Patient's Clinical Presentation and CPPopt Availability

Patient's clinical presentation and CPPopt availability: any association?

A. Liberti [1,2], E. Beqiri [2,3], A. Ercole [4], M. Cabeleira [3], J. Tas [1], FA. Zeiler [4,5-8], M. Czosnyka [3], P. Smielewski [3*], MJ. Aries [1*] , CENTER-TBI High Resolution Sub- Study Participants and Investigators

[1] Department of Intensive Care, University Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands

[2] Department of Physiology and Transplantation, Milan University, Milan, Italy

[3] Brain Physics Laboratory, Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge

[4] Cambridge, UK University of Cambridge, Division of anesthesia, Cambridge, UK

[5] Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Canada

[6] Department of Anatomy and Cell Science, Rady Faculty of Health Sciences, University of Manitoba, Canada

[7] Biomedical Engineering, Faculty of Engineering, University of Manitoba, Canada

[8] Centre on Aging, University of Manitoba, Canada

* senior authors contributed equally

Correspondence to:

Annalisa Liberti

Email: liberti.annalisa@gmail.com

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Summary

Background. The 'optimal' CPP (CPPopt) concept is based on the vascular pressure reactivity index called PRx. The feasibility and effectiveness of CPPopt guided therapy in severe traumatic brain injury (TBI) patients is currently being investigated prospectively in the COGiTATE trial. At the moment there is no clear evidence that certain admission and treatment characteristics are associated with CPPopt availability (yield).

Objective. To test the relation between patients' admission and treatment characteristics and the average CPPopt yield.

Methods. Retrospective analysis of 230 patients from the CENTER-TBI high Resolution database with ICP measured using intraparenchymal probe. CPPopt was calculated using the algorithm set for COGiTATE study. CPPopt yield was defined as the percentage of CPP monitored time (%) when CPPopt is available. Variables in the statistical model were:

age, admission GCS, gender, pupil response, hypoxia and hypotension at the scene, Marshall CT score, decompressive craniectomy, ISS score and 24-hr TIL score.

Results. The median CPPopt yield was 80.7% (IQR 70.9-87.4%). None of the selected variables showed a significant statistical correlation with the CPPopt yield.

Conclusion. In this retrospective multicenter study none of the selected admission and treatment variables were related to the CPPopt yield.

Introduction

Cerebral autoregulation (CA) is defined as the ability of the cerebrovascular system to maintain adequate cerebral blood flow (CBF) despite fluctuations in cerebral perfusion pressure (CPP) [6]. In patients with severe traumatic brain injury (TBI), CA is often impaired and related to worse outcome. Over the years, the new concept of personalized therapy based on patient's autoregulation has been introduced. Autoregulation based individualized management of CPP promises to be a successful strategy and it has already been proven from retrospective analysis that it might be related with outcome [1]. One of the methods created to estimate CA continuously at the bedside is the Pressure Reactivity index (PRx) [4]. PRx is calculated as the moving Pearson correlation between the slow waves of intracranial pressure (ICP) and mean arterial pressure (MAP) and it has proven to be able to detect the lower limit of autoregulation in animal models [3]. Several retrospective observations have shown correlations between average PRx and worse outcome when PRx values are above 0.2-0.3 [7,10,11]. In 2002, the CPPopt concept was introduced by plotting the values of PRx against CPP over the whole monitoring period for TBI patients [12]. The PRx/CPP relationship showed a U-shape curve with its nadir corresponding to the CPP at which PRx is the lowest and therefore the pressure reactivity is best preserved (CPPopt). Recent developments have made it possible to assess CPPopt automatically in individual patients and display it continuously at the bedside in real time (Fig.1) [1,8]. CPPopt guided therapy might therefore improve autoregulation and its feasibility, safety and effectiveness are currently being tested in a randomized controlled trial in 4 European centers (CPPOpt Guided Therapy: Assessment of Target Effectiveness, COGiTATE, www.cppopt.org) [2].

In the traditional CPPopt calculations based on 4-hours moving window, the yield was shown to be 50-60% of the total CPP monitored time [1]. With the weighted multi-window approaches the CPPopt availability improved to 94% ±2.1% (mean±SD) [8]. The importance of achieving high yield is crucial for management of TBI patients in the light of future trial as it is important to know whether there are particular categories that are not likely to benefit from this approach, because CPPopt might not be ready available most of the time (Fig. 2A-2B). This led to our research question to investigate the relationship between demographics, clinical and admission factors and the average CPPopt yield.

Material and methods

This retrospective analysis has been performed using ICP and ABP waveforms from the High Resolution cohort of the

the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study. Patients in this cohort were not treated taking PRx or CPPopt information into account. The total cohort contained 271 TBI patients. After exclusion of 41 patients who had ICP monitoring by an external ventricular drainage system with noisy or unreliable signals (due to continuous or intermittent CSF drainage), 230 patients were left for analysis. CPPopt was calculated with ICM+ software (https:// icmplus.neurosurg.cam.ac.uk) using the weighted multi-window approach with the calculation criteria used in the COGiTATE study [2]. Several admission variables were selected: sex, age, hypoxia and hypotension at the trauma scene, Marshall CT score, admission GCS, injury severity score (ISS), therapeutic intensity level (TIL) for the first 24 hours, pupil reactivity and decompressive craniectomy (DC) (Table 1-2). The admission variables hypoxia, hypotension and pupils were dichotomized in present or absent. Pupils reactivity was scored as 'bilateral reactive', 'bilateral unreactive', or 'unilateral unreactive'. Pupils were then reclassified binary into 'normal' if both pupils were reactive and 'pathological' when one or both pupils were not reactive to light. The Glasgow Coma Scale (GCS) at admission was divided in two groups above and below 8 as an estimate of initial head trauma severity (mild/moderate if GCS was >8 and severe if GCS was ≤8). CPPopt yield was considered as the percentage of monitored time (%) with CPPopt available given the presence of CPP. The TIL score was considered as an estimate of intracranial hypertension severity and need for intensive treatment [9]. The aim of TIL is to produce a quantitative estimate of the interventions by assigning numerical scores to each TIL intervention and summating these. The maximum score is 38. DC was investigated as a contributing factor as there are worries that the pressure-volume characteristics necessary for reliable PRx calculations are violated [13]. In this cohort of patients, DC refers to both primary and secondary craniectomy. Statistical analysis was done with R Studio software (version 3.5.1). Non parametric tests were used after testing the distribution of the variables through the Shapiro-Wilk test. Linear regression models were used comparing the CPPopt yield (%) to continuous variables (age, ISS and 24-hr TIL score for the 1st day). Mann-Whitney U and Kruskal Wallis tests were used to compare CPPopt yield (%) for categorical and ordinal variables. A p-value <0.05 was considered for statistical significance.

Results

The patient characteristics are listed in table 1-2. The median CPPopt yield was 80.7% (IQR 70.9-87.4) for the whole ICP/CPP monitoring period, suggesting the availability of CPPopt values during most of the recording period. All variables had a non-parametric distribution showing the heterogeneity of the TBI population in this multicenter cohort. In the cohort analyzed the median 24-hr TIL score for the 1st day was 6 (IQR 4-9) and the median ISS score was 34 (IQR 25-43). No statistical relationship between any of the considered variables and CPPopt yield was found (table 3).

Discussion

None of the admission demographic variables correlated with the CPPopt yield over the whole monitored period in a multicenter cohort of TBI patients. The importance of the CPPopt guided therapy concept lies on the fact that it could

potentially improve CA and therefore it could possibly improve the clinical outcome in TBI patients [5]. An important prerequisite of the application of the CPPopt concept at the bedside is the continuous availability of the automatically generated values of CPPopt, so that they could be used as clinical CPP targets. The first observation by Steiner et al. in 2002 about the CPPopt concept considered the total monitored time period identifying one single CPPopt value for all the patients and thus not ready for the clinical use at the bedside [12]. Over the years the CPPopt algorithm and the bedside software interface have been modified using initially a 4 hours moving single window [1] and later with a weighted multi-window algorithm approach to improve the yield and the stability of the CPPopt target [2-8]. Weersink et al. investigated the relationship between the absence of a CPPopt curve and physiological and therapy variables in a two center study [14]. Conditions related to the absence of a CPPopt curve were: high amount of sedative drugs, administration of high dose vasopressors, using neuromuscular blockers, low variance in slow ABP waves and status after decompressive craniectomy. The absolute ICP values were also associated with absence of CPPopt. CPPopt appeared more frequently in period with higher ICP levels perhaps due to fact that a stronger association is present between slow fluctuations in ABP and ICP in the steep part of pressure-volume curve, therefore producing possibly more robust pressure reactivity values [4]. The multi window approach increased the yield considerably (reaching values above 90%) [8]. This algorithm was adapted to the prospective bedside use within the COGiTATE study introducing safety and stability measures that decreased the yield from the original multi window algorithm [2]. However, the retrospective analysis performed in this multicenter database showed that a high overall CPPopt yield is found (>80% of monitored time) with the algorithm suggested for prospective use by the COGiTATE study. Moreover, the yield was neither negatively influenced by admission criteria including demographic variables as sex and age, or clinical variables as hypoxia and hypotension at the trauma scene, Marshall CT score, admission GCS, pupil reactivity and DC. Furthermore, the 24 hours ISS and TIL scores - as an estimate of (head) trauma severity – were not related to the CPPopt yield.

Conclusions

This retrospective analysis showed no association between CPPopt yield and demographics, clinical and management characteristics.

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CENTER-TBI High Resolution (HR ICU) Sub-Study Participants and Investigators:

Audny Anke, Ronny Beer, BoMichael Bellander, Andras Buki, Marco Carbonara, Arturo Chieregato, Giuseppe Citerio, Endre Czeiter, Bart Depreitere, Shirin Frisvold, Raimund Helbok, Stefan Jankowski, Danile Kondziella, Lars-Owe Koskinen, Ana Kowark, David K. Menon, Geert Meyfroidt, Kirsten Moeller, David Nelson, Anna Piippo-Karjalainen, Andreea Radoi, Arminas Ragauskas, Rahul Raj, Jonathan Rhodes, Saulius Rocka, Rolf Rossaint, Juan Sahuquillo, Oliver Sakowitz, Nino Stocchetti, Nina Sundström, Riikka Takala, Tomas Tamosuitis, Olli Tenovuo, Peter Vajkoczy, Alessia Vargiolu, Rimantas Vilcinis, Stefan Wolf, Alexander Younsi

Disclosure

Authors MC and PS have financial interest in part of the licensing fees for ICM+ software

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Tables

Table 1. Categorical demographic, clinical and admission variables.

Categorical Variables	**N (%)**
Gender	Male 178 (77.4) Female 51 (22.2) NA 1 (0.4)
Hypoxia at trauma scene	Yes 16 (6.9) No 213 (92.6) NA 1 (0.4)
Hypotension at trauma scene	Yes 7 (3) No 222 (96.9)
Marshall CT score	I 7 (3) II 71 (30) III 13 (5.7) IV 3 (1.3) V 6 (2.6) VI 71 (30) NA 59 (25.7)
Pupil reactivity	Bilateral reactive 159 (69.1) Unilateral reactive 19 (8.2) Both unreactive 39 (17) NA 13 (5.7)
Decompressive craniectomy#	Yes 48 (20.1) No 180 (78.3) NA 2 (0.9)

[#] This variables consists of primary and secondary decompressive craniectomies.

NA= Not Available

Table 2. Continuous demographic and clinical variables.

Variables	**Median (IQR)**
Age, yrs	49 (30-63)
Intracranial Pressure (first 24 hours), mmHg	11.9 (8.6-15.9)
Cerebral Perfusion Pressure (whole recorded period), mmHg	71.4 (64.9-77.9)
'Optimal' Cerebral Perfusion Pressure (whole recorded period), mmHg	72.0 (65.4-77.4)
Admission Glasgow Coma Score	6 (3-15)
24-hr Therapeutic Intensity Level (TIL) of the 1st day	6 (4-9)
Injury Severity Score (ISS)	34 (25-43)

Table 3: Univariate analysis of selected variables and CPPopt yield

Continuous Variables		
Variable	**CPPopt yield correlation coefficient (r)**	**p-value**
Age, yrs	-0.09	0.16

ISS	0.03			0.64
24-hr TIL (day 1)	0.03			0.59
Categorical Variables				
Variables	**CPPopt yield % (Median (IQR))**			**p-value**
Sex	Male		80.6 (71.3-88.3)	0.48[a]
	Female		81.1 (69.9-85.9)	
Hypoxia	Present		76.6 (56.4-83.8)	0.14[a]
	Absent		81.1 (71.9-87.6)	
Hypotension	Present		86.2 (81.7-88.4)	0.16[a]
	Absent		80.7 (70.5-87.3)	
Marshall CT Score	I II III IV V VI		83.3 (75.5-87.3) 81.3 (72-87.8) 79.2 (74.5-86.1) 78.7 (75.6-83.9) 59 (52.1-68.6) 78.4 (71.6-86.7)	0.99[b]
Admission GCS	GCS≤8		80.9 (71.6-87)	0.85[a]
	GCS>8		81.9 (66.8-87.6)	
Pupil Reactivity	Normal	Bilateral reactive	77.1 (63.8-85.6)	0.97[a]-0.33[b] #
	Pathological	Unilateral reactive	83 (70.9-87.7)	
		Unreactive	81.6 (72-88)	
Decompressive Craniec-tomy	Present		80.8 (71.6-86.3)	0.99[a]
	Absent		80.7 (70.5-87.6)	

[a] Mann-u Whitney test used
[b] Kruskal Wallis test used

We dichotomized pupil reactivity in 'normal' (both pupils reactive) or 'pathological' (unilateral or bilateral unreactive) using Mann-Whitney U test. A further analysis tested three categories (bilateral reactive/unilateral reactive/bilateral not reactive) through Kruskal-Wallis test.

Figure legends

Figure 1 The CPP-PRx error bar over a certain period in one single patient with a fitted U-shape curve (for more information about CPPopt and the fitting process visit the website www.cppopt.org). In this example the CPPopt would be around 92 mmHg.

Figure 2 Examples of CPPopt time trends generated by the continuous automated algorithm: CPPopt (thick line), CPP (thin line), PRx risk bar (with dark values indicating impaired autoregulation). PRx and CPP are selected for plotting the error bar chart. **A** An example when the (multi-window and weighted) CPPopt time trend has several gaps limiting its use for CPP individualized management. Of note, the PRx/CPP relationship chart over this selected monitored period does not indeed form a proper U-shape curve. **B** In this example, the CPPopt value is almost always available. Of note, the PRx/CPP plot over the selected period in this example shows a U-shape curve.