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Original Research Article

Association between the outcome of traumatic brain injury patients and cerebrovascular autoregulation, cerebral perfusion pressure, age, and injury grades

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ABSTRACT

Background and objective: The aim of this study was to explore the association of cerebrovascular autoregulation (CA) and optimal cerebral perfusion pressure (CPP) managing conditions with the outcome of traumatic brain injury (TBI) patients including additional information about the patients' age and grade of diffuse axonal injury (DAI).

Materials and methods: The CA monitoring of 28 TBI patients was performed by using ICM+ software (Cambridge, UK). The CA status estimating pressure reactivity indexes (PRx) and CPP data were processed in order to obtain information on the patient-specific treatment conditions by calculating the optimal CPP.

Results: There was a negative correlation between the Glasgow outcome scale (GOS) score and PRx ($r = -0.448$ at hospital discharge and $r = -0.402$ after 6 months). The estimated threshold value PRx of >0.24 was associated with mortality. The correlation coefficients between the GOS score and the difference CPP-optimal CPP were 0.549 at hospital discharge and 0.484 after 6 months. The threshold value of CPP declination from ΔCPPopt per −6 mmHg was associated with mortality. Poorer outcome was predicted for elderly TBI patients (aged >47 years) and patients having a DAI grade of 3.

Conclusions: The association of the GOS score with CPP, CA impairment conditions, age and diffuse axonal injury (DAI) grade showed that the outcomes of TBI patients were associated with patient-specific CPP management and better outcomes were obtained for younger patients, for patients having lower DAI grade and for patients whose CPP was kept within the range from the optimal CPP to the optimal CPP + 10 mmHg.

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1. Introduction

Although the outcome of patients with traumatic brain injury (TBI) is highly associated with the severity of brain injury and many other factors [1,2], it might be improved by optimizing treatment strategies [3–6]. The main factors influencing the possibility to treat the patient for leading to a better outcome are cerebral perfusion pressure (CPP), cerebrovascular autoregulation (CA), age and brain injury severity. The initial state of a TBI patient is estimated according to the Glasgow coma scale (GCS), which together with other factors (age, pupils, computed tomography [CT] scans, etc.) might provide rough prognosis of the outcome [7,8]. Moreover, such prediction of the patient's outcome based on the initial GCS does not contain the patient's treatment information. The impairment of CA has a strong impact on the outcome of the traumatic brain injury (TBI) patients, therefore, it is essential to know the real-time status of CA [9,10]. The consensus has already been achieved that the cerebral blood flow (CBF) autoregulatory state of TBI patients has to be monitored and the individualized treatment strategy should be re-valuated regularly over the time course of CBF autoregulation status [11,12].

The clinically practical method for continuous CA assessment is to calculate a pressure-reactivity index (PRx) as a moving linear correlation coefficient between the reference arterial blood pressure (ABP) and invasively or non-invasively measured intracranial pressure (ICP) slow waves [13–17]. PRx reflects the ability of cerebral vessels to change the diameter in response to the changes in the ABP, while maintaining a stable cerebral blood flow [13]. It is proved that the PRx increased above the critical thresholds is associated with brain vascular deterioration leading to the fatal outcome [18,19]. Different PRx thresholds for the survival (when the averaged PRx is below 0.2–0.25) and for a favorable outcome (when the averaged PRx is below 0.05) were reported in the recent studies [19,20]. Moreover, PRx can be used as a variable for setting the individual target for optimal CPP management [21,22]. Continuous PRx monitoring might help to identify the optimal CPP under the condition of the strongest cerebrovascular autoregulation. The optimal CPP is determined by plotting PRx against CPP 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 PRx is minimal [22]. Minimal PRx reflects the conditions of intact CA. The patients with greater deviation between their averaged CPP and post hoc assessed optimal CPP have worse outcomes after head trauma [22–24]. However, there are a few limitations of practical usage of PRx and optimal CPP-based treatment strategies:

- Statistically determined PRx thresholds for survival are rough due to the usage of averaged PRx values for threshold calculation. In most cases the real-time monitored PRx values varies considerably above and below determined PRx thresholds, therefore, it complicates patients specific treatment decision making. In recent studies it is shown that time of CA impairment (when PRx >0 or PRx is above specific thresholds of mortality) is also important factor associated with the patients' outcome and should be taken into account during patients' treatment [23,25].
- Determination of the optimal CPP requires more time for more accurate and precise estimation (3–6 h). Therefore, delay in making patient's treatment decision might be critical. The real-time monitored CPP value always varies with the delay respectively to the optimal CPP and the differences between the real-time monitored CPP and the optimal CPP are not investigated enough.
- Additional important factors, as age and brain injury rate, influence the patient's outcome and should be taken into account in choosing patient specific treatment strategies [26,27].

The aim of this study was to explore the influence of the CA impairment and the optimal CPP managing conditions on TBI patients' outcome including additional information about the patient's age and the rate of TBI injury as well as to identify the threshold for the difference between the real-time monitored CPP and the optimal CPP.

2. Materials and methods

A total of 28 severe traumatic brain injury patients in different pathophysiological states were monitored simultaneously by using the ICP monitor (Codman) and the ABP monitor (Datex) at Republican Vilnius University Hospital (Lithuania). The data from the ICP monitor and the ABP monitor were collected and processed by using software ICM+ (Cambridge, UK). This software was used for online real-time calculation of the PRx index as well as for determination of optimal CPP values (Fig. 1). All data were used to perform the post hoc analysis in order to extract additional information and optimize monitoring and real-time algorithms.

The following parameters of the monitored data were calculated:

- PRx was calculated as the moving linear correlation coefficient between the ABP and ICP spontaneous slow waves within a 10-min time window. The real time artifacts were rejected from the ABP and ICP data and only the artifact-free data were used for PRx calculation.
- CPP was calculated as the difference between the mean ABP and ICP 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 6 h monitoring window. The minimum point of the U shape was kept as an optimal CPP value. The optimal CPP values were rejected in the cases if the U shape fitting was not reliable.
- The difference between the real-time CPP and the optimal CPP was calculated as $\Delta CPPopt = CPP - CPPopt$.
- The total time in percentage of CA impairment when the PRx value exceeded threshold associated with mortality was calculated for each patient.

The Glasgow outcome scale (GOS) score was determined after hospital discharge (GOS_{HD}) and 6 months (GOS_{6M}). The patients' outcome was described as follows: 1, death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, low disability. The outcome was considered

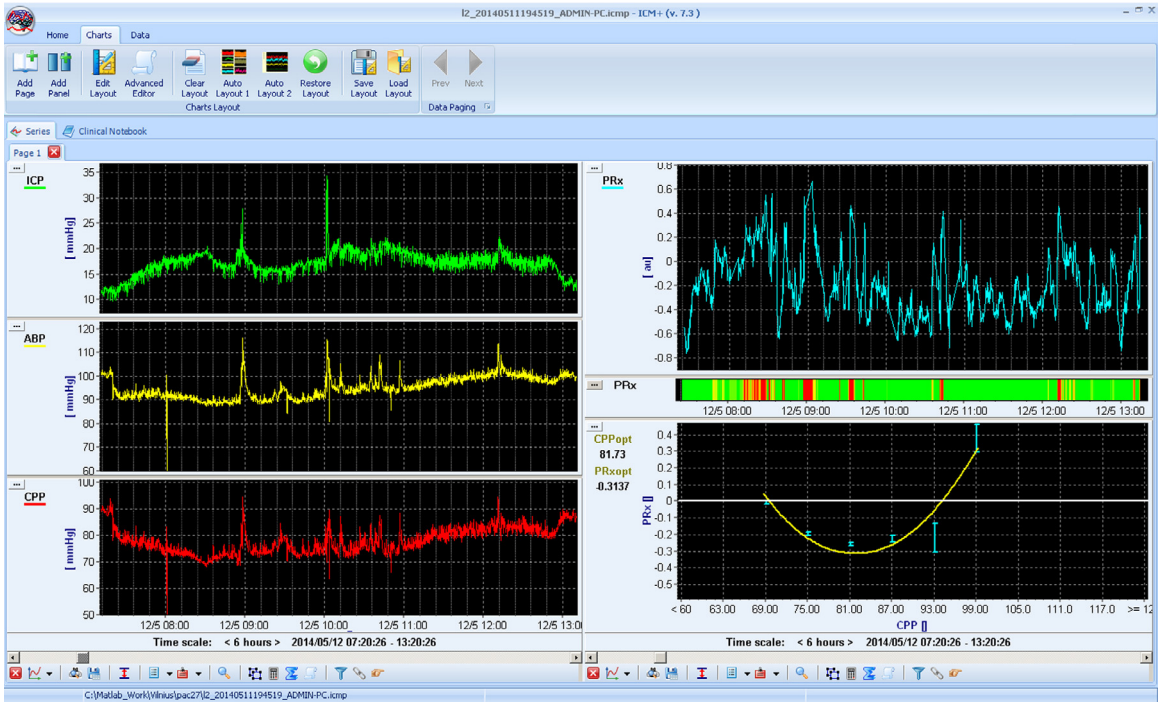

Fig. 1 – Windows of ICM+ software (Cambridge, UK) used for continuous ICP(t), ABP(t), CPP(t), PRx(t) monitoring and optimal CPP determination.

good if the GOS score was 4 or 5 and unfavorable if the GOS score was 1 or 2.

Magnetic resonance imaging (MRI) and CT scans were performed for some patients to estimate their diffuse axonal injury (DAI) grades according to the lesion location. DAI is classified into grades based on the severity of the injury: grade 1, widespread axonal damage is present, but no focal abnormalities are seen; grade 2, damage found in grade 1 is present in addition to focal abnormalities, especially in the corpus callosum; and grade 3, damage encompasses both grades 1 and 2 plus rostral brain stem injury and often tears in the tissue [27]. It is known that the exact location of brain lesions is statistically significant related to mortality and outcome of the survivors [2,28]. Although MRI and CT scans give useful information for patient treatment and prognosis, not all patients could be transferred to the MRI unit due to their critical state.

2.1. *Statistical analysis*

The Pearson chi-squared test (χ^2) was used to determine critical thresholds of the analyzed factors associated with unfavorable or favorable outcome. The series of 2×2 tables were created by grouping the patients according to the criteria of outcome (by distinguishing the patient groups with good [GOS score of 3, 4, and 5] vs. unfavorable outcome [GOS score of 1 and 2]) and influential factors (by distinguishing the patient groups with factor values greater than or smaller than the sequential thresholds) [19]. The tables were reconstructed by changing the influential factors within their range, and the Pearson chi-square was calculated for each of such tables. For each outcome measure, the respective threshold of all analyzed factors (PRx, ΔCPPopt, age) returning the highest chi square score was assumed to have the best discriminative value [19]. The additional plots of GOS association with PRx, ΔCPPopt, age and DAI grade were accompanied by fitting linear regression and calculating the Pearson correlation coefficient r. Multiple correlation coefficients were also calculated for the relationships between GOS indexes and multiple input factors (ΔCPPopt, age, DAI grade) by using Matlab software, Surface fitting tool. The significance was set at $P < 0.05$.

3. Results

The patients' age ranged from 18 to 66 years; the mean age was 37.6 years. There were 25 male and 3 female patients. The patients' outcomes after the hospital discharge were as follows: 4 cases had a GOS score of 1; 6 cases, 2; 12 cases, 3; and 4 cases had a GOS score of 4. The outcomes at 6 months after brain injury were as follows: 7 cases had a GOS score of 1; 1 case, 2; 7 cases, 3; 10 cases, 4; and 3 cases, 5. The outcome indexes GOS_{HD} and GOS_{6M} were plotted in comparison with the mean values of PRx indexes, time of CA impairments and ΔCPPopt showing an association between GOS and these factors (Figs. 2–4). The correlation coefficients between PRx and GOS were −0.448 ($P = 0.008$) at hospital discharge and −0.402 ($P = 0.017$) after 6 months.

ΔCPPopt correlated significantly with the GOS score at hospital discharge ($r = -0.549$, $P = 0.001$) and after 6 months ($r = -0.484$, $P = 0.004$). The calculated PRx thresholds for mortality outcome were 0.19 ($\chi^2 = 4.492$, $P = 0.0345$) at hospital discharge and 0.24 ($\chi^2 = 4.795$, $P = 0.0288$) after 6 months. The threshold value PRx of >0.24 was used to define conditions of

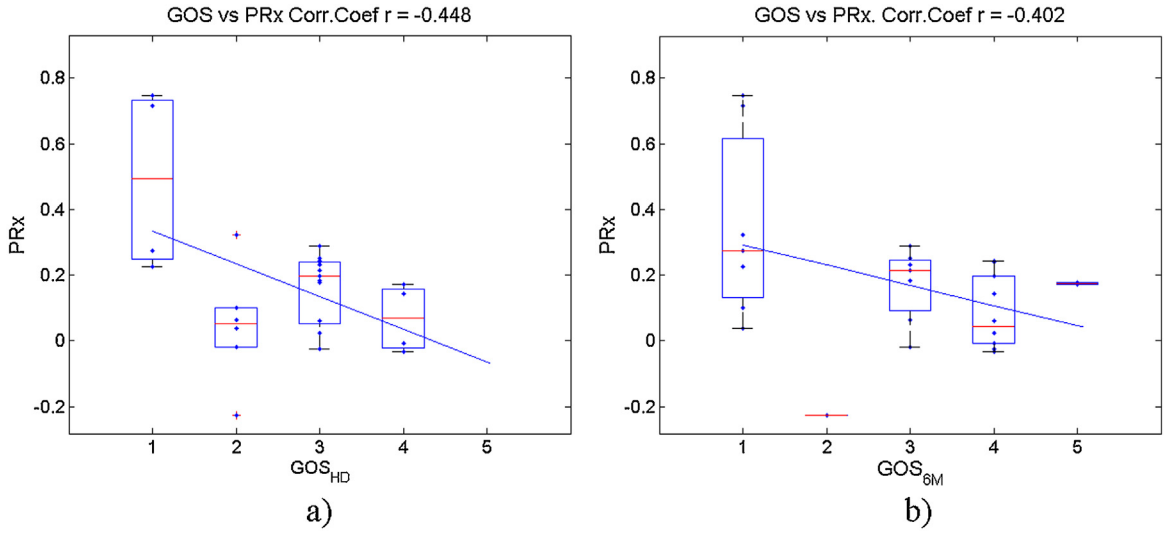

Fig. 2 – Association between GOS and PRx. GOS correlated negatively with PRx ($r = -0.448$, $P = 0.008$ at hospital discharge and $r = -0.402$, $P = 0.017$ after 6 months). Threshold value of PRx >0.24 was associated with mortality.

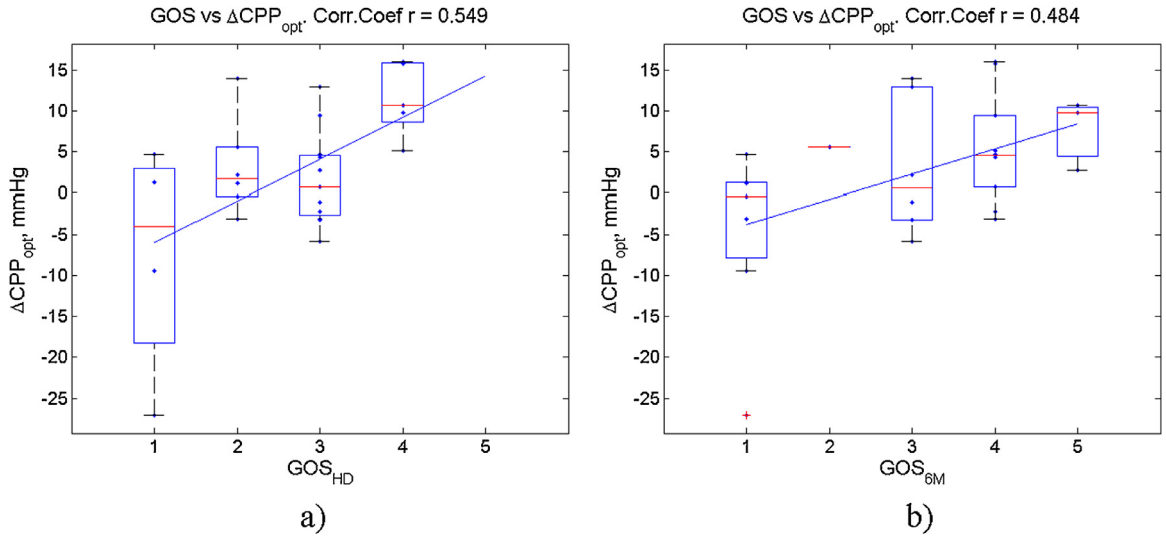

Fig. 3 – Association between GOS and ΔCPPopt. The correlation coefficients between the GOS and ΔCPPopt were 0.549 ($P = 0.001$) at hospital discharge and 0.484 ($P = 0.004$) after 6 months. The threshold value of ΔCPPopt <−6 mmHg was associated with mortality. Better outcomes were obtained when CPP was kept above CPPopt per ~5–10 mmHg.

CA impairment and to calculate the total time of CA impairment under these conditions. There was a significant correlation between the GOS score and the total time of CA impairment at hospital discharge ($r = -0.443$, $P = 0.008$) and after 6 months ($r = -0.442$, $P = 0.017$).

The PRx thresholds of good outcomes (GOS score of 4 or 5) were not determined. The statistically significant differences among the vegetative, severe disabilities and good outcomes were not found. The calculated ΔCPPopt thresholds for the mortality outcome were −4 mmHg ($\chi^2 = 5.147$, $P = 0.0233$) at hospital discharge and −6 mmHg ($\chi^2 = 6.171$, $P = 0.012$) after 6 months.

Additionally, the associations between age, brain injury rate and patients' outcome were checked. The plots indicating associations between the GOS score, age, and brain injury rate are show in Fig. 5a. The correlation coefficient between the age and the GOS_{6M} score was −0.585 ($P < 0.001$), and the age threshold separating poor outcomes (GOS scores of 1 or 2) was 47 years ($\chi^2 = 5.989$, $P = 0.0142$). The plots of the association of GOS scores with the age and the brain injury rate are shown in Fig. 5b. The correlation coefficient between the DAI grade and the GOS_{6M} score was −0.518 ($P = 0.001$). These plots show that the prognosis of poorer outcome was associated with older age (age >47 years) and higher DAI grade (grade of 3).

4. Discussion

In this prospective study we showed an association between the GOS score and various factors such as CA indexes, CPP

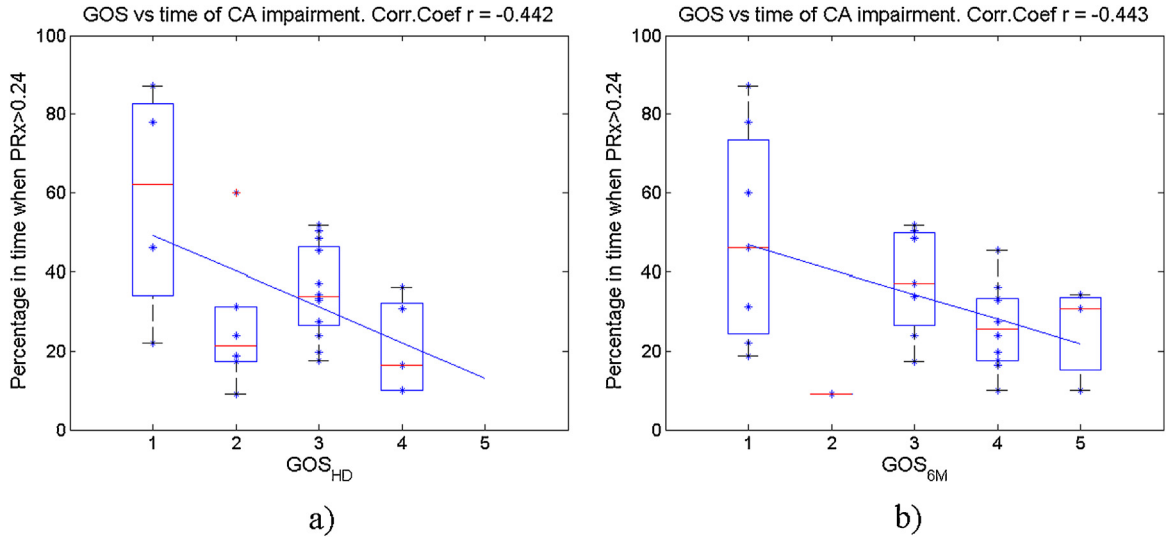

Fig. 4 – Association between GOS and total time of CA impairment under conditions when PRx >0.24 ($r = -0.442$, $P = 0.009$ at hospital discharge and $r = -0.443$, $P = 0.009$ after 6 months).

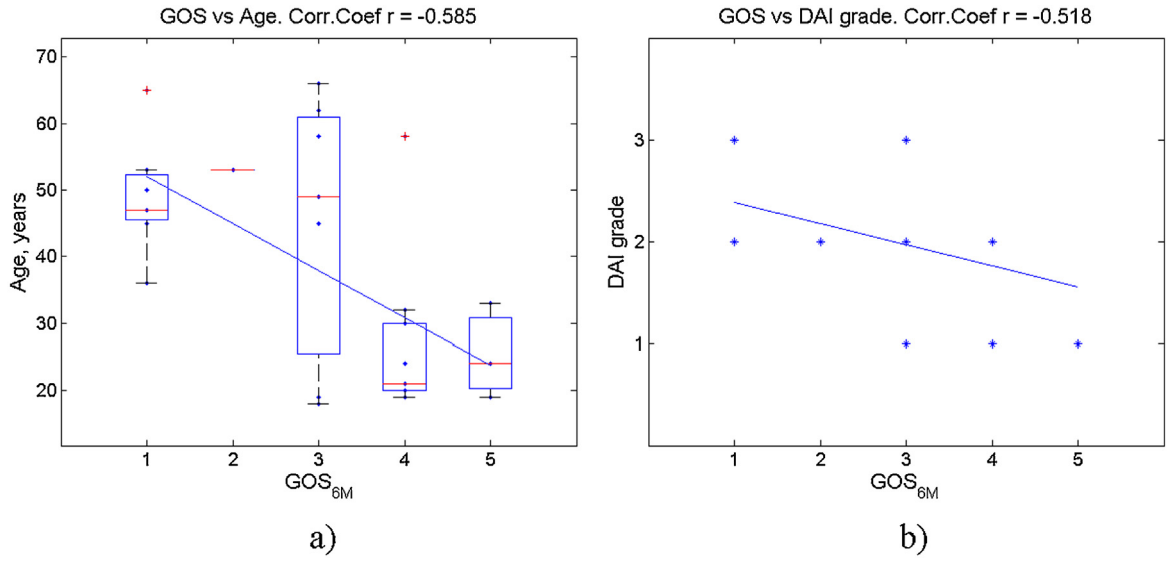

Fig. 5 – Associations of GOS_{6M} with age ($r = -0.585$, $P < 0.001$) and DAI grade ($r = -0.518$, $P = 0.001$). The poorer outcome was predicted for elderly TBI patients (age >47 years) and patients having DAI grade (grade 3).

declination from the optimal CPP, duration of CA impairment episodes, age and severity of brain injury. Analysis of separate one-dimensional associations of these factors showed a stronger or weaker association with the patient outcome and these results are in line with the results of other studies [19–24]. We showed that the correlation coefficient between analyzed factors and GOS indexes varied from 0.4 to 0.56, thus showing an indirect association between these factors and patients' outcome. The strongest correlations were between patient outcome and ΔCPPopt ($r = -0.549$ at hospital discharge and $r = -0.484$ after 6 months), age ($r = -0.585$, $P < 0.001$), and DAI grade ($r = -0.518$, $P = 0.001$).

We found that an acceptance of the treatment strategy in the way of keeping CPP close to optimal CPP might help to stabilize cerebrovascular autoregulation and to lead the patient to a better outcome. However, the age and DAI grade might act as limiting factors restricting the possibility of favorable outcome of TBI patients. We found that a poorer outcome was predicted for elderly TBI patients (age >47 years) and patients with higher DAI grade (grade 3).

The importance of the optimal CPP management is also highlighted in other studies [22,23]. They showed that CPP should be optimal, i.e., matched to an individually assessed value, which provides the best conditions for cerebrovascular reactivity and maximizes the ability of brain to protect itself from both ischemia and hyperemic injury [22]. However, the accessible limits of the allowed declination of CPP from the optimal value were not investigated deeply

enough. In recent studies it was suggested to monitor percentage time of CPP above and below optimal CPP. The authors of that study demonstrated that the fraction of time spent below the optimal CPP was significantly longer in the patients with poor outcome (76.0%) than in the patients with favorable outcome (28.0%) [23].

In our study we also found that the declination of CPP below optimal CPP for prolonged periods might lead to poorer outcome. In our study, the calculated critical threshold of ΔCPPopt associated with mortality was–6 mmHg.

In order to explore more deeply the importance of the optimal CPP management concept we expressed the outcome of TBI patients as a complex multi-dimensional function influenced by ΔCPPopt, DAI grade and age. The contour plots show of 3D surfaces show that the red area (good outcome, a GOS score of 5) is located in certain parts of the surface defining conditions for predicting and managing TBI patients' outcome. The color in the plots (Fig. 6a and b) represents the indexes of patients' outcome: the red color represents good outcome, i.e., a GOS score of 5; orange, a GOS score of 4; green, a GOS score of 3; light blue, a GOS score of 2, and dark blue, a GOS score of 1.

The contour plot of GOS association with ΔCPPopt and age clearly shows that a better outcome is expected for younger

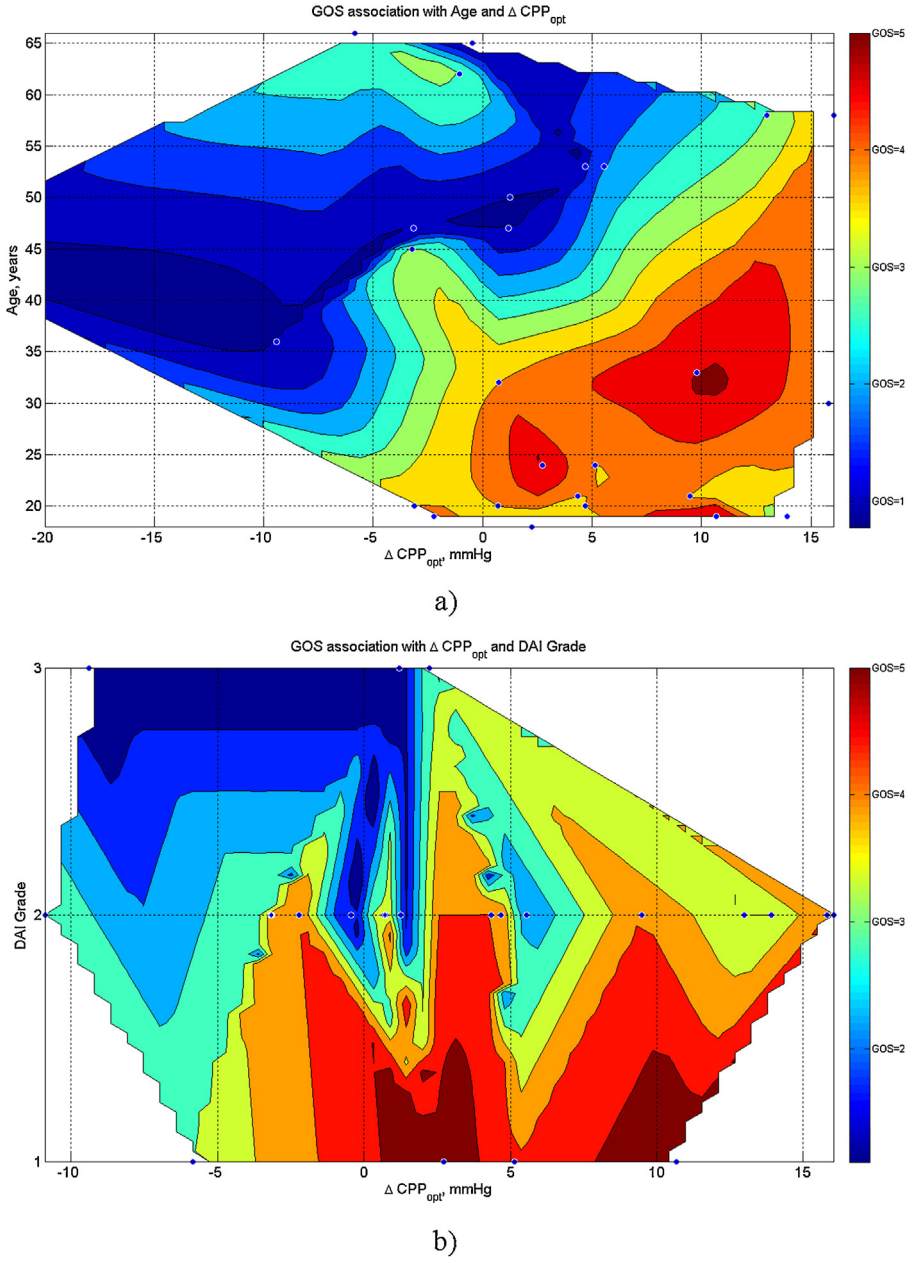

Fig. 6 – Contour plots of GOS association with the declination form CPPopt, age (a) and DAI grade (b). Better outcomes were obtained for younger patients when DAI grades were 1 and 2 and for those whose CPP was kept within the range from optimal CPP to optimal CPP + 10 mmHg. The multiple correlation coefficient between GOS and two input factors (ΔCPPopt and age) was 0.677 ($P < 0.001$). The multiple correlation coefficient between GOS and two input factors (ΔCPPopt and DAI grade) was 0.529 ($P = 0.007$).

patients and for those whose CPP was kept above the optimal CPP values (Fig. 6a). An additional plot of GOS association which included DAI grade information showed that better outcomes were obtained for DAI grades 1 and 2 and when CPP was kept within the range from the optimal CPP to the optimal CPP + 10 mmHg (Fig. 6b). The multiple correlation coefficient between GOS and two factors (ΔCPPopt and age) was 0.677 ($P < 0.001$) and the multiple correlation coefficient between GOS and two factors (ΔCPPopt and DAI grade) was 0.529 ($P = 0.007$).

4.1. *Limitations of the study*

The presented analysis was carried out on a limited number of 28 TBI patients. However, we found that the critical PRx threshold associated with the patients' mortality (PRx >0.24) calculated from our study was very close to the values obtained at other clinical centers: PRx >0.25 [19], PRx >0.2 [20].

Another limitation is also related to the inaccuracy of calculation of the optimal CPP value. A longer time (up to 6 h) is needed for obtaining the U-shaped approximation of PRx data as well as for calculation of the optimal CPP. However, a longer processing of the time series data for estimations of the optimal CPP is associated with the delay of making the patient's treatment decisions and with the inaccuracy of CPP management. It is proved that the declination of differences between the real-time monitored CPP and the optimal CPP toward the negative values might lead to poorer outcomes [23,24]. Therefore, the result that a better outcome might be expected by keeping CPP above the optimal CPP per some value (up to 10 mmHg in our cases) is expected and logical.

Methodological limitation is caused by usage of averaged values of CA related parameters which not reflect dynamics of variation of cerebrovascular autoregulation status and might hide some critical events. Real-time PRx monitoring and optimal CPP identification technology has to be created in order to overcome such limitations.

5. Conclusions

The analysis of GOS association with CA impairment conditions, CPP, age and DAI grade showed that outcomes of TBI patients were associated with patient-specific CPP management and better outcomes were obtained for the patients whose CPP was kept within the range from the optimal CPP to the optimal CPP + 10 mmHg, for younger patients, and for patients having lower DAI grade. Impairment of CA status and declination of CPP below optimal CPP value were associated with poor outcomes. The determined critical thresholds associated with mortality of TBI patients were PRx >0.24 and ΔCPPopt <−6 mmHg. The age limit associated with poorer outcome was above 47 years.

Conflict of interest

The authors state no conflict of interest.

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