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Comparison of Performance of Different Optimal Cerebral Perfusion Pressure Parameters for Outcome Prediction in Adult TBI: A CENTER-TBI Study

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Abstract:

It has been postulated previously, that individualized cerebral perfusion pressure (CPP) targets can be derived from cerebrovascular reactivity indices. Differences between real CPP and target CPP (named generically 'optimal CPP') has been linked to global outcome in adult traumatic brain injury (TBI). Different vascular reactivity indices can be utilized in the determination. The goal of this study is to evaluate optimal cerebral perfusion pressure (CPPopt) parameter, derived from three intra-cranial pressure (ICP) derived cerebrovascular reactivity indices, and determine which one is superior for 6 to 12-month outcome prediction. Using the prospectively collected data from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study, the following indices of cerebrovascular reactivity were derived: PRx (correlation between ICP and mean arterial pressure (MAP)), PAx (correlation between pulse amplitude of ICP (AMP) and MAP), and RAC (correlation between AMP and CPP). CPPopt was derived using each index. Univariate logistic regression models were created to assess the association between CPPopt with global dichotomized outcome at 6 to 12 months, as assessed by Glasgow Outcome Score – Extended (GOSE). Models were compared via area under the receiver operating curve (AUC) and Delong's Test. A total of 204 patients had available data. CPPopt derived from PRx, PAx and RAC performed variably in their association with outcomes. PRx and RAC based CPPopt performed similarly, with RAC parameters trending towards highest AUC values. PAx based CPPopt parameters failed to reach significant associations with dichotomized outcomes at 6 to 12-months. CPPopt parameters derived from PRx and RAC appear similar in their overall ability for 6 to 12-month outcome prediction in moderate/severe adult TBI. Keywords: Autoregulation, CPP optimum, ICP indices, outcome analysis

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Introduction:

Optimal cerebral perfusion pressure (CPPopt) has recently emerged as an attractive individualized cerebral perfusion pressure (CPP) target in adult traumatic brain injury (TBI).[1,2] This value is derived via determining the minimum of the parabolic relationship between cerebrovascular reactivity and CPP, over a moving window in time.[1,3,4] CPPopt theoretically indicates a midpoint between lower and upper limit of autoregulation on Lassen's autoregulatory curve.[5] Various retrospective single center series, and one multicentre,[6] to date have demonstrated a strong link between CPPopt values, and time spent away from CPPopt, with global patient outcome in TBI.[2]

Pressure reactivity index, the correlation between intra-cranial pressure (ICP) and mean arterial pressure (MAP),[7] is the most commonly utilized cerebrovascular reactivity index for CPPopt determination. However, two other ICP-derived indices exist: pulse amplitude index (PAx – correlation between pulse amplitude of ICP (AMP) and MAP)[8] and RAC (correlation (R) between AMP (A) and CPP (C)).[9] Both PRx and RAC have a documented association with 6-month global outcome in adult TBI using data from single-centre retrospective study.[10] Previously PAx showed the similar association [Aries- Pax paper]. Historically PRx has been shown experimentally to associate with lower limit ouf autoregulation.[11] Recently all three indices have been validated experimentally using similar technique[12] However, it remains unknown if CPPopt parameters, derived from one of PRx, PAx or RAC, provide superior global outcome prediction in adult TBI.

The goal of this multi-center study, using the high resolution intensive care unit (ICU) cohort from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study,[13] was to determine which CPPopt parameters, derived from three ICP indices of cerebrovascular reactivity, is superior in its association with 6 to 12-month global outcome in adult TBI.

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Methods:

Patient Population:

All patients with complete datasets (ie. high frequency digital physiologic signals and a 6 to 12 month outcome) from the multi-center CENTER-TBI high resolution ICU cohort were included for this study. These patients were prospectively recruited during the periods of January 2015 to December 2017. A total of 21 centers in the European Union (EU) recruited patients for this cohort. All patients were admitted to ICU for their TBI during the course of the study, with high frequency digital signals recorded from their ICU monitors during the course of their ICU stay. All patients suffered predominantly from moderate to severe TBI (moderate = Glasgow Coma Score (GCS) 9 to 12, and severe = GCS of 8 or less). A small percentage of patients suffered from minor TBI, with subsequent early deterioration leading to ICU admission for care and monitoring. All patients in this cohort had invasive ICP monitoring conducted in accordance with the BTF guidelines.[14]

Ethics: Data used in these analyses were collected as part of the CENTER-TBI study (IRAS No: 150943; REC 14/SC/1370). Participation in the study followed informed consent from all patients, or in the event they did not possess capacity, following discussions with a consultee, or with relative, according to local national regulations.

Data Collection:

As part of recruitment to the multi-center high resolution ICU cohort of CENTER-TBI,[13] all patients had demographics prospectively recorded. Similarly, all patients had high frequency digital signals from ICU monitoring recorded throughout their ICU stay, with the goal of initiating recording within 24 hours of ICU admission. All digital ICU signals were further processed (see Signal Acquisition/Signal Processing). For the purpose of this study, the following admission demographic variables were collected: age, sex and admission Glasgow Coma Scale (GCS – total and motor).

Signal Acquisition:

Arterial blood pressure (ABP) was obtained through either radial or femoral arterial lines connected to pressure transducers (Baxter Healthcare Corp. CardioVascular Group, Irvine,

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CA). ICP was acquired via an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA), parenchymal fiber optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, United States; https://www.integralife.com/) or external ventricular drain. All signals were recorded using digital data transfer or digitized via an A/D converter (DT9801; Data Translation, Marlboro, MA), where appropriate, sampled at frequency of 100 Hertz (Hz) or higher, using the ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) or Moberg CNS Monitor (Moberg Research Inc, Ambler, PA, USA) or a combination of both. Signal artifacts were removed using both manual and automated methods prior to further processing or analysis.

Signal Processing:

Post-acquisition processing of the above signals was conducted using ICM+. CPP was determined as CPP = MAP – ICP. AMP was determined by calculating the fundamental Fourier amplitude of the ICP pulse waveforms over a 10 second window, updated every 10 seconds. Ten second moving averages (updated every 10 seconds to avoid data overlap) were calculated for all recorded signals: ICP, ABP (which produced MAP), AMP and CPP.

Continuous indices of cerebrovascular reactivity were derived via the moving correlation coefficient between 30 consecutive 10 second mean windows of the parent signals, updated every minute. PRx was derived via the correlation between ICP and MAP. PAx was derived via the correlation between AMP and MAP. RAC was derived via the correlation between AMP and CPP.

CPPopt was calculated via the methodology describe by Aries et al.[1] In short, a 5-minute median CPP time trend was calculated along with each index: PRx, PAx and RAC. PRx, PAx and RAC values were averaged over 5 mm Hg bins of CPP, using 4 hours of data. Automatic parabolic curve fitting was applied (see previous publications for details),[1] determining the CPP value associated with the lowest PRx, PAx and RAC. This produced the CPPopt value. CPPopt was then calculated using a 4-hour moving window, updated every minute. Delta CPPopt was calculated by: median CPP – CPPopt; for each CPPopt derived from PRx, PAx and RAC.

Data was provided in minute-by-minute comma separated variable sheets for the entire duration of recording for each patient.

Data Processing:

Grand mean values of all physiologic variables were calculated per patient. In addition, the following post-ICM+ processing of this physiologic data occurred in R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/):

CPPopt Based on ICP Indices:

a. Mean CPPopt values derived from PRx, PAx and RAC were calculated. Mean delta CPPopt for each index was also calculated.

b. The % time spent greater than 5 mm Hg, 10 mm Hg and 15 mm Hg away from CPPopt was determined for each CPPopt values derived from PRx, PAx and RAC. This was determined for both above CPPopt and below CPPopt.

c. Hourly dose of CPP above 5 mm Hg from CPPopt and below 5 mm Hg from CPPopt for each index was calculated.

*Note: values for % time above CPPopt and hourly dose above CPPopt failed to yield statistically meaningful results in association with dichotomized 6 to 12-month outcomes and are thus not reported further within the manuscript.

Statistics:

All statistical analysis was conducted using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and XLSTAT (Addinsoft, New York, NY; https://www.xlstat.com/en/) add-on package to

Microsoft Excel (Microsoft Office 15, Version 16.0.7369.1323). Normality of continuous variables was assessed via Shapiro-Wilks test. For all testing described within, the alpha was set at 0.05 for significance.

Despite GOSE being collected at both 6 and 12 months post-injury in this cohort of patients, there was missing data present in both categories of outcome. Thus, we combined GOSE scores from both 6 and 12 months in order to provide a "6 to 12 Month" GOSE. For patients where GOSE was reported for both 6 and 12 months, the superior GOSE score was selected for analysis. GOSE was then dichotomized into the following categories: A. Alive (GOSE 2 to 8) vs. Dead (GOSE 1); and B. Favourable (GOSE 5 to 8) vs. Unfavourable (GOSE 4 or less). Demographics and physiologic variables were compared between each dichotomized group, via t-test, Mann-U and chi-square testing where appropriate.

Univariate logistic regression (ULR) was first conducted, comparing: mean CPPopt, delta CPPopt, % time/dose below CPP opt to the dichotomized outcomes was conducted. Again, superiority was assessed via AUC and Delong's Test.

Given this study is a preliminary multi-center validation study of previous single center retrospective univariate relationships, we did not correct for multiple comparisons as we felt it not to be appropriate for such an initial preliminary exploratory report. The goal was merely to investigate the univariate associations between CPPopt variables and outcome, in order to determine if previous single center results could be confirmed in a multi-center international data set. Thus, some p-values near the threshold for significance (ie. 0.05) may not remain significant if one were to correct for multiple comparisons, via Bonferroni of false discovery rate methodologies. Much further multi-variable statistical analysis on CPPopt will occur using the CENTER-TBI high-resolution data set, as part of separate sub-projects within this specific work package. During these future studies such statistical methodologies will be adopted, as appropriate for such analyses.

Results:

Patient Population

A total of 204 patients from the CENTER-TBI high resolution ICU cohort had complete data sets, including: 6 to 12-month GOSE and high frequency physiologic signals containing at least ICP and ABP for ICP cerebrovascular index derivation. 159 did not undergo decompressive craniectomy (DC). The analysis was conducted for both the: total

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population (n=204) and the non-DC cohort (n=157), with similar results found for both cohorts. The patient demographics for the entire cohort can be found summarized in Table 1. In addition, Mann-U and chi-square testing comparing various variables between alive/dead and favourable/unfavourable outcome groups can be found in Appendix A of the supplementary materials. Furthermore, the non-DC Patient cohort demographic and comparison between groups can be found in Appendix B of the supplementary materials.

Various CPPopt parameters were derived, using each of PRx, PAx and RAC to determine CPPopt. These variables are summarized in Table 1. The differences between the dichotomized outcome groups can be seen in Appendix A and B of the supplementary materials.

*Table 1 here

Examples of CPPopt calculations based on PRx, PAx and RAC can be seen in Figure 1, displaying a patient example of CPPopt determination via the three indices. Similarly, Figure 2 displays error bar plots for the total population, displaying the parabolic relationship between PRx, PAx and RAC with CPP, highlighting the potential for RAC to provide more visually distinct CPPopt curves. This is in keeping with the initial description of RAC in a large retrospective TBI cohort.[9]

Comparison Between Dichotomized Outcome Groups

Identical statistically significant differences between dichotomized outcome groups were noted in both the total population and the non-DC cohort (see Appendix A and B). In general, for the alive/dead outcome groups the following were statistically higher for the death group: age, the % time spent below CPPopt (ie. <5 mm Hg, <10 mm Hg, or <15 mm Hg), based on CPPopt from PRx and RAC, were higher in those who died. Comparing favourable/unfavourable outcome groups, the statistically significant differences in variables were the same, with the exception for ICP based variables (mean ICP, % time with ICP > 20 mm Hg and > 22 mm Hg), where these were not significantly different between groups.

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*Figure 1 here

*Figure 2 here

Univariate Logistic Regression Analysis – CPPopt Based Variables

All CPPopt based variables were calculated using each of PRx, PAx and RAC for CPPopt determination. The results of the ULR analysis were identical for both the total population (Table 2) and the non-DC cohort (Appendix C of the supplementary materials). The CPPopt variables based on RAC displayed higher AUC's for both dichotomized outcomes, compared to CPPopt variables derived from PRx, and PAx. However, when comparing the AUC's between PRx and RAC derived CPPopt variables via Delong's test, there was no statistically significant difference, despite the trend to higher AUC's with RAC variables. PAx based CPPopt variables rarely reached statistically significant associations with either dichotomized outcome, suggesting the PAx is inferior in outcome prediction capacity within this population.

Only the mean hourly dose of CPP 5 mm Hg or more below CPPopt, as determined through RAC, was statistically significantly different compared to similar variables derived from PRx or PAx. This suggests that RAC may provide superior predictive capacity for 6 to 12-month favourable/unfavourable outcome, over PRx and PAx. Table 2 displays the AUC's and p-values for the logistic regression analysis.

*Table 2 here

Discussion:

We have performed a basic analysis of the outcome prediction capacity of CPPopt parameters estimated using three ICP-derived cerebrovascular reactivity indices (PRx, PAx and RAC) in adult moderate/severe TBI using data from multiple European centers. The patient management protocols naturally differed from centre to centre. Yet the results obtained are in good agreement with previous, single centre, publications with respect to PRx and its derived CPPopt, and that fact alone is reassuring and note-worthy. In addition, analysis of the other indices of reactivity, PAx and RAC produced some interesting results, which deserve further highlighting.

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First, CPPopt variables, as derived from each of PRx, PAx and RAC, displayed some distinct trends. PAx performed poorly, with little to no statistically significant association between PAx based CPPopt variables and outcome, alive/dead or favourable/unfavourable. This raises the question of the utility of PAx for CPPopt estimation. Though, we acknowledge again, that this may be secondary to small population numbers and treatment heterogeneity.

Second, PRx and RAC based CPPopt variables performed similarly in their association with both dichotomized outcomes, with RAC display higher AUC's. However, there was no statistically significant difference between AUC's when tested. This suggests that PRx and RAC are comparable for CPPopt estimation and outcome association. However, dose of CPP 5 mm Hg or more below CPPopt (based on RAC) was statistically associated with favourable/unfavourable outcome, where similar PRx and PAx variables were insignificant. This suggests that RAC may be superior for favourable/unfavourable outcome prediction in adult TBI, though further analysis is required.

Finally, the % of time below CPPopt, for CPPopt based on PRx or RAC, was associated with worse outcome, death and unfavourable outcome. These results are in keeping with prior publications indicating that the time spent below CPPopt is associated with worse outcome.[1–4,15] Further to this, the % time and dose above CPPopt failed to reach a meaningful association with any of the dichotomized outcomes, and were thus not mentioned further in the manuscript. The lack of meaningful association to dichotomized outcomes has also been seen in these previous publications. Thus, it remains unclear the impact of CPP values above CPPopt on patient outcome in TBI. Further work in this area is required.

Limitations

There are limitations which require addressing. First, despite having prospective multi-center data, patient numbers for both cohorts are quite low. This likely impacted the lack of statistical significance when comparing AUC's. Thus, the results here are only preliminary and require further validation. Therefore, no conclusive comments on which index is superior for CPPopt parameter calculation can be made at this time.

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Second, CENTER TBI was a prospective observational study. Treatment heterogeneity may have impacted the signal values and associations seen. In particular, we did not analyzed strategies for CPP manipulation, i.e. use of vasopressors and/or fluids for CPP augmentation, or other pharmacological interventions, as deep sedation, which may have caused vasodilation and CPP reduction. Accordingly, strategies for ICP reduction (with consequent CPP improvement) are not the object of this investigation. In addition, we don't identify active CPP manipulations during the recording, given difficulties in obtaining accurate annotation regarding these events. These particular aspects could explain why some of the CPPopt variables tested failed to demonstrate strong, or in some cases any, statistical significance with global outcome at 6 to 12 months. This is one of the main difficulties with these types of observational studies, that despite prospective collection of data, there still exists the potential for heterogeneity in therapies and response, which may impact the recorded MAP, ICP and derived signals. Such analysis of the impact of various treatment strategies is important, and will be the focus of future more complex statistical methodologies applied to the CENTER-TBI high-resolution cohort data. The goal of this basic univariate analysis project was just to confirm that the results of previous studies on CPPopt weren't just a function of single center results. With the results from this current univariate analysis on CPPopt, we will now be able to move forward with confidence that CPPopt is a variable of prognostic significance, now validated on multi-center data, and apply more complex methodologies in order to determine the impact of various treatments, and if any sub-populations of TBI patients exist where CPPopt determination is more feasible than others. These aims are currently the focus of separate sub-projects within the CENTER-TBI high-resolution ICU cohort work package.

Third, the population chosen was that with an outcome recorded at 6 to 12 months and high frequency digital signals, hence the low patient numbers overall. Given this, we focused only on univariate models comparing various variables to dichotomized outcomes. Consequently, further analysis in larger higher resolution data cohorts is required to confirm if these relationships hold true in multi-variable models. Finally, we re-emphasized that the results here are preliminary only. Further analysis of the feasibility of CPPopt parameter calculation with PAx and RAC needs to be conducted prior to the widespread

adoption of these indices for this purpose. This will require larger patient cohorts with high frequency digital signal data and is currently planned.

Conclusion:

CPPopt outcome associations have been confirmed in a multicenter (multi-protocol) database. CPPopt parameters derived from PRx and RAC appear similar in their overall ability for 6 to 12-month outcome prediction in moderate/severe adult TBI. RAC may be superior in the prediction of favourable versus unfavourable outcome, based on CPPopt parameters derived from RAC. PAx based CPPopt parameters were poorly correlated with patient outcome.

Disclosures:

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Table 1: Patient Demographics – Total Population – Additional CPPopt Based Physiologic Variables

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		Mean/Median (+/-sd or IQR)
Number of Patients		204
Age (years)		46.6 (19.3)
Sex	***Male***	163
	Female	41
Admission GCS (Total)		7 (4 to 13)
Admission GCS Motor		4 (2 to 6)
Mean PRx Based CPPopt [mm Hg]		71.7 (9.3)
Mean PAx Based CPPopt [mm Hg]		69.0 (11.2)
Mean RAC Based CPPopt [mm Hg]		68.9 (9.9)
Mean PRx Based Delta CPP [mmHg]		-0.515 (3.9)
Mean PAx Based Delta CPP [mm Hg]		-0.358 (3.9)
Mean RAC Based Delta CPP [mm Hg]		2.5 (6.4)
PRx Based CPPopt Measures		
% Time Spent with CPP >5 mm Hg Above CPPopt		32.1 (20.3)
% Time Spent with CPP >10 mm Hg Above CPPopt		17.7 (14.3)
% Time Spent with CPP >15 mm Hg Above CPPopt		7.1 (8.3)
% Time Spent with CPP >5 mm Hg Below CPPopt		34.4 (22.0)
% Time Spent with CPP >10 mm Hg Below CPPopt		20.3 (16.8)
% Time Spent with CPP >15 mm Hg Below CPPopt		9.1 (10.6)
Mean Hourly Dose of CPP >5 mm Hg Above		108.6 (102.2)

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CPPopt [mm Hg]	
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt [mm Hg]	-108.1 (92.9)
PAx Based CPPopt Measures	
% Time Spent with CPP >5 mm Hg Above CPPopt	21.7 (16.1)
% Time Spent with CPP >10 mm Hg Above CPPopt	7.0 (10.1)
% Time Spent with CPP >15 mm Hg Above CPPopt	2.3 (5.9)
% Time Spent with CPP >5 mm Hg Below CPPopt	23.9 (19.1)
% Time Spent with CPP >10 mm Hg Below CPPopt	8.2 (12.5)
% Time Spent with CPP >15 mm Hg Below CPPopt	3.5 (9.7)
Mean Hourly Dose of CPP >5 mm Hg Above CPPopt [mm Hg]	49.3 (57.7)
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt [mmHg]	-57.8 (66.8)
RAC Based CPPopt Measures	
% Time Spent with CPP >5 mm Hg Above CPPopt	45.3 (23.8)
% Time Spent with CPP >10 mm Hg Above CPPopt	26.4 (18.3)
% Time Spent with CPP >15 mm Hg Above CPPopt	11.3 (11.4)
% Time Spent with CPP >5 mm Hg Below CPPopt	25.1 (23.0)
% Time Spent with CPP >10 mm Hg Below	15.5 (18.0)

CPPopt	
% Time Spent with CPP >15 mm Hg Below CPPopt	7.5 (11.8)
Mean Hourly Dose of CPP >5 mm Hg Above CPPopt	153.1 (135.6)
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-77.5 (92.9)

AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP, sd = standard deviation. Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC).

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Table 2: Univariate Logistic Regression Analysis – Total Population – CPPopt Based Parameters

Model	**AUC Alive/Dead (95% CI)**	**p-value**	**AUC Favourable/Unfavourable (95% CI)**	**p-value**
Delta CPPopt				
Mean PRx Based Delta CPPopt	0.702 (0.107-0.795)	**<0.0001**	0.640 (0.563-0.718)	**0.0020**
Mean PAx Based Delta CPPopt	0.586 (0.489-0.683)	0.2760	0.550 (0.470-0.630)	0.7500
Mean RAC Based Delta CPPopt	0.763 (0.686-0.840)	**<0.0001**	0.689 (0.615-0.764)	**0.0001**
% Time Below CPPopt				
PRx				
% Time >5 mm Hg Below PRx Based CPPopt	0.692 (0.595-0.788)	**<0.0001**	0.632 (0.556-0.710)	**0.0021**
% Time >10 mm Hg Below PRx Based CPPopt	0.679 (0.583-0.776)	**0.0002**	0.648 (0.571-0.725)	**0.0035**
% Time >15 mm Hg Below PRx	0.693 (0.600-0.787)	**0.007**	0.650 (0.573-0.727)	**0.0348**

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Based CPPopt				
PAx				
% Time >5 mm Hg Below PAx Based CPPopt	0.569 (0.468-0.670)	0.1500	0.559 (0.479-0.639)	0.3090
% Time >10 mm Hg Below PAx Based CPPopt	0.496 (0.395-0.598)	0.6210	0.552 (0.473-0.631)	0.6910
% Time >15 mm Hg Below PAx Based CPPopt	0.478 (0.388-0.569)	0.5040	0.582 (0.510-0.654)	0.8040
RAC				
% Time >5 mm Hg Below RAC Based CPPopt	0.765 (0.690-0.840)	**<0.0001**	0.706 (0.633-0.780)	**0.0002**
% Time >10 mm Hg Below RAC Based CPPopt	0.751 (0.673-0.829)	**<0.0001**	0.725 (0.653-0.797)	**0.0003**
% Time >15	0.711 (0.631-	**0.0146**	0.712 (0.639-0.785)	0.0585

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mm Hg Below RAC Based CPPopt	0.792)			
Hourly Dose Below CPPopt				
Mean Dose >5 mm Hg Below PRx CPPopt	0.523 (0.423-0.622)	0.5910	0.569 (0.489-0.648)	0.1470
Mean Dose >5 mm Hg Below PAx CPPopt	0.503 (0.401-0.605)	0.6680	0.552 (0.473-0.632)	0.4130
Mean Dose >5 mm Hg Below RAC CPPopt	0.640 (0.550-0.729)	0.0904	0.680 (0.605-0.754)	**0.0113**

A/D = alive/dead, AMP = pulse amplitude of ICP, AUC = area under the receiver operating curve, CPP = cerebral perfusion pressure, CPPopt = CPP optimum, CI = confidence interval, F/U = Favourable/Unfavourable outcome (ie. Favourable = Glasgow Outcome Scale of 5 to 8; Unfavourable = Glasgow Outcome Scale of 1 to 4), ICP = intra-cranial pressure, IMPACT = International Mission for Prognosis and Analysis of Clinical Trials, MAP = mean arterial pressure, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP. CORE model consisted of age, admission Glasgow Coma Scale motor score and pupil response (normal bilaterally, unilateral unreactive, or bilaterally unreactive). Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC).

Figure Legends:

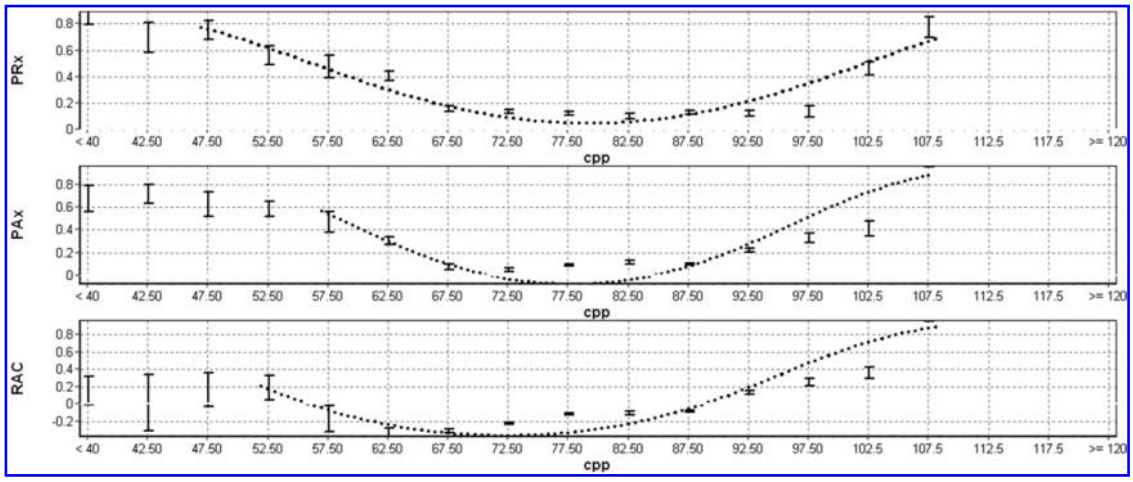

Figure 1: Patient Examples of CPPopt Determination Using PRx PAx or RAC.

AMP = pulse amplitude of ICP, a.u. = arbitrary units, CPP = cerebral perfusion pressure, CPPopt = CPP optimum, ICP = intra-cranial pressure, mm Hg = millimeters of Mercury, MAP = mean arterial pressure, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP.

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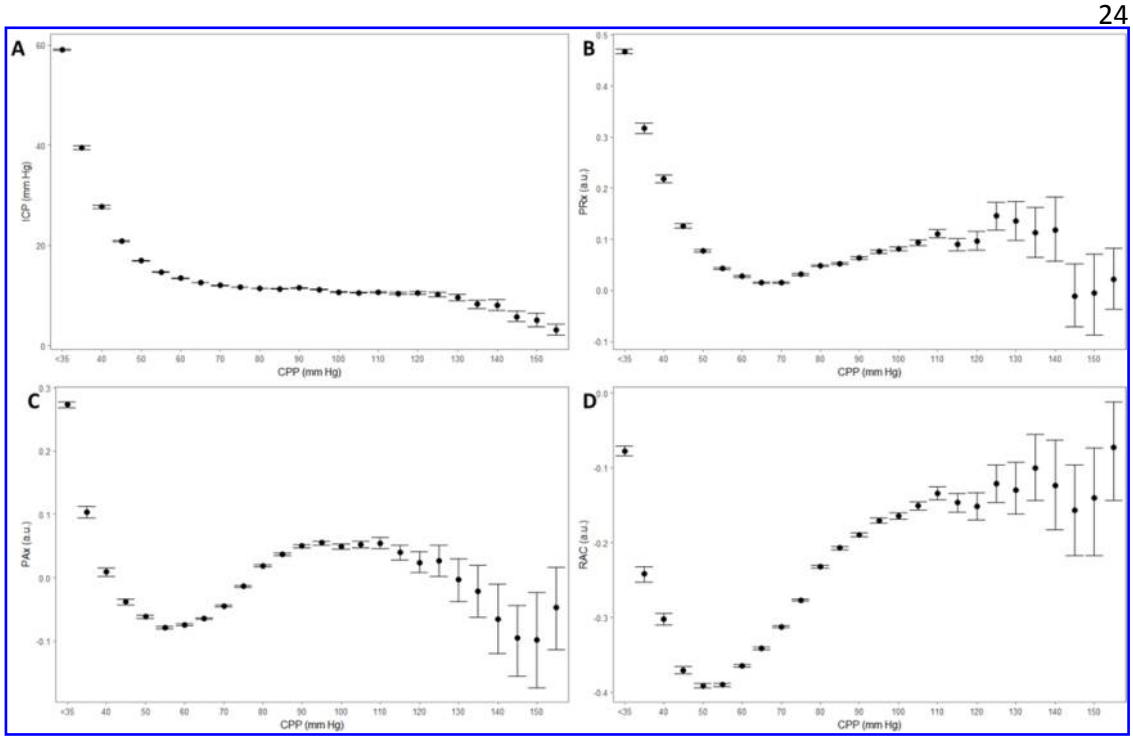

Figure 2: Total Population – ICP, PRx, PAx and RAC versus CPP – Binned data

AMP = pulse amplitude of ICP, a.u. = arbitrary units, CPP = cerebral perfusion pressure, CPPopt = CPP optimum, ICP = intra-cranial pressure, mm Hg = millimeters of Mercury, MAP = mean arterial pressure, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP. Figure derived from using 5 mm Hg bins of CPP, determining the average ICP, PRx, PAx and RAC values for each bin, then plotting using error-bar plots. Panel A: ICP versus CPP error bar plot, Panel B: PRx versus CPP error bar plot, Panel C: PAx versus CPP error bar plot, Panel D: RAC versus CPP error bar plot.

Appendix A: Total Population – Comparison of Demographics Between Dichotomized Outcomes

1. Comparison of Demographics and Physiologic Variables Between Dichotomized Outcome Groups – Alive/Dead Dichotomization

   **Note: % time spent with CPP >5, >10 and >15 mm Hg above CPPopt for PRx, PAx and RAC failed to be associated with poor outcome. As such, these values were not included in the tables to follow*

Alive/Dead Dichotomized Groups – Additional CPPopt Based Physiologic Parameters – Mann-U and Chi-Square Comparison Between Groups

		Mean/Median (+/-sd or IQR)		**p-value**
		Alive	**Dead**	
Number of Patients		155	49	
Age (years)		43.5 (18.4)	56.6 (18.7)	**<0.0001**
Sex	***Male***	128	35	0.089
	Female	27	13	
Admission GCS (Total)		7 (5 to 13)	8 (3 to 13)	0.707
Admission GCS Motor		4 (2 to 5)	4 (1 to 6)	0.863
Duration of High Frequency Physiologic Recording (hours)		164.1 (118.5)	145.1 (96.6)	0.472
Mean PRx Based CPPopt		71.1 (8.8)	74.1 (10.6)	**0.035**
Mean PAx Based CPPopt		69.7 (8.7)	66.4 (16.7)	0.790
Mean RAC Based CPPopt		67.8 (9.5)	72.8 (10.3)	**0.001**
Mean PRx Based Delta CPP		0.4 (5.3)	-3.7 (5.9)	**<0.0001**
Mean PAx Based		-0.2 (5.9)	-0.9 (4.2)	0.105

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Delta CPP			
Mean RAC Based Delta CPP	3.7 (6.0)	-1.8 (5.9)	**<0.0001**
PRx Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	30.9 (19.8)	46.2 (24.9)	**0.001**
% Time Spent with CPP >10 mm Hg Below CPPopt	17.8 (14.9)	28.9 (19.7)	**0.001**
% Time Spent with CPP >15 mm Hg Below CPPopt	7.6 (9.9)	14.3 (11.4)	**0.001**
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-106.1 (91.5)	-114.3 (98.2)	0.321
PAx Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	22.8 (18.8)	27.4 (19.8)	0.132
% Time Spent with CPP >10 mm Hg Below CPPopt	8.0 (12.6)	9.0 (12.5)	0.855
% Time Spent with CPP >15 mm Hg Below CPPopt	3.3 (9.7)	4.4 (10.0	0.535
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-56.7 (67.0)	-61.4 (66.6)	0.788
RAC Based CPPopt Measures			

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% Time Spent with CPP >5 mm Hg Below CPPopt	20.4 (20.5)	40.6 (24.1)	**<0.0001**
% Time Spent with CPP >10 mm Hg Below CPPopt	12.3 (15.7)	26.2 (20.5)	**<0.0001**
% Time Spent with CPP >15 mm Hg Below CPPopt	11.5 (11.6)	6.2 (11.6)	**<0.0001**
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-71.2 (95.4)	-97.5 (82.2)	**0.001**

AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP, sd = standard deviation. Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC). Bolded p-values are those reaching statistical significance (ie. p<0.05).

2. Comparison of Demographics and Physiologic Variables Between Dichotomized Outcome Groups – Favourable/Unfavourable Dichotomization

   **Note: % time spent with CPP >5, >10 and >15 mm Hg above CPPopt for PRx, PAx and RAC failed to be associated with poor outcome. As such, these values were not included in the tables to follow*

   Favourable/Unfavourable Dichotomized Groups – Additional CPPopt Based Physiologic Parameters – Mann-U and Chi-Square Comparison Between Groups

	Mean/Median (+/-sd or IQR)		**p-value**
	Favourable	**Unfavourable**	
Number of Patients	95	109	

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Age (years)		40.9 (17.3)	51.6 (19.6)	**<0.0001**
Sex	***Male***	85	78	0.463
	Female	10	31	
Admission GCS (Total)		8 (6 to 13)	7 (4 to 11)	0.136
Admission GCS Motor		5 (3 to 6)	4 (1 to 6)	0.110
Duration of High Frequency Physiologic Recording (hours)		151.6 (119.1)	166.5 (108.8)	0.125
Mean PRx Based CPPopt		70.1 (8.4)	73.2 (9.9)	**0.023**
Mean PAx Based CPPopt		69.7 (8.6)	68.4 (13.0)	0.772
Mean RAC Based CPPopt		66.7 (9.0)	70.9 (10.3)	**0.002**
Mean PRx Based Delta CPP		0.8 (5.4)	-1.7 (5.7)	**0.001**
Mean PAx Based Delta CPP		-0.3 (4.1)	-0.4 (3.8)	0.275
Mean RAC Based Delta CPP		4.4 (6.3)	0.7 (6.1)	**<0.0001**
<u>PRx Based CPPopt Measures</u>				
% Time Spent with CPP >5 mm Hg Below CPPopt		29.2 (20.3)	39.0 (22.5)	**0.001**
% Time Spent with CPP >10 mm Hg Below CPPopt		16.6 (15.7)	23.7 (17.0)	**0.001**
% Time Spent with CPP >15 mm Hg Below CPPopt		7.4 (11.3)	10.7 (9.9)	**0.001**

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Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-97.9 (86.1)	-117.0 (98.1)	0.098
PAx Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	22.4 (19.9)	25.2 (18.3)	0.150
% Time Spent with CPP >10 mm Hg Below CPPopt	7.8 (14.0)	8.5 (11.1)	0.227
% Time Spent with CPP >15 mm Hg Below CPPopt	3.4 (11.2)	3.7 (8.4)	0.050
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-53.7 (69.4)	-61.4 (64.6)	0.280
RAC Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	18.4 (21.8)	31.0 (22.5)	**<0.0001**
% Time Spent with CPP >10 mm Hg Below CPPopt	10.3 (15.9)	20.1 (18.4)	**<0.0001**
% Time Spent with CPP >15 mm Hg Below CPPopt	9.0 (10.2)	10.3 (15.9)	**<0.0001**
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-59.1 (89.2)	-93.6 (93.4)	**<0.0001**

AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg =

millimeters of mercury, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP, sd = standard deviation. Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC). Bolded p-values are those reaching statistical significance (ie. p<0.05).

Appendix B: Non-DC Population – Patient Demographics and Comparison of Parameters Between Dichotomized Outcome Groups

1. Entire Population Demographics

Patient Demographics – Total non-DC Population – Additional CPPopt Based Physiologic Parameters

		Mean/Median (+/-sd or IQR)
Number of Patients		159
Age (years)		48.2 (19.6)
Sex	***Male***	123
	Female	36
Admission GCS (Total)		8 (5 to 13)
Admission GCS Motor		5 (2 to 6)
Duration of High Frequency Physiologic Recording (hours)		150.5 (109.3)
Mean PRx Based CPPopt		71.8 (9.9)
Mean PAx Based CPPopt		70.0 (11.5)
Mean RAC Based CPPopt		68.8 (10.6)
Mean PRx Based Delta CPP		-0.8 (5.9)
Mean PAx Based Delta CPP		-0.7 (4.1)
Mean RAC Based Delta CPP		2.3 (6.7)
PRx Based CPPopt Measures		
% Time Spent with CPP >5 mm Hg Above CPPopt		31.4 (20.9)
% Time Spent with CPP >10 mm Hg Above CPPopt		17.8 (14.8)
% Time Spent with CPP >15 mm Hg Above CPPopt		7.1 (8.4)
% Time Spent with CPP >5 mm Hg Below CPPopt		35.8 (22.7)

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% Time Spent with CPP >10 mm Hg Below CPPopt	21.4 (17.4)
% Time Spent with CPP >15 mm Hg Below CPPopt	9.8 (11.2)
Mean Hourly Dose of CPP >5 mm Hg Above CPPopt	106.5 (103.1)
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-111.1 (90.4)
PAx Based CPPopt Measures	
% Time Spent with CPP >5 mm Hg Above CPPopt	20.6 (15.3)
% Time Spent with CPP >10 mm Hg Above CPPopt	6.8 (9.8)
% Time Spent with CPP >15 mm Hg Above CPPopt	2.3 (6.1)
% Time Spent with CPP >5 mm Hg Below CPPopt	25.3 (20.1)
% Time Spent with CPP >10 mm Hg Below CPPopt	9.2 (13.7)
% Time Spent with CPP >15 mm Hg Below CPPopt	4.1 (10.8)
Mean Hourly Dose of CPP >5 mm Hg Above CPPopt	45.4 (52.1)
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-60.8 (71.3)
RAC Based CPPopt Measures	
% Time Spent with CPP >5 mm Hg Above CPPopt	45.3 (24.5)
% Time Spent with CPP >10 mm Hg Above CPPopt	26.7 (18.6)

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% Time Spent with CPP >15 mm Hg Above CPPopt	11.3 (11.4)
% Time Spent with CPP >5 mm Hg Below CPPopt	26.1 (24.7)
% Time Spent with CPP >10 mm Hg Below CPPopt	16.3 (19.2)
% Time Spent with CPP >15 mm Hg Below CPPopt	8.1 (12.6)
Mean Hourly Dose of CPP >5 mm Hg Above CPPopt	153.4 (136.5)
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-78.1 (92.5)
6 to 12 Month GOSE	5 (2 to 5)
Number Alive – 6 to 12 Months	121
Number Dead – 6 to 12 Months	38
Number Favourable Outcome – 6 to 12 Months (GOSE 5 to 8)	82
Number Unfavourable Outcome – 6 to 12 Months (GOSE 1 to 4)	77

AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, DC = decompressive craniectomy, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP, sd = standard deviation. Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC).

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2. Comparison of Demographics and Physiologic Variables Between Dichotomized Outcome Groups – Alive/Dead Dichotomization

**Note: % time spent with CPP >5, >10 and >15 mm Hg above CPPopt for PRx, PAx and RAC failed to be associated with poor outcome. As such, these values were not included in the tables to follow*

Alive/Dead Dichotomized Groups – non-DC cohort - Additional CPPopt Based Physiologic Parameters – Mann-U and Chi-Square Comparison Between Groups

		Mean/Median (+/-sd or IQR)		p-value
		Alive	**Dead**	
Number of Patients		121	38	
Age (years)		44.8 (18.6)	59.0 (18.9)	**0.001**
Sex	***Male***	97	26	0.131
	Female	24	12	
Admission GCS (Total)		8 (5 to 13)	9 (4 to 13)	0.530
Admission GCS Motor		5 (3 to 6)	4 (1 to 6)	0.592
Duration of High Frequency Physiologic Recording (hours)		156.6 (114.5)	131.2 (85.1)	0.264
Mean PRx Based CPPopt		71.0 (9.3)	67.4 (11.5)	0.074
Mean PAx Based CPPopt		69.9 (8.9)	66.2 (17.4)	0.721
Mean RAC Based CPPopt		67.7 (10.1)	72.6 (11.4)	**0.013**
Mean PRx Based Delta CPP		0.3 (5.5)	-4.4 (5.8)	**<0.0001**
Mean PAx Based Delta CPP		-0.6 (3.9)	-0.9 (4.6)	0.299
Mean RAC Based		3.6 (6.3)	-1.9 (6.4)	**<0.0001**

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Delta CPP			
PRx Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	31.4 (20.8)	50.1 (23.5)	**<0.0001**
% Time Spent with CPP >10 mm Hg Below CPPopt	18.3 (15.5)	31.7 (19.5)	**0.001**
% Time Spent with CPP >15 mm Hg Below CPPopt	8.0 (10.6)	15.9 (11.1)	**<0.0001**
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-108.2 (89.6)	-120.6 (93.2)	0.199
PAx Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	10.7 (13.5)	24.4 (19.8)	0.252
% Time Spent with CPP >10 mm Hg Below CPPopt	8.7 (13.8)	10.7 (13.5)	0.663
% Time Spent with CPP >15 mm Hg Below CPPopt	3.6 (10.6)	5.5 (11.2)	0.245
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-59.5 (71.3)	-65.1 (72.1)	0.797
RAC Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below	21.0 (22.1)	43.1 (25.7)	**<0.0001**

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CPPopt			
% Time Spent with CPP >10 mm Hg Below CPPopt	12.7 (16.5)	28.5 (22.4)	**<0.0001**
% Time Spent with CPP >15 mm Hg Below CPPopt	6.7 (12.5)	12.5 (12.0)	**<0.0001**
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-72.2 (95.1)	-97.1 (82.1)	**0.004**

AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP, sd = standard deviation. Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC). Bolded p-values are those reaching statistical significance (ie. p<0.05).

3. Comparison of Demographics and Physiologic Variables Between Dichotomized Outcome Groups – Favourable/Unfavourable Dichotomization

   **Note: % time spent with CPP >5, >10 and >15 mm Hg above CPPopt for PRx, PAx and RAC failed to be associated with poor outcome. As such, these values were not included in the tables to follow*

   Favourable/Unfavourable Dichotomized Groups – non-DC cohort - Additional CPPopt Based Physiologic Parameters – Mann-U and Chi-Square Comparison Between Groups

	Mean/Median (+/-sd or IQR)		**p-value**
	Favourable	**Unfavourable**	
Number of Patients	82	77	
Age (years)	41.9 (17.3)	54.8 (19.7)	**<0.0001**

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Sex	***Male***	66	57	0.331
	Female	16	20	
Admission GCS (Total)		8 (6 to 13)	8 (4 to 13)	0.231
Admission GCS Motor		5 (4 to 6)	4 (2 to 6)	0.159
Duration of High Frequency Physiologic Recording (hours)		150.3 (123.5)	150.6 (92.5)	0.427
Mean PRx Based CPPopt		70.4 (8.8)	73.2 (10.8)	0.108
Mean PAx Based CPPopt		69.7 (8.9)	68.2 (13.8)	0.933
Mean RAC Based CPPopt		67.0 (9.5)	70.9 (11.4)	**0.026**
Mean PRx Based Delta CPP		0.6 (5.6)	-2.3 (5.8)	**0.001**
Mean PAx Based Delta CPP		-0.6 (4.2)	-0.8 (3.9)	0.378
Mean RAC Based Delta CPP		4.2 (6.6)	0.3 (6.4)	**<0.0001**
<u>PRx Based CPPopt Measures</u>				
% Time Spent with CPP >5 mm Hg Below CPPopt		29.9 (21.4)	42.2 (22.6)	**0.001**
% Time Spent with CPP >10 mm Hg Below CPPopt		17.5 (16.6)	25.6 (17.5)	**0.001**
% Time Spent with CPP >15 mm Hg Below CPPopt		8.1 (11.9)	11.6 (10.2)	**0.003**
Mean Hourly Dose of		-103.0 (90.8)	-120.0 (89.7)	0.132

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CPP >5 mm Hg Below CPPopt			
PAx Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	24.0 (20.7)	26.7 (19.5)	0.240
% Time Spent with CPP >10 mm Hg Below CPPopt	8.5 (14.8)	9.9 (12.5)	0.316
% Time Spent with CPP >15 mm Hg Below CPPopt	3.6 (11.7)	4.6 (9.6)	0.068
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-57.3 (73.2)	-64.5 (69.4)	0.447
RAC Based CPPopt Measures			
% Time Spent with CPP >5 mm Hg Below CPPopt	19.1 (23.1)	33.7 (24.2)	**<0.0001**
% Time Spent with CPP >10 mm Hg Below CPPopt	10.9 (16.9)	22.1 (19.9)	**<0.0001**
% Time Spent with CPP >15 mm Hg Below CPPopt	6.3 (14.1)	10.0 (10.4)	**<0.0001**
Mean Hourly Dose of CPP >5 mm Hg Below CPPopt	-62.1 (94.8)	-95.2 (87.5)	**0.001**

AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intra-cranial pressure, IQR = inter-quartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index (correlation between AMP and

MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP, sd = standard deviation. Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC). Bolded p-values are those reaching statistical significance (ie. p<0.05).

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Appendix C: Univariate Logistic Regression Analysis – non-DC cohort – CPPopt Based Measures

Model	**AUC A/D (95% CI)**	**p-value**	**AUC F/U (95% CI)**	**p-value**
PRx CPPopt	0.591 (0.479-0.702)	0.0766	0.570 (0.479-0.660)	0.0772
PAx CPPopt	0.539 (0.412-0.667)	0.0977	0.513 (0.420-0.605)	0.4160
RAC CPPopt	0.628 (0.518-0.739)	**0.0181**	0.597 (0.508-0.687)	**0.0228**
Delta CPPopt				
Mean PRx Based Delta CPPopt	0.728 (0.630-0.826)	**<0.0001**	0.654 (0.566-0.742)	**0.0028**
Mean PAx Based Delta CPPopt	0.560 (0.445-0.675)	0.639	0.545 (0.454-0.635)	0.736
Mean RAC Based Delta CPPopt	0.740 (0.647-0.833)	**<0.0001**	0.689 (0.604-0.774)	**0.0006**
% Time Below CPPopt				
PRx				
% Time >5 mm Hg Below PRx Based CPPopt	0.732 (0.634-0.829)	**<0.0001**	0.663 (0.578-0.749)	**0.0010**
% Time >10 mm Hg Below PRx Based CPPopt	0.721 (0.626-0.816)	**0.0002**	0.664 (0.578-0.750)	0.0053
% Time >15 mm Hg Below PRx Based CPPopt	0.741 (0.648-0.835)	**0.0009**	0.652 (0.565-0.739)	0.0579
PAx				
% Time >5 mm	0.550 (0.432-	0.3230	0.552 (0.460-	0.3960

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Hg Below PAx Based CPPopt	0.668)		0.643)	
% Time >10 mm Hg Below PAx Based CPPopt	0.518 (0.401-0.636)	0.4510	0.554 (0.463-0.645)	0.5060
% Time >15 mm Hg Below PAx Based CPPopt	0.443 (0.338-0.547)	0.3600	0.591 (0.508-0.673)	0.5390
RAC				
% Time >5 mm Hg Below RAC Based CPPopt	0.763 (0.678-0.849)	**<0.0001**	0.709 (0.627-0.791)	**0.0004**
% Time >10 mm Hg Below RAC Based CPPopt	0.755 (0.666-0.843)	**<0.0001**	0.719 (0.636-0.801)	**0.0007**
% Time >15 mm Hg Below RAC Based CPPopt	0.731 (0.646-0.817)	**0.0255**	0.722 (0.641-0.804)	0.0781
Hourly Dose Below CPPopt				
Mean Dose >5 mm Hg Below PRx CPPopt	0.552 (0.445-0.658)	0.4580	0.575 (0.486-0.665)	0.2400
Mean Dose >5 mm Hg Below PAx CPPopt	0.496 (0.377-0.616)	0.6740	0.541 (0.450-0.633)	0.5240
Mean Dose >5 mm Hg Below RAC CPPopt	0.633 (0.532-0.734)	0.1540	0.676 (0.591-0.760)	**0.0292**

A/D = alive/dead, AMP = pulse amplitude of ICP, AUC = area under the receiver operating curve, CPP = cerebral perfusion pressure, CPPopt = CPP optimum, CI = confidence interval, DC = decompressive craniectomy, F/U = Favourable/Unfavourable outcome (ie. Favourable

= Glasgow Outcome Scale of 5 to 8; Unfavourable = Glasgow Outcome Scale of 1 to 4), ICP = intra-cranial pressure, IMPACT = International Mission for Prognosis and Analysis of Clinical Trials, MAP = mean arterial pressure, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP. CORE model consisted of age, admission Glasgow Coma Scale motor score and pupil response (normal bilaterally, unilateral unreactive, or bilaterally unreactive). Note: Delta CPP = median CPP – CPPopt (where CPPopt can be derived from PRx, PAx or RAC). Bolded p-values are those reaching statistical significance (ie. p<0.05).

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