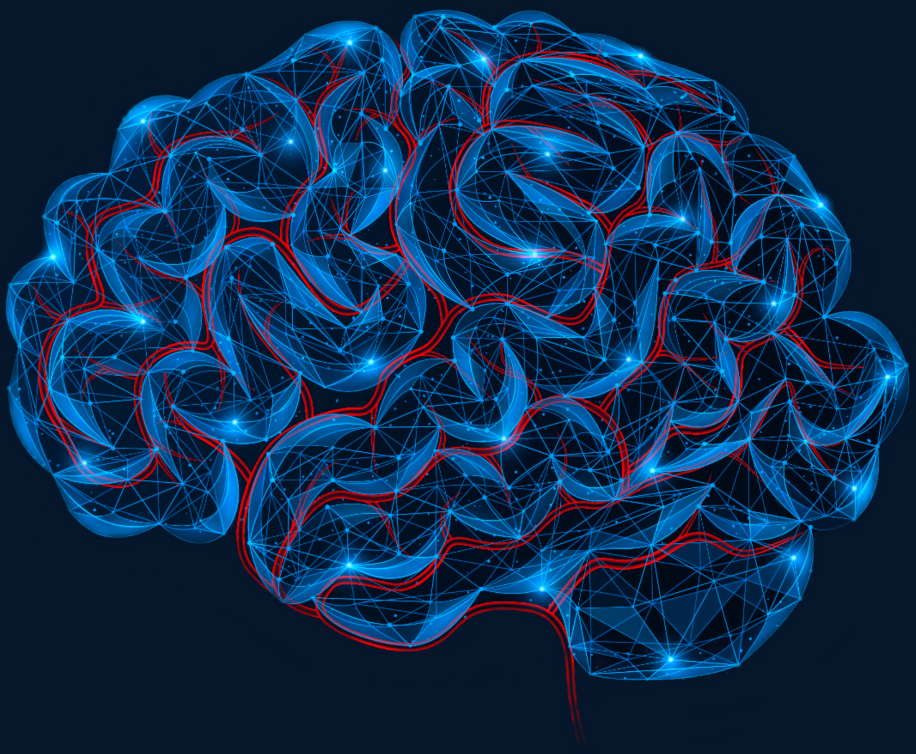
Quantifying Cerebral Autoregulation in Children with Severe Traumatic Brain Injury



MSc thesis

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Quantifying Cerebral Autoregulation in Children with Severe Traumatic Brain Injury

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Preface

While this thesis is my personal graduation project it was certainly a team effort. Therefore it is only fitting to start with acknowledgments. The seed for this thesis was planted three years ago during my first technical medicine internship. Jan Willem Kuiper suggested focusing on traumatic brain injury and Naomi Ketharanathan proposed including a cerebral autoregulation parameter in the research. Studying the relationship with outcome would not have been possible without Rogier de Jonge his expertise on statistical analysis. The quality of this research was greatly improved by Jan Willem, Rogier and Naomi's close involvement and their critical and constructive feedback. Alfred Schouten provided technical supervision and shared fresh insights from an engineering perspective while maintaining a strong focus on ensuring that the research was clinically relevant. Eris van Twist, my daily supervisor, was always available for the day to day challenges of conducting research, but made sure that the focus remained on the end goal of graduating. I would furthermore like to extend my gratitude to Maayke Hunfeld for her willingness to participate as a member of the graduation committee.

My friends and family became unofficial research advisers and career mentors during my graduation internship which I greatly appreciate. I am grateful that we get to navigate the ups and downs of life together. Unfortunately, it is not common for girls born in Suriname to get the chance to attend higher education. The chances that I got which have led me to write this thesis are due to a combination of incredible luck and hard work and sacrifices made by my parents. The warm and stable foundation they provided together with my grandparents is invaluable. As we say in Suriname, *gran tangi*.

Tahisa Robles

Rotterdam, September 2023

Abstract

Introduction

Traumatic brain injury is a leading cause of mortality in children worldwide. Defining optimal treatment targets for pediatric severe traumatic brain injury (sTBI) is challenging because of scarce scientific research on the disease in children. Cerebral autoregulation, quantified using the pressure reactivity index (PRx), may enable personalized treatment targets. The aims of this thesis are i. to investigate whether the relationship between PRx and outcome in the Erasmus MC Sophia pediatric intensive care unit (PICU) cohort is similar as to what is described in the literature ii. to develop an algorithm which utilizes PRx to determine dynamic and personalized cerebral perfusion pressure (CPP) targets iii. to assess if there is a correlation between these personalized CPP targets and outcome.

Method

The PRx was retrospectively generated for sTBI patients admitted to the PICU of the Erasmus MC Sophia Children's Hospital between 2016 and September 2023. An algorithm was written which utilizes PRx to generate a personalized optimal CPP value and CPP range every minute. Outcome was determined 1 year after the injury using the pediatric cerebral performance category (PCPC) and was dichotomized as favorable (PCPC 1-2) or unfavorable (PCPC 3-6). Secondary analyses were done for mortality and outcome in survivors (good outcome PCPC 1-2 vs. poor outcome PCPC 3-5).

Results

Fifty patients were included. Increased mean PRx was significantly associated with unfavorable outcome (OR 1.54; 95% CI 1.14 – 2.08) and mortality (OR 2.49; 95% CI 1.39 – 4.45). When determining the percentage of time that PRx was increased, a threshold of 0.3 had the strongest association with outcome (OR 1.05; 95% CI 1.01 – 1.09 for unfavorable outcome and OR 1.06; 95% CI 1.02 – 1.11 for mortality). There was no significant association between PRx and outcome in survivors. A CPPopt algorithm was developed which generates an personalized optimal CPP value and optimal CPP range every minute. A decreased percentage of time that CPP is within the optimal range was significantly associated with unfavorable outcome (OR 0.97; 95% CI 0.95 – 1.00) and mortality (OR 0.96; 95% CI 0.93 – 0.99). The percentage of time that CPP was within the optimal range was not significantly associated with outcome in survivors.

Conclusion

In the Erasmus MC Sophia PICU cohort increased PRx is a significant predictor of unfavorable outcome and mortality. A decreased percentage of time that CPP is within the optimal range is significantly associated with unfavorable outcome and mortality. Prospective multi-center research is needed to evaluate if outcome can be improved by autoregulation guided therapy.

Introduction

Traumatic Brain Injury (TBI) is a type of acquired brain injury caused by an external force. Globally, TBI is a main cause of mortality in children. TBI is classified based on the level of consciousness assessed through the Glasgow Coma Scale (GCS). The classifications include mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 3-8) TBI. [1] The incidence of moderate and severe TBI in children in the Netherlands is 14 per 100.000 person years. [1] To limit secondary injury patients with severe TBI (sTBI) are admitted to the intensive care unit for neuromonitoring and supportive measures. Treating pediatric sTBI is challenging, as there is a paucity of high level evidence on neuromonitoring and treatment. Subsequently, recommendations used in pediatric sTBI are mostly based on research in adults, although it is known that the anatomy and physiology of the pediatric brain is significantly different. [2] Cerebral autoregulation can play a crucial role in a better understanding of the sTBI disease process and enable personalized treatment.

Cerebral autoregulation is the physiological neuroprotective process in which cerebral blood vessels ensure a constant cerebral blood flow over a range of arterial blood pressures by vasodilation and vasoconstriction. This mechanism can become impaired after trauma. In the current clinical practice, cerebral autoregulation is not regularly monitored. The most widely studied parameter regarding cerebral autoregulation in both children and adults is the pressure reactivity index (PRx), which quantifies the correlation between intracranial pressure (ICP) and mean arterial pressure (MAP). An increased PRx represents impaired autoregulation and is associated with unfavorable outcomes in both adults and children. [3-14] PRx is especially clinically relevant as it can be used to determine personalized cerebral perfusion pressure (CPP) targets. [4, 15-19]

The pediatric intensive care unit (PICU) of the Erasmus MC Sophia Children's Hospital has started a research project in which retrospective data analysis is performed to identify appropriate thresholds for neuromonitoring of pediatric sTBI. While the current ICP and CPP thresholds are static and either the same for all patients or based on age categories this research aims to develop personalized, dynamic thresholds. The long term goal is to develop a dashboard on which the neuromonitoring parameters, derived parameters and personalized thresholds can be visualized. The aims of this thesis are i. to investigate whether the relationship between PRx and outcome in the Erasmus MC Sophia PICU cohort is similar as to what is described in the literature ii. to develop an algorithm which utilizes PRx to determine dynamic and personalized cerebral perfusion pressure (CPP) targets iii. to assess if there is a correlation between these personalized CPP targets and outcome.

Background

As described previously, sTBI is an acquired brain injury caused by external force. The primary injury is irreversible and caused by the impact of this external physical force. After the primary injury a cascade of cellular, biochemical and metabolic reactions take place which can lead to further damage to the brain tissue causing secondary injury. In this process, cerebral edema can occur. Because there is limited space in the skull swelling can cause compression of brain tissue. The swelling can result in brain herniation, leading to compression of the brain stem, which is fatal if left untreated. [2] To limit secondary injury and to support vital functions, patients with sTBI are admitted to the intensive care unit. In addition to vital function monitoring, continuous neuromonitoring is performed by measuring the intracranial pressure (ICP) and the cerebral perfusion pressure (CPP). The treatment is titrated based on the monitored values whereby if the parameters are not in the desired range, interventions such as hyperventilation, the administration of hypertonic saline, the administration of barbiturates and surgical interventions can be performed.

Intracranial pressure (ICP)
The pressure inside the skull is determined by the volume of three constituents : brain parenchyma, blood and cerebrospinal fluid. In the physiological setting the ICP is fairly constant because a small increase in volume of one constituent can be compensated by a decrease in volume of another and vice versa. [20] In the case of trauma the ICP can increase as an effect of rapid changes in volume due to edema or bleeding. A quick rise in ICP is a medical emergency as it can cause brain tissue to herniate with compression of the brain stem as a result. The threshold used for pathological ICP in children is based on research in adults and is set at 20 mmHg. [2]

Cerebral perfusion pressure (CPP)
CPP is the driving force behind perfusion of the brain, and is defined as

$$CPP = MAP - ICP$$

where MAP is the mean arterial pressure. The sTBI protocol focuses on maintaining the CPP above the age appropriate value as insufficient perfusion causes ischemia. [2] The thresholds used on the Sophia PICU are shown in table 1. There is also evidence that a high CPP causes unfavorable outcome, as increased blood flow can lead to additional cerebral edema. [21, 22]

Table 1 Age appropriate CPP used in current clinical practice

Age	*CPP*
0 – 1 month	40 mmHg
Through 6 months	45 mmHg
Through 4 years	50 mmHg
Through 10 years	55 mmHg
10 years and older	60 mmHg

Pressure regulation index (PRx)
In a physiological state cerebral blood vessels ensure stable blood flow amongst a range of arterial blood pressures through vasoconstriction and vasodilatation (see figure 1). This process is called autoregulation and contributes to maintaining a nearly constant volume and therefore constant pressure in the skull. [2] If the arterial blood pressure is outside of the range where cerebral blood vessels are reactive to changing

pressures, cerebral blood flow is entirely dependent on the blood pressure. Autoregulation can become impaired after sTBI. [2] In 1997 PRx was introduced as a way to quantify autoregulation. PRx is calculated by determining the Pearson correlation between 5 minute windows of ICP and MAP. When autoregulation is intact, the PRx is either zero or negative. In theory when autoregulation is impaired, there is a positive correlation between ICP and MAP, and PRx is a positive number. [23]

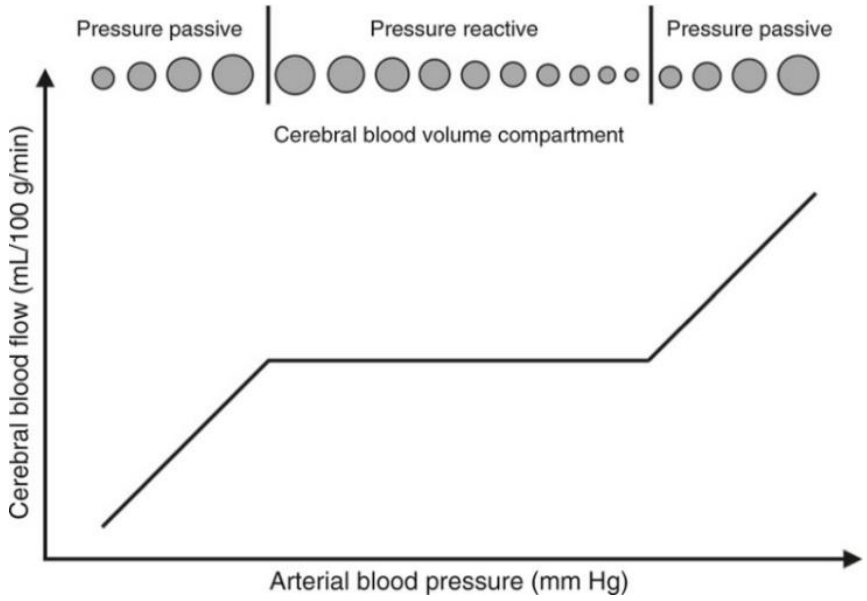

Figure 1 Cerebral autoregulation: There is a range of arterial blood pressures amongst which cerebral vessels can ensure a constant blood flow through vasodilatation of vasoconstriction. This range is the horizontal part of the curve. At both extremes of this curve cerebral blood flow is dependent on blood pressure, which can lead to inadequate blood flow. The grey circles above the curve represent the changing diameter of the cerebral blood vessels. Figure adapted from Rhee et al. (2018) [24]

CPPopt

In 2002 CPP was plotted against PRx by Steiner et al. [25] They described a U-shaped curve like the example in figure 2. Given that, theoretically, the lowest possible PRx is the most desirable, the personalized optimal CPP can be determined by finding the lowest point in this curve. [16, 25] Since this proposition researchers have been developing a CPPopt algorithm, which can be used clinically to determine personalized CPPopt target values. [16, 17, 19]

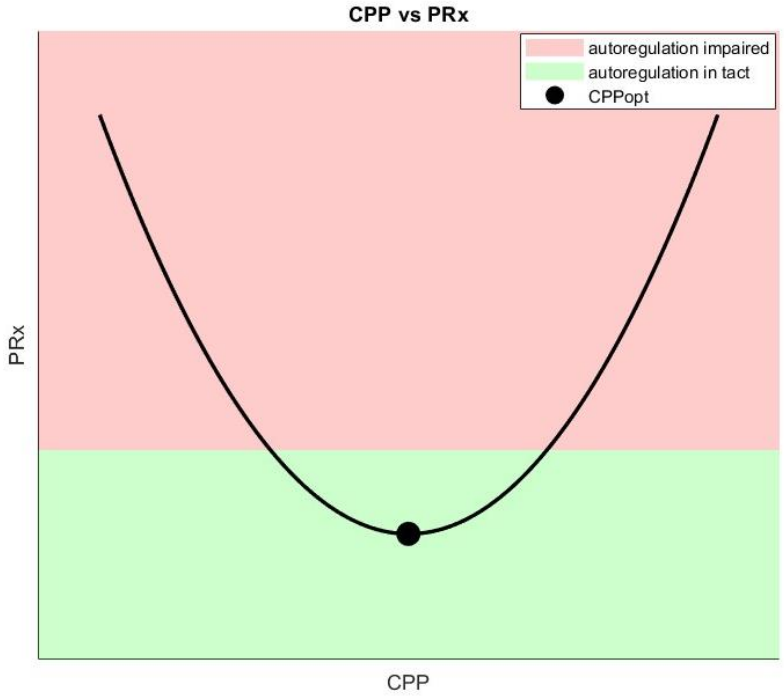

Figure 2 The relationship between CPP and PRx: Increased PRx values, in the red shaded are of the curve, represent impaired autoregulation. In the green shaded are of the curve autoregulation is intact. The vertex, or lowest point, of the curve is the optimal CPP.

Methods

Patient population

Retrospective data analysis was conducted in patients with sTBI admitted to the PICU for intracranial pressure monitoring from January 2016 until September 2023. Patients admitted to the PICU of the Erasmus MC Sophia Children's Hospital range in age from 0 to 18 years. All patients with at least 3 hours of continuous ICP and MAP data, as well as outcome data 1 year post-injury were eligible for inclusion in data analysis. There were no exclusion criteria.

Data collection

ICP was measured using an intraparenchymal probe (Codman Microsensor® ICP Transducer, Integra, Princeton, US; Pressio® Catheter, Sophysa, Orsay, France; Camino® Catheter, Nautus Medical Inc., Middleton, US). Arterial blood pressure was measured through an arterial line (Becton and Dickinson, Franklin Lakes, US). The Dräger monitor (Dräger, Lübeck, Germany) generates the MAP from the arterial blood pressure and sends the monitoring data to a secure Erasmus MC server. Patient characteristics such as age, gender and trauma mechanism were retrieved from the electronic health record (HiX, Chipsoft, Amsterdam, the Netherlands).

Patients receive follow up care at a specialized outpatient clinic which also provides the opportunity to collect long term outcome data. Outcome was determined 1 year after the injury and was classified using the Pediatric Cerebral Performance Category (PCPC). [26] An elaboration on the PCPC score is given in appendix A. All patients were assigned a PCPC score by the same clinical expert. For the primary analysis outcome was dichotomized as favorable (PCPC 1-2) or unfavorable (PCPC 3-6). Secondary analyses were done for mortality and outcome in survivors (good outcome PCPC 1-2 vs. poor outcome PCPC 3-5).

Data analysis

The code used for data pre-processing was written by preceding researchers. Artefacts are automatically removed after which the data is averaged over 10-second intervals to mitigate high frequency noise from respiration and pulse rate. Artefacts are defined as sudden increases or decreases (± 25 % for MAP and ± 10 mmHg for ICP) and values outside the pathophysiological range (30 mmHg - 160 mmHg for MAP and 0.01 mmHg – 60 mmHg for ICP). Artefacts are replaced by the mean of the surrounding 100 samples. If the artefacts included the surrounding 100 samples, the artefact is replaced by the values measured before the onset of the artefact. The raw data has a sampling frequency of 1 Hz and the cleaned and filtered data has a sampling frequency of 0.1 Hz.

PRx was generated by determining the Pearson correlation between ICP and MAP using a moving window of 300 seconds as described by Czosnyka et al. [23] As the objective was to compare the results in the Erasmus MC Sophia PICU cohort to the literature PRx metrics were chosen based on the literature. Mean PRx, median PRx and percentage of time that PRx was increased were determined for each patient. Both mean and median PRx are used in previous studies. [3-5, 7, 14] Multiple thresholds were used to define increased PRx to evaluate which threshold has the strongest association with outcome in the Erasmus MC Sophia PICU cohort. The thresholds 0, 0.2, 0.25 and 0.3 were chosen based on the results of recent PRx research in a large pediatric cohort. [14]

A CPPopt algorithm was written which determines the optimal CPP every minute. The optimal CPP was defined as the CPP value where the lowest PRx is expected. The algorithm was written based on descriptions in the literature and developed in close collaboration with clinicians. [15-17, 27] In previous adult and pediatric studies the difference between measured CPP and CPPopt (ΔCPP) is calculated to analyze the relationship with outcome. [4, 15-19, 27-29] However, as the width of the CPP range in which autoregulation is intact is different in every patient, ΔCPP was not deemed a desirable metric to compare patients. Therefore, an optimal CPP range was calculated for each patient. The optimal range is determined every minute and is defined as the CPP values where the optimal PRx values are expected based on the patient's individual CPP-PRx curve (see figure 3). The percentage of time that CPP is within the optimal range was calculated per monitoring day. This was done for days 1-4 as the median monitoring time in the Sophia PICU is 5 days. [30] Because the algorithm needs at least 8 hours of monitoring data there is a delay and day 4 of CPPopt monitoring can actually be day 5 of the hospitalization.

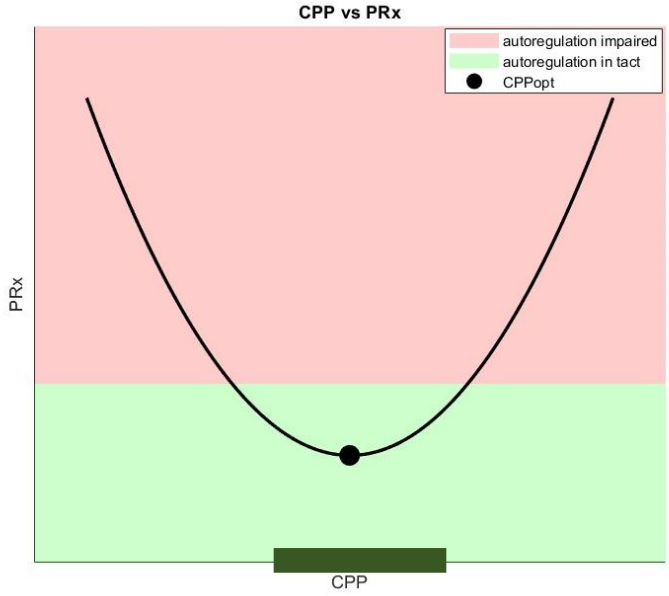

Figure 3 CPPopt and CPP range: The black dot in the vertex of the curve is the single value which is the optimal CPP. The green bar on the CPP-axis represent the optimal CPP range.

Statistical analysis

Data analysis and subsequent statistical analysis were performed using Matlab 2021b (Mathworks, Natick, US). Descriptive statistics were reported as count (percentage) and mean. Statistical significance was set at a two-sided p value of less than 0.05. Histograms were made to inspect the distribution of the data. Scatter plots were made to inspect the relationship between PRx parameters and outcome. Univariable logistic regression was performed to evaluate the relationship between PRx and outcome. For accurate interpretation of the odds ratio's mean and median PRx were multiplied by 10. In doing so, this the odds ratio reflect the change in odds as PRx transitions from 0 to 0.1 instead of 0 to 1.This was also done in previous research. [4, 14] As the percentage of time that CPP is within the optimal range was calculated per day it is a multi-level parameter. Therefore, to analyze the relationship with outcome an univariable mixed-effects model was used.

Results

Between January 2016 and September 2023, 67 children were admitted to the PICU with sTBI. Of these patients 50 were eligible for inclusion (figure 4). Patient characteristics are shown in table 2.

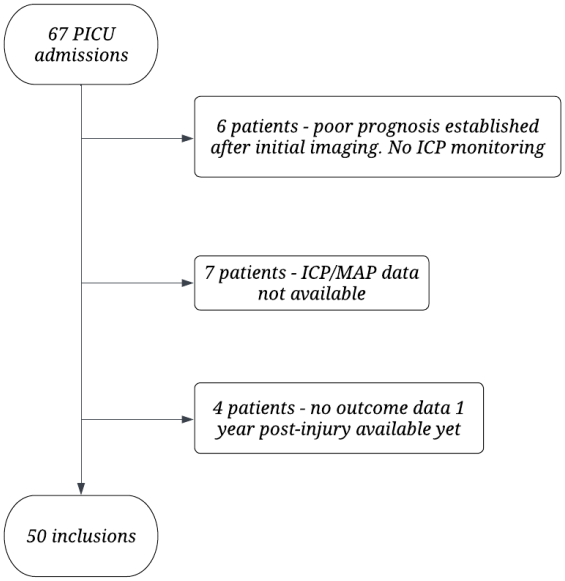

Figure 4 Flowchart of patient inclusion

Table 2 Patient characteristics. Note that patients with PCPC scores 1 and 2 are survivors with good outcome, patients with PCPC scores 3-5 are survivors with poor outcome and patients with PCPC score 6 are non-survivors.

	Favorable outcome	**Unfavorable outcome**	
	Survivors with a good outcome	*Survivors with a poor outcome*	*Non-Survivors*
N Patients **Patient characteristics**	31	10	9
Mean age	10.17	9.60	11.42
Female	35.48%	50%	44.44%
Trauma mechanism			
Bicycle rider	35.48 %	30 %	33.33 %
Fall	16.13 %	30 %	22.22 %
Car passenger	9.68 %	20 %	11.11 %
Pedestrian	29.03 %	10 %	11.11 %
Other	9.68 %	10 %	22.22 %

Pressure reactivity index

PRx was retrospectively generated for all included patients. The average percentage of time per day that PRx could not be generated was 3.65% (53 minutes) and was mainly caused by either missing ICP or MAP values. Examples of the PRx waveform for individual patients can be found in appendix B. Figures 5-7 show the mean PRx, median PRx and percentage of time that PRx is greater than 0.3 for all patients with each dot representing a patient and the color representing the outcome. The figures for percentage of time that PRx is increased using different thresholds can be found in appendix C.

Univariable logistic regression analysis was performed to analyze the relationship between PRx and outcome (tables 3-5). Increased mean and median PRx are significant predictors of both unfavorable outcome and mortality with odds ratios of respectively 1.54 (95% CI 1.14 – 2.08) and 1.44 (95% CI 1.22 – 1.85) for unfavorable outcome and 2.49 (95% CI 1.39 – 4.45) and 2.35 (95% CI 1.35 – 4.06) for mortality. The percentage of time that PRx is increased is also a significant predictor of outcome. The PRx threshold 0.3 has the strongest association with unfavorable outcome. The PRx thresholds 0.2, 0.25 and 0.3 have identical odds ratios of 1.06 when predicting for mortality. None of the PRx metrics researched are significantly associated with outcome in survivors. Histograms of the metrics used in the logistic regression analysis can be found in appendix D.

In figure 5 it is visible that all but one patient with a mean PRx greater than 0.3 have an unfavorable outcome. It is worth noting that this outlier with a high mean and median PRx, but a surprisingly favorable outcome had a complicated disease course for which a second ICP monitoring period was necessary. Only the first ICP monitoring period was included for this research. In figure 6 it is noticeable that all patients with a mean or median PRx less than 0.2 survive.

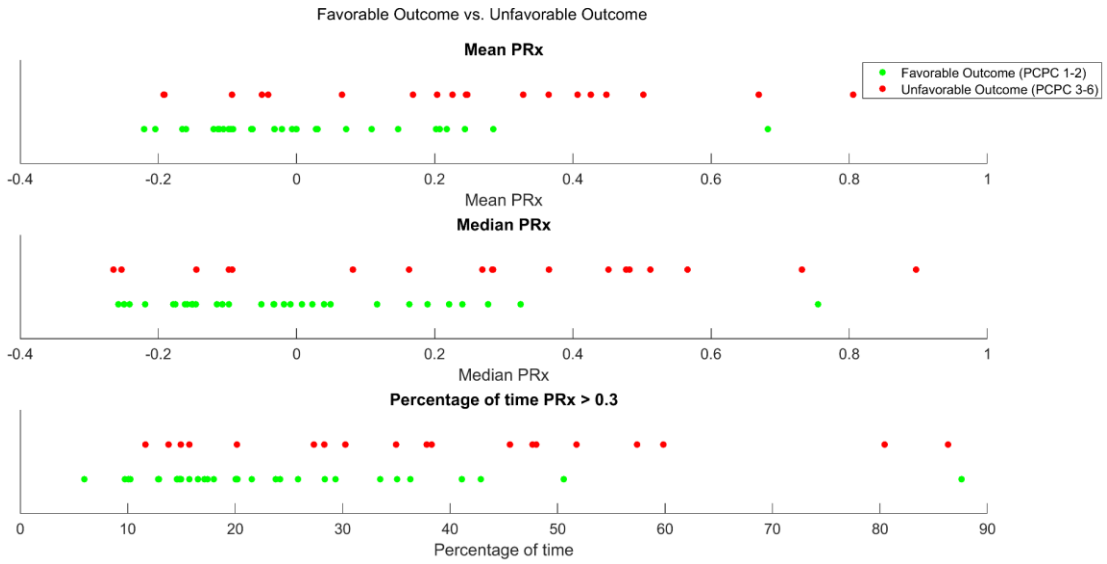

Figure 5 The mean PRx, median PRx and percentage time that PRx is greater than 0.3 for each patient. Green dots represent patients with a favorable outcome, red dots represent patients with an unfavorable outcome. PCPC = Pediatric Cerebral Performance Category

Table 3 Logistic regression analysis for different PRx metrics as predictors and dichotomized outcome as response (favorable outcome vs. unfavorable outcome)

	OR	*95% CI*	*p-value*
Mean PRx	1.54	1.14 – 2.08	< 0.01
Median PRx	1.44	1.22 – 1.85	< 0.01
% time PRx > 0.3	1.05	1.01 – 1.09	0.014
% time PRx > 0.25	1.04	1.01 – 1.08	0.016
% time PRx > 0.2	1.04	1.01 – 1.08	0.019
% time PRx > 0	1.03	1.00 – 1.06	0.074

OR = odd's ratio, 95% CI = 95% confidence interval

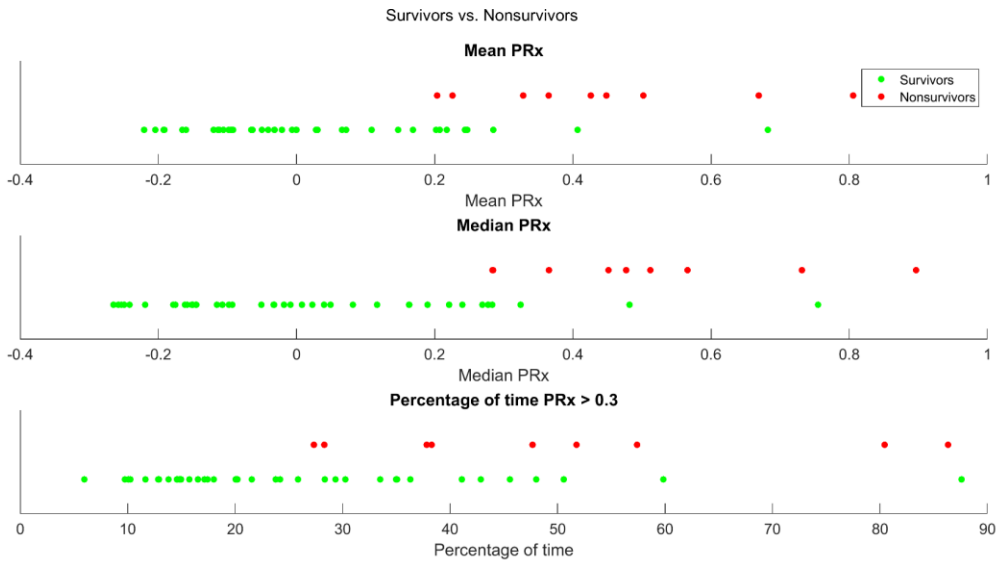

Figure 6 The mean PRx, median PRx and percentage of time that PRx is greater than 0.3 for each patient. Green dots represent patients who survived, red dots represent patients who did not survive.

Table 4 Logistic regression analysis for different PRx metrics as predictors and mortality as response

	OR	*95% CI*	*p-value*
Mean PRx	2.49	1.39 – 4.45	< 0.01
Median PRx	2.35	1.36 – 4.06	< 0.01
% time PRx > 0.3	1.06	1.02 – 1.11	< 0.01
% time PRx > 0.25	1.06	1.02 – 1.11	< 0.01
% time PRx > 0.2	1.06	1.02 – 1.10	< 0.01
% time PRx > 0	1.05	1.00 – 1.09	0.03

OR = odd's ratio, 95% CI = 95% confidence interval

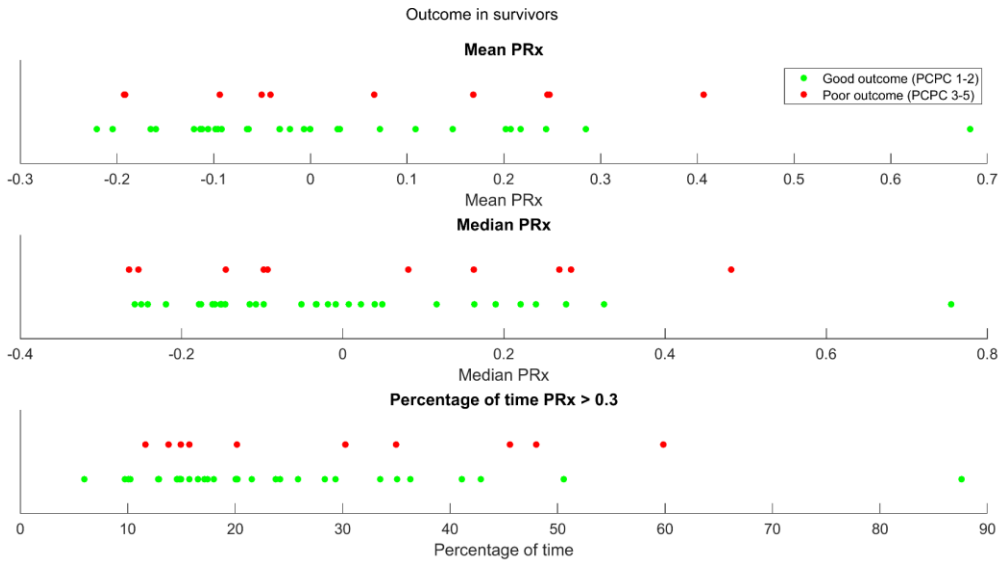

Figure 7 The mean PRx, median PRx and percentage of time that PRx is greater than 0.3 for each patient. Green dots represent survivors with a good outcome, red dots represent survivors with a poor outcome. PCPC = Pediatric Cerebral Performance Category

Table 5 Logistic regression analysis for different PRx metrics as predictors and outcome in survivors as response

	OR	*95% CI*	*p-value*
Mean PRx	1.12	0.78 – 1.62	0.54
Median PRx	1.10	0.80 – 1.50	0.56
% time PRx > 0.3	1.02	0.98 – 1.06	0.36
% time PRx > 0.25	1.02	0.98 – 1.07	0.38
% time PRx > 0.2	1.02	0.98 – 1.06	0.39
% time PRx > 0	1.01	0.97 – 1.05	0.55

CPPopt

The resulting CPPopt algorithm generates a CPP target every minute using the following steps

1. Mean CPP is calculated using a 5 minute window, resulting in a parameter containing one average CPP value per minute. This parameter is used for further calculations.
2. Mean PRx is calculated using a 1 minute window, resulting in a parameter containing one average PRx value per minute. This parameter is used for further calculations.
3. CPP and PRx data of the previous hour is extracted.
4. CPP bins with a binwidth of 5 mmHg are made. For each CPP data point the corresponding PRx value is collected after which the mean and standard deviation of PRx can be determined for every CPP bin.
5. An error bar chart is plotted of the mean and standard deviation of PRx for each CPP bin. A second order polynomial curve is fitted over the CPP bins that contain at least 1% of the data. The lowest point of this curve is the CPPopt. See figure 8 for an illustration of this step.
6. Steps 3-6 are repeated for different time windows: 2 hours, 4 hours, 6 hours, 8 hours.
7. The result of each time window is evaluated. If autoregulation is not intact (PRx > = 0.2) the CPPopt value is rejected and replaced by NaN.
8. The weighted average of the results is used to determine the CPPopt. In this approach, the CPP with the lowest PRx (and thus the best autoregulation) weighs heavier compared to the results of the other time windows. To achieve this, first, the average of all results is determined ($CPP_{\text{average of all results}}$). Then, the weighted average is calculated by determining the average between the $CPP_{\text{average of all results}}$ and the $CPP_{\text{with the lowest PRx}}$. An illustration of the trend of the resulting CPPopt is given in figure 9.

In the development of this algorithm deviations from the descriptions in the literature were made. Donnelly et al. used 36 time windows to determine CPPopt every minute (from 2 hours to 8 hours in 10 minute increments), which uses significant computational power resulting in a long run time of the code. [31] As this is considered undesirable for real time bedside use, larger increments inspired by Depreitere et al. were used (1 hour, 2 hours, 4 hours, 6 hours and 8 hours). [17] This did not have a large effect on the resulting CPPopt trend, as can be seen in appendix E. While Depreitere et al. also included 12 hour and 24 hour windows, these were not used, as data from 12 or 24 hours ago were deemed not representative of the current clinical condition given the dynamic nature of the disease. In the algorithm described by Beqiri et al. more recent time windows had a stronger weight in step 8.[27] This was not applied, because if cerebral autoregulation becomes impaired, it is undesirable that these windows have a stronger weight in determining the CPPopt. In the algorithm described in the literature a CPPopt chosen from a flat curve (PRx variation less than 0.2) was rejected. [27] This condition was not adopted because, as a result, curves in which a patient has a stable low PRx amongst all CPP values (indicating intact autoregulation) would be rejected. If there is little PRx variation in the curve because autoregulation is impaired amongst all CPP values, this curve is already rejected in step 7 of the algorithm. The PRx cutoff of 0.2 used in step 7 of the CPPopt algorithm was chosen based on the prominent cut off in figure 5 where it stands out that all patients with a mean PRx lower than 0.2 survive the hospitalization. In adults studies, a PRx cutoff is also used, with one study using a range from -0.3 to 0.6 and another using a threshold of 0.3. [27, 31]

To evaluate the relationship between a personalized CPP target and outcome an optimal CPP range was determined every minute using the following steps:

1. The error bar chart of the 8-hour time window is used.

2. An optimal PRx range is generated: the lowest mean PRx is the lower limit, the upper limit is the lower limit + 0.2. If this calculation results in a range with increased PRx values (PRx > 0.25) calculations are discarded and no range can be determined.
3. The measured CPP is considered in range if it belongs to a CPP bin in which the mean PRx is between the lower limit and upper limit of the optimal PRx range. If no range could be determined the measured CPP is automatically out of range.

For the calculation of the CPP range a threshold of 0.25 was used to define increased PRx. This differs from the threshold of 0.2 used in the determination of the single value CPPopt, because using 0.2 would mean that a range can only be determined when the lowest PRx is negative. Figure 10 visualizes the determination of the CPP range.

CPPopt was retrospectively generated for 49 patients (n=49/50, 98%). One patient was excluded because their autoregulation was completely impaired. Consequently, the algorithm could not determine a single CPPopt value and returned an empty array as a result. The algorithm is unable to generate a result 100% of the time as at least 8 hours of data and intact cerebral autoregulation are necessary to determine a CPPopt. The algorithm produced a result 62.37% of the time in patients with an unfavorable outcome and 89.78% of the time in patients with a favorable outcome. In non-survivors the algorithm produced a result 35.96% of the time, while in survivors a result was produced 88.26% of the time.

The average percentage of time that CPP was within the optimal range was calculated per day for each patient. Average values of each outcome group were calculated (figures 11-13). A mixed model analysis was performed to evaluate the relationship between the percentage of time that PRx is within the optimal range and outcome (table 6). A decreased percentage of time that CPP is within the optimal range is significantly associated with for both unfavorable outcome (OR 0.97; 95% CI 0.95 – 1.00) and mortality (OR 0.96; 95% CI 0.93 – 0.99). The percentage of time that CPP is within the optimal range decreases between day 1 and 2 in patients with an unfavorable outcome, while it increases in patients with a favorable outcome (figure 12). In non-survivors the percentage of time that CPP is within the optimal range decreases over the course of the hospitalization, while it increases for survivors (figure 13). The percentage of time that CPP is within the optimal range is not a significantly associated with outcome in survivors.

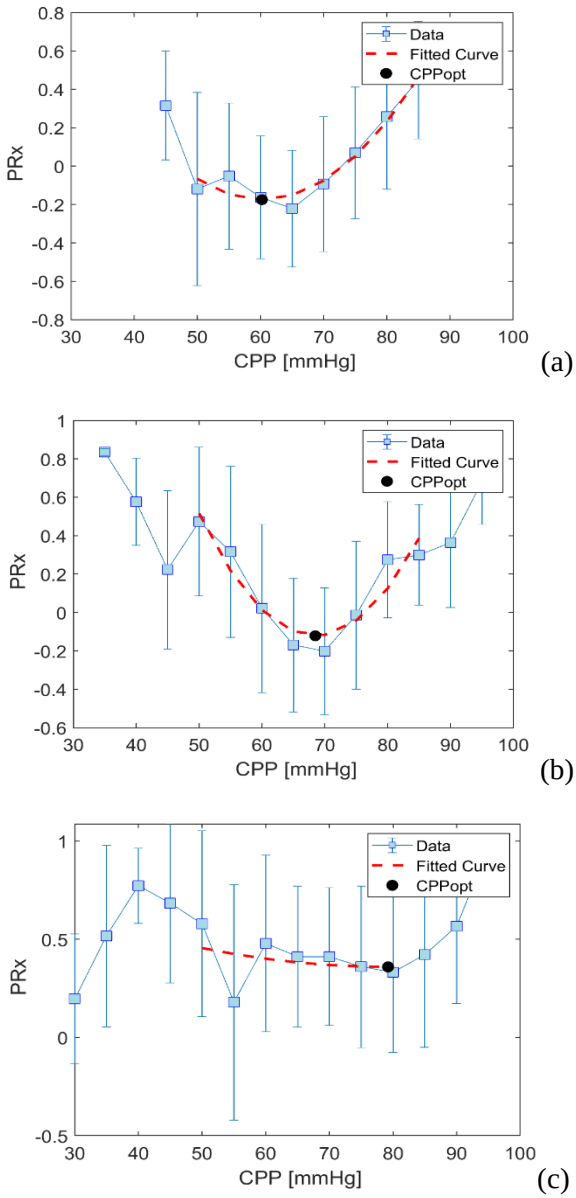

Figure 8 The CPP – PRx curve fitting step of the CPPopt algorithm: Note that for the illustrative purposes of this figure the data of the entire monitoring period of three different patients is used. The three patients have similar ages and were all treated with a CPP target of 60 mmHg. The fitted curve does not cover all data bins as the curve is only fitted over bins containing more than 1% of the data. (a) data from a survivor with a good outcome (b) data from a survivor with a poor outcome (c) data from a non-survivor, the resulting CPPopt of this curve would be rejected as the corresponding PRx is greater than 0.2

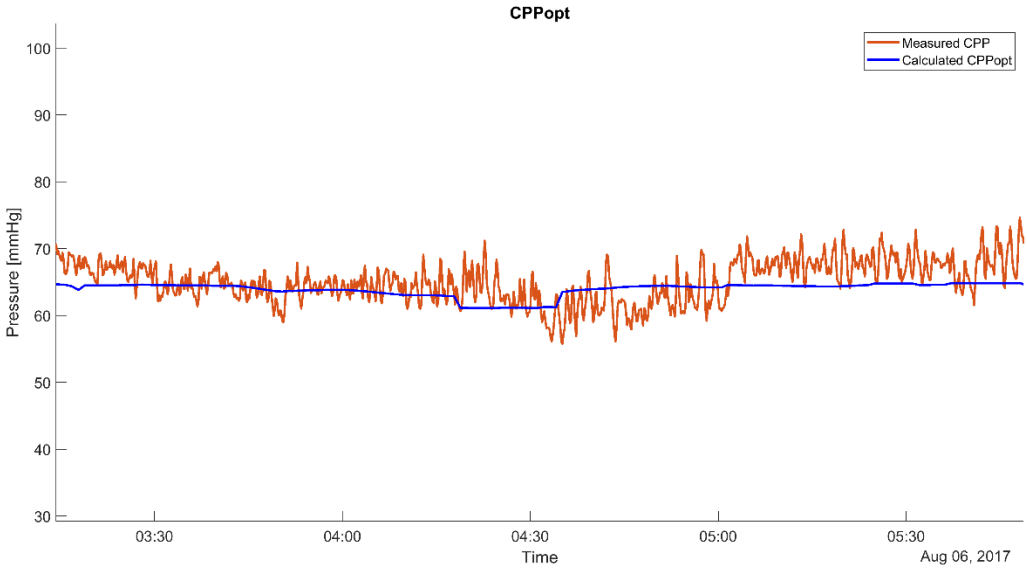

Figure 9 CPPopt trend. An example of the CPPopt trend (blue line) plotted against the measured CPP

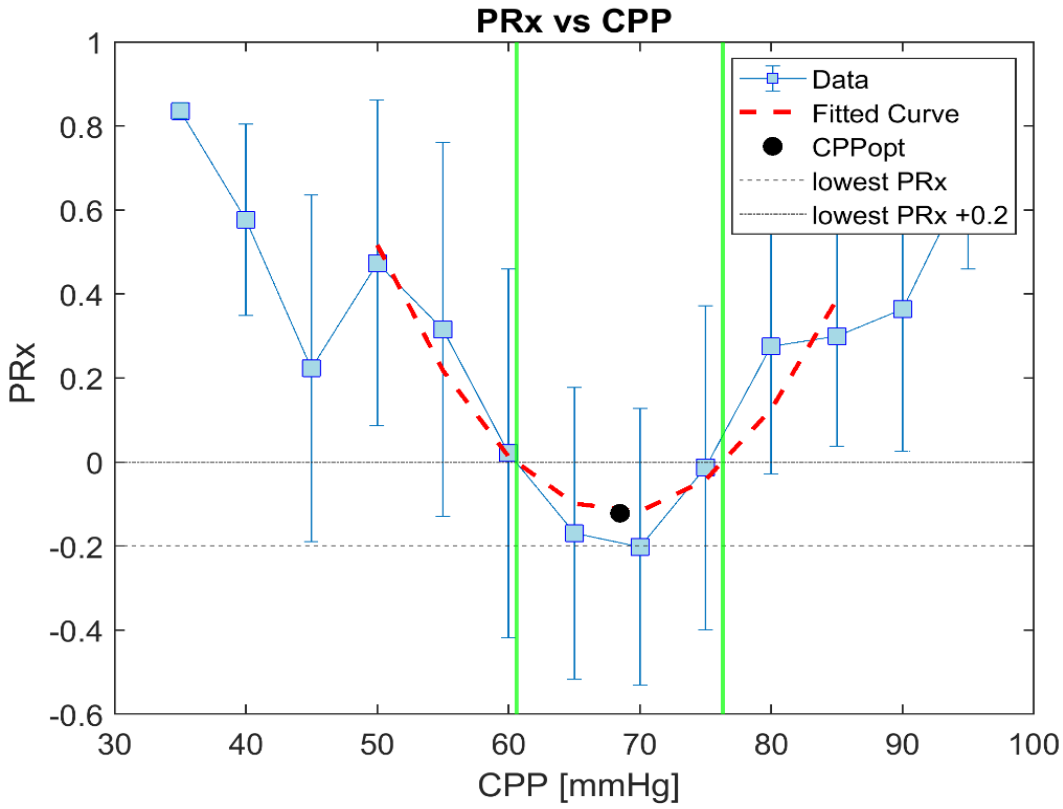

Figure 10 Determination of the optimal CPP range. First, the PRx limits of the range are determined; the lowest mean PRx is the lower limit, 0.2 is added to the lower limit to find the upper limit. The optimal CPP range (between the green vertical lines) consists of CPP values belonging to a CPP bin of which the mean PRx is within the visualized PRx range. For the illustrative purposes of this figure data of an entire hospitalization is used.

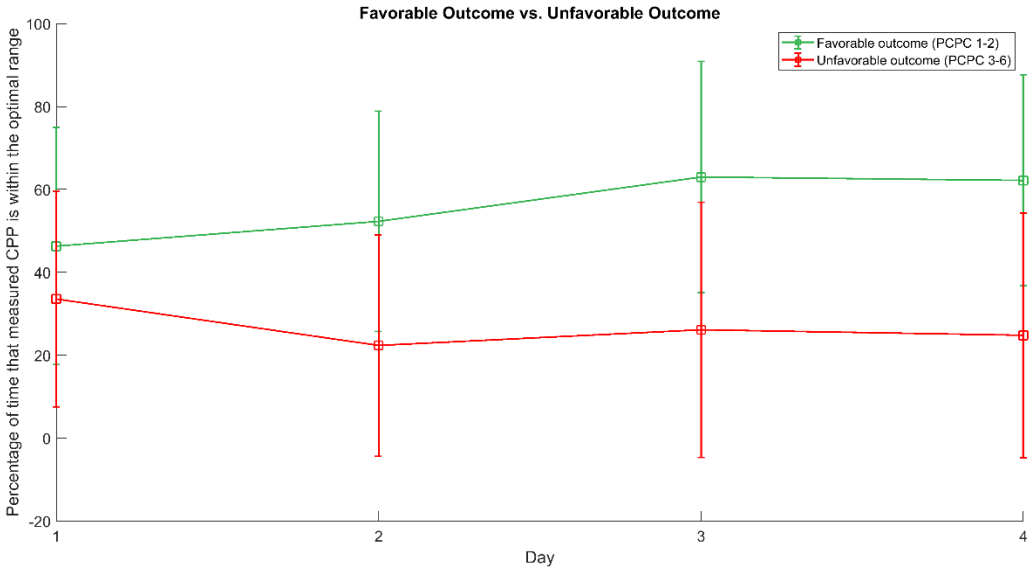

Figure 11 Percentage of time that CPP is within the optimal range. The average and standard deviation of the percentage of time that measured CPP is within the optimal range for days 1 through 4. The green line represents patients with a favorable outcome and the red line represents patients with an unfavorable outcome.

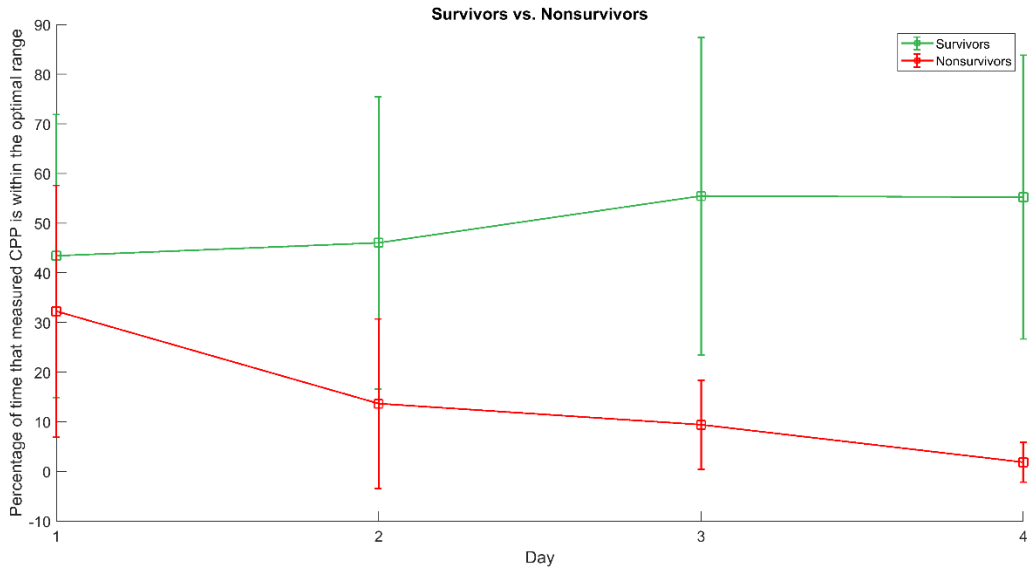

Figure 12 Percentage of time that CPP is within the optimal range. The average and standard deviation of the percentage of time that measured CPP is within the optimal range for days 1 through 4. The green line represents survivors and the red line represents non-survivors.

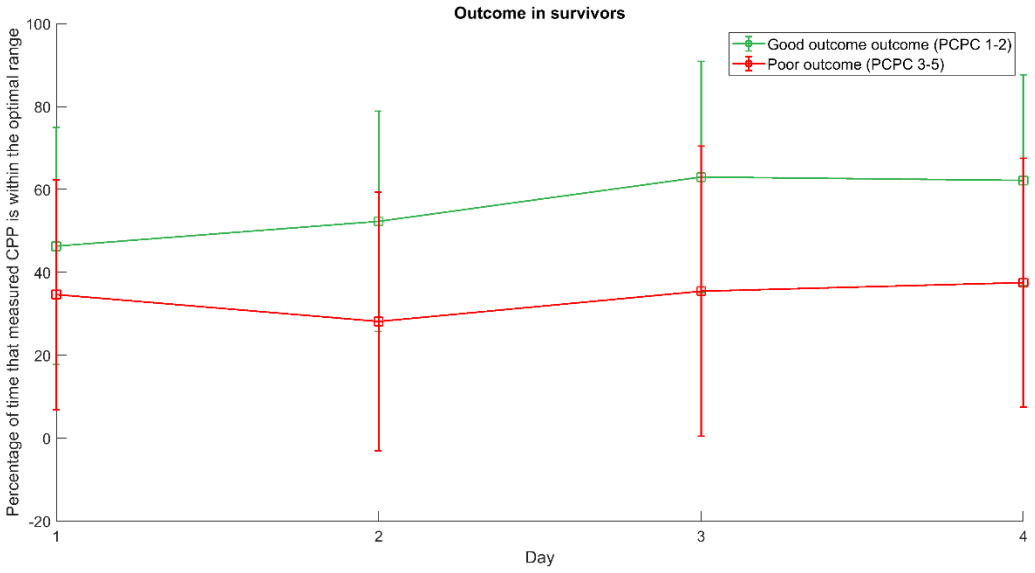

Figure 13 Percentage of time that CPP is within the optimal range. The average and standard deviation of the percentage of time that measured CPP is within the optimal range for days 1 through 4. The green line represents survivors with a good outcome and the red line represents survivors with a poor outcome.

Table 6 Results of the mixed model analysis with the percentage of time that CPP is within the optimal range as a predictor for outcome

	OR	*95% CI*	*p-value*
Favorable vs. unfavorable outcome	0.97	0.95 – 1.00	0.03
Mortality	0.96	0.93 – 0.99	0.02
Survivors with a good outcome vs. survivors with a poor outcome	0.98	0.95 – 1.01	0.25

OR = odd's ratio, 95% CI = 95% confidence interval

Discussion

This thesis studied cerebral autoregulation in children admitted to the PICU with sTBI, with the goal to gain insight in the pathophysiology of the disease and to explore the possibility of personalized dynamic CPP thresholds. The results of this study support the existing hypothesis that increased PRx as a measure of impaired cerebral autoregulation correlates with unfavorable outcome and mortality. The results in this cohort suggest that the association between PRx and unfavorable outcome is due to the association with mortality, as PRx is not significantly associated with outcome in survivors. This study further suggests that deviations from dynamic personalized CPP thresholds are associated with unfavorable outcome and mortality.

Pressure reactivity (PRx)

The association found between increased PRx and both unfavorable outcome and mortality is the same as in previous research. [3-7, 14] In both pediatric and adult research a PRx threshold of 0.25 is described to have the best discrimination for mortality.[8, 14] This is consistent with the results of the Sophia PICU cohort. Unfortunately, due to the small sample size, it was not possible to analyze the relationship between PRx and outcome adjusted for possible confounders. Although previous pediatric research has shown that the relationship between PRx and outcome is independent of age, post resuscitation Glasgow Coma Scale, median ICP and median CPP, we cannot confirm these results in this cohort. [14] It is reported in both adult and pediatric research that PRx is not related to the GCS on admission. [14, 16, 25] It is suggested that this could be because PRx is not influenced by the primary injury, but that it is a marker for secondary injury. [14] This hypothesis could explain why PRx is not associated to outcome in survivors in the Erasmus MC Sophia PICU cohort. In survivors secondary injury could be limited by the medical interventions, with the long term outcome being mainly dependent on the primary injury. An argument against this hypothesis that PRx is not related to GCS, because the GCS on admission is influenced by medical interventions in the pre-hospital setting. [25] In previous research the relationship between PRx and outcome in survivors is not studied.

During visual inspection of the PRx waveform it was noticed that PRx has a pulsating waveform in all patients. The almost 1 point increase in short time frames which is seen in the figures in appendix B was not expected. However, this is similar to exemplary figures in both adult and pediatric studies.[4, 25] There are multiple possible explanations for this. It may be possible that in the acute phase after a trauma no patient has perfect cerebral autoregulation. Alternatively, the correlation between ICP and MAP may show a similar waveform in healthy persons. It is also possible that noise from the respiratory and cardiovascular systems disturb the ICP signal. For future clinical use, it is valuable to know that the clinically relevant information seems to lie in the mean or median value.

CPPopt

The results of this research suggest that a decreased percentage of time that CPP is within the optimal range correlates with unfavorable outcome and mortality. Similarly to PRx, the percentage of time that CPP is within the optimal range is not a predictor of outcome in survivors. This is as expected given that the CPPopt range is based on PRx. These findings should be considered in light of the study's limited cohort size and the scarcity of similar research in the pediatric population. The development of the CPPopt algorithm was done in close collaboration with clinicians using data of the retrospective cohort to ensure clinical relevance. While there is careful consideration behind each adjustment made in the

development of the algorithm it is desirable that multiple iterations are tried to further optimize the algorithm.

The calculation of the CPP range is a first exploration for the analysis of the relationship with outcome. There is no similar research on determining a CPP range based on PRx values. There has been research in both adults and children on determining the CPP belonging to the lower limit of autoregulation (the lowest CPP in which PRx is lower than a set threshold). [6, 31, 32] While the CPP range used is this research is also based on PRx values, instead of a single threshold an dynamic range is used based on the lowest PRx for the individual patient. In this calculation additional iterations are needed as well to optimize the parameter, especially due to the clinical relevance of knowing the margin around the calculated CPPopt. CPPopt is challenging to compare with the current clinical practice of an age appropriate CPP as it is a dynamic target. Determining the percentage of time that CPPopt is lower than the age appropriate CPP or the percentage of time that the age appropriate CPP is not within the optimal personal range could be methods for comparison in future research.

In addition to the resulting CPPopt there is more clinically relevant information that can be extracted from the CPPopt algorithm. There are notable differences between the different CPP-PRx curves shown in figure 8. Comparing figures 8a and 8b it is noticeable that the first curve is less steep as there is a broad range of CPP values where PRx is negative. This illustrates that ΔCPP is not a suitable parameter to compare patients. With a ΔCPP of, for example 10 mmHg, some patients will stave have intact cerebral autoregulation based on the slope of the CPP-PRx curve, while in other patients this change can mean autoregulation becomes impaired. In figure 8c, the flat curve with increased PRx values for each CPP bin illustrates a complete impairment of cerebral autoregulation. This visualization may be helpful in clinical practice. Additionally, it may be insightful to compare the curve from the same patient over different time periods to visualize the disease course.

In the cohort of patients with unfavorable outcomes, it occurred more frequently that the algorithm is unable to generate a CPPopt. Although this difference was not statistically evaluated, it aligns with clinical expectations. It also supports the hypothesis that impaired autoregulation correlates with unfavorable outcomes as the algorithm does not yield results when the PRx expected with the calculated CPPopt is 0.2 or greater. This suggests that the absence of a CPPopt value could serve as a potential prognostic marker in future clinical applications. More importantly, this underscores that the CPPopt algorithm does not replace clinical decision making by the medical team as the algorithm cannot produce a result 100% of the time.

Strengths and limitations

The Erasmus MC Sophia cohort is unique as both continuous monitoring data and long term outcome data is available. The availability of high quality outcome data 1 year after the injury sets this research apart from other studies where outcome is mostly determined at 6 months post injury. It is described in previous research and also observed in the Sophia cohort that recovery after sTBI takes more than 6 months. [33] The development of a local CPPopt algorithm has the advantages that there is full insight in the calculations and future adjustments are easy to facilitate.

The main limitation in this study is the small sample size of the cohort. In addition, sTBI is a heterogeneous disease in which trauma mechanism, additional injuries and complications vary. Due to the small sample size of the cohort, subgroup analysis and adjustment for confounders was not possible. An inherent limitation of retrospective research is the potential confounding bias. In all patients, medical interventions that influence ICP and CPP such as mechanical ventilation, inotropic medication, deep

sedation and the administration of hypertonic saline and in some cases surgical intervention were performed.

Clinical recommendation and future research

The clinical relevance of both PRx and CPPopt are closely linked to the need of additional research. Prospective research in a large cohort of children is necessary to gain high level evidence to support autoregulation monitoring and the use of personalized thresholds. Due to small patient volumes in individual centers like the Erasmus MC Sophia PICU, multicenter research is the only way to comprehensively research cerebral autoregulation in children. A prospective multicenter observational study is currently being conducted in the United Kingdom to study the relationship between PRx, CPPopt and outcome in children. [34] In adults, cerebral autoregulation research is more advanced with studies demonstrating that CPPopt targeted therapy is safe and associated with better outcome. [35, 36] Determining when to implement cerebral autoregulation monitoring in clinical practice is complex as on one hand high level evidence is desirable, but on the other hand it will most likely take years for trials with a large pediatric cohort to be completed. Hereby, it is important to realize that in the current pediatric sTBI guidelines there is no recommendation with level I evidence. Taking this all into consideration, the recommendation is to continue with the development of the local sTBI dashboard and especially focus on the technical steps needed to enable PRx and CPPopt use in real-time while awaiting the results of the large studies currently being conducted.

Development of an sTBI dashboard

From a technical standpoint, the code necessary to pre-process neuromonitoring data, create figures and generate PRx and CPPopt is fully automated. To be able to use the code in clinical practice the main adjustment necessary is the continuous loading of new data. This requires changes in the code, but also a new data pipeline in which data is transferred from the monitor to the software used for the dashboard in real time. Depending on the software used to create the dashboard it might be necessary to translate the code from Matlab to another programming language. While a preliminary design of the dashboard has been made in preceding research the end-users have to be consulted to co-create a final design.

If a dashboard becomes available at the bedside it is important to consider adding safety thresholds to the CPPopt algorithm so that CPP values that the medical team deems unsafe are not presented on the dashboard. The age based CPP values from the current protocol could be used as a lower limit for example. However, if the algorithm suggests a CPPopt lower than the age based target and this requires less medical intervention it may also lower the risk of iatrogenic injury. Because such considerations should be made clinically no limits were integrated in the current algorithm. Additionally, it is expected that the algorithm will be used in a research setting first and will not be available directly at the bedside.

Pathophysiology of pediatric sTBI

Cerebral autoregulation is just one of the puzzle pieces to deepen the understanding of sTBI. To further unravel pediatric sTBI, other promising advanced neuromonitoring parameters such as cumulative ICP, intracranial compliance, compensatory reserve weighted ICP and parameters in conjunction have to be studied.

Cerebral autoregulation

Cerebral autoregulation is a promising research topic beyond sTBI. Especially as it can also be monitored non-invasively. A recent publication used diffuse correlation spectroscopy to measure cerebral

autoregulation and demonstrated that impaired autoregulation is associated with higher radiographic neurologic injury in children on extracorporeal membrane oxygenation (ECMO). [37] Joram et al. used near-infrared spectroscopy (NIRS) to study cerebral autoregulation in children on ECMO and similarly found that impaired autoregulation is associated with neurological complications. They also demonstrated that it is feasible to determine personalized MAP targets (MAPopt) based on autoregulation. [38] Calculating MAPopt using autoregulation indexes determined through the NIRS signal has also been studied in children after cardiac arrest.[39] Furthermore, cerebral autoregulation has been studied in preterm neonates and neonates with hypoxic-ischemic encephalopathy, intraventricular hemorrhage and during surgery for congenital heart disease. [24, 40]

Conclusion

Impaired autoregulation indicated by an increased PRx is associated with unfavorable outcome and mortality in children with sTBI from the Erasmus MC Sophia PICU cohort. In an initial exploratory analysis of CPPopt in our cohort a decreased percentage of time that CPP is within the optimal range is associated with unfavorable outcome and mortality. Both PRx and the percentage of the time that CPP is within the optimal range are not associated with outcome in survivors. These results call for prospective research to evaluate if outcome can be improved by implementing autoregulation guided therapy.

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Appendix A – Pediatric Cerebral Performance Category

The Pediatric Cerebral Performance Category (PCPC) is a score which can be used to categorize children based on level of morbidity. A child functioning at an age appropriate level is scored PCPC 1. Each step represents increasing morbidity and the highest score, PCPC 6, represents death. [26]

Table 1. Pediatric Cerebral Performance Category scale

Score	Category	Description
1	Normal	Normal; at age-appropriate level; school-age child attending regular school classroom
2	Mild disability	Conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom, but grade perhaps not appropriate for age; possibility of mild neurologic deficit
3	Moderate disability	Conscious; sufficient cerebral function for age-appropriate independent activities of daily life; school-age child attending special education classroom and/or learning deficit present
4	Severe disability	Conscious; dependent on others for daily support because of impaired brain function
5	Coma or vegetative state	Any degree of coma without the presence of all brain death criteria; unaware, even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles
6	Brain death	Apnea, areflexia, and/or electroencephalographic silence

Table adapted from Fiser et al. (2000) [26]

Appendix B – PRx waveform

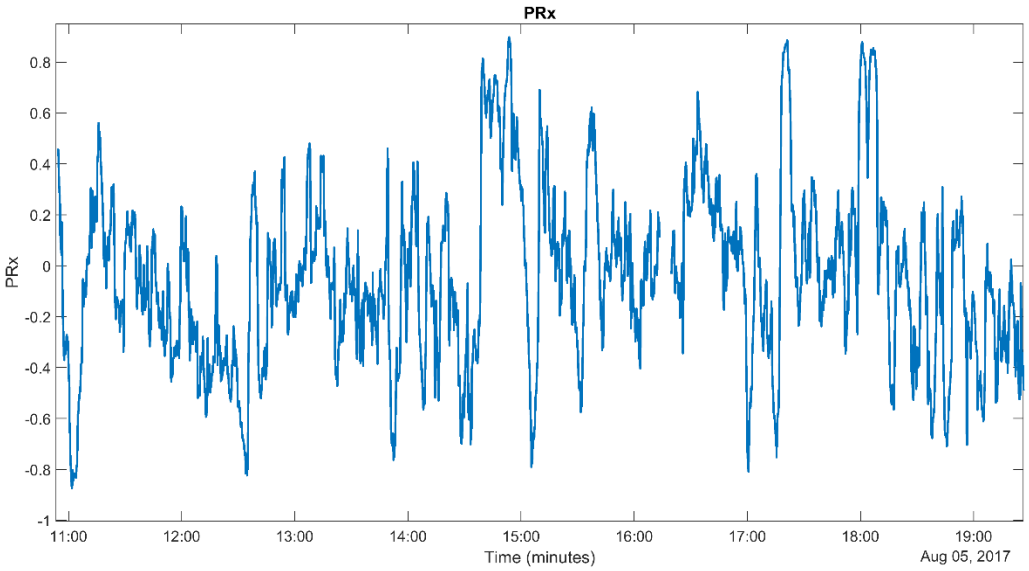

Figure 1a. Pressure reactivity index (PRx) waveform
The PRX waveform from a patient with a favorable outcome

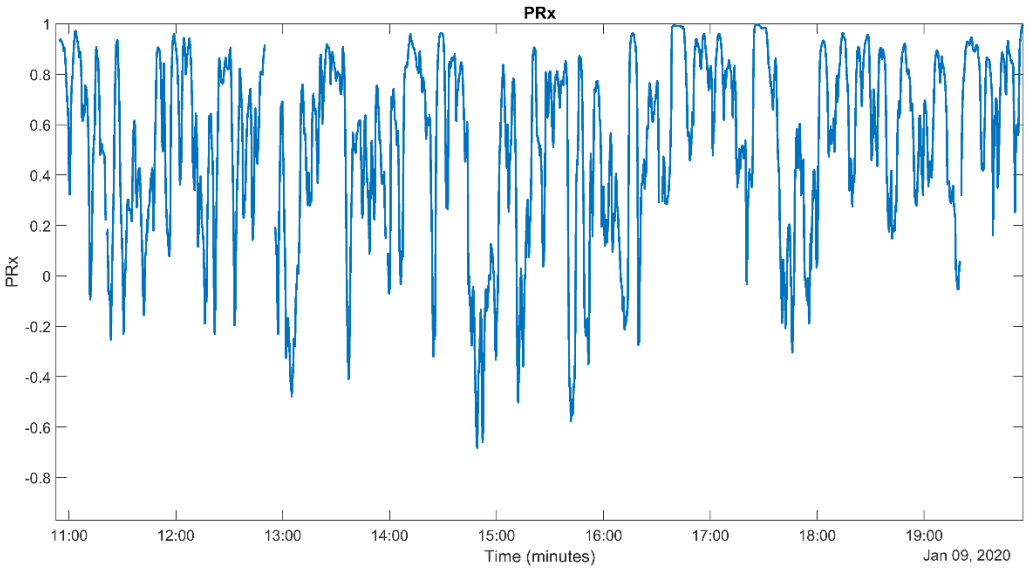

Figure 1b. Pressure reactivity index (PRx) waveform
The PRx waveform from a patient with an unfavorable outcome

Appendix C – PRx thresholds

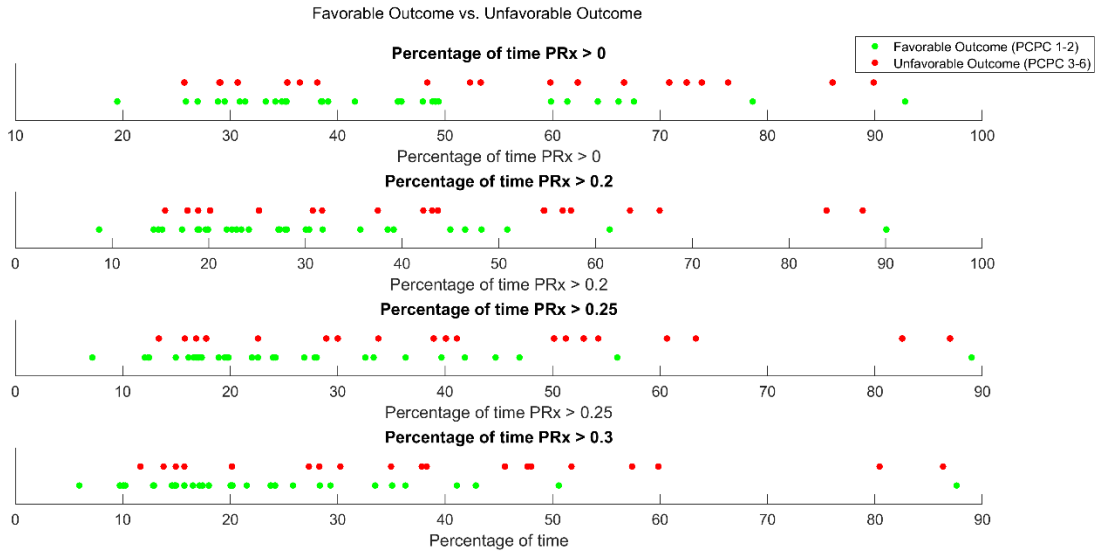

Figure 1a: Pressure reactivity index (PRx) thresholds The % time that PRx is greater than 0, 0.2, 0.25 and 0.3 for each patient. Each dot represents a patient with the color representing the outcome (favorable outcome vs. unfavorable outcome).

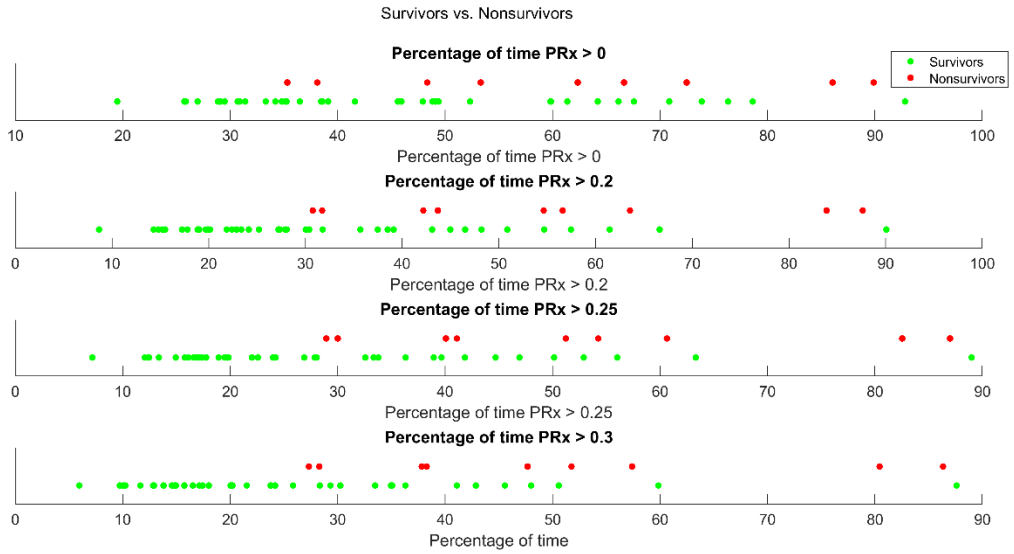

Figure 1b: Pressure reactivity index (PRx) The % time that PRx is greater than 0, 0.2, 0.25 and 0.3 for each patient. Each dot represents a patient with the color representing the outcome (survivors vs. non survivors).

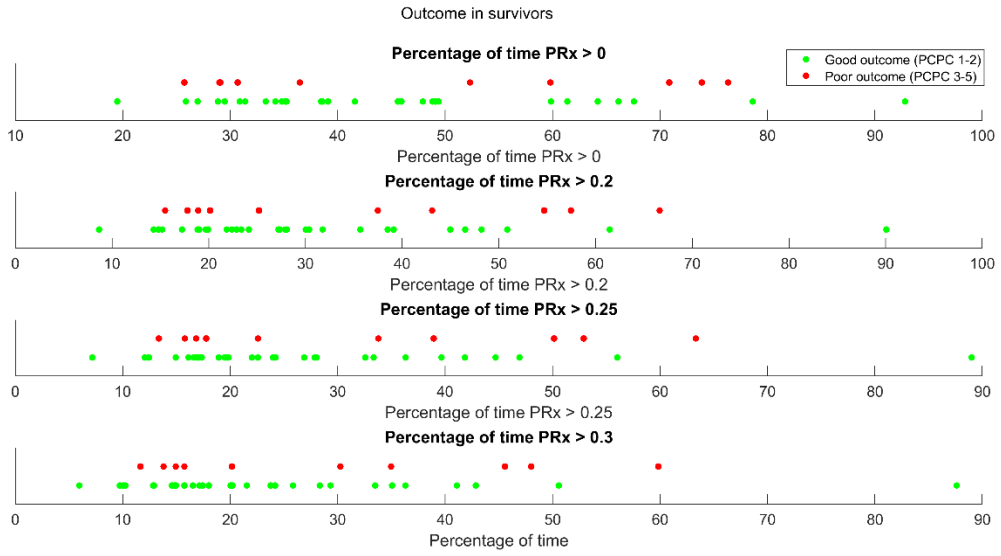

Figure 1c: Pressure reactivity index (PRx) The % time that PRx is greater than 0, 0.2, 0.25 and 0.3 for each patient. Each dot represents a patient with the color representing the outcome (survivors with good outcome vs. survivors with poor outcome).

Appendix D - Histograms of data distribution

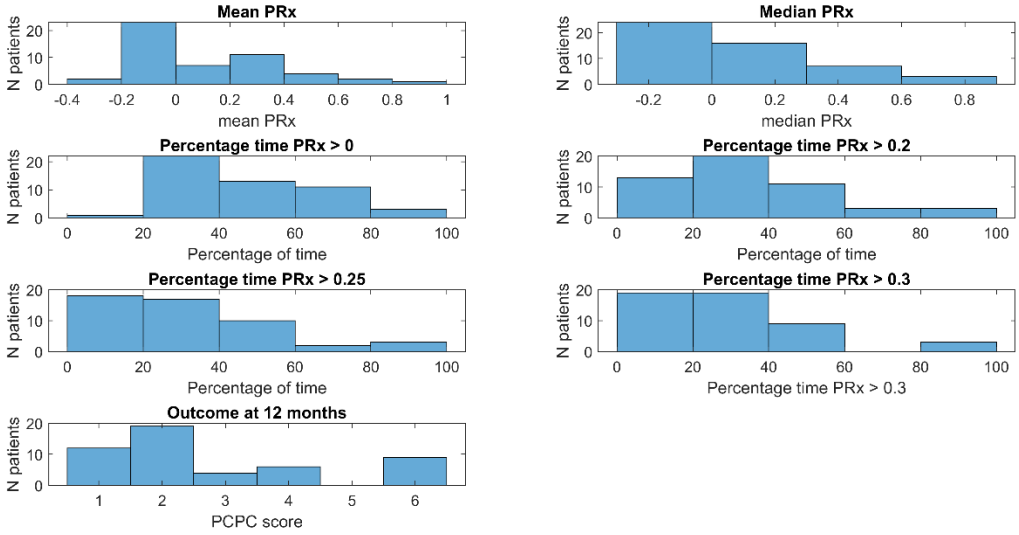

Figure 1: Histograms of used metrics in logistic regression analysis From left to right: mean PRx, median PRx, % time that PRx is greater than 0, % time that PRx is greater than 0.2, % time that PRx is greater than 0.25, % time that PRx is greater than 0.3 and outcome 1 year after the injury.

Appendix E – CPPopt time windows

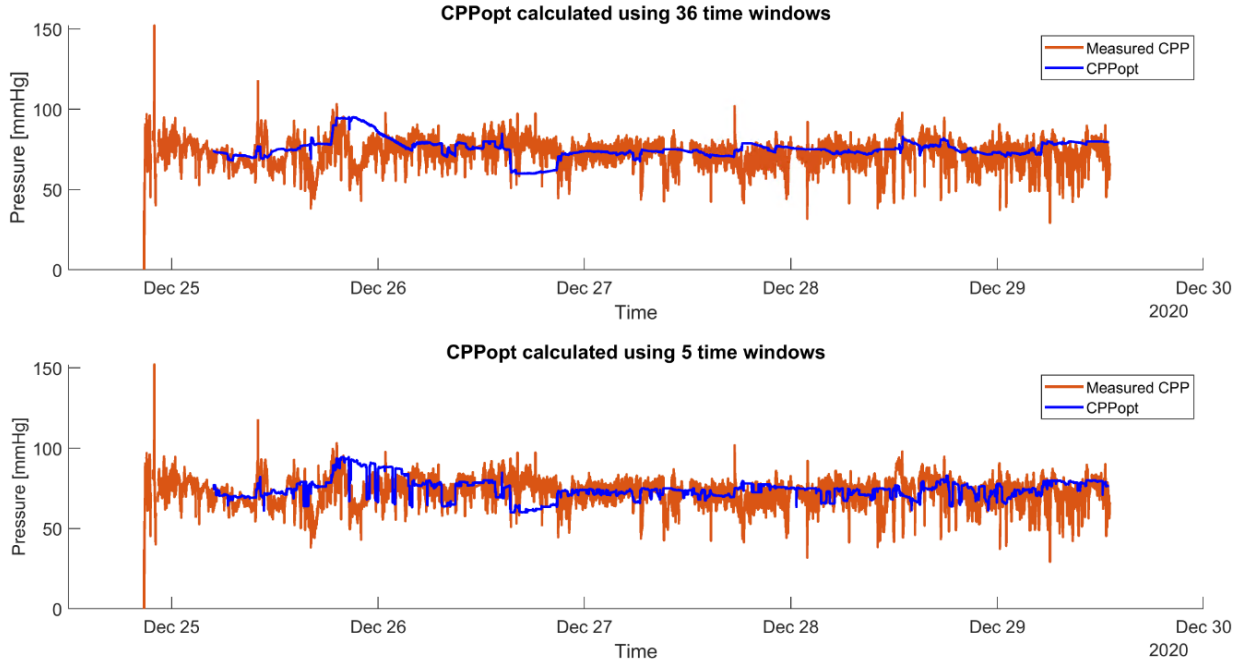

Figure 1. Time windows used in the CPPopt algorithm. An example of the CPPopt trend over the entire hospitalization, on the top image when using 36 time windows in the algorithm and on the bottom when using 5 time windows. Note that for the first hours of the hospitalization no CPPopt is generated as the algorithm needs 8 hours of data.