Optimal Cerebral Perfusion Pressure Assessed with a Multi-Window Weighted Approach Adapted for Prospective Use

Optimal cerebral perfusion pressure assessed with a multi-window weighted approach adapted for prospective use: a validation study

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Summary

Background. PRx-CPP relationship over a given time period can detect a value of CPP at which PRx shows best autoregulation (CPPopt). Algorithms for continuous assessment of CPPopt in TBI patients reached desired high yield with the multi-window approach (CPPopt_MA). However, the calculations were tested on retrospective manually cleaned datasets. Moreover, CPPopt false positive values can be generated from non-physiological variations of ICP and ABP. Therefore, the algorithm robustness was improved making it suitable for prospective bed-side application (COGiTATE trial).

Objective. To validate the CPPopt revised algorithm in a large single-centre retrospective cohort of TBI patients.

Methods. 840 TBI patients were included. CPPopt yield, stability and ability in discriminating outcome groups were compared to CPPopt_MA and the BTF guidelines reference.

Results. CPPopt yield was lower than CPPopt_MA yield (85% and 90%, $p<0.001$), but, importantly, with increased stability ($p<0.0001$). The Δ(CPP-CPPopt) could distinguish the mortality and survival outcome ($t= -6.7$, $p<0.0001$) with a statistical significance higher than the ΔCPP calculated with the guidelines reference (CPP-60) ($t= -4.5$, $p < 0.0001$).

Conclusion. This study validates on a large cohort of patients the new algorithm proposed for prospective use of CPPopt as a CPP target at the bedside.

Key words and/or reference phrases (4 – 10 keywords/phrases)

CPPopt; autoregulation; TBI; neuromonitoring; precision medicine

Introduction

Cerebrovascular pressure reactivity (PRx)- cerebral perfusion pressure (CPP) relationship over a given time period can detect an optimal value of CPP at which PRx shows the best autoregulation (CPPopt). Algorithms for continuous automated assessment of CPPopt in traumatic brain injury (TBI) patients reached desired high yield with the multi-window approach (CPPopt_MA, published by Liu X et al., 2017 [6]). However, the calculations were tested on retrospective datasets, in which artefacts were removed manually and CPP was scarcely managed according to CPPopt.

Moreover, CPPopt 'false positive' values can be generated from non-physiological variations of intracranial pressure (ICP) and arterial blood pressure (ABP) [3]. Therefore, the algorithm was fine-tuned to improve the robustness and making it more suitable for prospective bedside application (currently used in the COGiTATE trial – www.cppopt.org [2]). The aim of this study was to validate the CPPopt revised algorithm in a large single-center retrospective cohort of TBI patients by testing its relationship with outcome and comparing it with the current BTF guidelines [4] .

Materials and Methods

We performed a retrospective analysis of ICP and ABP waveforms and Glasgow Outcome Score (GOS) at 6 months data of Traumatic Brain Injury (TBI) patients requiring ICP monitoring admitted in Addenbrooke's Neuro critical care unit from 1996 to 2018. Patients who underwent craniectomy were excluded. ICP and ABP waveforms were processed with ICM+ software (https://icmplus.neurosurg.cam.ac.uk). For each patient, only the first 5 days from the date of injury were considered. For each recording the following variables were calculated: CPPopt, CPPopt_MA, Target, Yield, Stability, ΔCPPopt, ΔCPP60 and ΔTarget (figure 2), defined as in table I.

Details about the algorithm used to calculate CPPopt are shown in figure 1 and further explanations are available in the website cppopt.org. Here the main differences from the previous algorithm (CPPopt_MA) are highlighted.

First of all, the CPP values taken into account for generating the curve are filtered so that scarcely represented values given by short spikes and drops (which are common in the clinical daily environment and would have been manually removed in the retrospective analysis), but not given by the physiological trend, will be disregarded. A 5 min duration median filter is applied to CPP before dividing the data points into bins of 5 mmHg. Furthermore, the percentage of the total data count that each bin of CPP must represent has been increased to 3%.

Secondly, when the 2nd order polynomial is fitted in the PRx-CPP plots over a certain time window, the curves might appear only in their descending or ascending part, not including the nadir, named here Non-Parabolic. These fits, by their nature, result in 'optimum' values at the extreme ends of the available CPP bins range, and are usually produced by relatively short periods of transient up- and down- swings of CPP. Including these in the combined, weighted average calculations, leads often to sudden discontinuities in resulting CPPopt, of magnitude more than 10 mmHg. It's unlikely that the physiology of autoregulation changes in this way. Therefore, in the new algorithm, only U-shape parabolic curves are considered, decreasing the overall yield, but increasing substantially stability of the calculation and ensuring physiological values of CPPopt.

Finally, the U-shape curves generated by the PRx-CPP plots were screened for their determination coefficient R^2_{full} which gives a measure of the variability explained by the fitting curve compared to the total variability of the data. The 'full' subscript denotes that the calculations of R^2 are done on the complete set of bins, rather than only on the subset selected for the curve fitting process, as part of the fitting algorithm heuristics. The curves that produce values of $R^2_{full} < 0.2$ are rejected. All the remaining curves were combined using R^2_{full} as a weighting factor in the weighted average.

In COGiTATE protocol, the clinicians would adopt new recommendations of CPP management target only at fixed review times, and not adjust it until the next such time. These were scheduled once every 4 hours. In addition, the new target value would have been restricted to the clinically safe range of 50-100 mmHg and not allowed to change by more than 10 mmHg at a time. To simulate this in our retrospective analysis we have introduced a new variable called Target, which was only updated once every 4 hours and, truncated at that safety zone margins and with the imposed limit on change, of 10 mmHg (figure 2).

Student's t-test was used to assess ΔCPPopt, ΔCPP60 and ΔTarget ability in discriminating mortality and survival. AUC (CI 95%) were calculated and compared with the DeLong Test.

Results

813 TBI patients were included; 74% of the patients had a severe TBI (GCS <9) (table I); 23% were dead at the GOS assessment at 6 months (table II). CPPopt showed lower yield (83 % (range 75-90)) compared with CPPopt_MA (89% (range 81-93)), $p<0.001$, however the stability was significantly increased with the new algorithm ($p<0.001$). ΔCPPopt and ΔTarget work better in distinguishing mortality and survival outcome than ΔCPP60 ($p<0.05$ and $p<0.001$, table III).

Discussion

We validated in a large cohort of TBI patients a new algorithm, proposed for prospective use of automated CPPopt at the bedside as part of COGiTATE study. This CPPopt algorithm seems more stable and robust and able to distinguish between outcome groups.

A large amount of retrospective work has been done on improving the technology for the continuous assessment of CPPopt in TBI patients. With the multi-window approach inspired by Depretiere et al [5], and implemented in ICM+ by Liu et al. (CPPopt_MA)[6], the yield was considerably improved if compared with the previous four-hourly based algorithm[1]. CPPopt_MA could be available for more than 90% of time, calculated on the whole monitored time. This made it clinically useful, making it possible to start thinking on the prospective use of CPPopt assessed continuously

and automatically at the bedside, therefore the COGiTATE study was designed - the first randomized control trial assessing the feasibility and safety of managing CPP according to CPPopt in TBI patients.[2] The fact that CPPopt needed to be assessed prospectively in real time at the bedside and that clinical recommendation for treating patients would be managed according to CPPopt values, brought up two issues: 1) CPPopt was previously largely studied in retrospective cohorts, where waveform's artifacts were cleaned both manually and automatically; 2) the individual values generated by the automatic semi-continuous algorithm would need to be reliable enough and, more importantly, safe enough to make it suitable for clinical use. Therefore, the algorithm was modified and implemented with heuristics chosen for their ability in discriminating between estimations performed on the original versus surrogate (randomized) signals. We checked the robustness of the calculation (low inter-point variability), avoidance of unphysiological sudden jumps in the CPPopt time trend, and the reliability of the values in reflecting the cerebral autoregulation status.

The combination of the new heuristics made the algorithm more robust and stable, suitable for bedside use, but the relationship previously found with outcome had not been re-apprised. For this reason, we validated the new algorithm against outcome and we showed that the average deviation from CPPopt calculated with this algorithm, for the first 5 days from the date of injury, could distinguish mortality and survival, and performed better than the current guidelines threshold. The down side of using the more restrictive criteria is that the yield of CPPopt would decrease, as our analysis showed. However, the yield here is still higher than when using the single window approach, and at 83% it should still be clinically useful.

This validation study is still retrospective and the dataset is a large cohort of TBI patients admitted in a single center over a large time span. The data was partially cleaned manually and partially not. However, the results are comparative with the previous algorithm (CPPopt_MA), and both analysis were subject to the same limitation.

Conclusion

We demonstrated that the new algorithm is not only more robust and stable, but it also maintains the ability of discriminating outcome groups superior to that of fixed BTF guidelines. We believe it is therefore suitable for prospective use in TBI patients for future prospective trials.

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Conflict of interest

PS and MC have financial interest in a part of ICM+ software (htpps://icmplus.neurosurg.cam.ac.uk) licensing fee.

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Tables

Variable	Explanation
CPPopt	PRx-CPP relationship is assessed with the multi-window approach using a selected set of calculation heuristics, which were chosen based on their performance in a selected datasets and greatest discrimination from values generated from surrogate signals (figure 1).
CPPopt_MA	PRx-CPP relationship is assessed with the multiwindow approach using the calculation heuristics as described by [2].
Target	CPPopt value sampled every 4 hours, in order to simulate the CPP target provided to the clinical team as per COGiTATE protocol[2], which included a clinical 'safe range' of 50 to 100 mmHg imposed on the target and a limit of maximum change of ±10 mmHg from the previous target value (figure 2).
Yield	% of total CPP recorded time with CPPopt (or CPPopt_MA) values available.
Stability	standard deviation of the difference of two consecutive values of CPPopt (or CPPopt_MA).
ΔCPPopt	average deviation from CPPopt (ΔCPPopt=CPP- CPPopt) (figure 2).
ΔCPP60	average deviation from BTF guidelines 60 mmHg (ΔCPP60=CPP – 60) (figure 2).
ΔTarget	average deviation from the Target (ΔTarget = CPP- Target) (figure 2).

Table I. Calculated variables and their brief description

Variable		N (or median)	% (or IQR)
Age		38	24-89
GCS	**14-15**	37	5
	9-13	166	22
	1-8	569	74
GOS 6 months	**D**	191	23
	VS	15	2
	SD	259	32
	MD	202	25
	GR	146	18

Table II. Demographic and outcome characteristics. GCS, Glasgow coma score; GOS, Glasgow Outcome Score; D, dead; VS, Vegetative State; SD, Severe Disability; MD, Mild Disability; GR, Good Recovery.

Variable	Dead	Alive	P	AUC (CI 95%)
ΔCPPopt	-1.73	1.1	<0.001	0.65 (0.60-0.70)
ΔCPP60	15.4	18	0.001	0.58 (0.53-0.63)
Δtarget	-2	1.6	< 0.001	0.66 (0.62-0.71)
DeLong test				**p**
ΔCPPopt vs ΔCPP60				0.014
Δtarget vs ΔCPP60				<0.001

Table III. Assessment of the ability in distinguishing outcomes groups. P values of the t-test (dead vs alive) and AUC values are presented for ΔCPPopt, ΔCPP60 and ΔTarget. The DeLong test shows that both ΔCPPopt and ΔTarget could offer an advantage over ΔCPP60. ΔCPPopt, delta CPPopt = CPP-CPPopt; ΔCPP60, delta CPP as per BTF guidelines= CPP-60 mmHg; ΔTarget, delta CPP target = CPP- target.

Figure Legends

Figure 1. CPPopt calculation. At each time point, 36 PRx-CPP (5min median filter) plots are generated from past data windows of increasing duration ranging from 2 h to 8 h, using incremental steps of 10 min. The data points are divided into groups corresponding to CPP bins of 5 mmHg length, within 40-120 mmHg range of CPP. For each bin, mean PRx and CPP values are used to fit a 2nd order polynomial describing the theoretical U-shape, with its nadir determining CPPopt, according to the curve fitting criteria. This process is repeated for each progressively longer data window. Only parabolic curves (P= parabolic; NP = non parabolic) with R^2 full ≥ 0.2 are then combined using weighted average operation. The calculations are repeated every minute and the resulting time series is finally subjected to an exponentially weighted average filter of 2h of duration forming the CPPopt time. The missing data limit of the calculation is set at 50%, therefore at least 4 h of data are necessary to generate the first CPPopt value.

Figure 2. CPP trend is shown along with CPPopt, the CPPopt target value, and the BTF guidelines limit (60 mmHg). The target is assessed as CPPopt value sampled every 4 hours, in order to simulate the CPP target provided to the clinical team as per COGiTATE protocol; each target cannot be higher or lower than 10 mmHg from the previous one. Target values range from 50 to 100 mmHg.

Figures

Figure 1

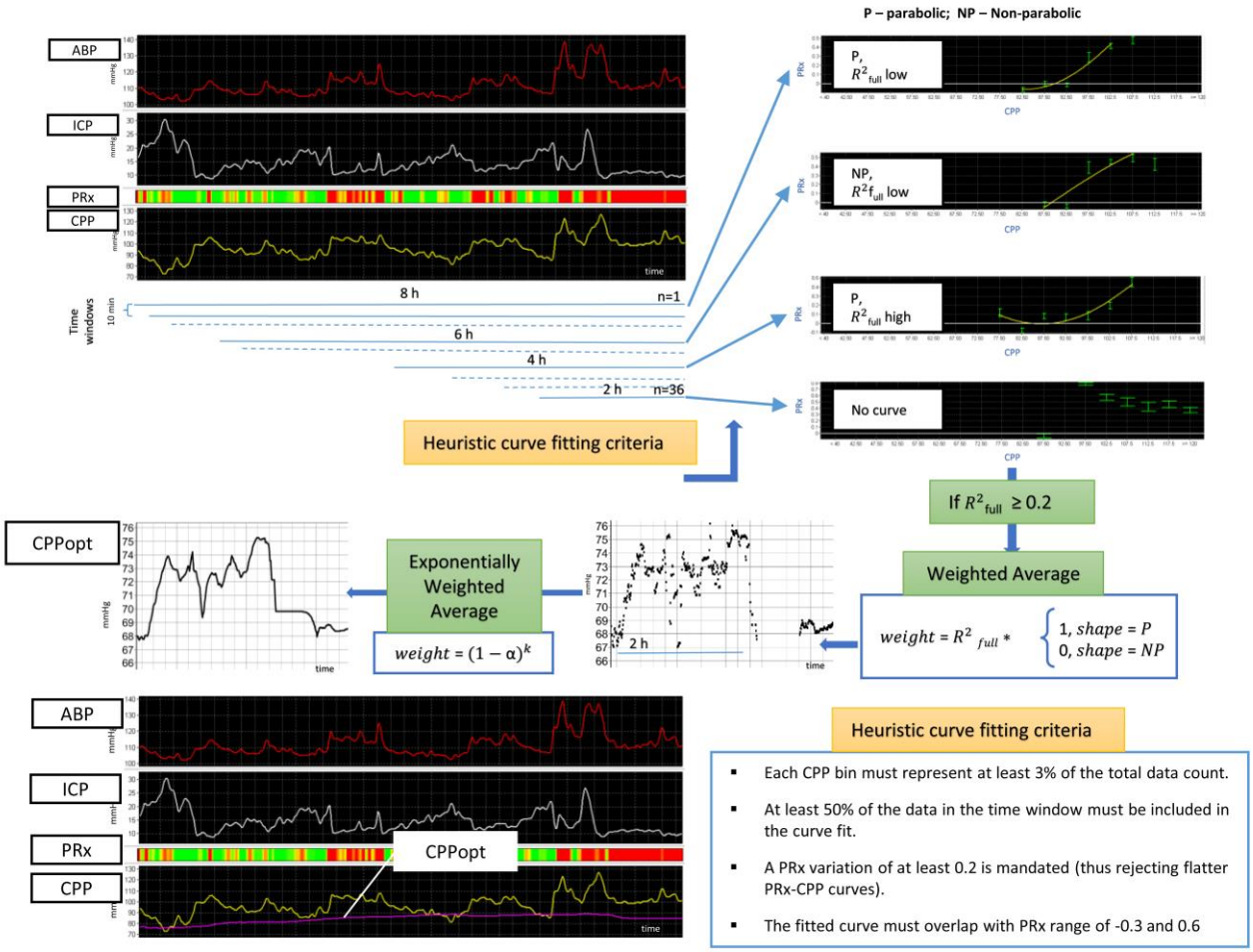
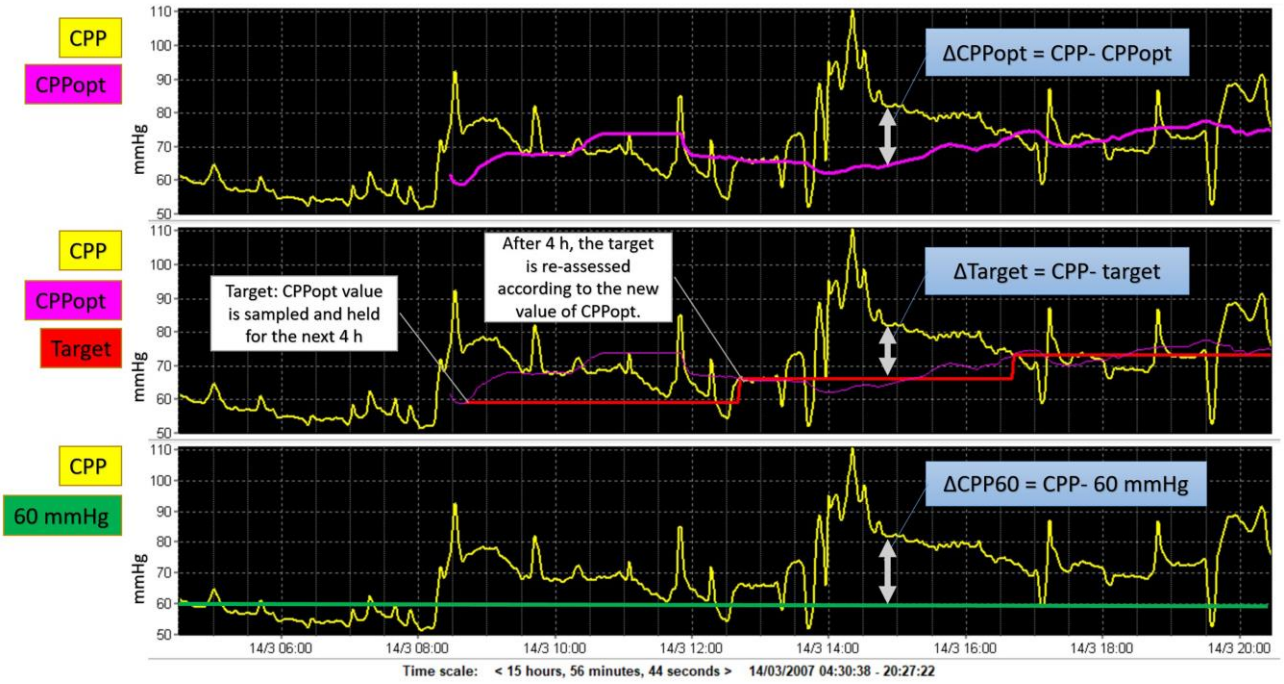


Figure 2


CPP
CPPopt
ΔCPPopt = CPP- CPPopt
CPP
CPPopt
Target
Target: CPPopt value is sampled and held for the next 4 h
After 4 h, the target is re-assessed according to the new value of CPPopt.
ΔTarget = CPP- target
CPP
60 mmHg
ΔCPP60 = CPP- 60 mmHg
mmHg
110
100
90
80
70
60
50
14/3 06:00
14/3 08:00
14/3 10:00
14/3 12:00
14/3 14:00
14/3 16:00
14/3 18:00
14/3 20:00
Time scale: < 15 hours, 56 minutes, 44 seconds > 14/03/2007 04:30:38 - 20:27:22