable for suggesting distinct minimal and ideal treatment thresholds and thus the suggestion of a treatment window; currently, treatment thresholds in neurocritical care are conceptualized as single, discrete values. We contend that these may oversimplify the conceptual association between measured values and outcome. We must also caution that in striving for higher $P_{bt}O_2$ values treating clinicians must take into account potential toxicities associated with higher oxygen values.[8,9,14] Thus, the potential physiological benefits of achieving higher $P_{bt}O_2$ values must be balanced against the risks.

Limitations

A number of limitations must be considered in interpreting this study. Patient outcomes (GOS scores) were measured at the time of hospital discharge, as analysis at a later time point was not possible due to a high rate of loss to follow-up in this trauma population at our county hospital. Additionally, time was relative to ICU admission and not the time of injury. This time point is clinically relevant, however. This study does not inform the optimal intracerebral site at which to monitor $P_{bt}O_2$ and does not allow analysis of the treatment threshold based on distance from focal brain lesions.[13] Additionally, this study does not exclude the possibility that individual patients or some disease pathologies have a different relationship between specific $P_{bt}O_2$ values and outcome. Ultimately, it will be necessary to validate candidate treatment thresholds prospectively. There are important limitations to such a study, however, as a limited number of thresholds can be studied concurrently, and it is unethical to randomize patients to thresholds believed to be suboptimal.

Conclusions

Although this study does not provide evidence for a causal relationship, it substantially informs the nature of the relationship between $P_{bt}O_2$ values and neurological outcome. The proportion of measures below treatment threshold was more strongly associated with outcome than average $P_{bt}O_2$. Moreover, our study supports the concept of a $P_{bt}O_2$ treatment window in TBI recovery, with suggested minimum and ideal treatment thresholds. Indeed, our results suggest that a minimum $P_{bt}O_2$ treatment threshold of 19 mm Hg may be considered and that values as high as 33 mm Hg or 45 mm Hg may be of additional benefit if they can be achieved. Validation of these results in a prospective study is needed.

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ABBREVIATIONS

AUC	area under the curve
BTF	Brain Trauma Foundation

GCS	Glasgow Coma Scale
GLM	generalized linear model
GOS	Glasgow Outcome Scale
TBI	traumatic brain injury
$P_{bt}O_2$	partial pressure of oxygen in brain tissue
ROC	receiver operating characteristic

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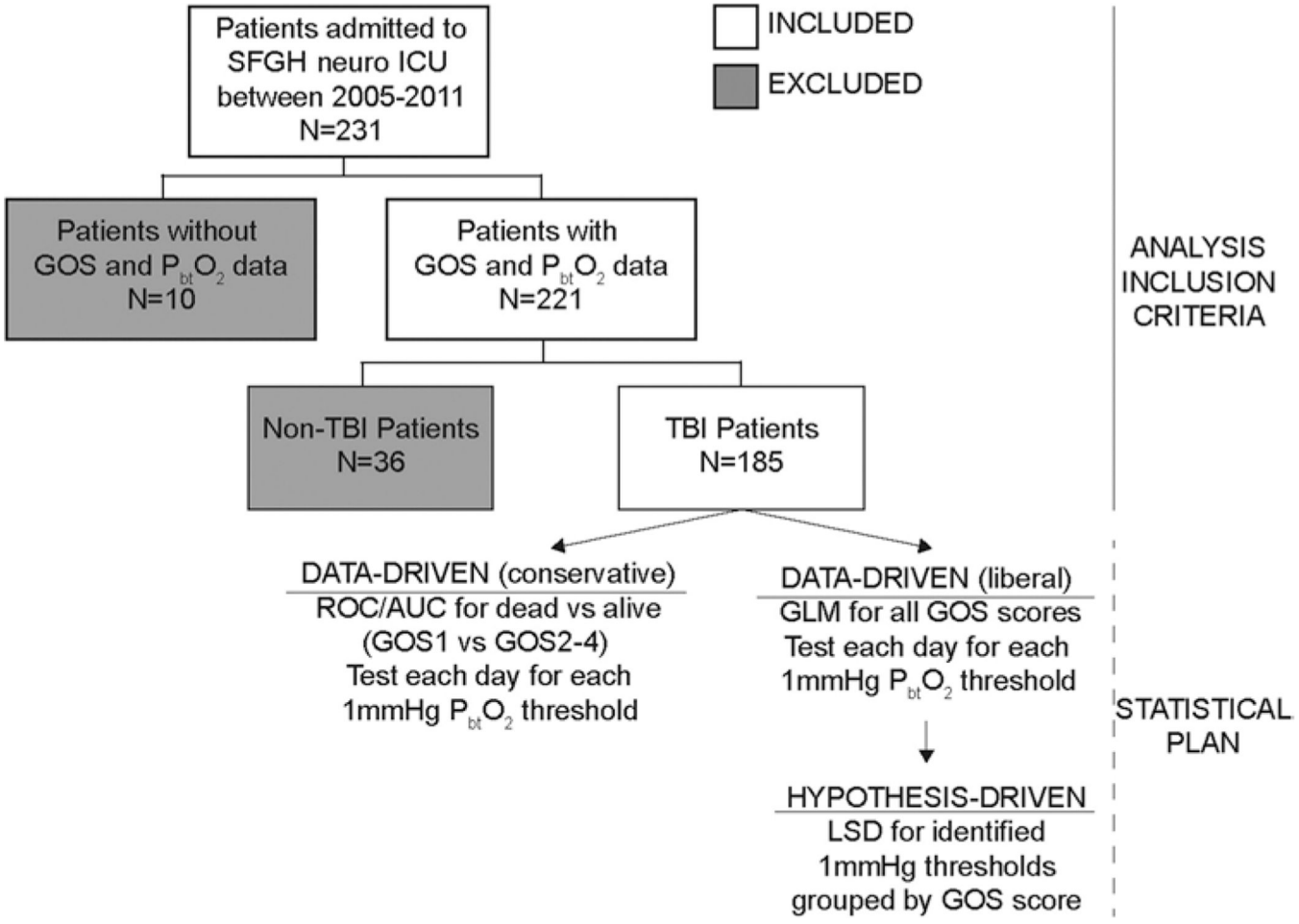

FIG. 1.

Analysis of inclusion criteria and flowchart. Patients with $P_{bt}O_2$ data and GOS scores at discharge with a confirmed TBI were included in the analyses. A first wave of conservative data-driven analyses was performed using ROC/AUC to test whether specific treatment thresholds predicted mortality (GOS score 1 vs > 1). A second wave of liberal data-driven analyses was performed using GLM to test the same hypothesis, followed by post hoc testing using the least significant difference (LSD) for thresholds with significant predictors on GOS scores.

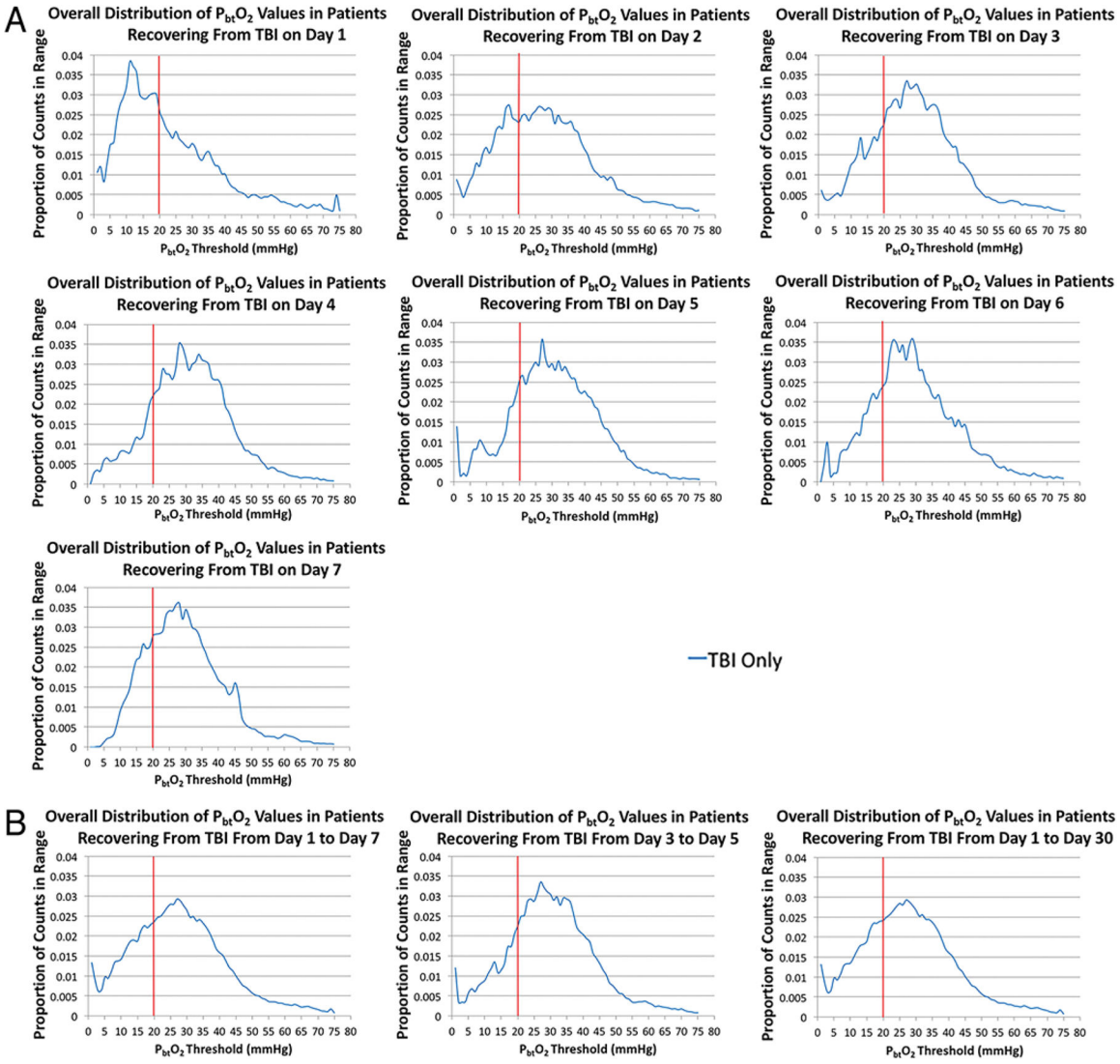

FIG. 2.

Distribution of $P_{bt}O_2$ values demonstrating that a high proportion of measures were consistently below treatment threshold throughout the first 30 days after ICU admission. $P_{bt}O_2$ values were measured using the Licox system, and measures are plotted within 1–mm Hg ranges. **A:** Individual days. **B:** Multiday epochs. The *vertical red line* indicates a possible treatment threshold of 19 mm Hg. The *blue line* includes patients recovering specifically from TBI (n = 190). The indicated time is in reference to the time of ICU admission.

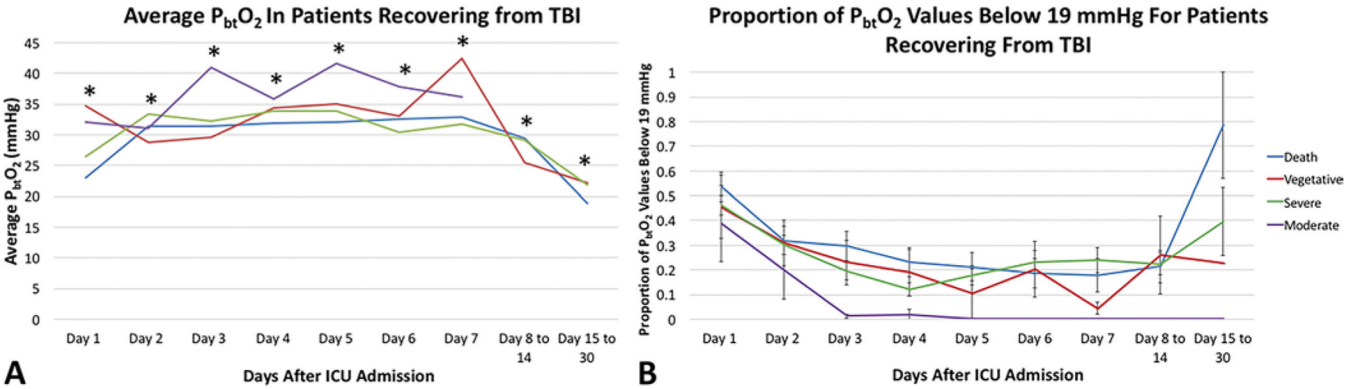

FIG. 3.

Patient outcome is more strongly associated with the proportion of time spent below treatment thresholds than it is with mean $P_{bt}O_2$ values. The proportion of $P_{bt}O_2$ values < 19 mm Hg is associated with outcome from days 1 to 4 in TBI patients. **A:** Values were measured using the Licox system, and average $P_{bt}O_2$ values are plotted in relation to time after ICU admission. **B:** The proportion of $P_{bt}O_2$ values below a potential threshold of 19 mm Hg are plotted. The "n" used in statistical testing in (A) is the number of $P_{bt}O_2$ measures, while the "n" in (B) is the number of patients. Mean values are shown. The *error bars* represent SEM. *Significant on analysis.

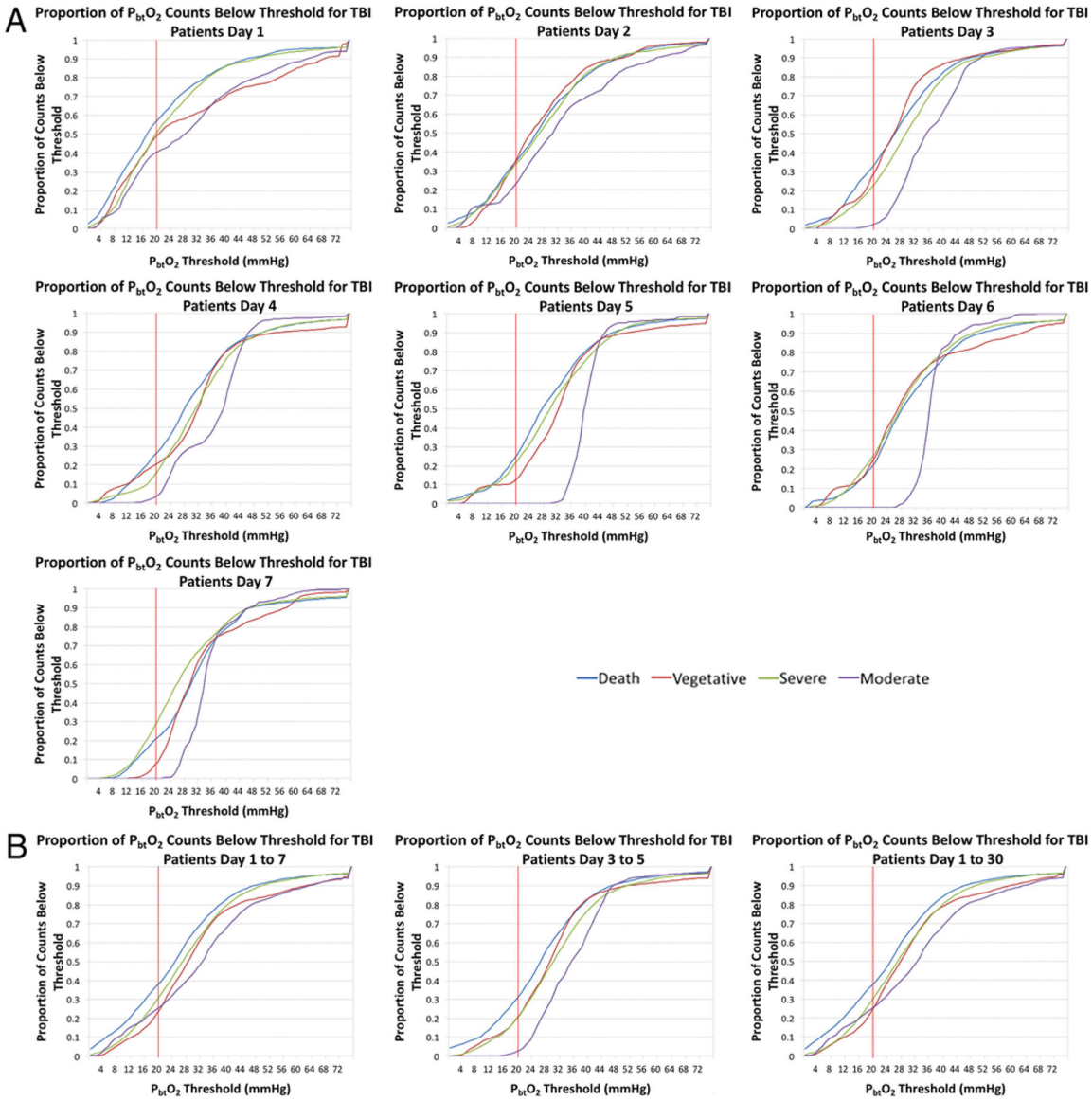

FIG. 4.

The amount of time spent at lower $P_{bt}O_2$ (< 45 mm Hg) values is associated with poorer neurological outcome after injury. Plots display thresholds at 1–mm Hg increments. All TBI patients with GOS values (n = 185) are reported. Values were measured using the Licox $P_{bt}O_2$ monitoring system and time is relative to ICU admission. **A:** Individual days. **B:** Multiday epochs. The *vertical red line* at 19 mm Hg indicates counts below a proposed threshold of 19 mm Hg.

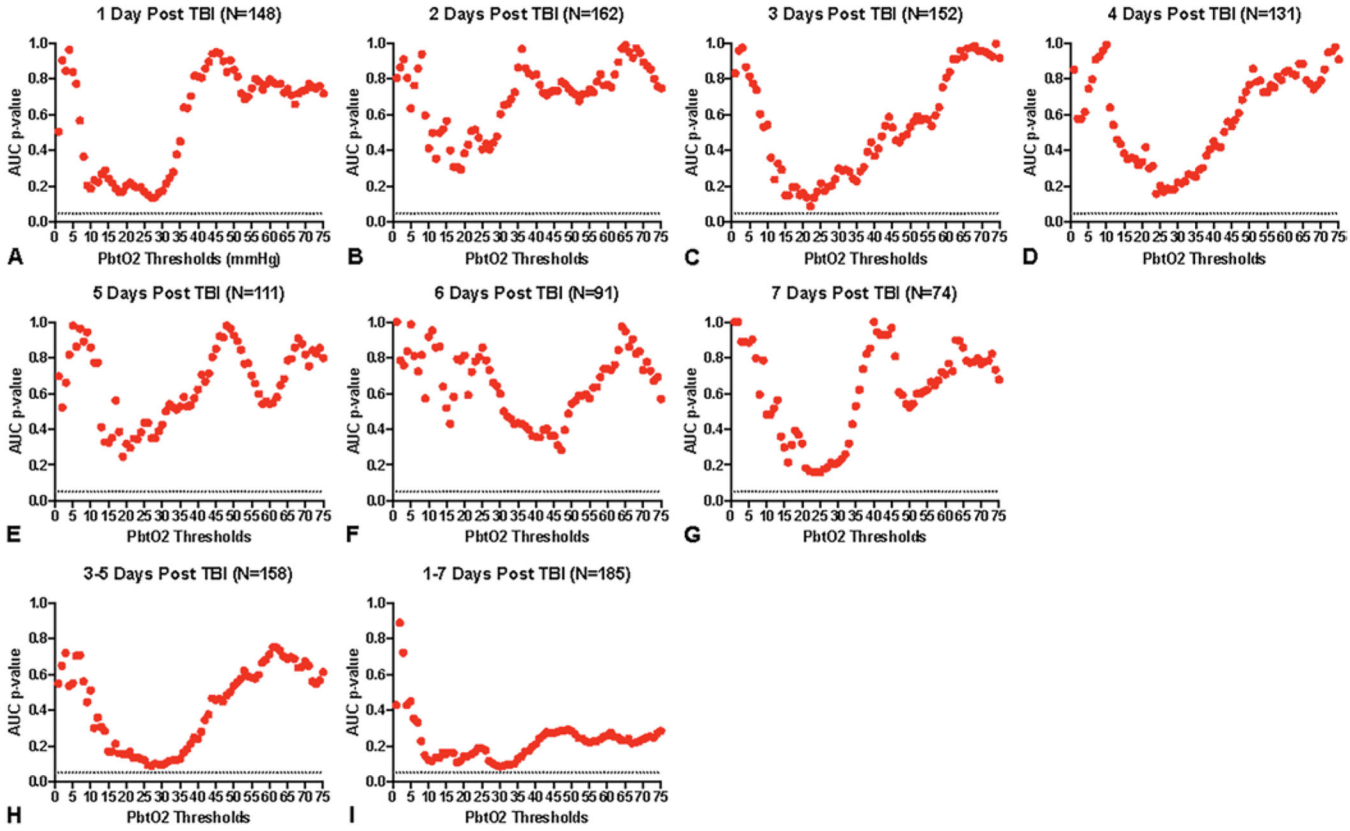

FIG. 5.

Data-driven identification of potential treatment thresholds to predict mortality of TBI patients based on $P_{bt}O_2$ proportions below each value using ROC analysis. $P_{bt}O_2$ data for each TBI patient were analyzed using the ROC curve to calculate the AUC to test whether the proportion of events below each 1–mm Hg threshold could predict mortality (GOS score 1 vs GOS scores 2–4). p values from AUC results are plotted on the y-axis and 1–mm Hg thresholds on the x-axis to identify windows of vulnerability in the ICU for 7 days after admission to the ICU post-TBI (**A–G**). Patient numbers drop off each day, most likely due to discharge or death. The increase in patients on day 2 indicates that Licox monitoring was not initiated until 2 days after coming into the hospital for some patients. Data for all days, either 3–5 (**H**) or 1–7 (**I**), were combined to calculate proportions below each threshold for each duration, highlighting the average dip in p values that occurs between 15 and 40 mm Hg on days 3–5.

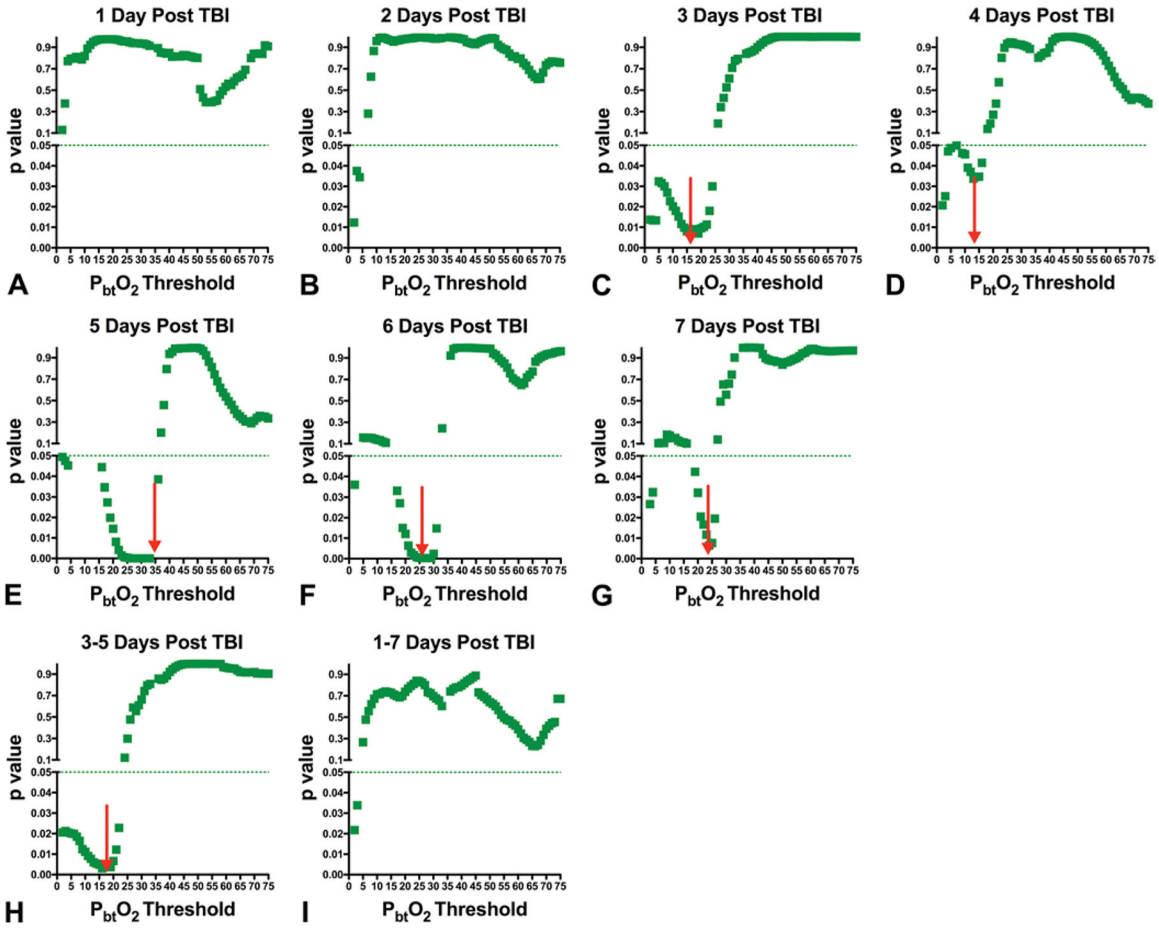

FIG. 6.

Data-driven identification of potential treatment thresholds to predict mortality of TBI patients based on $P_{bt}O_2$ proportions below each value using GLM analysis. $P_{bt}O_2$ data for each TBI patient were analyzed using GLM to test whether the proportion of events below each 1–mm Hg threshold could predict the GOS score at discharge (all groups combined/ main effect). p values from GLM are plotted on the y-axis and 1–mm Hg thresholds on the x-axis, similar to Fig. 5, to identify windows of vulnerability in the ICU for 7 days after admission to the ICU post-TBI (**A–G**). Data for all days, either 3–5 (**H**) or 1–7 (**I**), were combined to calculate proportions below each threshold. The y-axis is plotted to emphasize the locations where the p values fall into significance ($p < 0.05$), with *red arrows* indicating the lowest point of the drop in p values.

TABLE 1.

Characteristics of 185 patients studied, stratified by outcome

	Died (GOS score 1)	Vegetative (GOS score 2)	Severe Disability (GOS score 3)	Moderate Disability (GOS score 4)	p Value
No. of patients	51	15	110	9	
Male sex (%)	40 (78.4)	11 (73.3)	93 (84.5)	9 (100)	0.520
Mean age, yrs	56.4	36.1	37.0	31.7	<0.0001
Mean total time monitored, hrs	236.3	520.3	347.2	127.0	<0.0001
Mean total $P_{bt}O_2$ time monitored, hrs	128.8	149.9	126.7	53.4	0.117

Of all patients studied, 185 were recovering from TBI and had a GOS score available at the time of hospital discharge; characteristics of these 185 patients are stratified by outcome. ANOVA was used to analyze a difference between means while binomial logistic regression was used for categorical data.

TABLE 2.

Benchmarking validity of predictors on outcome—optimal regression

	Standardized Coefficients				
	Beta	**Estimate of SE**	**df**	**F**	**p Value**
Age	−0.572	0.076	10	56.013	<0.001 *
Proportion below $P_{bt}O_2$ of 19 mm Hg	−0.197	0.095	1	4.325	0.040 *
TBI type (focal or diffuse)	0.027	0.070	1	0.150	0.699
GCS score in field	0.210	0.264	1	0.631	0.429
GCS score at ED	0.032	0.278	2	0.013	0.987

ED = emergency department.

An optimal regression was developed to benchmark the predictive validity of the 19 mm Hg $P_{bt}O_2$ threshold from days 3 to 5 on GOS score at discharge against other putative predictors of outcome including age, type of injury (focal or diffuse), and injury severity (GCS scores from the field and emergency department). Age was the strongest predictor of outcome, and the $P_{bt}O_2$ threshold of 19 mm Hg was the only other significant predictor (p = 0.040).

* Statistically significant.