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Individualising thresholds of cerebral perfusion pressure using estimated limits of autoregulation

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Abstract

Objectives—In severe traumatic brain injury (TBI), cerebral perfusion pressure (CPP) management based on cerebrovascular pressure reactivity (PRx) has the potential to provide a personalised treatment target to improve patient outcomes. So far, the methods have focused on identifying *one* autoregulation guided CPP target – called CPPopt. We investigated whether a CPP autoregulation range - which uses a continuous estimation of the ‘lower’ and ‘upper’ CPP limits of cerebrovascular pressure autoregulation (PRx) - has prognostic value.

Design—Single-centre retrospective analysis of prospectively collected data

Setting—The neurocritical care unit at a tertiary academic medical centre

Patients—Data from 729 severe TBI patients admitted between 1996 and 2016 were used. Treatment was guided by controlling intracranial pressure and CPP according to a local protocol.

Interventions—None

Methods and Main Results—CPP-PRx curves were fitted automatically using a previously published curve-fitting heuristic from the relationship between PRx and CPP. The CPP values at which this ‘U-shaped curve’ crossed the fixed threshold from intact to impaired pressure reactivity

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ICM+ is a software licensed by Cambridge Enterprise Ltd, UK. PS and MC have financial interest in a fraction of the licensing fee.

(PRx =0.3) were denoted automatically the ‘Lower’ and ‘Upper’ CPP Limits of Reactivity (LLR and ULR), respectively. The % of time with CPP below (%CPP<LLR), above (%CPP>ULR) or within these reactivity limits (%CPP WLR) was calculated for each patient and compared across dichotomised Glasgow Outcome Scores.

After adjusting for age, initial GCS, and mean ICP, %CPP<LLR was associated with unfavourable outcome (OR %CPP<LLR 1.04, 95%-CI 1.02-1.06, $p < 0.001$) and mortality (OR 1.06 95%-CI 1.04-1.08, $p < 0.001$).

Conclusions—Individualised autoregulation-guided CPP management may be a plausible alternative to fixed CPP threshold management in severe TBI patients. Prospective randomized research will help to define which autoregulation guided method is beneficial, safe and most practical.

Keywords

Traumatic brain injury; intracranial pressure; cerebral haemodynamics; autoregulation; brain chemistry; cerebral perfusion pressure

Introduction

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 ischaemia 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) minus intracranial pressure (ICP)) above a certain limit may help decrease cerebral ischaemia but a CPP that is driven too high may contribute to cerebral oedema or precipitate systemic complications (6). On this basis, current Brain Trauma Foundation (BTF) 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-minute 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 (figure 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 utility 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 individualised CPP recommendation method to determine continuously and automatically the CPP range with intact pressure reactivity in a single centre 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.

Methods

Patients

836 severe TBI patients entering the neurocritical care unit (NCCU) with computerized ICP monitoring (September 1996 - June 2016) were selected. 107 patients were removed (<12 hours (ICP) monitoring data, age ≤ 12 years old, no PRx available, Glasgow Outcome Score (GOS) not available), leaving 729 patients for final analysis. Pupil reactivity information was only available in 207 (28%) of patients. 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 < 20 mm Hg and CPP > 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 Health- care 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 minute) 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 one-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-hours) to produce the CPP-PRx curve variables (CPPopt, LLR, ULR, WLR), multiple calculation windows were applied from a period of 2 hours to 8 hours (in 10-minute increments) to yield up to 36 estimations. The mean of these estimates was calculated and updated every minute.

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

Automated estimation of the lower and upper CPP limits of reactivity (figure 1)

The defined CPP-PRx curve was extrapolated to both sides to include the full range of plausible CPP values (from 40 -120 mm Hg) to obtain the CPP values at which the curve crossed the threshold PRx value for impaired pressure reactivity ($PRx = +0.30$). The value of CPP at these two points of intersection were 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 (less than 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 thresholds: 1. recent guideline CPP thresholds (lower = 60; upper = 70 mm Hg), 2. the CPPopt-based thresholds (lower= a CPP more than 10 mm Hg below CPPopt or CPPopt < -10; upper= a CPP more than 10 mm Hg above CPPopt or CPPopt > +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 dichotomised outcome groups. Unfavourable outcome was defined as death, vegetative state or severe disability. Univariate outcome relationships were performed by comparing Receiver Operating Curves (ROC) attributes.

For each CPP threshold approach multivariable logistic regression models were constructed for outcome prediction. Available covariates in our 1996-2016 cohort were age, GCS 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 (AIC) (18). We used the R language and software environment for statistical computation (R Core Team 2015 version 2.12.1) using the following packages: dplyr (20), ggplot2 (21), bestglm(18). The significance level was set at 0.05.

Results

Patient characteristics (table 1)

Summary demographic data of the 729 patients in this analysis are shown in table 1. The mean age was $42 (\pm 17)$. Mean ICP was $15.1 (\pm 6.2)$ mm Hg and was significantly higher in those that 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 from the time of first estimate) increased significantly with the multi-window approach ($60\% \pm 14$ vs. $93\% \pm 8$ 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 (figure S1, S2)

The mean CPP LLR and ULR for the cohort were $59.3 (\pm 7.3)$ mm Hg and $96.0 (\pm 7.5)$ mm Hg while 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. The interrelationships between flexible CPP thresholds and other physiologic variables are depicted in a correlation matrix (supplemental figure 1). 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 which might indicate a rightward shifted and narrower autoregulation plateau.

Prognostic significance of CPP: fixed vs flexible CPP thresholds (figure 2 and 3)

Spending more time with $CPP < 60$ was related to death (figure 2), whereas spending more time with $CPP > 70$ was not (in fact inversely related). These findings were confirmed in AUC analysis (figure 3, Table S1). In all outcome groups, the % of time within the guideline CPP range was low (figure 2, mean $19.1\% \pm 13.1$).

Time with $CPP_{opt} < -10$ was significantly related to mortality, whereas spending more time with $CPP_{opt} > +10$ was not (similar to $CPP > 70$, there was an inverse relationship) (figure 2, Table S1). In ROC analysis, time with $CPP_{opt} < -10$ significantly predicted mortality (AUC 0.66, 95%-CI 0.61-0.72, $p < 0.001$) and favourable outcome (AUC 0.56, 95%-CI 0.51-0.61, $p < 0.001$).

The % of time with $CPP < LLR$ was a significant predictor of both unfavourable outcome (AUC 0.60, 95%-CI 0.56-0.64, $p < 0.001$) and mortality (AUC 0.73, 95%-CI 0.68-0.77, $p < 0.001$) (figure 3, Table S1). The % of time with $CPP > ULR$ predicted unfavourable outcome (AUC 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 (table 2)

Based on the univariate analyses, % time with CPP below each threshold was included in initial models predicting mortality, whereas % time with CPP above and below each threshold were included in the initial models predicting unfavourable outcome. After applying the best subset algorithm, % time with CPP above the upper thresholds were not present in any model. Multivariate models using the flexible CPP reactivity limits (rather than fixed CPP or CPPopt limits) showed the best ability to predict unfavourable 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 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.

Characterizing CPP limits of pressure reactivity using the CPP-PRx curve

Similar to the recently developed visualisation method of the CPP-PRx landscape (22), 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. While 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(23). 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 (24, 25).

The CPP-PRx curve- a pragmatic and prognostically important relationship

The time spent with CPP < LLR and (10 mm Hg) deviation below CPPopt were significantly related to adverse outcome (table 1-2, figure 2-3), fitting with the clinical maxim that periods with low CPP should be avoided in severe TBI patients (9, 26, 27). There is evidence that even short periods of cerebral hypoperfusion contribute to secondary brain injury and are related to unfavourable outcome (28). 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 (29–31). The sequelae of having a CPP > ULR and (10 mm Hg) deviation above CPPopt are less clear; in this large cohort, only modest relationship to unfavourable outcome was found (table 1, figure 2). While 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 (figure S2), 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 $CPP < LLR$ is grouped by patient outcome, the major differences are between those that 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 CRASH database (32, 33), 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, figure 2). Similar observations can be found in other recent studies (34–36)

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 strategies. Specifically, modelling the CPP-PRx relationship using a 2nd 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 multi-window 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 multi-window 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 (37–41) – like CO₂ levels - and are not currently considered in the current concept and related management. However, the analysis of multimodal data (like in the high resolution CENTER-TBI study) might give insights in the near future (42).

Given that the monitoring data (including the single window CPP-PRx curve) was 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 a 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 physiological 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.

Conclusion

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. 2013; 9:231–6. [PubMed: 23443846]
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; 27:1343–53. [PubMed: 20392140]
3. Maas AIR, Menon DK. Traumatic brain injury: Rethinking ideas and approaches. *Lancet Neurol*. 2012; 11:12–13. [PubMed: 22172614]
4. Donnelly J, Budohoski KP, Smielewski P, et al. Regulation of the cerebral circulation: bedside assessment and clinical implications. *Crit Care*. 2016; 20:129. [PubMed: 27145751]
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. [PubMed: 23328942]
6. Robertson C. Management of cerebral perfusion pressure after traumatic brain injury. *Anesthesiology*. 2001:1513–1517. [PubMed: 11748413]
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. [PubMed: 11940737]

9. Aries MJH, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury*. *Crit Care Med.* 2012; 40:2456–2463. [PubMed: 22622398]
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; 120:1451–7. [PubMed: 24745709]
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. [PubMed: 26132743]
12. Young AMH, Donnelly J, Czosnyka M, et al. Continuous Multimodality Monitoring in Children after Traumatic Brain Injury—Preliminary Experience. *PLoS One.* 2016; 11:e0148817. [PubMed: 26978532]
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.* 2016; 8 Epub ahead of print.
14. Menon DK. Cerebral protection in severe brain injury: physiological determinants of outcome and their optimisation. *Br Med Bull.* 1999; 55:226–58. [PubMed: 10695089]
15. Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet.* 1975; II:480–484.
16. Donnelly J, Aries MJH, Czosnyka M. Further understanding of cerebral autoregulation at the bedside: possible implications for future therapy. *Expert Rev Neurother.* 2015; 15:169–185. [PubMed: 25614952]
17. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocrit Care.* 2012; 16:258–66. [PubMed: 21964774]
18. McLeod AI, Xu C. Bestglm: Best Subset GLM. R Packag version 036. 2017
19. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2015. [Internet]. Available from: <http://www.r-project.org/>
20. Wickham H, Francois R. dplyr: A Grammar of Data Manipulation. [Internet]. R Packag version 050. 2016 Available from: <http://cran.r-project.org/package=dplyr>.
21. Wickham, H. *Elegant Graphics for Data Analysis*. New York: Springer-Verlag; 2009.
22. Aries MJH, Wesseling R, Elting JWJ, et al. Enhanced visualization of optimal cerebral perfusion pressure over time to support clinical decision making. *Crit Care Med.* 2016 In press.
23. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med.* 1999; 27:2086–2095. [PubMed: 10548187]
24. Eker C, Asgeirsson B, Grande P, et al. Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. *Crit care.* 1998
25. Rosner MJ, Rosner SD, Johnson aH. Cerebral perfusion pressure: management protocol and clinical results. *J Neurosurg.* 1995; 83:949–62. [PubMed: 7490638]
26. 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
27. Brain Trauma Foundation. Guidelines for the Management of Severe Traumatic Brain Injury 3rd Edition. *J Neurotrauma.* 2007; 24(Suppl 1):S37–44. [PubMed: 17511544]
28. 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. [PubMed: 25894624]
29. 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. [PubMed: 9833824]
30. 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. [PubMed: 10986755]
31. Donnelly J, Czosnyka M, Harland S, et al. Cerebral haemodynamics during experimental intracranial hypertension. *J Cereb Blood Flow Metab.* 2016

32. 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. [PubMed: 18270239]
33. 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. discussion e165. [PubMed: 18684008]
34. 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. [PubMed: 20415526]
35. Griesdale DEG, Örtengwall 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. [PubMed: 25179411]
36. Dias C, Silva MJ, Pereira E, et al. Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. *Neurocrit Care*. 2015
37. Donnelly J, Czosnyka M, Sudhan N, et al. Increased Blood Glucose is Related to Disturbed Cerebrovascular Pressure Reactivity After Traumatic Brain Injury. *Neurocrit Care*. 2014; 22:20–25.
38. 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; 23:210–6. [PubMed: 25894454]
39. 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. [PubMed: 25273515]
40. Smirl JD, Tzeng Y-C, Monteleone BJ, et al. Influence of cerebrovascular resistance on the dynamic relationship between blood pressure and cerebral blood flow in humans. *J Appl Physiol*. 2014
41. Lavinio A, Timofeev I, Nortje J, et al. Cerebrovascular reactivity during hypothermia and rewarming. *Br J Anaesth*. 2007; 99:237–244. [PubMed: 17510046]
42. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI). *Neurosurgery*. 2015; 76:67–80. [PubMed: 25525693]

Figure 1. Schematic depicting the theoretical relationships between CPP and PRx including estimation of 'optimal' CPP (CPPopt), CPP LLR, and CPP ULR

The relationship between CPP and PRx can be approximated by fitting a U-shaped curve (2nd order polynomial) whereby with both high or low values of CPP, the PRx is impaired (top right panel). With impaired PRx there is a positive correlation between changes in MAP and changes in ICP (normally calculated over a 5-minute window). However, for intermediate CPP values, PRx is (probably) efficient (bottom right panel), and the CPP at which PRx is most negative is termed the CPPopt (as indicated by the 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 lower and upper CPP limits of reactivity (LLR and ULR respectively). Summarising the relationships between CPP and the variables (LLR, ULR, CPPopt), we can appreciate how far a patient's CPP is from their autoregulation guided target or range.

CPP - cerebral perfusion pressure; PRx - Pressure reactivity index; MAP - Mean arterial pressure; ICP - intracranial pressure; CPPopt - CPP optimal; PRxopt - PRx optimal. ULR - Upper limit of reactivity; LLR - Lower limit of reactivity

Figure 2. Comparison of %time spent in different ‘zones’ of CPP as defined by fixed thresholds (left), optimal CPP based thresholds (middle), or flexible limits of reactivity (right)

A. Using the BTF 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 that died, the proportion of time with CPP > 70 mm Hg was lowest, and proportion of time with CPP < 60 mm Hg the highest.

B. The CPP_{opt}-based thresholds were estimated as follows: lower threshold was a CPP more than 10 mm Hg below CPP_{opt} (CPP_{opt} < -10); while the upper threshold was a CPP more than 10 mm Hg above CPP_{opt} (CPP_{opt} > +10). Those with severe disability or vegetative state spent the most amount of time above the upper CPP_{opt} threshold, while those who died spent the most time with CPP below the lower CPP_{opt} threshold.

C. Referencing patients current CPP to their individually estimated lower and upper limits of reactivity (LLR and ULR respectively) 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.

GR-good recovery; MD-moderate disability; SD-severe disability; VS- vegetative state; D- death; GOS- Glasgow outcome score; CPP- cerebral perfusion pressure; LLR-Lower limit of reactivity; ULR-upper limit of reactivity; WLR-within limits of reactivity; CPP_{opt} - CPP- CPP_{opt}; BTF- Brain Trauma Foundation

A Mortality

B Unfavourable outcome

Figure 3. Comparison of receiver operator characteristic (ROC) curves for predicting mortality (top) and unfavourable outcome (bottom).

Percentage of time with CPP below the lower limit of reactivity (%CPP <LLR) was the strongest predictor of mortality and unfavourable outcome.

CPP- Cerebral perfusion pressure; CPPopt- CPP minus CPPopt; LLR- Lower limit of reactivity; ULR- Upper limit of reactivity

Table 1
Demographic and physiological description of cohort

Variable	GR	MD	SD/VS	D	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
Sex (%)					0.025
Female	32 (23)	27 (15)	66 (26)	28 (18)	
Male	107 (77)	156 (85)	187 (74)	126 (82)	
Admission GCS (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 hours (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
ICP [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
% CPPopt < -10 (mean (sd))	14.13 (8.33)	16.54 (10.31)	15.56 (11.07)	23.20 (14.53)	<0.001
% CPPopt ± 10 (mean (sd))	61.89 (10.50)	60.07 (11.07)	58.43 (12.22)	57.89 (12.47)	0.011
% CPPopt > 10 (mean (sd))	23.97 (11.15)	23.39 (11.20)	26.01 (13.42)	18.90 (12.60)	<0.001

GR-good recovery; MD-moderate disability; SD-severe disability; VS- vegetative state; D-death; ICP- intracranial pressure; CPP- cerebral perfusion pressure; PRx-pressure reactivity index; LLR-lower limit of reactivity; ULR-upper limit of reactivity; WLR-within CPP limits of reactivity; CPPopt = CPP-CPPopt; GCS – Glasgow coma score

Table 2
Binary logistic regression models (odds ratios) for prediction of unfavourable outcome and mortality

Variable	Unfavourable outcome			Mortality	
	(1)	(2)	(3)	(4)	(5)
% CPPopt < -10 mm Hg	1.02. (1.00-1.03)			1.04 ^{**} (1.03-1.06)	
% CPP < 60 mm Hg		1.03 [*] (1.01-1.06)			1.03 [*] (1.01-1.05)
%CPP < LLR			1.04 ^{**} (1.02-1.06)		1.06 ^{**} (1.04-1.08)
Age	1.04 ^{**} (1.03-1.05)	1.04 ^{**} (1.03-1.05)	1.04 ^{**} (1.03-1.05)	1.04 ^{**} (1.03-1.06)	1.04 ^{**} (1.03-1.06)
GCS	0.82 ^{**} (0.76-0.87)	0.82 ^{**} (0.77-0.87)	0.82 ^{**} (0.77-0.87)	0.85 ^{**} (0.78-0.92)	0.87 ^{**} (0.80-0.94)
ICP	1.06 ^{**} (1.03-1.09)	1.05 [*] (1.02-1.09)	1.06 ^{**} (1.03-1.09)	1.13 ^{**} (1.09-1.16)	1.11 ^{**} (1.07-1.15)
Log Likelihood	-431.33	-432.89	-424.34	-296.04	-282.18
Akaike Inf Criteria.	872.66	875.79	858.69	602.08	574.36
AUROC	0.737	0.742	0.75	0.793	0.777

Note: *p<0.05; **p<0.01; ***p<0.001

CPP-Cerebral perfusion pressure; CPPopt- CPP minus CPPopt; LLR- Lower limit of reactivity; GCS-Glasgow coma scale; ICP- intracranial pressure, AUROC-area under the receiver operating curve