

Patient's Clinical Presentation and CPPopt Availability: Any Association?



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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) [1]. In patients with severe traumatic brain injury (TBI), CA is often impaired and related to worse outcomes. Over the years, the new concept of personalized therapy based on a 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 to outcome [2]. One of the methods created to estimate CA

continuously at the bedside is the pressure reactivity index (PRx) [3]. 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 [4]. Several retrospective observations have shown correlations between average PRx and worse outcome when PRx values are above 0.2–0.3 [5–7]. In 2002, the CPPopt concept was introduced by plotting the values of PRx against CPP over the whole monitoring period for TBI patients [8]. The PRx/CPP relationship showed a U-shaped 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) [2, 9]. CPPopt guided therapy might therefore improve

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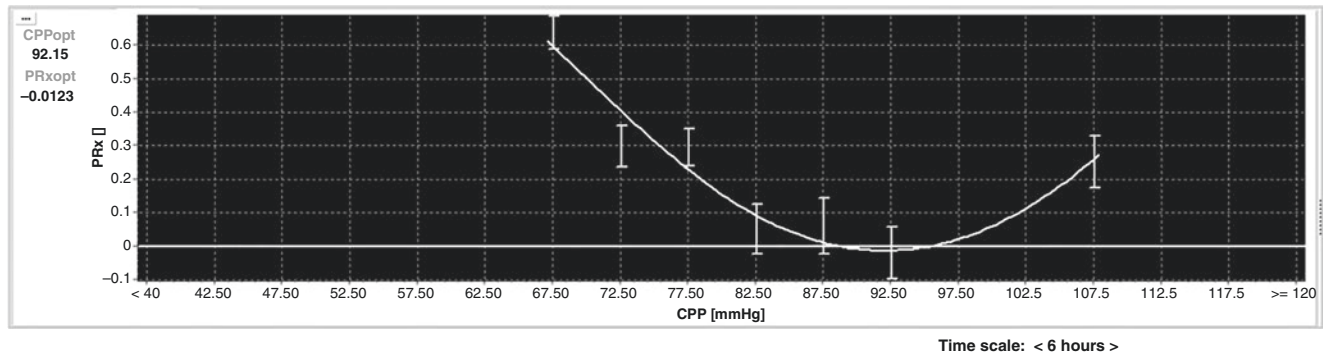


Fig. 1 The CPP-PRx error bar over a certain period in a single patient with a fitted U-shaped curve (for more information about CPPopt and the fitting process, visit the website www.cppopt.org). In this example, the CPPopt would be around 92 mmHg

autoregulation, and its feasibility, safety, and effectiveness are currently being tested in a randomized controlled trial in four European centers (CPPOpt Guided Therapy: Assessment of Target Effectiveness, COGiTATE, www.cppopt.org) [10].

In the traditional CPPopt calculations based on a 4-h moving window, the yield was shown to be 50–60% of the total CPP monitored time [2]. With the weighted multiwindow approaches, the CPPopt availability improved to $94 \pm 2.1\%$ (mean \pm SD) [9]. The importance of achieving high yield is crucial for the management of TBI patients in the light of future trials because it is important to know whether there are particular categories that are not likely to benefit from this approach, because CPPopt might not be readily available most of the time (Fig. 2a, b). This prompted our research question to investigate the relationship between demographic, clinical, and admission factors and the average CPPopt yield.

Material and Methods

This retrospective analysis was performed using ICP and ABP waveforms from the high-resolution cohort of 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 the exclusion of 41 patients who received ICP monitoring by an external ventricular drainage system with noisy or unreliable signals (due to continuous or intermittent Cerebrospinal fluid (CSF) drainage), 230 patients were left for analysis. CPPopt was calculated with ICM+ software (<https://icmplus.neurosurg.cam.ac.uk>) using a weighted multiwindow approach with the calculation criteria used in the COGiTATE study [10]. Several admission variables were selected: sex, age, hypoxia and hypotension at the trauma scene, Marshall computed tomography (CT) score, admission Glasgow Coma Scale (GCS), injury severity score (ISS), therapeutic intensity

level (TIL) for the first 24 h, pupil reactivity, and decompressive craniectomy (DC) (Tables 1 and 2). The admission variables hypoxia, hypotension, and pupils were dichotomized into present or absent. Pupil reactivity was scored as bilateral reactive, bilateral unreactive, or unilateral unreactive. Pupils were then reclassified as a binary into normal if both pupils were reactive and pathological when one or both pupils were not reactive to light. The GCS at admission was divided into two groups, above and below 8, as an estimate of initial head trauma severity (mild/moderate if $GCS > 8$ and severe if $GCS \leq 8$). 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 the need for intensive treatment [11]. The aim of TIL is to produce a quantitative estimate of the interventions by assigning numerical scores to each TIL intervention and summing these. The maximum score is 38. DC was investigated as a contributing factor because there are worries that the pressure-volume characteristics necessary for reliable PRx calculations are violated [12]. 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). Nonparametric tests were used after testing the distribution of the variables through a Shapiro-Wilk test. Linear regression models were used comparing the CPPopt yield (%) to continuous variables (age, ISS, and 24-h TIL score for the first 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 Tables 1 and 2. The median CPPopt yield was 80.7% (interquartile range (IQR) 70.9–87.4) for the whole ICP/PPP monitoring period, suggesting the availability of CPPopt values during most of the

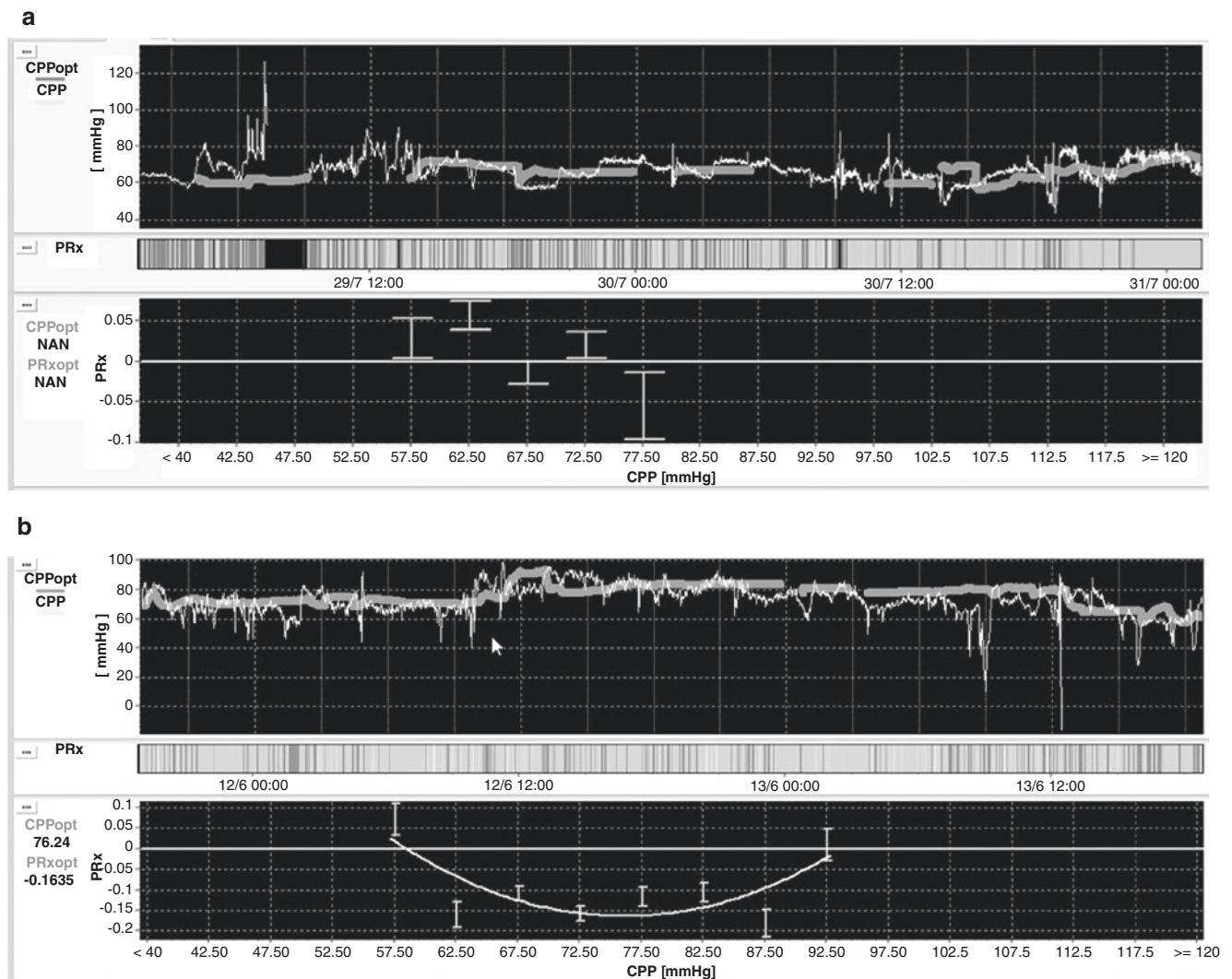


Fig. 2 Examples of CPPopt time trends generated by continuous automated algorithm: CPPopt (thick line), CPP (thin line), PRx risk bar (with bold values indicating impaired autoregulation). PRx and CPP are selected for plotting the error bar chart. (a) An example when the (multiwindow and weighted) CPPopt 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 in fact form a proper U-shaped 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-shaped curve

recording period. All variables had a nonparametric distribution, showing the heterogeneity of the TBI population in this multicenter cohort. In the cohort analyzed, the median 24-h TIL score for the first 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 in the fact that it might improve CA and, therefore, could improve the clinical outcome in TBI patients [13]. 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 a single CPPopt value for all the patients and thus not ready for clinical use at the bedside [8]. Over the years the CPPopt algorithm and the bedside software interface have been modified using initially a 4-h moving single window [2] and later with a weighted multiwindow algorithm approach to improve the yield and stability of the CPPopt target [9, 10]. Weersink et al. investigated the relationship

Table 1 Categorical demographic, clinical, and admission variables

Categorical variable	<i>N</i> (%)
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)
Pupil reactivity	NA 59 (25.7)
	Bilateral reactive 159 (69.1)
	Unilateral reactive 19 (8.2)
	Both unreactive 39 (17)
Decompressive craniectomy ^a	NA 13 (5.7)
	Yes 48 (20.1)
	No 180 (78.3)
	NA 2 (0.9)

NA Not available

^aThese variables consist of primary and secondary decompressive craniectomies

Table 2 Continuous demographic and clinical variables

Variable	Median (IQR)
Age, years	49 (30–63)
Intracranial pressure (first 24 h), 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-h therapeutic intensity level (TIL) of first day	6 (4–9)
Injury severity score (ISS)	34 (25–43)

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 a high amount of sedative drugs, administration of high-dose vasopressors, using neuromuscular blockers, low variance in slow ABP waves, and status after DC. The absolute ICP values were also associated with an absence of CPPopt. CPPopt appeared

Table 3 Univariate analysis of selected variables and CPPopt yield

Continuous Variables			
Variable	CPPopt yield correlation coefficient (<i>r</i>)	<i>p</i> -value	
Age, years	−0.09	0.16	
ISS	0.03	0.64	
24-h TIL (day 1)	0.03	0.59	
Categorical variables			
Variable	CPPopt yield % (Median (IQR))	<i>p</i> -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	83.3 (75.5–87.3)	0.99 ^b
	II	81.3 (72–87.8)	
	III	79.2 (74.5–86.1)	
	IV	78.7 (75.6–83.9)	
	V	59 (52.1–68.6)	
	VI	78.4 (71.6–86.7)	
Admission GCS	GCS ≤ 8	80.9 (71.6–87)	0.85 ^a
	GCS > 8	81.9 (66.8–87.6)	

Table 3 (continued)

Continuous Variables				
Variable	CPPopt yield correlation coefficient (<i>r</i>)		<i>p</i> -value	
Pupil Reactivity	Normal	Bilateral reactive	77.1 (63.8–85.6)	0.97 ^a –0.33 ^{b,c}
		Unilateral reactive	83 (70.9–87.7)	
	Unreactive	81.6 (72–88)		
Decompressive craniectomy	Present		80.8 (71.6–86.3)	0.99 ^a
	Absent		80.7 (70.5–87.6)	

^aMann-Whitney *U* test used

^bKruskal Wallis test used

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

more frequently in periods with higher ICP levels, perhaps owing to fact that a stronger association is present between slow fluctuations in ABP and ICP in the steep part of pressure-volume curves, thereby producing possibly more robust pressure reactivity values [3]. The multiwindow approach increased the yield considerably (reaching values above 90%) [9]. This algorithm was adapted to prospective bedside use within the COGiTATE study, introducing safety and stability measures that decreased the yield from the original multiwindow algorithm [10]. However, the retrospective analysis performed in this multicenter database showed that a high overall CPPopt yield was 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 like sex and age or clinical variables like hypoxia and hypotension at the trauma scene, Marshall CT score, admission GCS, pupil reactivity, and DC. Furthermore, the 24-h ISS and TIL scores—as an estimate of (head) trauma severity—were not related to CPPopt yield.

Conclusions

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

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