Pressure reactivity based optimal cerebral perfusion pressure in a traumatic brain injury cohort

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Abstract

Objectives: Retrospective data from severe traumatic brain injured (TBI) patients indicate that deviation from the continuously calculated pressure reactivity based 'optimal' cerebral perfusion pressure (CPPopt) is associated with worse patient outcome. The objective of this study was to assess the relationship between prospectively collected CPPopt data and patient outcome after TBI.

Methods: We prospectively collected intracranial pressure (ICP) monitoring data from 231 severe TBI patients at Addenbrooke's Hospital, UK. Uncleaned arterial blood pressure and ICP signals were recording using ICM+ ® software on dedicated bedside computers. CPPopt was determined using automatic curve fitting procedure of the relationship between pressure reactivity index (PRx) and CPP using a 4-hour window as previously described. The difference between an instantaneous CPP value and its corresponding CPPopt value was denoted every minute as ΔCPPopt. A negative ΔCPPopt that was associated with impaired PRx (> + 0.15) was denoted as being below the Lower Limit of Reactivity (LLR). Glasgow outcome scale was assessed at 6 months post ictus.

Results: When ΔCPPopt was plotted against PRx and stratified by GOS groupings, data belonging to patients with more unfavourable outcome had a U-shaped curve that was shifted upwards. More time spent with a ΔCPPopt value below the LLR was positively associated with mortality (AUROC = 0.76 (0.68-0.84)).

Conclusions: In a recent cohort of severe TBI patients the time spent with a CPP below the CPPopt derived LLR is related to mortality. Despite aggressive CPP and ICP oriented therapies, TBI patients with fatal outcome spend a significant time with a CPP below their individualized CPPopt, indicating a possible therapeutic target.

Introduction:

Maintaining an adequate cerebral perfusion pressure (CPP) is imperative to prevent cerebral hypoperfusion and ischaemia after severe traumatic brain injury (TBI). However, defining what might be an optimal CPP is uncertain, a CPP too low risks hypoperfusion, whereas a CPP too high risks cerebral hyperaemia. As such the brain trauma foundation recommend keeping CPP somewhere between 50 and 70 mm Hg [1]. However, applying rigid thresholds may not be appropriate for all patients [2].

Various physiological markers have been proposed as guides as to what may an optimal CPP including cerebral microdialysis, brain tissue oxygenation, or cerebral autoregulation. Estimating at which CPP cerebral autoregulation is most efficient is an attractive avenue as cerebral autoregulation *per se* is related to patient outcome and it can be estimated continuously using the pressure reactivity index (PRx) [3]. Previous investigations using retrospective datasets have ascertained that continuously estimating the optimal CPP (CPPopt) is feasible and has some relationship with outcome [4–8]

The aim of this study was to ascertain whether prospectively collected CPP optimal data collected at the bedside, without any post-processing manual artefact removal, has any relationship with patient outcome after severe TBI. This is a short version based on oral presentation during Intracranial Pressure 2016 Symposium in Boston, USA. The paper containing full analysis of acquired data is currently in submission to Critical Care medicine (2016).

Materials and Methods:

Patients:

231 severe TBI patients between 2010 and 2015 from the Addenbrooke's hospital neurocritical care unit who had computeristed intracranial pressure (ICP) monitoring were selected for this analysis. National ethical approval was obtained (29 REC 97/291) and patients were treated according to published protocolised guidelines [9] with attempts to maintain ICP < 20 and CPP between 50-70 mmHg [1].The Glasgow outcome scale (GOS) was assessed at 6 months by outpatient assessment [10]. The primary outcome of this study was survival at 6-months.

Data Acquisition and Analyses

ICP was monitored with an intraparenchymal sensor inserted into the frontal cortex (Codman ICP Micro- Sensor, Codman & Shurtleff, Raynham, MA) via a burr hole and arterial blood

pressure (ABP) was monitored in the radial or femoral artery zeroed at the level of the right atrium (Baxter Health- care CA, USA; Sidcup, UK). In patients with head elevation, no corrections were made for hydrostatic pressure differences. Data were sampled at 100 Hz with proprietary data acquisition software which was also used to calculate PRx and CPPopt on-line (ICM+©, http://www.neurosurg.cam.ac.uk/icmplus Cambridge Enterprise, Cambridge, UK).

PRx was calculated over a 5 minute moving window as the Pearson correlation of 30 consecutive 10-second average values of ABP and ICP as previously described [11] and CPPopt was calculated as described previously (see appendix Aries et al. 2012). ΔCPPopt was calculated as the mean CPP calculated over a 5-minute buffer, minus the current CPPopt value estimate.

Analysis of CPPopt data

A method to incorporate information about PRx into CPPopt assessment was developed on the basis of initial exploratory analysis of the minute-by-minute ΔCPPopt and PRx data (Fig 1). First, each PRx value was dichotomised into intact and impaired vascular reactivity using a threshold of +0.15 a.u. Then, each continuously derived ΔCPPopt value was coupled with its time-aligned dichotomised PRx value to give an estimate of whether the current CPP was above, or below the limits of working cerebrovascular pressure reactivity. The percentage time each patient spent with their CPP below the lower reactivity limits (LLR) was calculated using the total time CPPopt was available as the denominator. These percentage times were compared across GOS groups.

Statistical analysis

The relationship between time spent with CPP below the LLR and mortality was assessed using a ROC analysis with area under the curve descriptives. The ability of time spent below LLR to differentiate between survivors and non-survivors was compared with time spent with below fixed thresholds of 50, 60 and 70 mm Hg by comparing AUC values. Delongs test was used to detect statistically significant differences. All data manipulation and statistical analyses were conducted in the R language and software environment for statistical computation (version 2.12.1) (R Core Team 2015). The following packages were used: dplyr [13] , ggplot2 [14], MASS [15], and pROC. The significance level was set at $p<0.05$.

Results:

Mean age of the cohort was 42 years with 19% female. Of the 231 patients 21% died, 33 were severely disabled, 28% had moderate disability, and 17% had a good recovery. CPPopt calculated at the bedside was available on average 60% (IQR 50.2 to 68.4).
When the difference between CPP and CPPopt was plotted against PRx, a U shaped curve was obtained, and the patients eventual outcome seemed to determine the vertical position of these curves (Figure 1). Those that ended up dying had a ΔCPPopt -PRx curve that was shifted upwards and with steeper edges indicating that in these patients a narrower range of CPP with adequate pressure reactivity.

Using a cut-off for intact PRx of +0.15, those with better outcome spent a smaller amount of time with a ΔCPPopt below the LLR (GR 13.7%, MD 18.6%, SD 16.5%, Dead 33.3%. The amount of time with CPP below the LLR was superior to using the fixed threshold of 50 or 70 mm Hg in differentiating survivors from non-survivors and showed a tendency towards being superior to a fixed threshold of 60 mm Hg (%time CPP<LLR AUC =0.76 (0.68-0.84), %time CPP <50 mm Hg AUC= 0.64 (0.54-0.74), %time CPP <60 AUC=0.67 (0.57-0.77),%time CPP<70 mm Hg AUC= 0.58 (0.48-0.69); Table 1)

Discussion:

In this study, we demonstrate that CPPopt calculated at the bedside has prognostic importance after severe TBI. In addition, post-hoc analysis revealed that time spent with CPPopt below the individualised LLR may be a practical and prognostic metric for the adequacy of a patients CPP.
Retrospective studies assessing a PRx based CPPopt and outcome are limited to one large analysis (330 patients) [5] and several smaller pilot studies [6, 16, 17]. In addition, Depretiere et al. have shown prognostic importance of an alternative method for determining CPPopt [7, 8]. For the current PRx based method to be of practical use after TBI, the algorithm must be validated in a large cohort that is independent from the dataset used to derive the current CPPopt algorithm.
In this cohort, the time spent with a CPP below the LLR was associated with patient outcome. Importantly, the time spent with a CPP below the LLR was superior to fixed thresholds 50 or 70 mm Hg and showed a tendency towards being superior than a threshold

of 60 mm Hg (Table 1). This provides initial evidence that individualised autoregulation guided CPP management may be beneficial after severe TBI

The precise threshold of PRx that indicates impaired cerebrovascular reactivity is largely unclear; a PRx < 0 is thought to indicate working pressure reactivity [18] and has been associated with favourable outcome [19], while a PRx > 0.3 was strongly associated with mortality in TBI patients [19]. In light of these considerations, we used a value between these cut-points (PRx = +0.15) as our threshold for dividing between working and impaired pressure reactivity.

Limitations:

In the current study, CPPopt was only available on average for 60% of the monitoring time. This low yield limits the practical utility of the current CPPopt methodology. However, one method has been proposed that produces a yield of almost 100% of the time [7], and similar approaches are currently under development.

Furthermore, although the current study used prospectively collected CPPopt data from the bedside and showed an effect on outcome, whether targeting CPPopt will improve outcome remains to be elucidated. Furthermore, the safety of a CPPopt based therapy is as yet unknown. Thus, studies investigating the feasibility, clinical safety should be performed before conducting a randomised controlled trial of CPPopt targeted therapy.

Conclusion:

In this large severe TBI study the time CPP below the lower limits of cerebral vascular reactivity was associated with increased mortality 6-month after ictus and seemed to be superior to time spent below fixed thresholds of CPP. Further studies should focus on clinical safety and feasibility of an autoregulation based CPP management.

Table and figure legends

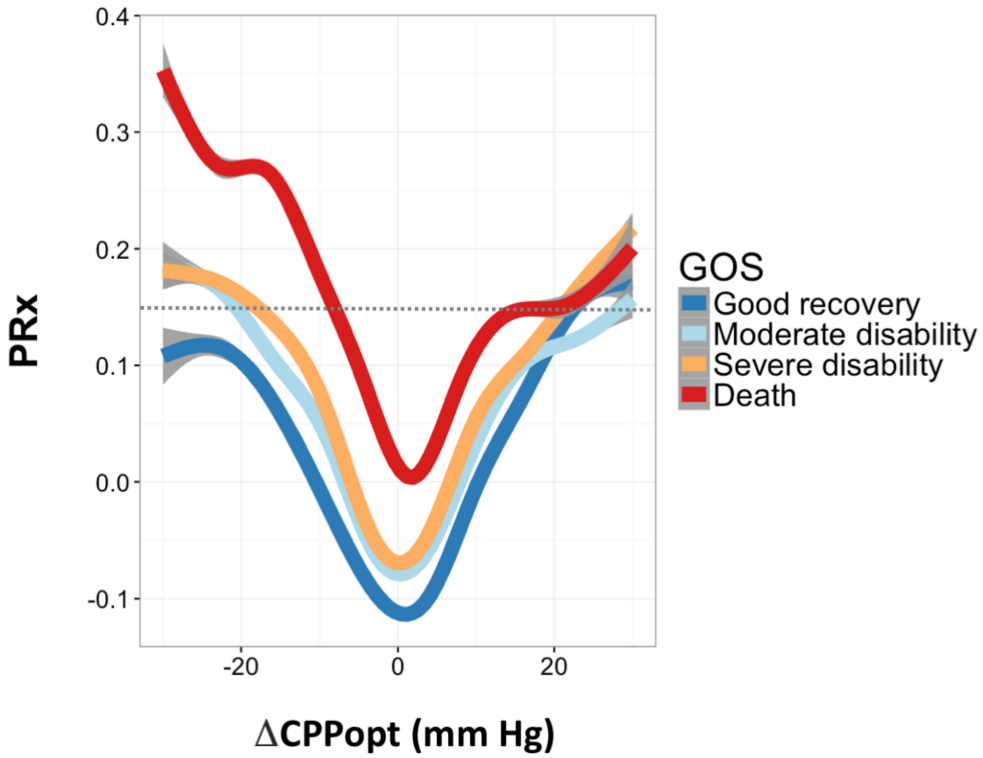
0.4
0.3
0.2
0.1
0.0
-0.1
PRx
-20
0
20
ΔCPPopt (mm Hg)
GOS
Good recovery
Moderate disability
Severe disability
Death

Figure 1 Relationship between the difference between CPP and CPPopt (ΔCPPopt) and PRx, stratified by 6 month glasgow outcome score

From top to bottom the fitted (generalised additive model) curves represent data from patients who subsequently died, had severe disability, had moderate disability, or had a good recovery. With increasing burden of disability, the U-shaped relationship between ΔCPPopt and PRx is shifted superiorly indicating a narrower range of ΔCPPopt values associated with good PRx**.** For subsequent calculations, an individualised dichotomisation of whether a patients CPPopt value was below the individualised lower limit of reactivity (LLR) was devised. Using a cut-pff for impaired PRx of 0.15 a.u. (dotted line), a CPP below the LLR was defined as a CPP that was lower than CPPopt and associated with a PRx greater than 0.15 a.u.

Table 1. Area under the Receiver operating characteristic curve for differentiating survivors from non-survivors comparing the time spent with individualised CPP below LLR with time spent below fixed thresholds of CPP

% TIME	AUC SURVIVORS VS. NON-SURVIVORS	P-VALUE FIXED THRESHOLD VS. INDIVIDUALISED LLR
CPP < LLR	0.76 (0.68-0.84)	
CPP <50	0.64 (0.54-0.74)	0.046
CPP <60	0.67 (0.57-0.77)	0.11
CPP <70	0.58 (0.48-0.69)	<0.001

**CPP- cerebral perfusion pressure; LLR- Lower Limit of Reactivity*

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