

Continuous Determination of the Optimal Bispectral Index Value Based on Cerebrovascular Reactivity in Moderate/Severe Traumatic Brain Injury: A Retrospective Observational Cohort Study of a Novel Individualized Sedation Target

BACKGROUND: We have sought to develop methodology for deriving optimal bispectral index (BIS) values (BISopt) for patients with moderate/severe traumatic brain injury, using continuous monitoring of cerebrovascular reactivity and bispectral electroencephalography.

METHODS: Arterial blood pressure, intracranial pressure, and BIS (a bilateral measure that is associated with sedation state) were continuously recorded. The pressure reactivity index, optimal cerebral perfusion pressure (CPPopt), and BISopt were calculated. Using BIS values and the pressure reactivity index, a curve fitting method was applied to determine the minimum value for the pressure reactivity index thus giving the BISopt.

RESULTS AND CONCLUSIONS: Identification of BISopt was possible in all of the patients, with both visual inspection of data and using our method of BISopt determination, demonstrating a similarity of median values of 44.62 (35.03–59.98) versus 48 (39.75–57.50) ($p = 0.1949$). Furthermore, our method outperformed common CPPopt curve fitting methods applied to BISopt with improved percent (%) yields on both the left side 52.1% (36.3–72.4%) versus 31.2% (23.0–48.9%) ($p < 0.0001$) and the right side 54.1% (35.95–75.9%) versus 33.5% (12.5–47.9%) ($p < 0.0001$). The BIS values and BISopt were compared with cerebral perfusion pressure, mean arterial pressure, and CPPopt. The results indicated that BISopt's impact on pressure reactivity was distinct from CPPopt, cerebral perfusion pressure, or mean arterial pressure. Real-time BISopt can be derived from continuous physiologic monitoring of patients with moderate/severe traumatic brain injury. This BISopt value appears to be unassociated with arterial blood pressure or CPPopt, supporting its role as a novel physiologic metric for evaluating cerebral autoregulation. BISopt management to optimize cerebrovascular pressure reactivity should be the subject of future studies in moderate/severe traumatic brain injury.

KEY WORDS: bispectral index; cerebrovascular reactivity; hemodynamic monitoring; neurocritical care; sedation; traumatic brain injury

Although current guideline-based treatments in moderate/severe traumatic brain injury (TBI) have improved outcomes over the past 25 years, mortality and morbidity remains high (1). Impaired cerebrovascular reactivity, a surrogate of cerebral autoregulation, has an emerging association with long-term outcomes in moderate/severe TBI, with recent work highlighting its independent link with 6-month outcomes (2–5). Evaluation of multimodal cerebral physiologic monitoring in TBI cohorts has demonstrated

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that a large portion of time spent in the ICU with physiologic dysfunction is dominated by impaired cerebrovascular reactivity (2, 3, 6–8). Despite improvements in the ability to reach intracranial pressure (ICP) and cerebral perfusion pressure (CPP) targets (8–10), current ICU-based therapeutic interventions in TBI have demonstrated little impact on continuously assessed cerebrovascular reactivity (1).

IV sedation is used as part of the standard treatment for moderate/severe TBI, to aid with mechanical ventilation, reduce cerebral metabolic demand, and attenuate ongoing secondary injury pathways (11, 12). However, evidence suggests that exposure to excessive sedation is linked with poor cognitive long-term outcomes in both TBI and general ICU populations (13–15), although the mechanisms for these associations is unclear. Recent work has suggested that titration of IV sedative agents has a negligible impact on cerebrovascular reactivity, both at the macrovascular and at the microvascular level (16–18). Yet, these studies have only compared dose-titration data directly to physiologic monitoring without accounting for patient-specific pharmacodynamic profiles that lead to variability in drug response (16–18). Thus, without objective quantifications of depth of sedation, the true impact of sedation on cerebrovascular reactivity is uncertain.

Finally, individualized optimal CPP (CPPopt) uses pressure reactivity index (PRx; correlation between ICP and mean arterial pressure [MAP]) (19) and CPP to demonstrate a parabolic relationship between CPP and PRx (20–22). Leveraging similar techniques, we have recently demonstrated that there is an association between individualized depth of sedation and cerebrovascular reactivity (23). Using continuous electroencephalogram-based entropy index (bispectral index [BIS]; BIS a potential route for depth of sedation monitoring) and PRx (19), we have shown that a parabolic relationship exists between BIS and PRx. The minimum of this parabolic curve represents the BIS value at which PRx was the most negative (i.e., cerebrovascular reactivity was most intact) and thus a potential route for individualized depth of sedation. However, it was unclear from this preliminary analysis whether this sedation effect on cerebrovascular reactivity was merely occurring through changes in MAP or acting as an independent physiologic metric.

We hypothesize that depth of sedation plays an important role in modulating cerebrovascular reactivity in TBI, independent from changes to CPP. The goal of this study

is to explore the concept of optimal BIS (BISopt; a potential route for optimal sedation depth) based on BIS and PRx monitoring in a prospective cohort of moderate/severe TBI patients, highlighting: A) the presence of this novel target, B) its relationship with MAP and CPPopt, and C) preliminary attempts at continuous derivation.

MATERIALS AND METHODS

Ethics

Data were collected following full approval by the University of Manitoba Health Research Ethics Board (H2017:181, H2017:188, and B2019:065) and the Health Sciences Centre Research Impact Committee (R2019:072).

Patient Population and Data Collection

This was a retrospective observational study, inclusion criteria for the study were adult patients (> 16 yr old) with moderate/severe TBI (Glasgow Coma Scale 12 or less), requiring invasive ICP monitoring as determined by the Brain Trauma Foundation guidelines (11).

Admission demographic information were extracted following the existing prognostic models in moderate and severe TBI (24).

High-frequency arterial blood pressure, ICP, and BIS data were collected, see **Supplementary File A** (<http://links.lww.com/CCX/A943>) for more details. Note, BIS and BISopt values were obtained from the hemisphere that had no frontal lobe contusion, overlying hematoma, or subgaleal/scalp hematoma, with visual inspection of the electromyography signal of the frontalis indicating no large firing potentials, ensuring no muscle artifacts were present. Finally, no patients had neuromuscular blockade agents administered during the periods of recorded physiology and paroxysmal sympathetic hyperactivity was not actively monitored for or clinically detected in this cohort (as such active treatment was not administer), both may impact BIS values.

Signal Processing

Signal processing was done after the data was recorded in the ICU, with all signal artifacts removed using manual methods. All signal analysis work was conducted using Intensive Care Monitoring (ICM+) software (Cambridge Enterprise Ltd, Cambridge, UK, <http://icmplus.neurosurg.cam.ac.uk>) and R statistical computing. (R

Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org/>) MAP and ICP were decimated over a 10-second nonoverlapping moving average filter. CPP was derived as MAP-ICP. PRx was derived using the standard Pearson correlation between 30 consecutive 10-second windows of ICP and MAP, updated every minute (1, 3, 25–27). CPPopt was determined in individual patients through the use of the published optimal Flex methodology, for more details, see **Supplementary File B** (<http://links.lww.com/CCX/A943>) (3, 28–30). All final data was output in a minute-by-minute updated frequency.

Optimal Depth of Sedation Determination (BISopt)

Similar to past work by Aries et al (20) in CPPopt determination, a custom-created automatic quadratic curve fitting method was applied to the binned 60-second BIS data and PRx to determine the BIS value with the lowest associated PRx values (for details, see **Supplementary File C**, <http://links.lww.com/CCX/A943>).

BISopt was first calculated over the entire recording period, for each patient, similar to the original CPPopt work by Steiner et al (21) (for results see **Supplementary Files D and E**, <http://links.lww.com/CCX/A943>).

Next, a continuous time trend of BISopt was calculated using the above-mentioned curve fitting methods, generated from a moving 4-hour time window updated every minute. The BISopt curve could be generated when at least 50% of the required data points of PRx were available, that is, after a minimum of 2 hours of monitoring, keeping with CPPopt (20–22, 29, 30).

Finally, to evaluate existing CPPopt algorithms, we used the multiwindow weighted optimal Flex methodology within ICM+ to determine a BISopt value. BIS values ranged from 20 to 80 arbitrary units (au) with a maximum window size of 20-hour window, where the BISopt was calculated. This was conducted to evaluate the performance of existing CPPopt methods when directly applied to our custom-created BISopt calculations.

Statistical Analysis

Statistical analysis was conducted using R statistical computing software (R Foundation for Statistical Computing). Descriptive analyses were of BISopt/BIS and its associations with other physiologic parameters of

interest in TBI care. All physiologic variables were found to be non-parametric in nature via Shapiro-Wilk testing. Alpha was set at 0.05 with no correction for multiple comparisons given the exploratory nature of this study.

Initially, patient characteristics and BISopt values were summarized using descriptive techniques. Visually obtained BISopt values from the entire recording period, for each patient, were compared with those derived from our quadratic curve fitting algorithm using Wilcoxon signed-ranked test.

Next, we found the percentage of time that BISopt could be determined over each patient using a sliding 4-hour window that produced an updating value every minute. This included only time where BIS was sufficiently recorded to achieve at least 2-hour of interference-free data (20). Thus, we calculated the % yield for our algorithmic method and optimal Flex. Compared % yield of BISopt calculation between the two methods using Wilcoxon signed-ranked test, to determine which had a more optimal % yield.

Using our method of determining BISopt, we also performed a subgroup analysis by finding the % yield of BISopt and its association with all recorded sedative agents/dose and vasopressor agents used in this cohort. The data were separated for times which BISopt could be found (i.e., both BIS and PRx was available), and the sedative agents/dose over this time were added from bedside nursing charts. Due to the variability in dose and its weak association with sedation depth, three categories of sedation dose were chosen for each agent (high, moderate, and low) (31, 32). See **Supplementary File G** (<http://links.lww.com/CCX/A943>) for more information.

The association between BISopt and both MAP and CPPopt was determined between the minute-by-minute data for the entire recording period. First, using the entire recording period BISopt, CPPopt, and mean MAP were determined for each patient. Scatterplots were derived for BISopt versus MAP and BISopt versus CPPopt, for the entire population. Linear regression analysis was subsequently performed.

Next, using continuously derived PRx, we determined when the patient had intact ($PRx < 0.2$) versus impaired ($PRx > 0.2$) cerebrovascular reactivity (2, 26, 33). The data were then dichotomized with each state of cerebral reactivity, the BISopt (based on our method) was then compared with the minute-by-minute derived MAP and CPPopt over impaired and intact

cerebrovascular reactivity using Kendall’s tau correlation (note the data dichotomization was only done comparing BIS relations to systemic pressure changes as the autoregulatory states may influence vascular response). Thus, we compared the minute-by-minute values of BIS to MAP using a Kendall’s tau correlation methodology over impaired and intact cerebrovascular reactivity, to confirm that the BIS values were sufficiently isolated from MAP phenomena.

Finally, BIS/BISopt were compared with ICP using the previously described methods for MAP/CPPOpt, see **Supplementary Files J and K** (<http://links.lww.com/CCX/A943>) for details.

RESULTS

Demographics and Grand Averages of Monitored Modalities

Thirty-two patients were recruited with characteristics summarized in **Table 1**. The sedative regimens used were fentanyl and/or propofol to achieve a baseline sedation level with the addition of ketamine in three patients.

TABLE 1.
Thirty-Two Patient Demographics

Demographics	Median (IQR) or No. of Patients
Age	43 (23–55)
Sex (% male)	87.5
Best admission GCS–total	6.5 (4–10)
Best admission GCS–motor	4 (2–5)
Number with hypoxia episode	10
Number with hypotension episode	6
Number with traumatic subarachnoid hemorrhage	30
Number with epidural hematoma	3
Pupils	
Bilateral unreactive	3
Unilateral unreactive	6
Bilateral reactive	23
Admission Marshall CT	
V	17
IV	3
III	9
II	3

GCS = Glasgow Coma Score, IQR = interquartile range.

The Richmond Agitation-Sedation Scale (RASS) was extracted from bedside charts and indicated to be –4 for nearly all time recorded, although this value was recorded often with over 4 hours of time between events and thus has a limited overall interpretation (34). The exact sedation regimen to reach the RASS goal of –4 was determined by the treating intensivist, without a defined algorithm present within our ICU.

BISopt for Entire Recording

The mean recording time per patient after the removal of artifacts and empty BIS bilateral data was 0.80 days (0.0–5.15 d), with all patients at least having one hemisphere of usable data. Overall, visualization determination of an individual BISopt over the entire recording period was possible in all patients using visual inspection, 84.4% on the left side and 71.9% on the right side, see additional information in **Supplementary File E** (<http://links.lww.com/CCX/A943>).

Using our custom algorithmic method, we could find a BISopt in all of the complete recordings (chosen as the most optimal bilateral BIS values) with **Figure 1** demonstrating histograms of our algorithmic method BISopt values versus direct visualization BISopt values from error bar plots. Often the BISopt values were within 5 au from one another, with our algorithmic method versus direct visualization, still consistently close as to fail the Wilcoxon test 44.62 (35.03–59.98) versus 48 (39.75–57.50) ($p = 0.1949$).

Continuous Derivation of BISopt—Comparison of Different Methods

The optimal Flex method produced slightly inaccurate results (see **Fig. 2** and **Supplementary File F**, <http://links.lww.com/CCX/A943>). When comparing the percent yield for BISopt over each patient, our method outperformed optimal Flex method as determined by % yield and a Wilcoxon test. The % yield for our method versus optimal flex on the left side was 52.1% (36.3–72.4%) versus 31.2% (23.0–48.9%) ($p < 0.0001$) and the right side 54.1% (35.95–75.9%) versus 33.5% (12.5–47.9%) ($p < 0.0001$).

Continuous Derivation of BISopt—Comparison of Different Agents

Supplementary File G (<http://links.lww.com/CCX/A943>) displays all the relationships between sedation

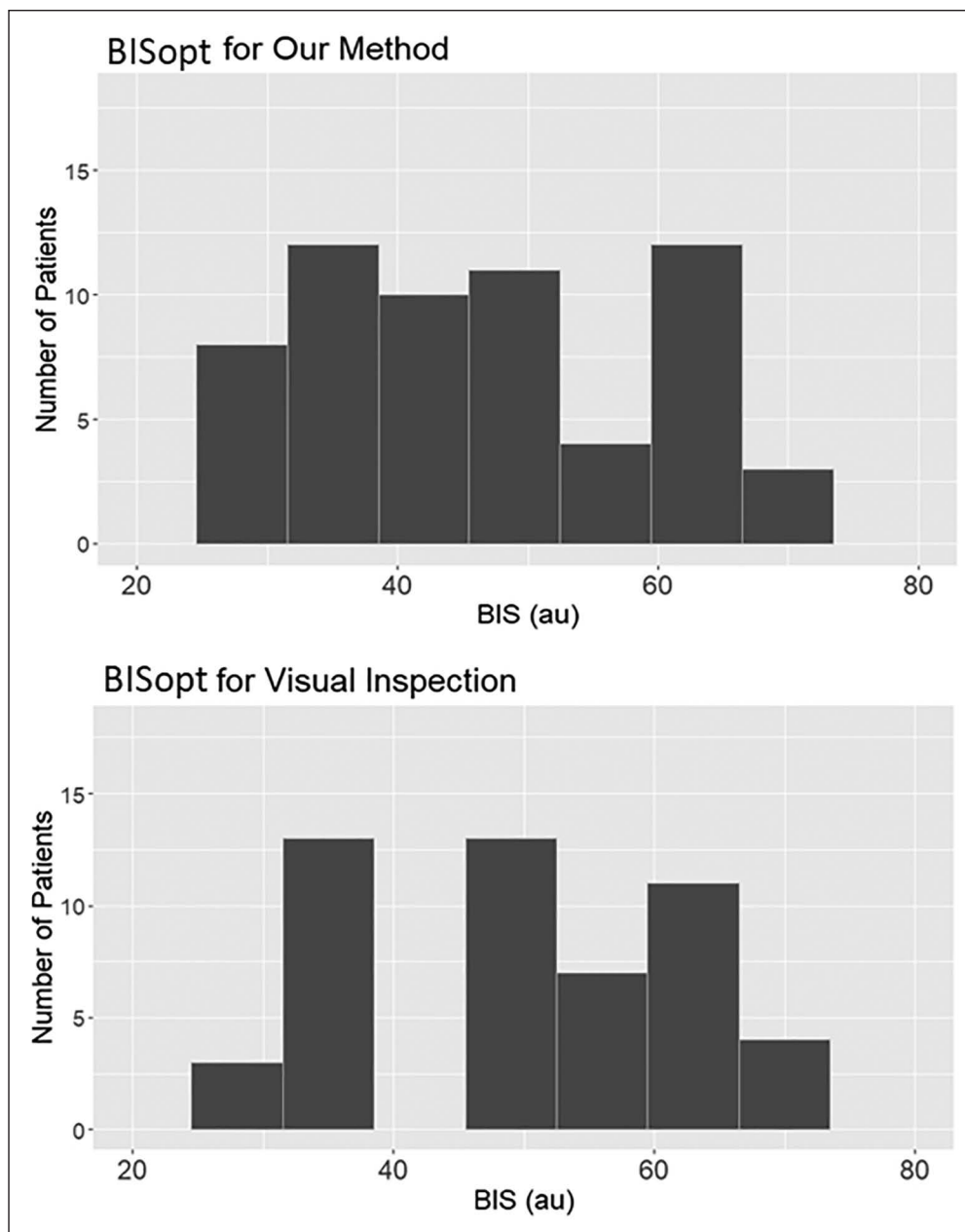


Figure 1. Optimal bispectral index (BISopt) through visual inspection and our method. The different bispectral index (BIS) values associated with each BISopt method. The Wilcoxon signed-ranked test of 0.1949 is the p value between these two histograms, demonstrating that the median values are similar. au = arbitrary units.

dose/agents and vasopressor agents with our method of determining BISopt % yield. This analysis demonstrated that fentanyl and propofol whether together or separate attained roughly the same % yield in BISopt, likewise no matter the combination of vasopressor agents BISopt had a similar % yield. High levels of sedation demonstrated a slight increase in % yield of BISopt calculation, with low BIS values demonstrating an increase in PRx.

BISopt Association With ICP, MAP, and CPPopt—Entire Recording Period

Figure 3 and Supplementary Files I and J (<http://links.lww.com/CCX/A943>), displays the BISopt versus CPPopt/MAP/ICP relationships, derived over the entire recording period. Linear regression analysis failed to demonstrate any significant relationships between BISopt and either CPPopt/MAP/ICP.

BISopt/BIS Association With ICP, MAP, and CPPopt—Minute-by-Minute Data

Through the comparisons of BISopt values to ICP, MAP, and CPPopt and comparisons of BIS values to ICP and MAP, using minute-by-minute data, there were no grossly significant relationships found through Kendall correlation analysis. Nearly, all correlation coefficients calculated were below 0.5, with no significant difference within the results. Analysis outputs can be found in **Supplementary Files H**

and K (<http://links.lww.com/CCX/A943>).

DISCUSSION

This study assessed and confirmed the presence of a BISopt value in individual patients suffering moderate/severe TBI, expanding on our prior work (23). Further, we assessed the relationship between BISopt and other important physiologic aspects in TBI and

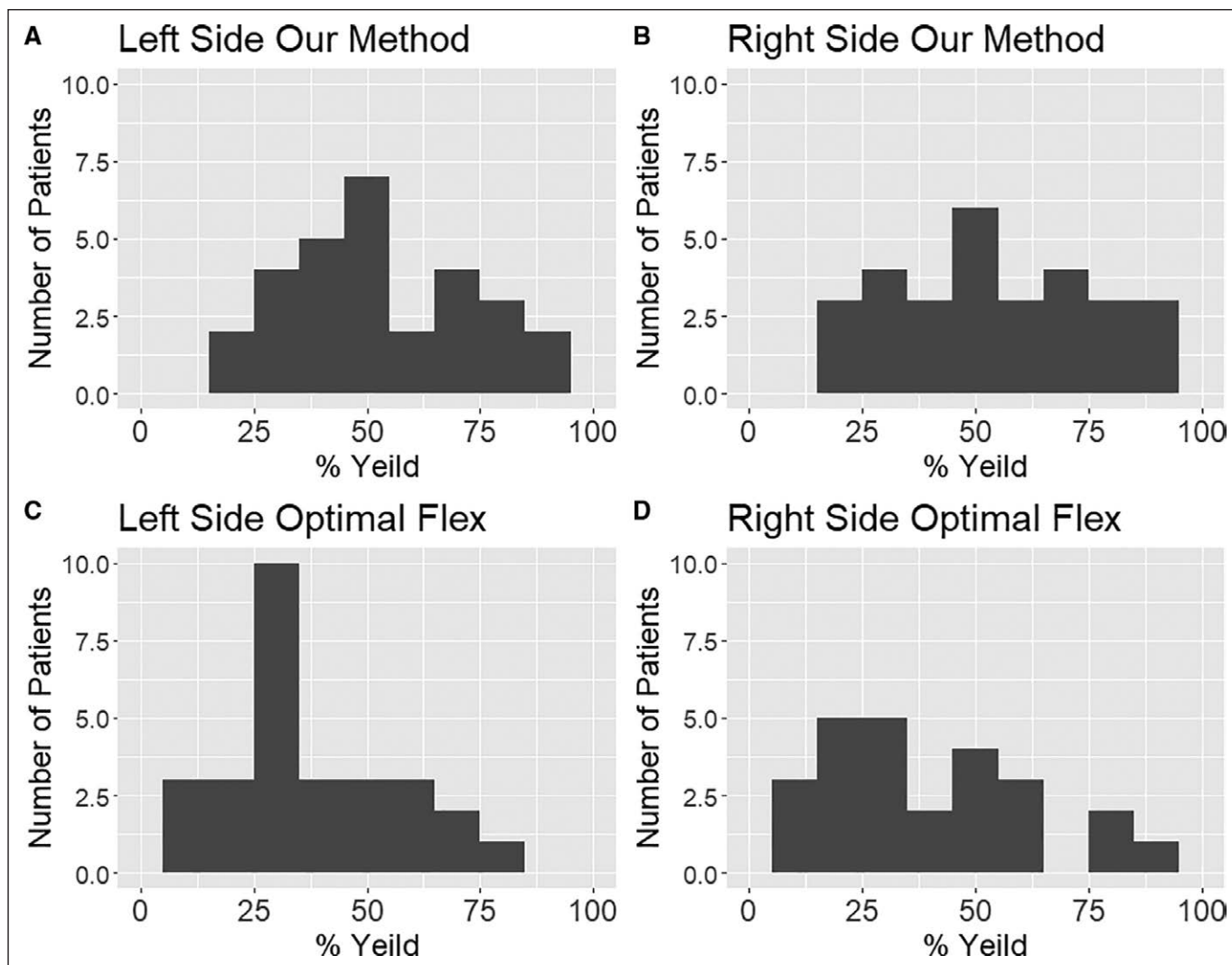


Figure 2. Histogram plots for % yield of different methods. **A** and **B**, The left and right side percent yield using our method for each patient. **C** and **D**, The left and right side of the percent yield of optimal Flex method for each patient.

critical care, namely MAP and CPPopt. By adapting previously described CPPopt curve fitting methods, we determined an BISopt value (a potential surrogate measure for depth of sedation) as attained by the lowest PRx value. This BISopt value was compared with ICP, MAP, and CPPopt in the entire cohort, showing no correlation. Individual BIS values were also compared with MAP and CPPopt using a Kendall's tau test over the entire recording period for each patient and dichotomized for intact and impaired autoregulation. Thus, we were able to highlight that BISopt was sufficiently uncoupled from CPPopt, suggesting BISopt as a potential distinct metric for personalized physiologic targeting in critical care. Finally, we outlined a method that can be used to derive a continuously updating BISopt value from patient data. Although the results here remain preliminary, some important aspects deserve highlighting.

First, nearly all of the patients within our cohort displayed a unique BISopt value that confirms our previous findings (23) and highlights the novel relationship between BIS values and cerebrovascular reactivity. This is despite past studies that have assessed sedation and cerebral autoregulation, where results were indeterminate (16, 18, 19, 35, 36). Within these prior studies, sedation state was determined through nursing assessed depth of sedation scores, which have limited reliability when assessing patients who are heavily sedated, with extended epochs between each sedation score collected. Thus, the prior attempts at evaluating the association between sedation depth and cerebral autoregulation have been limited, warranting further investigation using methods described in our study.

Our work suggests that a parabolic relationship may exist between BIS and PRx, facilitating the derivation

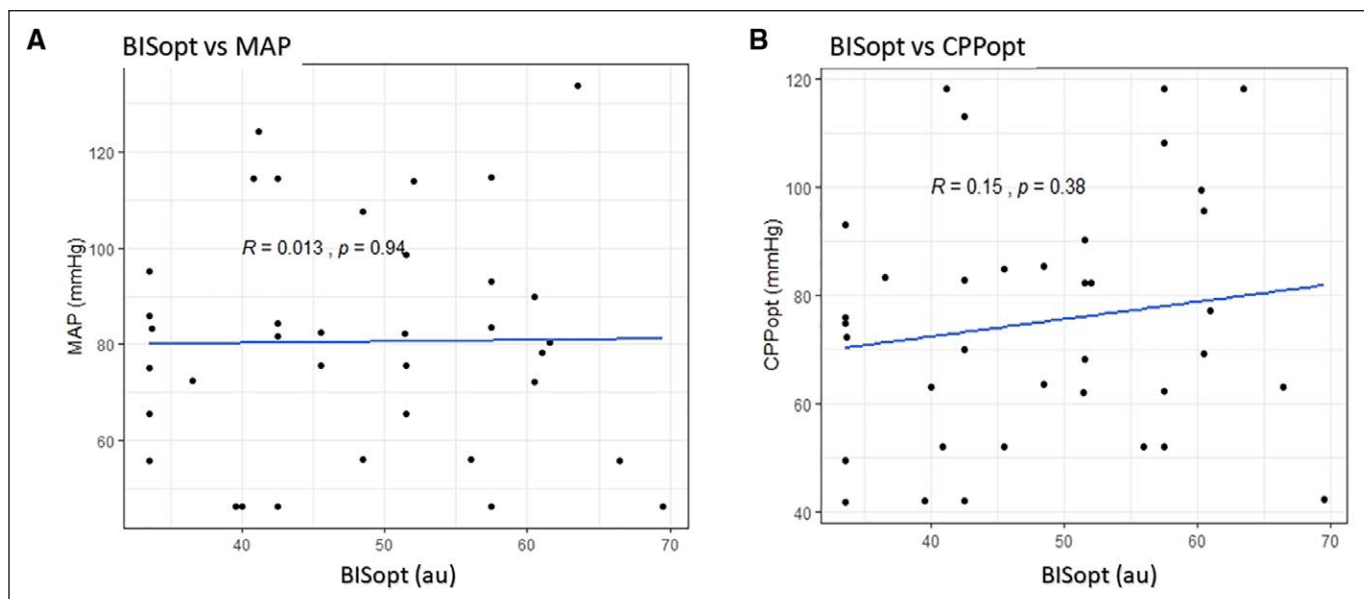


Figure 3. Scatter plot of optimal bispectral index (BISopt) and mean arterial pressure (MAP)/optimal cerebral perfusion pressure (CPPopt). **A**, BISopt versus mean MAP over the entire recording period for each patient with a Pearson correlation between the values, demonstrating no correlation between the values. **B**, BISopt versus CPPopt over the entire recording period for each patient with a Pearson correlation between the values, demonstrating no correlation between the values. au = arbitrary units, mm Hg = millimeter of mercury.

of a personalized BISopt value over time, which we propose is an BISopt level (which may represent an optimal depth of sedation) and could potentially balance the metabolic needs of cerebral vessels associated with an optimal PRx. It has been documented that the cerebrovascular response and blood flow are influenced by neurologic activity and metabolic demand, both of which are significantly linked to the sedation states of a patient (34, 36–40). Although the link between depth of sedation and cerebrovascular reactivity is still unclear, our work suggests the potential presence of an BISopt value where autoregulatory capacity remains the most intact. These findings may suggest that at very high levels of sedation (metabolic suppression levels) cerebral vessels may lose their innate ability to mediate vascular control and thus would demonstrate impaired PRx (39). In corollary, with less sedation in the post-TBI state, there may be an increase in metabolic demand, leading to the buildup of metabolic byproducts of anaerobic metabolism, which could cause vasodilation (39); alternatively, reduced sedation may increase sympathetic tone and vasoconstriction, both of these could have detrimental effects on cerebrovascular reactivity though this requires more study (16, 35, 41). BISopt may therefore offer an individualized threshold for sedation treatment and could lead to more effective management for

critical care patients requiring sedation infusions as part of their ICU care (see the following for terminology **Supplementary File L**, <http://links.lww.com/CCX/A943>). This is supported by the fact that improved PRx values (PRx < 0.2) have been demonstrated to show improved outcomes in a large number of studies, both in TBI and non-TBI illness (1, 9, 21, 26, 28, 42–49). Further, it is highlighted through recent developments in personalized CPP derivation in TBI care (20–22, 28, 50).

Second, in the determination of BISopt, it should be noted that like CPPopt, the BISopt value index may fluctuate over the time of care. Therefore, we have endeavored to build a continuously updating method to determine BISopt throughout the entire patient recording period. Based on the similarity between our algorithmic method (**Supplementary File C**, <http://links.lww.com/CCX/A943>) and direct visual inspection, a simple quadratic function appears to be sufficient for most scenarios. Furthermore, the improved percent yield of BISopt using our algorithmic method versus optimal Flex indicates that when endeavoring to identify an BISopt value, not all methods currently applied to CPPopt derivation necessarily apply to BISopt derivation. Although we adapted previously documented CPPopt methods for the continuous determination of BISopt, future work is required to achieve the most BISopt value.

Finally, there was a disassociation between any BIS values/BISopt and ICP, MAP, or CPPopt value. This helps confirm that the BISopt values appear to be independent from other currently explored aspects of personalized care in the ICU, namely MAP or CPPopt directed targets. As such, the preliminary findings here potentially indicate that individual sedation depth and systemic blood pressure-based measures are sufficiently independent and highlights the idea that BISopt may in fact have a separate and entirely unique relationship to PRx, which is distinct from CPPopt.

First limitation is the small, heterogeneous cohort available in this study, which warrants larger datasets with collaborations like Collaborative European NeuroTrauma Effectiveness Research in TBI (13), as well as investigation of non-TBI populations (14, 51, 52). Second, the nature of the BIS values and its relationship to sedation type, sedation depth, systemic blood pressure, and other confounding factors was only preliminarily commented. Although BISopt from different sedative agents appeared to be similar, this requires further exploration. Also, all patients suffered from trauma-induced alterations in level of consciousness, which may impact BIS; thus, non-TBI populations are required to verify our findings. Third, we could not comment on the association of BISopt with outcomes. Analysis of the relationship between BISopt and long-term outcome requires more than the typical course outcome metric seen in TBI studies, often consisting of point measures of the Glasgow Outcome Score. Studies have shown that sedative dose exposure and time in ICU care are associated with worse long-term cognitive function (15–17), any comparison of BISopt with outcome would necessitate comprehensive neurocognitive assessments. Fourth, although we have shown that the BISopt, MAP, and CPPopt appear to function independently, titrated levels of sedation often have secondary impacts on systemic hemodynamics; similarly, it is unclear how the manipulation of MAP with vasoactive agents affects BISopt. Future interventional studies are warranted to understand how these metrics of cerebral autoregulation interact with each other in real-time. Finally, the capturing of BIS values can be problematic within the ICU over long periods of time. A consistent issue we encountered were artifacts or loss of signals due in part to the fact that the pads used to capture the electroencephalogram signals often lose sufficient scalp contact to

capture signals. Such events require constant bedside attention to the electrodes and frequent changing of the disposable pads. If future large-scale adoption of BIS monitoring in the ICU is to occur, there will have to be improvements in disposable electrode design to facilitate longer artifact-free recording.

The method of CPPopt has completed its feasibility study, demonstrating that there were no significant differences between groups for therapy intensity level or for other safety endpoints, thus an individual and dynamic cerebral autoregulation-guided CPP is feasible and safe in TBI ICP patients (19). Based on these results, our similar method of BISopt may be equally feasible and safe.

Finally, future assessment in the association of BIS and other methods to sedation depth should be tested including other forms of the entropy electroencephalogram sedation measures, higher resolution full array electroencephalogram and entropy derivation at multiple channels. This should include the analysis of links to sedation, the impact of various cofactors as well as discrepancies within the methods. Such analysis will again require the evaluation of groups outside TBI populations and requires continuous physiologic and treatment information. Thus, future exploration into continuous data groups is advised.

CONCLUSIONS

Real-time BISopt can be identified during the continuous physiologic monitoring of patients with moderate/severe TBI. Real-time derivation of BISopt is possible, although future considerations on specific algorithmic methods for its calculation are required. BISopt appears to be unassociated with MAP or CPPopt, supporting it as a potentially unique individualized physiologic target in ICU care. BISopt management to optimize cerebrovascular pressure reactivity should be the subject of future studies in moderate/severe traumatic head-injury patients.

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