Individualizing Thresholds of Cerebral Perfusion Pressure Using Estimated Limits of Autoregulation

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Objectives: In severe traumatic brain injury, cerebral perfusion pressure management based on cerebrovascular pressure reactivity index has the potential to provide a personalized treatment target to improve patient outcomes. So far, the methods have focused on identifying "one" autoregulation-guided cerebral perfusion pressure target—called "cerebral perfusion pressure optimal". We investigated whether a cerebral perfusion pressure autoregulation range—which uses a continuous estimation of the "lower" and "upper" cerebral perfusion pressure limits of cerebrovascular pressure autoregulation (assessed with pressure reactivity index)—has prognostic value.

Design: Single-center retrospective analysis of prospectively collected data.

Setting: The neurocritical care unit at a tertiary academic medical center.

Patients: Data from 729 severe traumatic brain injury patients admitted between 1996 and 2016 were used. Treatment was guided by controlling intracranial pressure and cerebral perfusion pressure according to a local protocol.

Interventions: None.

Methods and Main Results: Cerebral perfusion pressure-pressure reactivity index curves were fitted automatically using a previously published curve-fitting heuristic from the relationship between pressure reactivity index and cerebral perfusion pressure. The cerebral perfusion pressure values at which this "U-shaped curve" crossed the fixed threshold from intact to impaired pressure reactivity (pressure reactivity index = 0.3) were denoted automatically the "lower" and "upper" cerebral perfusion pressure limits of reactivity, respectively. The percentage of time with cerebral perfusion pressure below (%cerebral perfusion pressure < lower limit of reactivity), above (%cerebral perfusion pressure > upper limit of reactivity), or within these reactivity limits (%cerebral perfusion pressure within limits of reactivity) was calculated for each patient and compared across dichotomized Glasgow Outcome Scores. After adjusting for age, initial Glasgow Coma Scale, and mean intracranial pressure, percentage of time with cerebral perfusion pressure less than lower limit of reactivity was associated with unfavorable outcome (odds ratio %cerebral perfusion pressure < lower limit of reactivity, 1.04; 95% CI, 1.02–1.06; $p < 0.001$) and mortality (odds ratio, 1.06; 95% CI, 1.04–1.08; $p < 0.001$).

Conclusions: Individualized autoregulation-guided cerebral perfusion pressure management may be a plausible alternative to fixed cerebral perfusion pressure threshold management in severe traumatic brain injury patients. Prospective randomized research

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will help define which autoregulation-guided method is beneficial, safe, and most practical. (*Crit Care Med* 2017; 45:1464–1471)
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Severe traumatic brain injury (TBI) is a major cause of global morbidity (1) with a quarter to a third of patients dying as a result of the injury (2). This high burden highlights the urgent need for research into improving management of severe TBI. Since TBI pathophysiology is heterogeneous across patients and over time, one attractive avenue is to individualize patient management during the intensive care admission (3, 4).

After the initial trauma, secondary insults such as cerebral ischemia contribute to poor outcome, and their early detection and amelioration are central to neurocritical care (5). Maintaining cerebral perfusion pressure (CPP; mean arterial blood pressure [MAP] – intracranial pressure [ICP]) above a certain limit may help decrease cerebral ischemia, but a CPP that is driven too high may contribute to cerebral edema or precipitate systemic complications (6). On this basis, current Brain Trauma Foundation guidelines recommend maintaining CPP between 60 and 70 mm Hg (7).

The cerebrovascular pressure reactivity index (PRx) has been proposed as a guide for individualizing CPP management (8). In this autoregulation-based technique, PRx (the moving correlation between slow fluctuations in MAP and ICP over a 5-min window) is plotted against trends in CPP to create a U-shaped CPP-PRx curve outlining the CPP at which pressure reactivity is more efficient—the 'optimal' CPP (CPPopt) (**Fig. 1**) (8, 9). This procedure is applied iteratively on moving calculations on recent patients' data to provide (semi) continuous CPP-PRx curves and CPP targets. Data supporting the usage of this approach, despite deriving from a relatively small number of retrospective analyses, are promising (9–13).

However, existing studies have focused on identifying one autoregulation-guided CPP target ignoring the fact that a broader CPP range might provide similar autoregulation benefit. As depicted on Figure 1, understanding the position and shape of CPP-PRx may help us identify the CPP below which PRx is impaired (the lower limit of reactivity [LLR]), the CPP above which PRx is again impaired (upper limit of reactivity [ULR]), and the CPP range associated with intact PRx (within limits of reactivity [WLR]).

Our aim was to extend our current individualized CPP recommendation method to determine continuously and automatically the CPP range with intact pressure reactivity in a single-center dataset of severe TBI patients (1996–2016). We compared the performance of these dynamic individual CPP autoregulation thresholds with the CPPopt target and the recommended fixed CPP thresholds by evaluating the relationships with outcome.

MATERIALS AND METHODS

Patients

Eight hundred thirty-six severe TBI patients entering the neurocritical care unit (NCCU) with computerized ICP monitoring (September 1996–June 2016) were selected. One hundred seven patients were removed (< 12-hr [ICP] monitoring data, age ≤ 12 yr old, no PRx available, Glasgow Outcome Score [GOS] not available), leaving 729 patients for final analysis. Pupil reactivity information was only available in 207 patients (28%). Use of computer-recorded data was approved by NCCU Users' Committee and conducted before 2000 as a part of anonymous clinical audit. After 2000, regional ethical approval was obtained (30 REC 97/291) for anonymized data recording. Patients were managed according to TBI guidelines (14) aimed at keeping ICP less than 20 mm Hg and CPP greater than 50–60 mm Hg. CPPopt or PRx-guided management was not part of the management algorithm. GOS was obtained at 6 months by outpatient assessment (15).

Data Acquisition and Processing

ICP was monitored with an intraparenchymal sensor (Codman ICP Micro-Sensor; Codman & Shurtleff, Raynham, MA). Arterial blood pressure (ABP) was zeroed at the level of the right atrium (Baxter Healthcare Health Care Corp. Cardio Vascular Group, Irvine, CA). No corrections were made for hydrostatic pressure influence. Data were sampled at 100 Hz with proprietary data acquisition and analysis software (ICM+, Cambridge Enterprise Ltd, Cambridge, UK; http://www.neurosurg.cam.ac.uk/icmplus). ABP and ICP signals were first averaged (mean) over a 10-second window; then, PRx was calculated as the moving Pearson correlation of 30 consecutive ABP and ICP, updated every minute (16).

Automated CPP-PRx Curve Fitting and CPPopt Determination

CPP-PRx curve fitting was calculated as described previously (9). Briefly, 5-minute periods of mean CPP (updated every min) were collected alongside 1-minute mean values of PRx. These PRx values were then binned into 5-mm Hg wide CPP intervals. These data were plotted as an error bar chart with CPP on the *x*-axis and PRx on the *y*-axis. A second-order polynomial curve was fitted after 4 hours of data collection with predefined heuristics, and the resulting local minimum was denoted CPPopt (Fig. 1). A moving window with 1-minute updates was used to generate a trend of CPPopt.

To address the issue of a relatively low yield of CPPopt curves introduced by the strict physiologic heuristic constraints of the curve-fitting process (9), we used the averaging method proposed by Depreitere et al (10). Instead of a single calculation window (of 4 hr) to produce the CPP-PRx curve variables (CPPopt, LLR, ULR, and WLR), multiple calculation windows were applied from a period of 2 to 8 hours (in 10-min increments) to yield up to 36 estimations. The mean of these estimates was calculated and updated every minute.

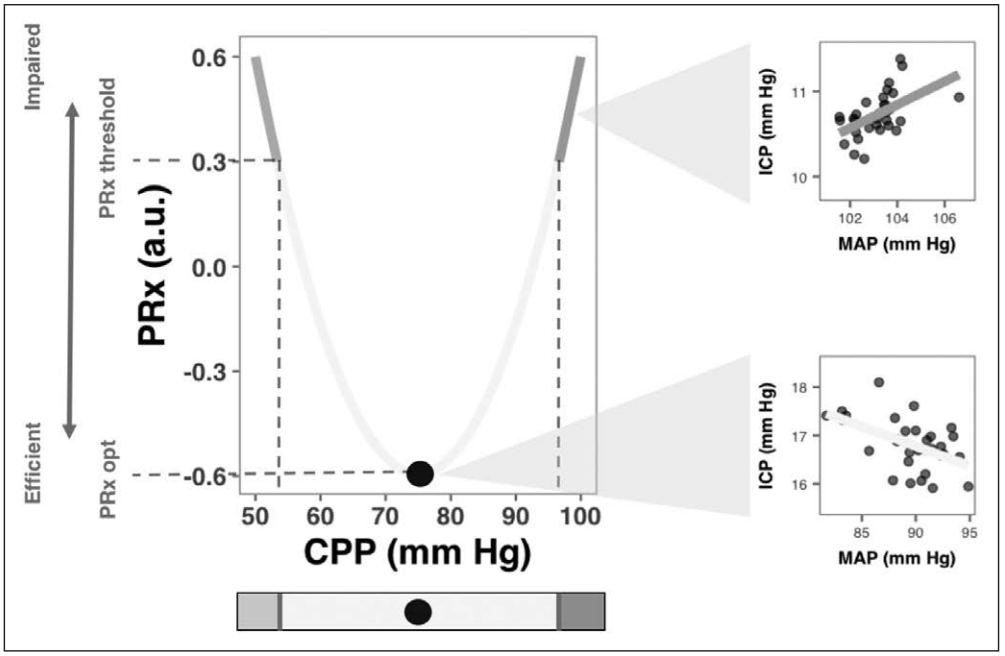

Figure 1. Schematic depicting the theoretical relationships between cerebral perfusion pressure (CPP) and pressure reactivity index (PRx) including estimation of 'optimal' CPP (CPPopt), CPP lower limit of reactivity (LLR), and CPP upper limit of reactivity (ULR). The relationship between CPP and PRx can be approximated by fitting a U-shaped curve (second-order polynomial) whereby with both high and low values of CPP, the PRx is impaired (*top right*). With impaired PRx, there is a positive correlation between changes in mean arterial pressure (MAP) and changes in intracranial pressure (ICP) (calculated over a 5-min window). However, for intermediate CPP values, PRx is (probably) efficient (*bottom right*), and the CPP at which PRx is most negative is termed the CPPopt (as indicated by the *large black dot*). By applying a threshold for impaired cerebral PRx (here, PRx = +0.30), the CPP at which PRx switches from being intact to impaired can be calculated to give an estimate of the CPP LLR and CPP ULR. Summarizing the relationships between CPP and the variables (LLR, ULR, and CPPopt), we can appreciate how far a patients' CPP is from their autoregulation-guided target or range. PRxopt = PRx optimal.

ΔCPPopt was calculated as the patients' CPP minus the calculated (multiwindow) CPPopt every minute. Positive and negative values were interpreted as the time a patient spent (%) with a CPP above or below the CPPopt, respectively. ΔCPPopt is independent on the level of head elevation, and therefore possible errors derived from hydrostatic influences are compensated for.

Automated Estimation of the LLR and ULR

The defined CPP-PRx curve was extrapolated to both sides to include the full range of plausible CPP values (from 40 to 120 mm Hg) to obtain the CPP values at which the curve crossed the threshold PRx value for impaired pressure reactivity (PRx = +0.30) (Fig. 1). The value of CPP at these two points of intersection was denoted automatically the LLR and ULR, respectively. If a curve was entirely above the PRx threshold, no intersection could be calculated, and thus, the LLR and ULR were set to equal the CPPopt. In addition, extreme values for the estimated LLR and ULR (< 40 and 120 mm Hg) were defaulted to 40 or 120 mm Hg, respectively. Furthermore, where the fitted CPP-PRx yielded a monotonically ascending or descending curve with no inflection point, no strict intersection with the PRx threshold could be calculated, and thus the LLR was taken to be 40 mm Hg and the ULR 120 mm Hg, respectively. For example, if a descending curve (no inflection point) crossed the threshold at a CPP of 50 mm Hg, the LLR would be denoted 50 mm Hg and the ULR would default to 120 mm Hg. The value of 0.3 as a threshold for PRx was chosen as it has been identified as a critical threshold for determining fatal outcome in a previous study of severe TBI patients in our cohort (17).

Statistical Analysis

We compared three CPP thresholds: 1) recent guideline CPP thresholds (lower = 60; upper = 70 mm Hg); 2) the CPPopt-based thresholds (lower = a CPP > 10 mm Hg below CPPopt or ΔCPPopt < –10; upper = a CPP > 10 mm Hg above CPPopt or ΔCPPopt > +10); and 3) the flexible CPP reactivity thresholds (lower = LLR; upper = ULR). For each patient, the amount of time (%) spent below the lower threshold, above the upper threshold, and between both thresholds was calculated and then compared across dichotomized outcome groups. Unfavorable outcome was defined as death, vegetative state, or severe disability. Univariate outcome relationships were performed by comparing receiver operating curves (ROCs) attributes.

For each CPP threshold approach, multivariable logistic regression models were constructed for outcome prediction. Available covariates in our 1996–2016 cohort were age, Glasgow Coma Scale, and mean ICP. The best subset selection algorithm was applied using an exhaustive method that searches the best model, based on the lowest Akaike information criterion (18). We used the *R* language and software environment for statistical computation (R Core Team 2015 version 2.12.1; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/) using the following packages: dplyr (19), ggplot2 (20), and bestglm (18). The significance level was set at 0.05.

RESULTS

Patient Characteristics

Summary demographic data of the 729 patients in this analysis are shown in **Table 1**. The mean age was 42 (± 17). Mean ICP was 15.1 (± 6.2) mm Hg and was significantly higher in those who died (18.4 ± 8.2 mm Hg; $p < 0.001$). Mean CPP was 78.2 ± 8.2 mm Hg and was lower in those who died (76.8 ± 9.5; $p = 0.008$). The mean CPPopt was 78.6 ± 7.9 mm Hg and was not different across outcome groups ($p = 0.74$). Compared with the single 4-hour window, the CPPopt availability (calculated

TABLE 1. Demographic and Physiologic Description of Cohort

Variables	Good Recovery	Moderate Disability	Severe Disability/ Vegetative State	Death	*p*
n	139	183	253	154	
Age, mean (SD)	33.91 (16.11)	35.28 (15.31)	39.98 (15.85)	45.03 (18.43)	< 0.001
Gender, *n* (%)					0.025
Female	32 (23)	27 (15)	66 (26)	28 (18)	
Male	107 (77)	156 (85)	187 (74)	126 (82)	
Admission Glasgow Coma Scale, median (IQR)	8.00 (5.50–10.00)	8.00 (5.00– 10.00)	6.00 (4.00–8.00)	5.00 (3.00– 8.00)	< 0.001
Monitoring hr, mean (SD)	116.84 (91.67)	139.40 (106.91)	151.63 (114.73)	122.13 (90.53)	0.004
% valid CPP-PRx curve multi window, mean (SD)	93.46 (7.01)	92.62 (7.90)	93.39 (7.72)	91.91 (10.28)	0.269
% valid CPP-PRx curve single window, mean (SD)	60.75 (13.77)	58.94 (13.54)	60.01 (14.18)	59.38 (13.96)	0.673
Intracranial pressure (mm Hg), mean (SD)	14.02 (4.51)	14.22 (4.80)	14.37 (5.05)	18.35 (8.15)	< 0.001
CPP (mm Hg), mean (SD)	79.55 (6.90)	78.63 (6.22)	79.68 (6.93)	76.77 (9.45)	0.001
CPPopt (mm Hg), mean (SD)	77.46 (6.91)	77.31 (6.32)	77.45 (7.32)	78.11 (7.79)	0.745
PRx, mean (SD)	0.01 (0.14)	0.03 (0.14)	0.06 (0.14)	0.16 (0.19)	< 0.001
CPP LLR (mm Hg), mean (SD)	58.63 (7.43)	58.66 (6.55)	58.94 (7.35)	62.34 (8.10)	< 0.001
CPP ULR (mm Hg), mean (SD)	96.43 (6.43)	96.04 (6.90)	95.56 (7.83)	94.56 (8.96)	0.166
WLR range (mm Hg), mean (SD)	37.80 (7.97)	37.37 (6.69)	36.62 (7.83)	32.22 (10.32)	< 0.001
%CPP < LLR, mean (SD)	6.46 (7.61)	7.80 (8.26)	8.37 (10.33)	21.06 (21.30)	< 0.001
%CPP within WLR, mean (SD)	81.95 (14.34)	80.14 (15.16)	77.26 (17.18)	65.84 (24.22)	< 0.001
%CPP > ULR, mean (SD)	11.58 (9.72)	12.07 (10.68)	14.36 (12.59)	13.10 (11.25)	0.071
%CPP < 60, mean (SD)	2.77 (3.13)	3.74 (5.06)	4.14 (7.15)	10.48 (15.56)	< 0.001
%CPP 60–70, mean (SD)	18.01 (13.34)	20.57 (13.33)	18.34 (12.70)	19.37 (12.87)	0.237
%CPP > 70, mean (SD)	79.22 (15.42)	75.69 (16.52)	77.52 (17.12)	70.15 (23.63)	< 0.001
%ΔCPPopt < −10, mean (SD)	14.13 (8.33)	16.54 (10.31)	15.56 (11.07)	23.20 (14.53)	< 0.001
%ΔCPPopt ± 10, mean (SD)	61.89 (10.50)	60.07 (11.07)	58.43 (12.22)	57.89 (12.47)	0.011
%ΔCPPopt > 10, mean (SD)	23.97 (11.15)	23.39 (11.20)	26.01 (13.42)	18.90 (12.60)	< 0.001

CPP = cerebral perfusion pressure, ΔCPPopt = CPP – optimal CPP (CPPopt) IQR = interquartile range, LLR = lower limit of reactivity, PRx = pressure reactivity index, ULR = upper limit of reactivity, WLR = within CPP limits of reactivity.

from the time of first estimate) increased significantly with the multiwindow approach (60% ± 14 vs 93% ± 8 of the monitoring period; $p < 0.001$) and was not different across outcome groups ($p = 0.27$). Excluding one patient, whose CPP did not reach above 30 mm Hg, all patients had at least some CPPopt availability.

The CPP Limits of Cerebrovascular Reactivity

The mean CPP LLR and ULR for the cohort were 59.3 (± 7.3) mm Hg and 96.0 (± 7.5) mm Hg, whereas the mean WLR was 36.8 ± 7.8 mm Hg. Two patient examples of the interaction between CPP and the CPP LLR and ULR are shown in **Figure S2** (Supplemental Digital Content 2, http://links.lww.com/CCM/C710—**legend**, Supplemental Digital Content 4, http://links.lww.com/CCM/C712). The interrelationships between flexible CPP thresholds and other physiologic variables are depicted in a correlation matrix (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C709—legend, Supplemental Digital Content 4, http://links.lww.com/CCM/C712). Notably, the WLR was significantly related to mean PRx ($r = –0.74$; $p < 0.001$). Older patients tended to have a smaller WLR range and a higher CPP LLR that might indicate a rightward shifted and narrower autoregulation plateau.

Prognostic Significance of CPP: Fixed Versus Flexible CPP Thresholds

Spending more time with CPP less than 60 was related to death (**Fig. 2**), whereas spending more time with CPP greater than 70 was not (in fact, inversely related). These findings were confirmed in area under ROC (AUROC) analysis (**Fig. 3** and Table S1, Supplemental Digital Content 3, http://links.lww.com/CCM/C711). In all outcome groups, the percentage of time within the recent guideline CPP range was low (mean 19.1% ± 13.1) (Fig. 2).

Time with ΔCPPopt less than −10 was significantly related to mortality, whereas spending more time with ΔCPPopt greater than +10 was not (similar to CPP > 70, there was an inverse relationship) (Fig. 2 and Table S1, Supplemental Digital Content 3, http://links.lww.com/CCM/C711). In ROC analysis, time with ΔCPPopt less than −10 significantly predicted mortality (AUROC, 0.66; 95% CI, 0.61–0.72; $p < 0.001$) and favorable outcome (AUROC, 0.56; 95% CI, 0.51–0.61; $p < 0.001$).

The percentage of time with CPP less than LLR was a significant predictor of both unfavorable outcome (AUROC, 0.60; 95% CI, 0.56–0.64; $p < 0.001$) and mortality (AUROC, 0.73; 95% CI, 0.68–0.77; $p < 0.001$) (Fig. 3 and Table S1, Supplemental Digital Content 3, http://links.lww.com/CCM/C711). The percentage of time with CPP greater than ULR predicted unfavorable outcome (AUROC, 0.54; 95% CI, 0.50–0.58; $p = 0.02$) but not mortality ($p = 0.89$).

For all three approaches, looking at absolute time (rather than %time as described here) gives quantitatively similar results (data not shown).

Multivariable Analysis

Based on the univariate analyses, percentage of time with CPP below each threshold was included in initial models predicting mortality, whereas percentage of time with CPP above and below each threshold was included in the initial models predicting unfavorable outcome. After applying the best subset algorithm, percentage of time with CPP above the upper thresholds was not present in any model. Multivariate models using the flexible CPP reactivity limits (rather than fixed CPP or ΔCPPopt limits) showed the best ability to predict unfavorable outcome (AUROC = 0.75) and mortality (AUROC = 0.82) (**Table 2**).

DISCUSSION

In this study of 729 severe TBI patients, we extended our autoregulation-guided CPP method with a novel technique that in addition to estimating the CPPopt value, also estimates the CPP limits of cerebral pressure reactivity. We demonstrated that deviation of CPP from the autoregulation-guided individual and flexible thresholds is related to patient outcome, even after adjusting for important TBI prognostic covariates.

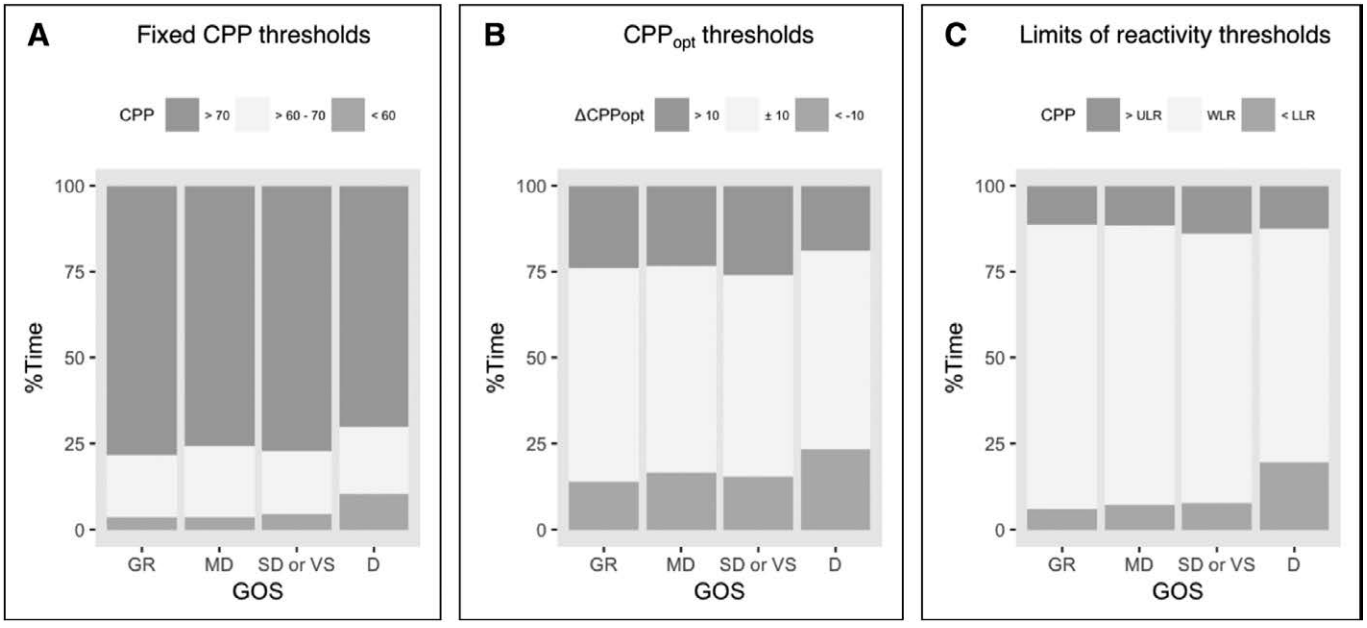

Figure 2. Comparison of %time spent in different "zones" of cerebral perfusion pressure (CPP) as defined by fixed thresholds (*left*), optimal CPP (CPPopt)–based thresholds (*middle*), or flexible limits of reactivity (lower limit of reactivity [LLR]) (*right*). **A**, Using the Brain Trauma Foundation recommended fixed CPP values of 60 and 70 mm Hg as lower and upper thresholds, most patients spent the majority of time with a CPP above the upper threshold. In those who died, the proportion of time with CPP > 70 mm Hg was the lowest and proportion of time with CPP < 60 mm Hg the highest. **B**, The CPPopt-based thresholds were estimated as follows: lower threshold was a CPP > 10 mm Hg below CPPopt (ΔCPPopt < −10), whereas the upper threshold was a CPP > 10 mm Hg above CPPopt (ΔCPPopt > +10). Those with severe disability (SD) or vegetative state (VS) spent the most amount of time above the upper CPPopt threshold, whereas those who died spent the most time with CPP below the lower CPPopt threshold. **C**, Referencing patients' current CPP to their individually estimated LLR and upper limit of reactivity (ULR) reveals the most consistent pattern; those patients with increasing burden of disability spent more time with a CPP below their LLR and above their ULR. D = death, GOS = Glasgow Outcome Score, GR = good recovery, MD = moderate disability, WLR = within limits of reactivity.

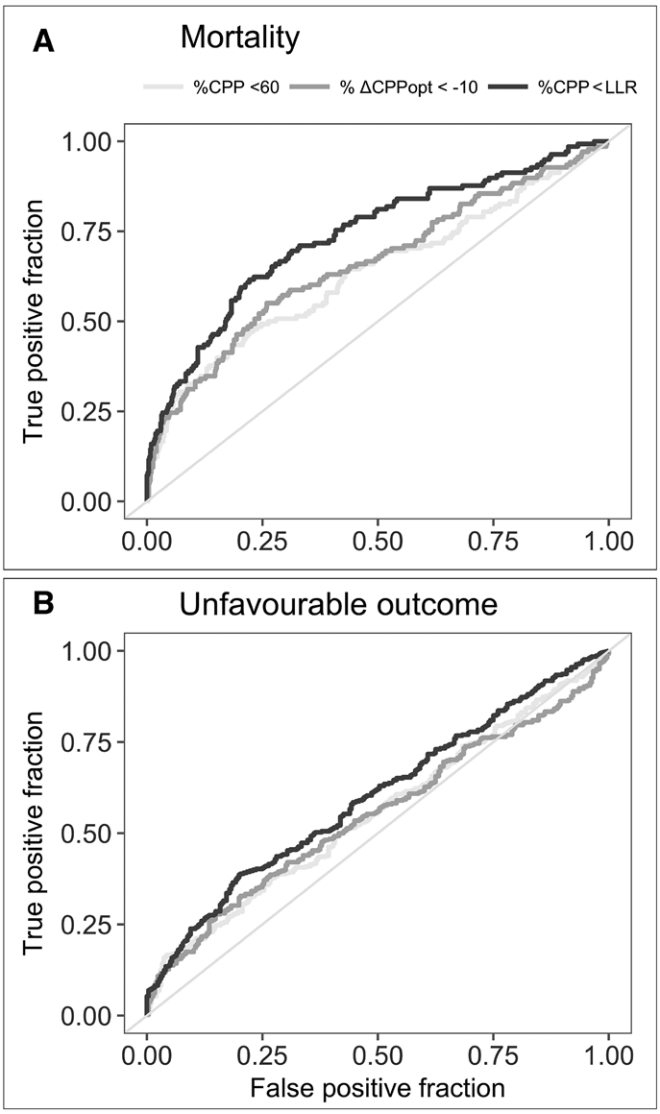

Figure 3. Comparison of receiver operator characteristic curves for predicting mortality (**A**) and unfavorable outcome (**B**). Percentage of time with cerebral perfusion pressure (CPP) below the lower limit of reactivity (LLR) (%CPP < LLR) was the strongest predictor of mortality and unfavorable outcome. ΔCPPopt = CPP − CPPopt.

Characterizing CPP Limits of Pressure Reactivity Using the CPP-PRx Curve

Similar to the recently developed visualization method of the CPP-PRx landscape (21), the continuous estimation of CPP LLR and ULR provides the clinician with more contextual information to the single CPPopt value and therefore may align better with clinical acumen. Although targeting the CPPopt is a practical option for a randomized clinical trial, there are clinical situations where strictly targeting the CPPopt continuously might be risky and may outweigh the overall potential benefit. For example, in a patient with a broad CPP pressure reactivity range, lower CPP targets can be accepted for a certain period limiting the need for administration of large doses of vasopressors and fluids, which reduces (microvascular) damage to other organ systems (22). In this scenario, management based on the individual autoregulation-guided CPP could be a compromise between the aggressive CPP-oriented therapy promulgated by Rosner et al and the more permissive Lund protocol (23, 24).

The CPP-PRx Curve–A Pragmatic and Prognostically Important Relationship

The time spent with CPP less than LLR and (10 mm Hg) deviation below CPPopt were significantly related to adverse outcome (Tables 1–2 and Figs. 2–3), fitting with the clinical maxim that periods with low CPP should be avoided in severe TBI patients (9, 25, 26). There is evidence that even short periods of cerebral hypoperfusion contribute to secondary brain injury and are related to unfavorable outcome (25). Indeed, a large body of evidence indicates that a low CPP is deleterious through a range of interrelated pathways including deranged cortical and global cerebral blood flow, oxygenation, and metabolism (27–29). The sequelae of having a CPP greater than ULR and (10 mm Hg) deviation above CPPopt are less clear; in this large cohort, only modest relationship to unfavorable outcome was found (Table 1 and Fig. 2). Although this could perhaps indicate that the morbidity caused by periods of "hyperperfusion" is outweighed by the morbidity engendered by periods of "hypoperfusion," it is also possible that deleterious effects of aggressively elevated CPP are not detected by our coarse outcome measures (GOS).

The observation that PRx was strongly positively related to LLR and negatively related to the WLR (Fig. S2, Supplemental Digital Content 2, http://links.lww.com/CCM/C710—legend, Supplemental Digital Content 4, http://links.lww.com/CCM/C712) has pragmatic implications: the complex concept of PRx can be translated into something immediately clinically meaningful—a number that represents margins of individual cerebral autoregulatory capacity. This idea fits with the current guidelines stating that higher and lower CPP values might be accepted dependent on autoregulation status (7).

It is notable that when time spent with CPP less than LLR is grouped by patient outcome, the major differences are between those who died and survived, rather than distinguishing between the individual categories of survival (GOS 2–5). A similar phenomenon was found with TBI prognostic models applied to the large Corticosteriod Randomisation After Significant Head Injury (CRASH) database (30, 31), highlighting the urgent need for further investigation into novel TBI prognostic markers. It is also striking that most patients spent significant periods of time with CPP above current recommendations (Table 1 and Fig. 2). Similar observations can be found in other recent studies (32–34).

Limitations

This study has several important limitations. By nature of its observational design, conclusions about whether an autoregulation-guided CPP protocol will improve patient physiology or outcome are not possible. Nevertheless, the extension of the method described here seems crucial for the design of different prospective trials. Practical and safety issues might guide choices between strict flexible targets, flexible thresholds, or even flexible ranges.

The algorithm for the CPP-PRx curve fitting and deriving the CPPopt and limits of reactivity as described here represents our current efforts but does not preclude modifications or alternative

TABLE 2. Binary Logistic Regression Models (Odds Ratios) for Prediction of Unfavorable Outcome and Mortality

	Unfavorable Outcome			Mortality		
Variable	(1)	(2)	(3)	(4)	(5)	(6)
%ΔCPPopt < −10 mm Hg	1.02[a] (1.00–1.03)			1.05[b] (1.03–1.07)		
%CPP < 60 mm Hg		1.03[a] (1.00–1.06)			1.05[a] (1.02–1.07)	
%CPP < lower limit of reactivity			1.04[c] (1.02–1.06)			1.06[c] (1.04–1.08)
Age	1.04[c] (1.03–1.05)	1.04[c] (1.03–1.05)	1.04[c] (1.03–1.05)	1.04[c] (1.03–1.06)	1.04[c] (1.03–1.06)	1.04[c] (1.03–1.06)
Glasgow Coma Scale	0.82[c] (0.76–0.87)	0.82[c] (0.77–0.87)	0.82[c] (0.77–0.87)	0.85[c] (0.78–0.92)	0.87[c] (0.80–0.93)	0.87[c] (0.80–0.94)
Intracranial pressure	1.06[c] (1.03–1.09)	1.05[b] (1.02–1.09)	1.06[c] (1.03–1.09)	1.13[c] (1.09–1.16)	1.11[c] (1.07–1.15)	1.13[c] (1.09–1.17)
Log likelihood	−431.33	−432.89	−424.34	−296.04	−308.90	−282.18
Akaike information criteria	872.66	875.79	858.69	602.08	627.80	574.36
Area under the receiver operating curve	0.737	0.742	0.75	0.793	0.777	0.820

CPP = cerebral perfusion pressure, ΔCPPopt = CPP − CPPoptimal.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.

strategies. Specifically, modeling the CPP-PRx relationship using a second-order polynomial may be an oversimplification, as may applying the same heuristic constraints to the LLR and ULR estimation as to CPPopt. Similar to a previous study, the multiwindow approach to the CPP-PRx curve fit significantly increased CPPopt (and LLR/ULR) availability (10). Although undoubtedly a significant step forward, further work must be undertaken to explore the relative merits of this multiwindow technique and other potential approaches to improve the CPP-PRx curve parameter availability. Further, factors other than ICP/CPP may also affect pressure reactivity or autoregulation (35–39)—like Co_2 levels—and are not currently considered in the current concept and related management. However, the analysis of multimodal data (like in the high-resolution Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury [CENTER-TBI] study; https://www.center-tbi.eu/) might give insights in the near future (40).

Given that the monitoring data (including the single-window CPP-PRx curve) were not hidden from the treating clinicians, it is possible that in some cases, patient management decisions could have been influenced by the clinician evaluating the CPP-PRx relationship despite this not being in the treatment protocol during the 1996–2016 period. Unfortunately, we do not have information on whether this was the case, and if so, the potential magnitude of the effect.

Finally, a detailed analysis of the effect of various clinical scenarios on the CPP-PRx relationship was not addressed in the current study including the influence of decompressive craniectomies, the influence of more complete initial injury severity descriptors (i.e., extracranial injury, pupil reactivity) or the specific type of TBI pathology, or indeed the time course of the studied physiologic relationships. These should be explored in future studies. In spite of these caveats, CPPopt deviation and CPP LLR threshold have been shown to be prognostically relevant in a large cohort of 729 patients.

CONCLUSIONS

By examination of the CPP-PRx relationship, we can not only estimate the CPPopt but also derive a continuous estimation of the CPP LLR and CPP ULR. Deviation of CPP from autoregulation-guided flexible thresholds is related to patient outcome. Prospective randomized research is needed to define which autoregulation-guided method is most beneficial, safe, and practical.

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REFERENCES

1. Roozenbeek B, Maas AI, Menon DK: Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013; 9:231–236

2. Stein SC, Georgoff P, Meghan S, et al: 150 years of treating severe traumatic brain injury: A systematic review of progress in mortality. *J Neurotrauma* 2010; 27:1343–1353
3. Maas AI, Menon DK: Traumatic brain injury: Rethinking ideas and approaches. *Lancet Neurol* 2012; 11:12–13
4. Donnelly J, Budohoski KP, Smielewski P, et al: Regulation of the cerebral circulation: Bedside assessment and clinical implications. *Crit Care* 2016; 20:129
5. Le Roux P: Physiological monitoring of the severe traumatic brain injury patient in the intensive care unit. *Curr Neurol Neurosci Rep* 2013; 13:331
6. Robertson CS: Management of cerebral perfusion pressure after traumatic brain injury. *Anesthesiology* 2001; 95:1513–1517
7. Carney N, Totten AM, O'Reilly C, et al: Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2016; 24:s1–s106
8. Steiner LA, Czosnyka M, Piechnik SK, et al: Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 2002; 30:733–738
9. Aries MJ, Czosnyka M, Budohoski KP, et al: Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med* 2012; 40:2456–2463
10. Depreitere B, Güiza F, Van den Berghe G, et al: Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. *J Neurosurg* 2014; 120:1451–1457
11. Lewis PM, Czosnyka M, Carter BG, et al: Cerebrovascular pressure reactivity in children with traumatic brain injury. *Pediatr Crit Care Med* 2015; 16:739–749
12. Young AM, Donnelly J, Czosnyka M, et al: Continuous multimodality monitoring in children after traumatic brain injury-preliminary experience. *PLoS One* 2016; 11:e0148817
13. Needham E, McFadyen C, Newcombe V, et al: Cerebral perfusion pressure targets individualized to pressure-reactivity index in moderate to severe traumatic brain injury: A systematic review. *J Neurotrauma* 2017; 34:963–970
14. Menon DK: Cerebral protection in severe brain injury: Physiological determinants of outcome and their optimisation. *Br Med Bull* 1999; 55:226–258
15. Jennett B, Bond M: Assessment of outcome after severe brain damage: A pediatric scale *Lancet* 1975; 305:480–484
16. Donnelly J, Aries MJ, Czosnyka M: Further understanding of cerebral autoregulation at the bedside: Possible implications for future therapy. *Expert Rev Neurother* 2015; 15:169–185
17. Sorrentino E, Diedler J, Kasprowicz M, et al: Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocrit Care* 2012; 16:258–266
18. McLeod AI, Xu C: bestglm: Best Subset GLM. R package version 0.36. 2017. Available at: https://CRAN.R-project.org/package=bestglm. Accessed June 30, 2017
19. Wickham H, Francois R: dplyr: A Grammar of Data Manipulation. R Package version 050, 2016. Available at: http://cran.r-project.org/package=dplyr
20. Wickham H: Elegant Graphics for Data Analysis. New York, NY, Springer-Verlag, 2009
21. Aries MJH, Wesselink R, Elting JWJ, et al: Enhanced visualization of optimal cerebral perfusion pressure over time to support clinical decision making. *Crit Care Med* 2016; 44:e996–e99
22. Robertson CS, Valadka AB, Hannay HJ, et al: Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 1999; 27:2086–2095
23. Eker C, Asgeirsson B, Grände PO, et al: Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. *Crit Care Med* 1998; 26:1881–1886
24. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: Management protocol and clinical results. *J Neurosurg* 1995; 83:949–962
25. Güiza F, Depreitere B, Piper I, et al: Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. *Intensive Care Med* 2015; 41:1067–1076
26. Brain Trauma Foundation: Guidelines for the management of severe traumatic brain injury 3rd edition. *J Neurotrauma* 2007; 24(Suppl 1):S37–S44
27. Vespa P, Prins M, Ronne-Engstrom E, et al: Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: A microdialysis study. *J Neurosurg* 1998; 89:971–982
28. al-Rawi PG, Hutchinson PJ, Gupta AK, et al: Multiparameter brain tissue monitoring–correlation between parameters and identification of CPP thresholds. *Zentralbl Neurochir* 2000; 61:74–79
29. Donnelly J, Czosnyka M, Harland S, et al: Cerebral haemodynamics during experimental intracranial hypertension. *J Cereb Blood Flow Metab* 2017; 37:694–705
30. Perel P, Arango M, Clayton T, et al: Predicting outcome after traumatic brain injury: Practical prognostic models based on large cohort of international patients. *BMJ* 2008; 336:425–429
31. Steyerberg EW, Mushkudiani N, Perel P, et al: Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008; 5:e165
32. Spiotta AM, Stiefel MF, Gracias VH, et al: Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. *J Neurosurg* 2010; 113:571–580
33. Griesdale DE, Örtenwall V, Norena M, et al: Adherence to guidelines for management of cerebral perfusion pressure and outcome in patients who have severe traumatic brain injury. *J Crit Care* 2015; 30:111–115
34. Dias C, Silva MJ, Pereira E, et al: Optimal cerebral perfusion pressure management at bedside: A single-center pilot study. *Neurocrit Care* 2015; 23:92–102
35. Donnelly J, Czosnyka M, Sudhan N, et al: Increased blood glucose is related to disturbed cerebrovascular pressure reactivity after traumatic brain injury. *Neurocrit Care* 2015; 22:20–25
36. Sekhon MS, Griesdale DE, Czosnyka M, et al: The effect of red blood cell transfusion on cerebral autoregulation in patients with severe traumatic brain injury. *Neurocrit Care* 2015; 23:210–216
37. Dias C, Gaio AR, Monteiro E, et al: Kidney-brain link in traumatic brain injury patients? A preliminary report. *Neurocrit Care* 2015; 22:192–201
38. Smirl JD, Tzeng YC, Monteleone BJ, et al: Influence of cerebrovascular resistance on the dynamic relationship between blood pressure and cerebral blood flow in humans. *J Appl Physiol (1985)* 2014; 116:1614–1622
39. Lavinio A, Timofeev I, Nortje J, et al: Cerebrovascular reactivity during hypothermia and rewarming. *Br J Anaesth* 2007; 99:237–244
40. Maas AI, Menon DK, Steyerberg EW, et al; CENTER-TBI Participants and Investigators: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A prospective longitudinal observational study. *Neurosurgery* 2015; 76:67–80