Journal of Critical Care 41 (2017) 49–55

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients

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ARTICLE INFO

Keywords:
Traumatic brain injury
Cerebrovascular reactivity
Optimal cerebral perfusion pressure
Cerebrovascular autoregulation

ABSTRACT

Purpose: The maintenance of patient-specific optimal cerebral perfusion pressure (CPPopt) is crucial for patients with traumatic brain injury (TBI). The goal of the study was to explore the influence of CPP declination from CPPopt value on the TBI patients' outcome.

Methods: The CPP and cerebrovascular autoregulation (CA) monitoring of 52 TBI patients was performed. Patient-specific CPPopt has been identified and the associations between the patients' outcome and complex influence of time of CPP declination from CPPopt value, age, and the duration of CA impairment episodes has been analyzed.

Results: The multiple correlation coefficient between the Glasgow outcome scale (GOS), duration of CA impairment events and percentage time, when $0 < \Delta CPPopt < 10$ mm Hg was $r = -0.643$ ($P < 0.001$). The multiple correlation coefficients between GOS, age, and percentage time of ΔCPPopt when $0 < \Delta CPPopt < 10$ mm Hg was $r = -0.587$ ($P < 0.001$).

Conclusion: The CPPopt-targeted patient-specific management might be useful for stabilizing CA in TBI patients as well as for improving their outcome. Better outcomes were obtained by maintaining CPP in light hyperperfusion condition (up to 10 mm Hg above CPPopt) when CPPopt is in the range of 60–80 mm Hg, and keeping CPP within the range of CPPopt +/− 5 mm Hg when CPPopt is above 80 mm Hg.

1. Introduction

The main objectives of critical care management of severe traumatic brain injury (TBI) are prevention and treatment of intracranial hypertension and a secondary brain injury by maintaining patient-specific cerebral perfusion and oxygenation [1,2]. The cerebral perfusion pressure (CPP) represents the pressure difference driving cerebral blood flow and thereby, oxygen and metabolite delivery to the brain [1]. Mathematically, CPP is defined as the difference between the mean arterial pressure (MAP) and the mean intracranial pressure (ICP). Universal targets of CPP associated with improved outcomes in severe TBI are not realistic and also the static targets per individual do not exist. It seems that safer CPP zones are changing in time, they are dynamic and depend on cerebrovascular autoregulation (CA) status.

Various clinical studies on CPP-targeted severe TBI management approaches present different outcome results [3-5]. The existing international guidelines by the Brain Trauma Foundation recommend keeping CPP between 60 and 70 mm Hg [6]. However, these common CPP limits are not optimal for every individual case [7]. Clinical studies show that the critical thresholds of CPP should be between 50 and 60 mm Hg, because lower CPP reduces the risk of vasogenic oedema and the elevated ICP [8]. However, too low CPP is associated with the reduction of cerebral blood flow and, consequently, cerebral ischemia or infarction [2,9,10]. Another study showed that CPP above 70 mm Hg is highly associated with the improved patients' outcome [8]. The maintenance of CPP higher than 70 mm Hg, however, increases the risk of pulmonary complications and the acute respiratory distress syndrome [11,12]. Moreover, the increase of CPP can cause hyperaemic insult, vasogenic oedema and a secondary rise of ICP in the case of disturbed cerebrovascular reactivity [13].

In the last decade, the new concept based on the individualized and optimal CPP (CPPopt) targeted management has been developed [14,15]. The pressure-reactivity index (PRx) calculated as a moving linear correlation coefficient between of the arterial blood pressure (ABP) and ICP slow waves [16] is proposed as an estimate of the CA status to identify the CPPopt value. The CPPopt(t) is determined by plotting PRx(t) against CPP(t) in individual cases (by the moving time window of 3 h or even up to 6 h) and by finding the CPP value or CPP range at which

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http://dx.doi.org/10.1016/j.jcrc.2017.04.029
0883-9441/

PRx is minimal [14,15]. The minimal PRx value if it is negative reflects the best achievable intact CA status for individual patient at CPP values which are close to patient-specific CPPopt.

The recent clinical studies show that both parameters CPPopt and PRx are significantly associated with the TBI patients' outcome [14-20]. The rise in PRx above some critical threshold value is associated with vascular deterioration leading to fatal outcomes. Various studies demonstrate that the time-average value of PRx above the critical threshold 0.2 to 0.25 is associated with mortality, while PRx below 0.05 is associated with favorable outcomes [18-21].

The difference between the actual CPP and CPPopt (ΔCPPopt = CPP − CPPopt) can also be used as an outcome predictor [17-20,22]. A better outcome was expected for the patients when a median CPP was within ±5 mm Hg from CPPopt [17]. A poor outcome was more frequent when a median CPP was >10 mm Hg from CPPopt [17]. A severe disability was particularly likely when a median CPP was higher than 5 mm Hg above CPPopt [17]. The mortality rate increases significantly when CPP shifts below the threshold of CPPopt. Various studies show that the ΔCPPopt below −4…−6 mm Hg is highly associated with mortality or a poor outcome [17,21-23].

However, the CPP, CPPopt and PRx based approach contains one major limitation. Many studies were based on the post-hoc analysis of association of the mean or median values of CPP, ΔCPPopt and PRx with the outcome. The calculation of the mean or median values over the whole monitoring period neglects the influence of critical events with extremely long temporal CA impairments and low ΔCPPopt values on the outcomes [24,25]. For example, while estimating the CA status, in most cases, the real-time monitored PRx values vary considerably above and below the determined averaged PRx value of critical thresholds. In the case of ΔCPPopt estimation, real CPP values vary above and below the CPPopt and critical thresholds. Such variances complicate the patient-specific treatment decision making. To avoid the usage of the averaged ΔCPPopt and PRx values, the methodologies of calculation of the percentage time of ΔCPPopt below and above some selected values (or thresholds) are often used [5,22,23,25]. In some studies, it was proposed to estimate the dose of all CA impairment events (or the area under the curve of PRx > 0) instead of calculating the averaged PRx values [26]. In our previous study, we also demonstrated that the outcome of a TBI patient is more significant associated with a single longest event of CA impairment than with the averaged PRx values [25].

This study is a continuation of our previous clinical studies that were based on the analysis of the influences of CA impairment events and CPP critical thresholds on TBI patients' outcome [21,25].

The objective of our study was to explore the influence of CPP declination from the CPPopt value on the TBI patients' outcome when CPPopt-targeted therapy has been used for severe TBI patients' management. Additional influential factors such as CPP range, duration of CA impairment events, and age were included into post-hoc analysis.

2. Materials and methods

Fifty-two patients with severe TBI (with Glasgow Coma Scale GCS < 8 and motor action < 5) were included in the study for monitoring, data collection and retrospective analysis of prospectively collected data. Optimal CPP targeted therapy has been used for treatment for all included patients. The patients were monitored by using the invasive ICP monitors (Codman) and ABP monitors (Datex). Ethical approvals No.158200-06-498-145, 2012-06-12 and No.158200-15-801-323, 2015-10-06 were granted for the clinical study in the intensive care unit of the Republican Vilnius University Hospital (Lithuania). The monitoring data from the ICP and ABP monitors were collected and processed by the ICM+ (Cambridge, UK) data collection and analysis software tool. The sampling frequency of raw ICP(t) and ABP(t) data was 200 Hz. This software tool was used for the online real-time estimation of PRx(t) and CPPopt(t). The following parameters were included in the post-hoc analysis:

- PRx(t) - the moving linear correlation coefficient between the ABP(t) and ICP(t) spontaneous slow waves. PRx(t) was averaged within 10 min by moving averaging.
- CPP was calculated as the difference between the mean ABP(t) and ICP(t) values within 10-min time window. The optimal CPP values were calculated by plotting the CPP values vs. PRx values, and fitting the U-shaped curve over the plotted points taken from 4 h monitoring window. The minimum point of the U shape was identified as an optimal CPP value. The optimal CPP values were rejected or corrected according to the last reliable CPPopt value in the cases if the U shape fitting was not found.
- The difference between the real-time CPP and the optimal CPP was calculated as ΔCPPopt(t) = CPP(t) − CPPopt(t).
- The total time in percentage when ΔCPPopt(t) was below −5 mm Hg; below 0 mm Hg and when it was within the range between 0 and +10 mm Hg was calculated.
- The duration of the longest CA impairment (LCAI) episodes, when PRx(t) continuously exceeded the positive value of 0.5, was estimated for each patient.

Table 1
Demographic characteristics, clinical findings, CPP and CA monitoring data, and outcome of TBI patients (a,b). Remarks:
a. IQR, interquartile range; GOC, Glasgow outcome scale; GOS6M, Glasgow outcome scale at 6 months after discharge; CPP, cerebral perfusion pressure, ΔCPPopt, declination of CPP from optimal CPP, LCAI, longest CA impairment; PRx(t), pressure reactivity index; SD, standard deviation.
b. Favorable outcomes after 6 months are good recovery (GOS = 5) or moderate disability (GOS = 6); unfavorable outcomes after 6 months are severe disability (GOS = 3), vegetative state (GOS = 2), or death (GOS = 1).
c. p-value of differences between the groups with favorable and unfavorable outcomes calculated by using Mann-Whitney U test (significant if $p < 0.05$).

	Favorable outcome (GOS_{6M} = 4-5)	Unfavorable outcome		Total	p-value
		(GOS_{6M} = 2-3)	Died (GOS_{6M} = 1)		
No patient (%)	24 (46.2)	9 (17.3)	19 (36.5)	52 (100)	-
Mean age (STD), years	30.7 (12.9)	44.7 (18.3)	45.0 (12.4)	38.3 (15.3)	0.002
Sex, M/F	19/3	7/2	12/4	37/10	-
GCS, median (IQR)	7 (5–8)	4 (4–6)	5 (3–7)	5 (4–7)	0.042
HCT, median (IQR)	5 (1–5)	7 (5–10)	8 (5–11)	5 (2–8)	<0.001
Only ICP senor placement procedure, (%)	15 (28.8)	3 (5.8)	11 (21.2)	29 (55.8%)	-
ICP senor placement plus open surgery, (%)	9 (17.3)	6 (11.5)	8 (15.4)	23 (44.2%)	-
Averaged PRx, mean (STD)	0.07 (0.09)	0.08 (0.16)	0.32 (0.36)	0.17 (0.27)	0.044
Averaged ΔCPPopt, mm Hg	2.71 (4.38)	-0.22 (4.03)	-0.33 (3.47)	1.09 (4.21)	0.009
Averaged CPP, mm Hg	86.96 (8.41)	85.96 (10.48)	74.56 (26.81)	82.25 (18.37)	0.155
Percentage time when ΔCPP < − 5 mm Hg, %, mean (STD)	27.32(13.11)	35.20 (17.52)	45.51 (26.04)	34.60 (20.48)	0.030
Percentage time when 0 < ΔCPP < 10 mm Hg, mean (STD)	32.55 (9.94)	25.37 (9.90)	23.32 (14.36)	28.66 (12.08)	0.044
Duration of LCAI (PRx > 0.5), min, mean (SD)	60 (38)	91 (78)	224 (155)	126 (126)	0.002