

Optimal Cerebral Perfusion Pressure

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Optimal Cerebral Perfusion Pressure: Targeted Treatment for Severe Traumatic Brain Injury

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Abstract

Identification of individual therapy targets is critical for traumatic brain injury (TBI) patients. Clinical outcomes depend on cerebrovascular autoregulation (CA) impairment. Here, we compare the effectiveness of optimal cerebral perfusion pressure (CPPopt)-targeted therapy in younger (<45 years of age) and elderly (≥45 years of age) TBI patients. Single-center multi-modal invasive arterial blood pressure(t), intracranial pressure (ICP)(t), cerebral perfusion pressure CPP(t), and CPPopt(t) monitoring ($n=81$) was performed. ICM+ software was used for continuous CPPopt(t) status assessment by identification of pressure reactivity index (PRx). The most significant prognostic factors were age, Glasgow Coma Scale, serum glucose, and duration of longest CA impairment event (LCAI) when PRx(t) >0.5 within 24 h after admission. The modeled accuracies for favorable and unfavorable outcome prediction were 86.5% and 90.9%, respectively. Age above 45 years and averaged ICP during all monitoring time above 21.3 mm Hg was associated with unfavorable outcome of an individual patient. Averaged CPP values close to CPPopt were associated with a better outcome in younger patients. Averaged Δ CPPopt <−5.0 mm Hg, averaged PRx >0.36, and LCAI >100 min were significantly associated with mortality for the younger patients. The critical values of averaged PRx >0.26 and LCAI >61 min were significantly associated with mortality for the elderly group. Autoregulation-guided treatment was important for individual TBI management, especially in younger patients. Further randomized multi-center studies are needed to prove final benefit.

Keywords: cerebrovascular autoregulation; critical care; optimal cerebral perfusion pressure; pressure reactivity index; traumatic brain injury

Introduction

THE ABILITY OF THE CEREBRAL VASCULAR SYSTEM TO stabilize cerebral blood flow (CBF) ensuring metabolic brain demand over a wide physiological cerebral perfusion pressure (CPP) or arterial blood pressure (ABP) ranges is called cerebrovascular autoregulation (CA).^{1,2} Impairments of this function followed after a severe traumatic brain injury (TBI), strongly affect clinical outcomes.^{3–7} Therefore, continuous bedside CA status monitoring in comatose TBI patients can help to establish optimal, individualized targeted treatment strategies.⁸ Such patient-specific treatment can be achieved by identifying an individual optimal CPP value (CPPopt) as a target for ensuring cerebrovascular reactivity and, consequently, cerebral perfusion within the optimal range.^{8–13} Continuous CPP maintenance close to CPPopt can eliminate the

possibility of detrimental CA impairment events, which can cause ischemic or hyperemic brain insults.⁹

Clinical CA assessment can be based on measuring cerebral vascular resistance or CBF changes relative to the changes in CPP.^{5,14,15} However, for a long-term and continuous severe TBI treatment in the intensive care unit (ICU), CA status is determined more often by calculating the pressure reactivity index (PRx) as Pearson's correlation coefficient between ABP(t) and intracranial pressure (ICP)(t) slow waves over a moving time window of a few or more minutes.^{4–7}

Negative PRx(t) values reflect normal CBF autoregulation accompanied by active reactions in the cerebral vessels, which change their diameter, thus maintaining stable CBF. Positive PRx(t) values show an impaired mechanism of CBF autoregulation, which fails to ensure an adequate metabolic supply to brain cells.

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This goes together with a passive response to ABP(t) in cerebral vessel diameters, resulting in close to almost synchronous fluctuation in ABP(t) and ICP(t) slow waves. The maximal value of PRx is +1.0, reflecting that a total loss of CA is associated with nearly 100% mortality.^{4,5,17,18} Therefore, PRx(t) monitoring facilitates the classification of CA status into impaired CA (PRx is getting more positive) or intact CA (PRx is more negative).

Even though a gold standard for CA monitoring is missing and a clear protocol of monitoring procedures has not yet been published, PRx(t) monitoring is already accepted in clinical practice as a robust identification of autoregulation estimates.⁸

CPPopt is identified as the minimum CPP value of the U-shaped relationship of PRx versus CPP^{10,11}; in other words, somewhere in the middle of the individual autoregulation plateau. CPPopt-targeted therapy of severe TBI patients is based on the promising idea⁹ that intact CBF autoregulation can be preserved if CPP is kept away from the dynamic lower and upper limits of autoregulation.^{9,19–21} Preservation of adequate CBF during the intensive care of severe TBI and septic encephalopathy is associated with better patient outcomes,^{21,22} but high-quality evidence is insufficient to recommend replacing the CPP targets of 60–70 mm Hg suggested by the Brain Trauma Foundation.²³ The existing evidence of the effectiveness of CPPopt-targeted therapy is mainly based on numerous retrospective studies.^{21,24–26} At the moment, the feasibility and effectiveness

TBI study is underway in four European centers (COGITATE [CPPopt Guided Therapy: Assessment of Target Effectiveness]). In this study, no restrictions regarding the tested patient population are applied.

It is well known that the patient's age and ICP are the strongest influential factors associated with poorer outcomes in patients with severe TBI.^{27–29} In this study, we carried out a retrospective analysis of the prospectively collected data in TBI patients undergoing optimal CPP-targeted therapy in the neurosurgical ICU. Our objective was to compare the effectiveness of CPPopt-guided therapy in younger and elderly severe TBI patients with normal and elevated ICP, taking into account prognostic factors like age, CPP deviation from the calculated CPPopt value (Δ CPPopt), ICP, TBI severity, glucose level in blood serum, and the duration of cerebrovascular autoregulation impairment events.

Methods

The study was conducted at Vilnius Republic University Hospital (Lithuania). The study was approved by the Vilnius Regional Biomedical Research Ethics Committee (protocol nos. 158200-06-498-145 and 158200-16-854-364, 2016-07-12).

Eighty-one patients with severe TBI which required continuous multi-modal monitoring in the ICU were enrolled in the study. ICM+ software was used for collecting, visualization, and real-time

TABLE 1. DEMOGRAPHIC AND MULTI-MODAL MONITORING DATA OF TBIPATIENTS

Data	Outcome			Overall
	Fatal	Survival	p-value	
Sex (M/F)	18/6	47/10	–	65/16
GCS	5 (3)	6 (3)	0.136	5 (3)
Age, years	47 (15)	36 (15)	<0.001	40 (16)
HCT	8 (5)	5 (5)	0.003	6 (5)
Glucose concentration in blood, mmol/L	10.8 (4.3)	7.1 (1.8)	<0.001	8.1 (3.1)
Patients (<45 years)	10	40	–	50
Patients (>45 years)	14	17	–	31
Averaged PRx (<45 years)	0.58 (0.30)	0.09 (0.14)	<0.001	0.19 (0.26)
Averaged PRx (>45 years)	0.28 (0.31)	0.02 (0.18)	0.018	0.13 (0.27)
Averaged Δ CPPopt, mm Hg (<45 years)	–21.5 (24.2)	1.4 (4.5)	<0.001	–3.2 (14.5)
Averaged Δ CPPopt, mm Hg (>45 years)	0.7 (4.9)	0.6 (6.3)	0.736	0.6 (5.6)
Averaged CPP, mm Hg (<45 years)	49.1 (30.4)	83.3 (9.8)	<0.001	76.5 (20.9)
Averaged CPP, mm Hg (>45 years)	83.9 (14.8)	87.2 (7.3)	0.796	85.7 (11.2)
Averaged CPPopt, mm Hg (<45 years)	63.9 (14.1)	81.9 (8.8)	<0.001	78.3 (12.3)
Averaged CPPopt, mm Hg (>45 years)	82.9 (15.7)	87.8 (8.7)	0.351	85.5 (12.4)
Duration of LCAI (PRx >0.5), min (<45 years)	316 (256)	41 (31)	0.002	97 (158)
Duration of LCAI (PRx >0.5), min (>45 years)	133 (182)	41 (34)	0.092	82 (131)
Patients (ICP <22 mm Hg)	13	51	–	67
Patients (ICP >22 mm Hg)	11	6	–	17
Averaged PRx (ICP <22 mm Hg)	0.18 (0.24)	0.06 (0.16)	0.147	0.09 (0.18)
Averaged PRx (ICP >22 mm Hg)	0.66 (0.22)	0.10 (0.13)	0.001	0.46 (0.33)
Averaged Δ CPPopt, mm Hg (ICP <22 mm Hg)	1.5 (4.0)	1.29 (5.0)	0.841	1.3 (4.8)
Averaged Δ CPPopt, mm Hg (ICP >22 mm Hg)	–20.5 (23.2)	0.1 (6.2)	0.010	–13.2 (21.2)
Averaged CPP, mm Hg (ICP <22 mm Hg)	87.4 (10.3)	84.9 (9.4)	0.494	85.4 (9.5)
Averaged CPP, mm Hg (ICP >22 mm Hg)	48.2 (27.9)	80.6 (7.1)	0.007	59.6 (27.5)
Averaged CPPopt, mm Hg (ICP <22 mm Hg)	86.9 (11.4)	84.1 (9.2)	0.559	84.7 (9.6)
Averaged CPPopt, mm Hg (ICP >22 mm Hg)	60.8 (12.1)	79.3 (8.3)	0.494	67.4 (14.0)
Duration of LCAI (PRx >0.5), min (ICP <22 mm Hg)	95.6 (183)	39 (28)	0.003	51 (87)
Duration of LCAI (PRx >0.5), min (ICP >22 mm Hg)	343 (213)	60 (52)	0.494	243 (220)

Values of averaged PRx, Δ CPPopt, CPP, CPPopt, duration of LCAI, and glucose concentration in blood are presented as means with the standard deviation in brackets. Values of GCS and HCT are medians with the interquartile range in brackets.

TBI, traumatic brain injury; M, male; F, female; GCS, Glasgow Coma Scale; HCT, Helsinki *Computed Tomography* score; PRx, pressure reactivity index; CPPopt, optimal cerebral perfusion pressure; CPP, cerebral perfusion pressure; LCAI, longest cerebrovascular autoregulation impairment event; ICP, intracranial pressure.

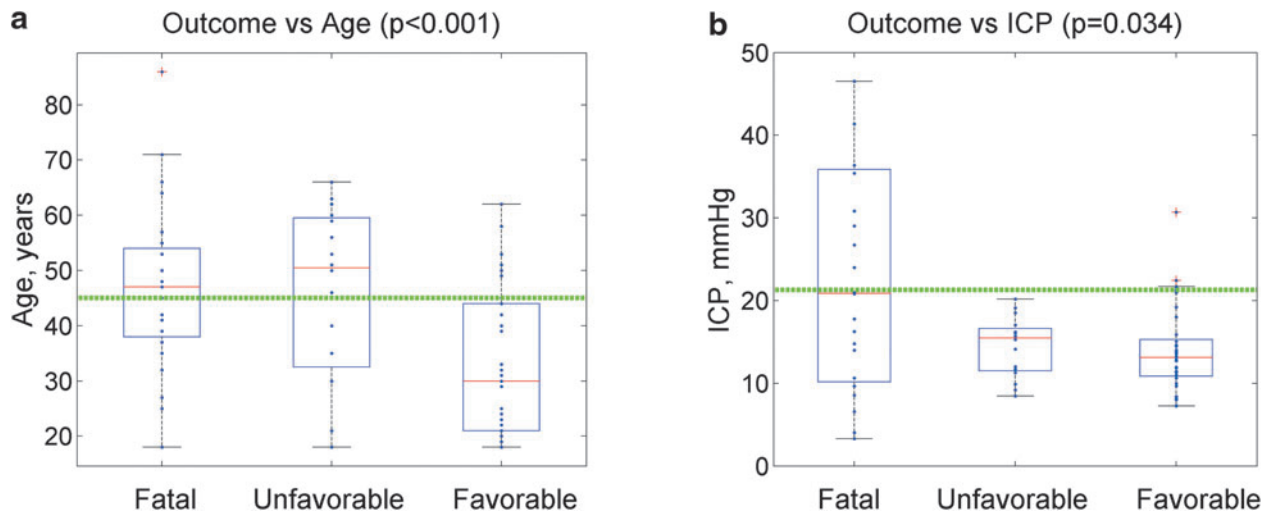


FIG. 1. TBI patient outcomes are statistically significant associated with age (**A**; Kruskal-Wallis test, $p < 0.001$) and averaged ICP (**B**; Kruskal-Wallis test, $p = 0.034$). Age above 45 years is associated with unfavorable and fatal outcome (**A**; $\chi^2 = 15.50$; $p = 0.0175$). Averaged ICP above 21.3 mm Hg is associated with fatal outcome ($\chi^2 = 16.86$; $p = 0.03$). ICP, intracranial pressure; TBI, traumatic brain injury. Color image is available online.

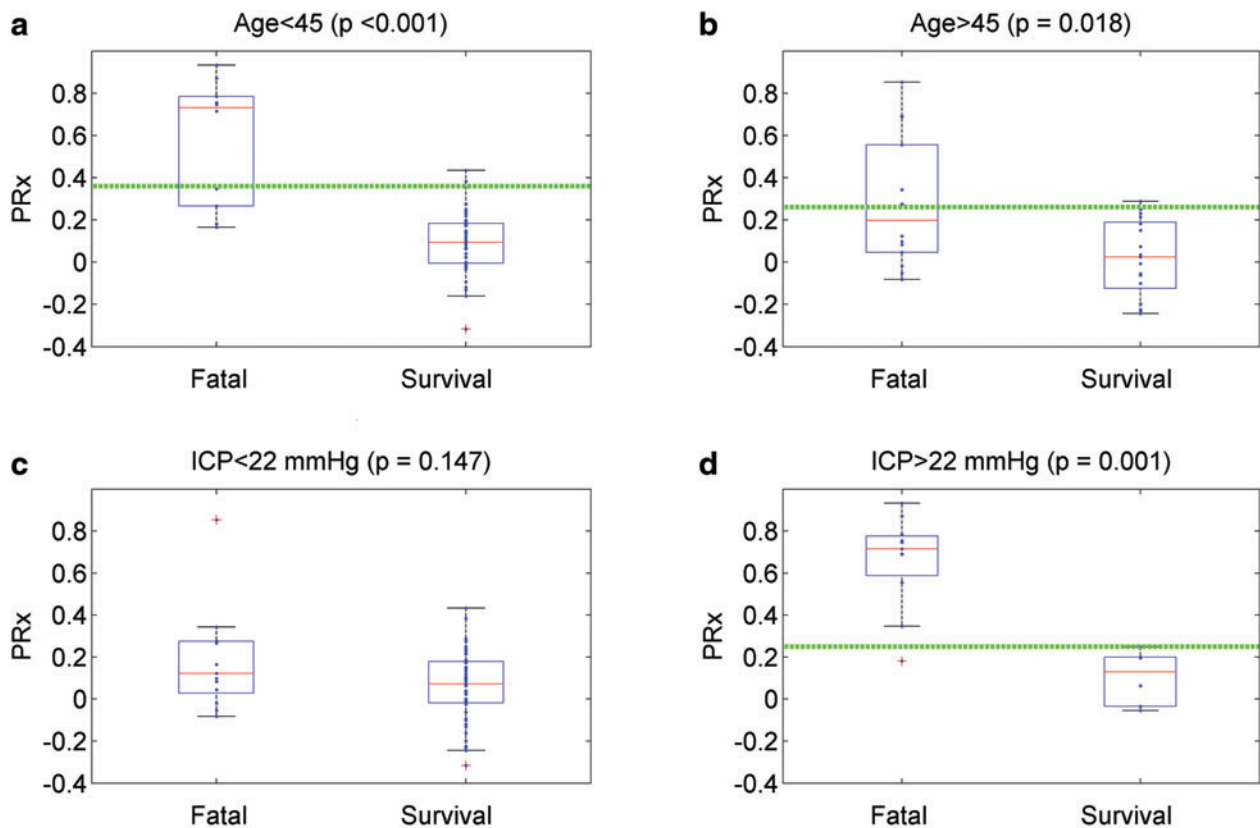


FIG. 2. Averaged PRx association with the outcome of younger (**A**; age < 45 years) and elderly (**B**; age > 45 years) TBI patients with normal (< 22 mm Hg) and elevated (> 22 mm Hg) averaged ICP (**C**, **D**). Averaged PRx above 0.36 is associated with fatal outcome for younger TBI patients (**A**; $\chi^2 = 18$; $p = 0.043$). Averaged PRx above 0.26 is associated with fatal outcome for elderly TBI patients (**B**; $\chi^2 = 7.8$; $p = 0.005$). Averaged PRx above 0.25 is associated with fatal outcome for patients with elevated ICP (**D**; $\chi^2 = 13.24$; $p = 0.005$). Statistically significant differences between the fatal and non-fatal patient groups were found for elderly and younger patients (Mann-Whitney U test, $p < 0.001$ [**A**] and $p = 0.018$ [**B**]) and for patients with elevated ICP ($p = 0.001$). ICP, intracranial pressure; PRx, pressure reactivity index; TBI, traumatic brain injury. Color image is available online.

processing of invasively monitored ICP(t) (Codman monitors with ventricular or parenchymal sensor) and ABP(t) (Datex Ohmeda monitor with pressure sensor in the radial artery) high-resolution data. PRx(t) and CPPopt(t) were estimated in real time over the entire treatment period at bedside. Invasively monitored CPPopt(t) values were used for decision-making treatment by the individual attending physicians. The post-hoc analysis was carried out by processing the following parameters:

The PRx(t) was calculated as a moving correlation coefficient between the ABP(t) and ICP(t) spontaneous slow waves within a 10-min averaging window. CA impairment events when PRx(t) continuously exceeded the value of +0.5 and the duration of the single longest CA impairment (LCAI) event were determined.

CPPopt(t) was identified by plotting the binned CPP values versus PRx values and identifying the minimum CPP value of the U-shaped fitting over the binned points as an optimal CPP. CPPopt(t) values were recalculated every 1 min from CPP and PRx data taken from the moving 4-h monitoring window. CPPopt(t) values were rejected in the cases of an unreliable U-shaped fitting and corrected by using the last reliable CPPopt value. The decline of real-time CPP from the optimal CPP was calculated as $\Delta\text{CPPopt}(t) = \text{CPP}(t) - \text{CPPopt}(t)$.

For each patient, the averaged values of PRx, ICP, CPP, and ΔCPPopt and the duration of LCAI event, when PRx(t) continuously exceeded the value of +0.5, were estimated and used for post-hoc analysis.

Patients were divided into three groups: fatal (Glasgow Outcome Scale [GOS] 1); unfavorable (GOS 2, 3); and favorable (GOS 4, 5).

For each group, distribution of calculated parameters and demographic factors was analyzed.

The Pearson chi-squared test (χ^2) was applied to calculate the critical thresholds in the analyzed parameters that separate the patients in different outcome groups. Thresholds were determined by creating series of 2×2 tables grouping the patients according to the analyzed factor into different outcome groups at different thresholds and identifying the best discriminative threshold according to the highest χ^2 score found.

Statistical analysis

The non-parametric Kruskal-Wallis test was used for calculating statistical differences between age and averaged ICP data in the groups with fatal, unfavorable, and favorable outcomes. The non-parametric Mann-Whitney U test was used for calculating statistical differences between the analyzed parameters (PRx, ΔCPPopt , and LCAI) in the groups with fatal outcome versus survivals for elderly and younger patients as well as for patients with normal and elevated ICP. Additionally, a multi-factorial logistic regression analysis was performed by using SPSS software (SPSS, Inc., Chicago, IL) for determining the most significant factors influencing TBI patients' outcome.

Results

TBI patients' outcomes, demographic data, and monitored physiological parameters are presented in the Table 1. Patients'

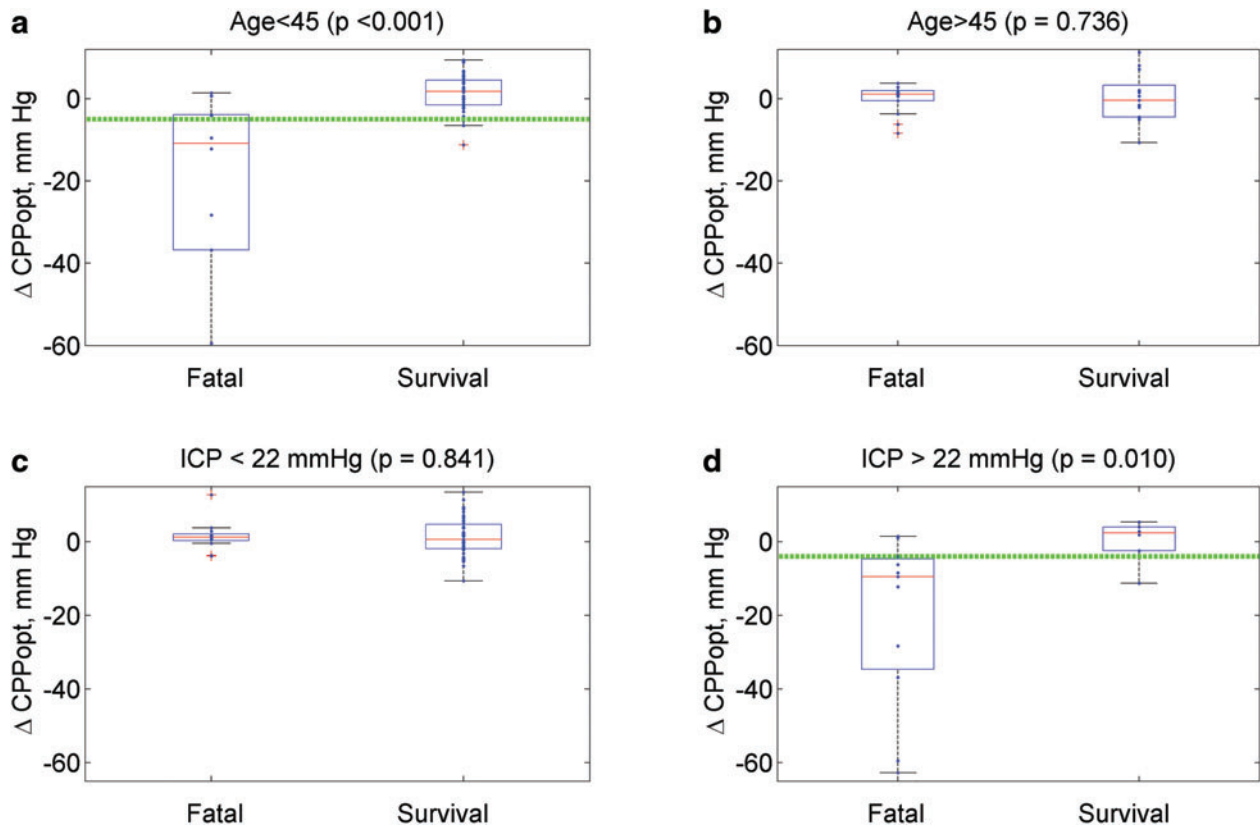


FIG. 3. Association of averaged ΔCPPopt with the outcome of younger (**A**; age <45 years) and elderly (**B**; age >45 years) TBI patients with normal (<22 mm Hg) and elevated (>22 mm Hg) averaged ICP (**C**, **D**). Averaged ΔCPPopt below -5 mm Hg is associated with fatal outcome for younger TBI patients (**A**; $\chi^2 = 14.94$; $p = 0.014$). Averaged ΔCPPopt below -4 mm Hg is associated with fatal outcome for TBI patients with elevated ICP (**D**; $\chi^2 = 6.8$; $p = 0.009$). Statistically significant differences between fatal and non-fatal patient groups were found for the younger group of patients (**A**; Mann-Whitney U test, $p < 0.001$) and for patients with elevated ICP (**D**; $p = 0.01$). CPPopt, optimal cerebral perfusion pressure; ICP, intracranial pressure; TBI, traumatic brain injury. Color image is available online.

outcomes after 6 months from TBI were as follows: 41 cases (50.6%) with favorable outcome (GOS 4, 5); 16 cases (19.8%) with unfavorable outcome (GOS 2, 3); and 24 cases (29.6%) of fatal outcome (GOS 1). The total number of survival cases was 57 (70.4%).

Outcome was significantly associated with age (Fig. 1A) and averaged ICP (Fig. 1B). Age above 45 years was associated with unfavorable and fatal outcome ($\chi^2 = 15.50$; $p = 0.0175$). Averaged ICP above 21.3 mm Hg was associated with fatal outcome ($\chi^2 = 16.86$; $p = 0.03$). This threshold was found close to the critical ICP threshold (ICP = 22 mm Hg) presented in the Brain Trauma Foundation,²³ which recommends ICP treatment because ICP values above this level are associated with increased mortality.

The 45-years threshold was used as a differentiating value between younger (50 patients) and elderly (31 patients) patient groups. The mortality rate in the younger patient group was 20% (10 fatal cases vs. 40 survival). The mortality rate for the elderly patient group was 45.2% (14 fatal cases vs. 17 survival).

We chose averaged ICP = 22 mm Hg threshold as a critical ICP threshold according to the Brain Trauma Foundation²³ for differentiating patients group with normal ICP (64 patients) and elevated ICP (17 patients). A mortality rate in the normal ICP patient group

was 20.3% (13 fatal cases vs. 51 survival). A mortality rate for the elevated ICP patient group was 65.7% (11 fatal cases vs. 6 survival).

The influences of averaged PRx, averaged Δ CPPopt, and duration of LCAI (PRx > 0.5) on patients' outcome were analyzed separately for younger and elderly patients as well as for patients with normal and elevated ICP. We found statistically significant differences between averaged PRx values in fatal and non-fatal patient groups, separately for younger and elderly patients ($p < 0.001$ and $p = 0.018$, respectively) and for patients with elevated ICP (Fig. 2). However, the PRx thresholds associated with fatal outcome differed depending on age. PRx thresholds above 0.36 and 0.26 were associated with fatal outcome for younger ($\chi^2 = 7.8$; $p = 0.005$) and elderly ($\chi^2 = 18$; $p = 0.043$) TBI patients, respectively (Fig. 2). PRx threshold above 0.25 was associated with fatal outcome for TBI patients with elevated ICP ($\chi^2 = 13.25$; $p = 0.005$; Fig. 2). No statistically significant difference was found for patients with normal ICP.

By analyzing the influence of averaged Δ CPPopt and duration of LCAI (PRx > 0.5), we found statistically significant differences between these parameters in fatal and non-fatal patients' groups, but only in the younger patient group and in patients with elevated ICP (Mann-Whitney U test, $p < 0.05$). The threshold

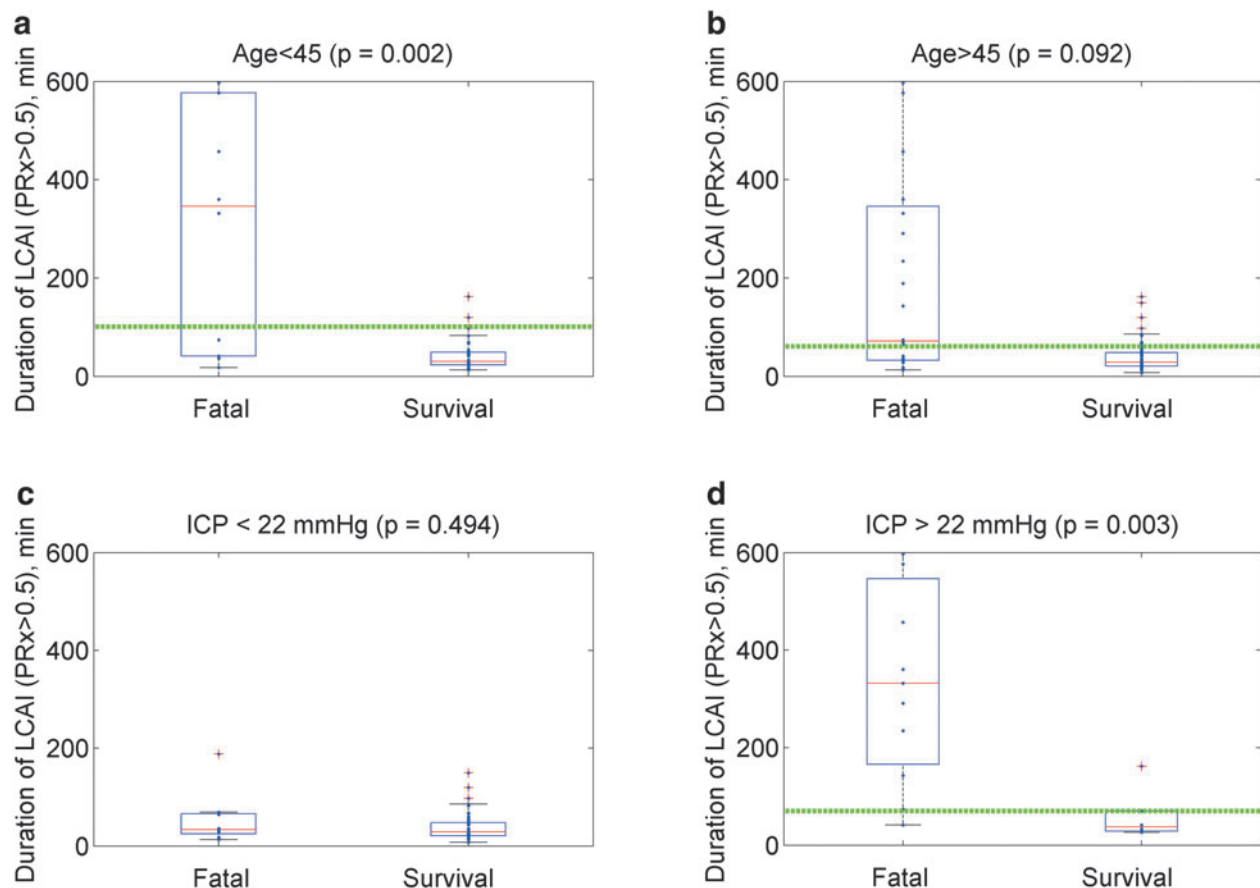


FIG. 4. Association of the duration of longest CA impairment (LCAI) event with the outcome of younger (**A**; age < 45 years) and elderly (**B**; age > 45 years) TBI patients with normal (< 22 mm Hg) and elevated (> 22 mm Hg) averaged ICP (**C, D**). LCAI longer than 100 min (PRx > 0.5) is associated with fatal outcome for younger TBI patients (**A**; $\chi^2 = 18$; $p = 0.043$). LCAI longer than 61 min (PRx > 0.5) is associated with fatal outcome for elderly TBI patients (**B**; $\chi^2 = 5.447$; $p = 0.0196$). LCAI longer than 70 min is associated with fatal outcome for TBI patients with elevated ICP (**D**; $\chi^2 = 9.370$; $p = 0.002$). Statistically significant differences between fatal and non-fatal patient groups were found for younger patients (**A**; Mann-Whitney U test, $p = 0.002$) and for patients with elevated ICP (**D**; $p = 0.003$). ICP, intracranial pressure; PRx, pressure reactivity index; LCAI, longest cerebrovascular autoregulation impairment event; TBI, traumatic brain injury. Color image is available online.

TABLE 2. THE MULTI-FACTORIAL LOGISTIC REGRESSION MODEL OF PREDICTING FAVORABLE AND UNFAVORABLE OUTCOMES OF TBI PATIENTS

Factor	Threshold	p value	OR	CI
Age, years	45	0.001	19.987	3.28–121.78
Duration of LCAI (PRx >0.5), min	58	0.012	29.622	2.09–419.07
Glucose concentration mmol/L	7.5	0.006	0.105	0.021–0.528
GCS	8	0.001	22.057	3.35–144.85
Nagelkerke R square				0.702
Model constant B				–2.411 (<i>p</i> = 0.011)
Prediction of favorable outcome (GOS 4, 5)				86.5%
Prediction of unfavorable outcome (GOS 1, 2, 3)				90.9%
Overall prediction accuracy				88.6%

TBI, traumatic brain injury; LCAI, longest cerebrovascular autoregulation impairment event; PRx, Pressure Reactivity Index; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; OR, odds ratio; CI, confidence interval.

associated with fatal outcome in the younger patient group was $\Delta\text{CPPopt} < -5$ mm Hg ($\chi^2 = 14.94$; $p = 0.014$; Fig. 3). A similar threshold associated with fatal outcome ($\Delta\text{CPPopt} < -4$ mm Hg ($\chi^2 = 6.80$; $p = 0.009$)) was found for patients with elevated ICP (Fig. 3).

The threshold associated with fatal outcome also differed for the duration of LCAI (Fig. 4). The duration of LCAI longer than 100 min ($\chi^2 = 18$; $p = 0.043$) was found to be associated with fatal outcome for younger TBI patients, whereas this threshold for elderly patients was 61 min ($\chi^2 = 5.447$; $p = 0.0196$). LCAI longer than 58 min is associated with fatal outcome for TBI patients with elevated ICP ($\chi^2 = 15.73$; $p = 0.019$; Fig. 4).

Multi-factorial model (*n* = 81 patients)

Multi-factorial binary logistic regression modeling was performed by analyzing the significance of input factors (age, sex, GCS, LCAI, ΔCPPopt , ICP, CPP, etc.). The input factors were binned according to threshold values that statistically separate the patients in different outcome group by applying a chi-square test.

The analysis showed that the statistically significant factors affecting TBI patients' mortality are age, GCS, glucose level in blood serum samples (determined within 24 h after admission), and duration of LCAI.

Other factors (such as ICP, CPP, ΔCPPopt , and Helsinki Computed Tomography score [HCT]) were not statistically significant and therefore did not improve model-predicting accuracy. The modeled accuracies for favorable and unfavorable outcome prediction were 82.5% and 90.9% respectively, whereas overall model accuracy was 88.6% (Table 2).

Discussion

We aimed to compare the effectiveness of CPPopt-targeted therapy in younger and elderly TBI patients with normal and elevated ICP. We found that the magnitude and duration of deviation from CPPopt were associated with increased mortality in the younger group (Fig. 3A). There was no statistically significant

association of these parameters with the outcomes of elderly patients (Fig. 3B). These data suggest that CPPopt-targeted therapy is more effective for younger patients.

Looking into other differences between the younger and elderly groups, we detected different thresholds associated with mortality for CA-related parameters (averaged PRx and duration of LCAI event): PRx >0.36 for younger patients versus PRx >0.26 for elderly patients (Fig. 2A,B); duration of LCAI >100 min for younger patients versus 61 min for elderly patients (Fig. 4A,B). The obtained thresholds are higher for younger patients, providing further evidence that younger patients can withstand and survive under more dangerous conditions of CA impairment.

By analyzing the influence of PRx, ΔCPPopt , and LCAI on patients' outcome in normal and elevated ICP patients' groups, we found statistically significant differences between survival and fatal patients' groups only for those who had elevated ICP. It clearly demonstrates that elevated ICP is associated with CA deterioration, thus leading to fatal outcomes (Figs. 2D, 3D, and 4D).

Given that both age and ICP are independent factors affecting TBI patients' outcome, we analyzed the influence of ICP on patients' outcome in younger and elderly patients' groups (Fig. 5). There, we found statistical significant difference between patients' outcome between survival and fatal outcome for the younger group with a critical threshold ICP = 20 mm Hg separating these patients' outcome groups (Fig. 5A). No statistically significant differences were found between outcome groups in elderly patients (Fig. 5B). Moreover, it is worth emphasizing that for elderly patients, both survival and fatal patients had averaged ICP less than the critical ICP threshold, 20 mm Hg (Fig. 5). This constitutes an additional evidence that younger patients may survive at higher ICP levels.

The limited number of patients (*n* = 81) and the heterogeneous population are limitations of the study. Also, CPPopt-targeted therapy was based on a local and unpublished protocol that limits the value of the found results. Therefore, the study provides preliminary results only. A greater number of patients are needed to perform more detailed analyses and to group patients according to age, sex, and severity of brain injury. A limitation of CPPopt-targeted treatment is the delay between the real-time CPP value measurements and CPPopt value determination. Typically, 3–4 h are needed for collection of PRx(CPP) data to obtain the U-shaped approximation. We were able to find an overall reliable CPPopt in 64% of total monitoring time in our cohort of patients. We decided to reject unreliable U-shaped curves, curves based on high PRx values (when PRx >0.5 at a minimum point), and periods of distorted ICP or ABP data caused by artefacts. However, in addition, we replaced non-reliable CPPopt(t) values by using the last available reliable CPPopt value taken from a 2-h time window. This increased the time of CPPopt detection up to 87%. These data were used for the analysis. We also assumed CPPopt = 50 mm Hg in the cases when CPPopt retrieved a value <50 mm Hg.

Processing of the time-series data for estimation of the optimal CPP value is associated with delayed treatment decisions. The uncertainty of the CPP measurement is another limiting factor. Systematic errors of CPP are eliminated by calculating the difference between CPP and CPPopt, but there will always be instrumental and methodological uncertainties related to the delay in CPPopt estimation.

The main influential factors affecting severe TBI treatment outcomes are patient age, GCS, blood glucose level, and the impairment of CA status during the first day after patient admission

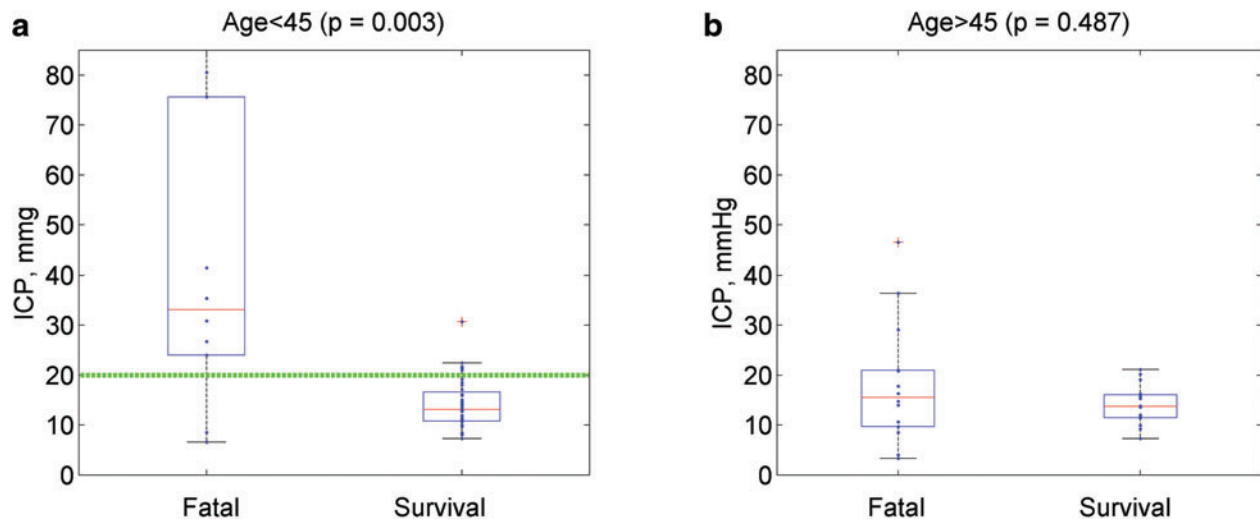


FIG. 5. Association of the averaged ICP with the outcome of younger (**A**; age <45 years) and elderly (**B**; age >45 years) TBI patients. ICP above 20 mm Hg is associated with fatal outcome for younger TBI patients (**A**; $\chi^2 = 16.766$; $p = 0.0290$). Statistically significant differences between fatal and non-fatal patient groups were found only for younger patients (**A**; Mann-Whitney U test, $p < 0.001$). ICP, intracranial pressure; TBI, traumatic brain injury. Color image is available online.

(Table 2). Although ICP was analyzed as one of the influential factors associated with patient outcome, the multi-factorial modeling revealed that it is not a statistically significant factor, which does not improve outcome prediction accuracy. Because of the fact that ICP affects CA status, the CA-related parameter (LCAI) was found as statistically significant in the outcome-predicting model.

CPPopt-targeted individualized treatment is useful for stabilizing CA in severe TBI patients. It may be especially beneficial to improve outcome for younger patients that are <45 years of age. Younger patients probably need higher CPP targets than currently recommended. Autoregulation monitoring in the first 24 h seems to be important, because, especially in older patients, impaired autoregulation was tolerated only for a shorter period of time than that in younger patients.

Autoregulation-guided treatment seems important for individual TBI management, especially in younger patients. Ongoing studies are working on an intervention protocol to test feasibility and effectiveness (COGITATE study). Randomized multi-center studies on the CPPopt concept are needed to prove a final benefit of autoregulation-targeted therapy.

Author Contributions

Arminas Ragauskas and Vytautas Petkus initiated the research. Aidanas Preiksaitis, Saulius Rocka, Saulius Vosylius, and Erika Zubaviciute collected the clinical data and prepared documents to obtain ethical approval. Vytautas Petkus, Edvinas Chaleckas, Romanas Chomskis, and Aidanas Preiksaitis gathered and processed patients' monitoring data. Romanas Chomskis, Saulius Vosylius, and Aidanas Preiksaitis supervised equipment and software used for clinical data monitoring. Vytautas Petkus, Jan-Oliver Neumann, and Marcel J. Aries contributed to the study methodology and writing of the manuscript. Jan-Oliver Neumann, Marcel J. Aries, Daiva Rastenyte, Arminas Ragauskas, and Saulius Rocka supervised the analysis of study results and contributed to the final manuscript. All authors discussed the study results and approved the final manuscript.

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Author Disclosure Statement

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References

- Paulson, O.B., Strandgaard, S., and Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev.* 2, 161–192.
- Chillon, J.M., and Baumbach, G.L. (2002). Autoregulation: arterial and intracranial pressure, in: *Cerebral Blood Flow and Metabolism*, 2nd ed. L. Edvinsson and D.N. Krause (eds). Lippincott Williams & Wilkins: Philadelphia, PA, pps. 395–412.
- Sviri, G.E., and Newell, D.W. (2010). Cerebral autoregulation following traumatic brain injury. *Open Neurosurg. J.* 3, 6–9.
- Czosnyka, M., Brady, K., Reinhard, M., Smielewski, P., and Steiner, L.A. (2009). Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocrit. Care* 10, 373–386.
- Czosnyka, M., Smielewski, P., Kirkpatrick, P., Laing, R.G., Menon, D., and Pickard, J.D. (1997). Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery* 41, 11–17.
- Preiksaitis, A., Krakauskaite, S., Petkus, V., Rocka, S., Chomskis, R., Dagi, T.F., and Ragauskas, A. (2016). Association of severe traumatic brain injury patient outcomes with duration of cerebrovascular autoregulation impairment events. *Neurosurgery* 79, 75–82.
- Sorrentino, E.J., Diedler, J., Kasprzewicz, M., Budohoski, K.P., Haubrich, C., Smielewski, P., Outtrim, J.G., Manktelow, A., Hutchinson, P.J., Pickard, J.D., Menon, D.K., and Czosnyka, M. (2012). Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocrit. Care* 2, 258–266.
- Le Roux, P., Menon, D.K., Citerio, G., Vespa, P., Bader, M.K., Brophy, G.M., Diringer, M.N., Stocchetti, N., Videtta, W., Armonda, R., Badjatia, N., Böesel, J., Chesnut, R., Chou, S., Claassen, J., Czosnyka, M., De Georgia, M., Figaji, A., Fugate, J., Helbok, R., Horowitz, D., Hutchinson, P., Kumar, M., McNett, M., Miller, C., Naidech, A., Oddo, M., Olson, D., O'Phelan, K., Provencio, J.J., Puppo, C., Riker, R., Robertson, C., Schmidt, M., and Taccone, F. (2014). Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in

- Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Med.* 40 Neurocrit Care. 21, Suppl. 2, S282–S296.
9. Czosnyka, M., Smielewski, P., Piechnik, S., Steiner, L.A., and Pickard, J.D. (2001). Cerebral autoregulation following head injury. *J. Neurosurg.* 95, 756–763.
 10. Aries, M.J.H., Czosnyka, M., Budohoski, K.P., Steiner, L.A., Lavinio, A., Koliass, A.G., Hutchinson, P.J., Brady, K.M., Menon, D.K., Pickard, J.D., and Smielewski, P. (2012). Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit. Care Med.* 40, 2456–2463.
 11. Steiner, L.A., Czosnyka, M., Piechnik, S.K., Smielewski, P., Chatfield, D., Menon, D.K., and Pickard, J.D. (2002). Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit. Care Med.* 30, 733–738.
 12. Petkus, V., Preiksaitis, A., Krakauskaite, S., Zubaviciute, E., Rocka, S., Rastenyte, D., Vosylius, S., and Ragauskas, A. (2017). Benefit on optimal cerebral perfusion pressure-targeted treatment for traumatic brain injury patients. *J. Crit. Care* 41, 49–55.
 13. Rasulo, F.A., Girardini, A., Lavinio, A., De Peri, E., Stefani, R., Cenzato, M., Nodari, I., and Latronico, N. (2012). Are optimal cerebral perfusion pressure and cerebrovascular autoregulation related to longterm outcome in patients with aneurysmal subarachnoid hemorrhage? *J. Neurosurg. Anesthesiol.* 24, 3–8.
 14. Czosnyka, M., Smielewski, P., Kirkpatrick, P., Menon, D.K., and Pickard, J.D. (1996). Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 27, 1829–1834.
 15. Eames, P.J., Blake, M.J., Dawson, S.L., Panerai, R.B., and Potter, J.F. (2002). Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J. Neurol. Neurosurg. Psychiatry* 72, 467–473.
 16. Spiegelberg, A., Preuß, M., and Kurtcuoglu, V. (2016). B-waves revisited. *Interdisc. Neurosurg.* 6, 13–17.
 17. Schmidt, B., Reinhard, M., Lezaic, V., McLeod, D.D., Weinhold, M., Mattes, H., and Klingelhöfer, J. (2016). Autoregulation monitoring and outcome prediction in neurocritical care patients: does one index fit all? *J. Clin. Monit. Comput.* 30, 367–375.
 18. Czosnyka, M., Czosnyka, Z., Momjian, S., and Pickard, J.D. (2004). Cerebrospinal fluid dynamics. *Physiol. Meas.* 25, R51.
 19. Steiner, L.A., Czosnyka, M., Piechnik, S.K., Smielewski, P., Chatfield, D., Menon, D.K., and Pickard, J.D. (2002). Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit. Care Med.* 30, 733–738.
 20. Aries, M.J., Koliass, A.G., Czosnyka, M., Budohoski, K.P., Steiner, L.A., Lavinio, A., Brady, K.M., Menon, D.K., Pickard, J.D., Hutchinson, P.J., and Smielewski, P. (2014). Optimal cerebral perfusion pressure-towards individualised treatment in severe traumatic brain injury. *J. Neurotrauma* 31, A62.
 21. Needham, E., McFadyen, C., Newcombe, V., Synnot, A., Czosnyka, M., and Menon, D. (2017). Cerebral perfusion pressure targets individualised to pressure-reactivity index in moderate to severe traumatic brain injury: a systematic review. *J. Neurotrauma* 34, 963–970.
 22. Zeiler, F.A., Thelin, E.P., Helmy, A., Czosnyka, M., Hutchinson, P.J.A., and Menon, D.K. (2017). A systematic review of cerebral microdialysis and outcomes in TBI: relationships to patient functional outcome, neurophysiologic measures, and tissue outcome. *ACTA Neurochir.* 159, 2245–2273.
 23. Carney, N., Totten, A.M., O'Reilly, C., Ullman, J.S., Hawryluk, G.W.J., Bell, M.J., Bratton, S.L., Chesnut, R., Harris, O.A., Kisooson, N., Rubiano, A.M., Shutter, L., Tasker, R.C., Vavilala, M.S., Wilberger, J., Wright D.W., and Ghajar, J. (2016). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 80, 6–15.
 24. Depreitere, B., Güiza, F., Van den Berghe, G., Schuhmann, M.U., Maier, G., Piper, I., and Meyfroidt, G. (2014). 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.* 120, 1451–1457.
 25. Kramer, A.H., Couillard, P.L., Zygun, D.A., Aries, M.J., and Gallagher, C.N. (2019). Continuous assessment of “optimal” cerebral perfusion pressure in traumatic brain injury: a cohort study of feasibility, reliability, and relation to outcome. *Neurocrit. Care* 30, 51–61.
 26. Howells, T., Smielewski, P., Donnelly, J., Czosnyka, M., Hutchinson, P.J.A., Menon, D.K., Enblad, P., and Aries, M.J.H. (2018). Optimal cerebral perfusion pressure in centers with different treatment protocols. *Crit. Care Med.* 46, e235–e241.
 27. Rosenblatt, K., Walker, K.A., Goodson, C., Olson, E., Maher, D., Brown, C.H., and Nyquist, P. (2019). Cerebral autoregulation-guided optimal blood pressure in sepsis-associated encephalopathy: a case series. *J. Intensive Care Med.* Feb 13. doi: 10.1177/0885066619828293. [Epub ahead of print]
 28. Hukkelhoven, C.W., Steyerberg, E.W., Rampen, A.J., Farace, E., Habbema, J.D., Marshall, L.F., Murray, G.D., and Maas, A.I. (2003). Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *J. Neurosurg.* 99, 666–673.
 29. Mannino, C., Glenn, T.C., Hovda, D.A., Vespa, P.M., McArthur, D.L., Van Horn, J.D., and Wright, M.J. (2018). Acute glucose and lactate metabolism are associated with cognitive recovery following traumatic brain injury. *J. Neurosci. Res.* 96, 696–701.

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