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# Monitoring of optimal cerebral perfusion pressure in traumatic brain injured patients using a multi-window weighting algorithm

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**Abstract**

Methods to identify an autoregulation guided 'optimal' cerebral perfusion pressure (CPPopt) for traumatic brain injury patients (TBI) have been reported through several studies. An important drawback of existing methodology is that CPPopt can be calculated only in approximately 50-60% of the monitoring time. In this study, we hypothesized that the CPPopt yield and the continuity can be improved significantly through application of a multi-window and weighting calculation algorithm, without adversely affecting preservation of its prognostic value. Data of 526 severe TBI patients admitted between 2003 and 2015 were studied. The multi-window CPPopt calculation was based on automated curve fitting in pressure reactivity index (PRx)-CPP plots using data from 36 increasing length time windows (2 to 8 hours). The resulting matrix of CPPopts was then averaged in a weighted manner. The yield, continuity, and stability of CPPopt were studied. The difference between patients' actual CPP and CPPopt (ΔCPP) was calculated and the association with outcome was analyzed.

Overall, the multi-window method demonstrated more continuous and stable presentation of CPPopt in this cohort. The new method resulted in a mean (±SE) CPPopt yield of 94% ± 2.1%, as opposed to the previous single-window-based CPPopt yield of 51% ± 0.94%. The stability of CPPopt across the whole monitoring period was significantly improved by using the new algorithm ($p<0.001$). The relation between ΔCPP according to the multi-window algorithm and outcome was similar to that for CPPopt calculated on the basis of a single window. In conclusion, this study validates the use of a new multi-window and weighting algorithm for significant improvement of CPPopt yield in TBI patients. This methodological improvement is essential for its clinical application in future CPPopt trials.

**Key words:** cerebral autoregulation, multi-window algorithm, optimal cerebral perfusion pressure, pressure reactivity index, traumatic brain injury

**Introduction**

Survival after traumatic brain injury (TBI) depends on the control of intracranial hypertension and the provision of haemodynamic support to achieve an "adequate" cerebral blood flow with cerebral perfusion pressure (CPP) being one of the main driving forces. Maintaining a CPP above 70 mm Hg was proposed as a method for preventing secondary injuries[1,2]. However, a large randomized controlled trial could not demonstrate a benefit of a fixed CPP-targeted therapy [3]. Over the years, a dynamic patient-targeted CPP protocol, based on the cerebral autoregulation (CA) ability of cerebral vasculature has been proposed [2]. Research to achieve this objective began over 20 years ago [4], attempting to assess CA by relating changes in CPP to changes in flow velocity. Later, changes in intracranial pressure (ICP) in response to mean arterial blood pressure (ABP) were studied, leading to the creation of the pressure reactivity index (PRx), calculated as a moving correlation coefficient between ABP and ICP [5]. Negative PRx values indicate intact CA, whereas positive values imply impairment[6,7]. As ICP and ABP are two commonly measured modalities in TBI, PRx has become widely accepted as a marker for CA status in many neurocritical care settings[8]. Moreover, plotting PRx against CPP will often generate a "U" shaped curve, the minimum of which represents the CPP corresponding to the smallest value of PRx, where the CA response is most active[9–11], the point termed CPPopt. Steiner et al. introduced the CPPopt concept in 2002 [9] and Aries et al. proposed and tested an automated CPPopt algorithm based on a moving 4 hour window [11]. Over the years, studies have confirmed that patients with median CPP closer to their CPPopt seem to have better clinical outcomes [10,12,13].

Problematic for the design of such a study is the fact that CPPopt can only be generated during approximately 44% of the monitoring time [14]. Weersink et al. identified six factors independently associated with absence of the CPPopt curve[15]. Depreitere et al. introduced an innovative multi-window-based algorithm for CPPopt calculation using minute-by-minute monitoring data[14].They used a low resolution version of PRx, and calculated a moving weighted-average value of CPPopts based on 7 windows of different length (1,2,4,6,8,12,24 hours), instead of a single 4 hour-long moving window. The weighting system was based on 2 criteria: the better a U-shaped curve could be fitted and the lower the autoregulation index value corresponding to the plot-specific CPPopt, the higher the weight of that window.

The present study aimed to extend this mathematical approach further by increasing the window number and applying a weighting system which incorporates more characteristics of the PRx-CPP plot, and validate it in a much larger population of TBI patients using a dataset containing high resolution recordings.

## Materials and Methods

### Patients' demographics

This retrospective study includes 526 TBI patients (307 males) admitted in the neurocritical care unit of Addenbrooke's Hospital between 2003 and 2015. Mean age (SD) was 38.6 ± 16.5 years old. Continuous recordings of ABP and ICP were part of the local monitoring protocol in severe TBI patients[16]. The computerized and anonymized data storage protocol was approved by the ethics committee (REC 30 97/291).

All patients were sedated, intubated, and mechanically ventilated during the recording period. A CPP/ICP-oriented protocol for TBI management was used with CPP maintained > 60 mm Hg and ICP < 20 mm Hg [16]. The baseline neurological status of each patient was determined using the Glasgow Coma Scale (GCS). The post-resuscitation GCS was used in patients who had sedation discontinuation immediately following hospital admission. In patients who were deemed too unstable to undergo formal neurological assessment on admission, the GCS score collected on scene was used. The clinical outcome was assessed at 6 months after hospital admission using the Glasgow Outcome Scale (GOS) [17].

### Data acquisition

ABP was monitored invasively through the radial or femoral artery using a standard pressure monitoring kit (Baxter Healthcare, CardioVascular Group, Irvine, CA), and was zeroed at the level of the right atrium. ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA) inserted into the frontal cortex. All signals were sampled at 30-240 Hz and recorded using ICM+® software (University of Cambridge, Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus) through an A/D converter (DT9801, Data Translation, Marlboro, MA) or digitally directly from GE Solar monitors. ICM+® was later used for the retrospective analysis. Artefacts introduced by tracheal suctioning, arterial line flushing or transducer malfunction were removed manually. Data were recorded and analyzed anonymously as part of a standard audit approved by the Neurocritical Care Users Group Committee.

**Preprocessing**

Time averaged values of ICP, ABP, and CPP (CPP = ABP-ICP) were calculated using waveform time integration over 60-sec intervals. Cerebrovascular PRx was calculated as a moving Pearson correlation coefficient between 30 consecutive, 10-sec averaged values of ABP and corresponding ICP signals [5]. Averages over 10 secs were used to suppress the influence of the pulse- and respiratory-frequency wave components.

**Traditional CPPopt calculation**

CPPopt was calculated according to a published curve-fitting algorithm using 4 hours of ABP and ICP recording[18]. In summary, a 5-min median CPP time trend was calculated alongside PRx. These PRx values were divided over and averaged within CPP bins spanning 5 mmHg. The upper limit and lower limit of CPP for CPPopt calculation were set at 40 and 120 mmHg, respectively. For each CPP bin, the corresponding values of PRx were assembled. The mean value and standard error (S.E.) of each bin were then plotted against the bin's mean CPP values in order to create the error bar chart representing the relationship between PRx and CPP. An automatic curve fitting method was applied to the error-bar plot to determine the CPPopt value automatically at the lowest associated PRx. The curve fitting error was calculated as the square root of average sum of the squared differences (SSE) between the 5 mmHg bin averaged PRx data and fitted values (Fig.1 B, left panel).

Theoretically this PRx-CPP relationship should form a smooth U-shaped curve, i.e., with the best CA at the lowest point (vertex). Importantly, before the curve fitting process, PRx data were first Fisher transformed, to achieve a normal distribution eliminating the ceiling effect of the maximum PRx value of 1.0 [19].

**Multi-window CPPopt calculation with weighting**

In this study, we applied a multi-window approach for CPPopt, with the length of the calculation window varying from 2 to 8 hours, increased in 10-minute steps. Hence, for each time point, 36 PRx-CPP plots were generated after 8 hours of monitoring. These plots were given a combined weight factor based on 3 rules (see below), and the final resulting

CPPopt value was computed as the weighted average of the 36 available CPP values (the minima of each curve). The weighting rules were as follows:

1. The longer the window duration, the lower the weight factor (Fig.1 A);

2. The smaller the curve 'fit error', the higher the weight factor (Fig.1 B, the thick black line); Here the full 'fit error' was calculated as the error between the original PRx data points and the fitted curve, instead of the 5 mm Hg bin average data and the fitted curve (Fig.1 B);

3. Fitted curves that doesnot include a vertex (the turning point with minimum value), i.e. non-parabolic curve, are given lower weight (Fig.1 C- Fig.1 D);

The weighting process can be described mathematically as:

$$= \frac{1}{\qquad} \times \frac{1}{\qquad} \times \quad \_ \qquad \text{(Equation 1)}$$

**Additional fit criteria**

To try and improve the quality of individual curve fitting, the following two extra calculation options were investigated:

1. inclusion of error weighting (the S.E. of the error bars) in the process of curve fitting (Fig.1 F) and
2. a criterion enforcing the curve to be (at least partially) included in the range of PRx values [-0.3,0.6] (Fig.1 E), thus forcing the algorithm not to return any CPPopt value when PRx was always very high (>0.6, complete loss of CA), or very low (<-0.3, entirely intact CA).

**CPPopt and outcome**

Previous published papers from our group were able to demonstrate that patients with average CPP close to CPPopt tended to have more favorable outcome[18]. We repeated this same analysis on a larger number of patients using the new multi-window weighted CPPopt calculation method as well the original single window (4hr) CPPopt calculation approach. To investigate the influence of the newly introduced parameters/options for the CPPopt calculation, the analysis was repeated several times as detailed in Table 1. The following naming convention was adopted for the suffix of CPPopt parameters labels:

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S – single window calculation;

M – multiple window calculation;

Y – enforcing the curve to overlap a specific range of PRx values (between -0.3 and 0.6; on the Y-axis);

E – (standard) error bar weighting as part of curve fitting;

W – using weighting algorithm; each plot was given a combined weight factor based on 3 rules (window length, full fit error and vertex presence; Equation 1);

A – average.

We calculated the difference between the median CPP (CPPmed) and each of the calculated CPPopt values every minute. Subsequently, for outcome analysis, these values were averaged over the whole monitoring period for each patient (ΔCPP). Outcome was dichotomized in two ways: favorable (good recovery and moderate disability) vs. unfavorable outcome (severe disability, persistent vegetative state, and death) and mortality vs. survival.

**Statistical Analysis**

Statistical analysis was performed using the IBM SPSS Statistics (version 21) software. The yield was calculated as the ratio between the count of CPPopt and the count of CPP across the whole monitoring period in every patient. The stability of CPPopt was calculated as the standard deviation of differences between two consecutive values of CPPopt over the whole monitoring period. Mortality and survival outcome groups were compared using the nonparametric Kruskal-Wallis test. ANOVA test was used to compare the yield of different CPPopt calculation methods (Table 1). We assumed $\alpha=0.05$. Receiver Operating Curves (ROC) were used to compare the ability of different CPPopts in distinguishing patient outcome, rendering an area under the ROC curve (AUC-ROC) for each parameter[20]. Bland-Altman plots were used to investigate the agreement between CPPopt_S and CPPopt_MA for the pooled data of all TBI patients.

## Results

### Patient Demographics

The group of patients included 219 females and 307 males, with their characteristics described in Table 2. Their mean age was 38.6 ± 16.5 (mean ± S.D.) years old, median GCS score was 7 (interquartile range [IQR]: 4-9). The GCS and GOS score were missing in 190 and 18 patients. The average ABP and ICP of this cohort was 93.6 ± 8.3 mmHg and 16.6 ± 9.9 mmHg, respectively. For the outcome analysis, patients with GOS score missing were excluded. The outcome was distributed as follows: good recovery, n= 84 ( 16.5%), moderate disability, n = 136 (26.8%), severe disability, n = 165 (32.5%); persistent vegetative state, n = 12 (2.3%); and death, n = 111 (21.9%). The mean recording time per patient after artefact removal was 142.0 hours (range from 1 hour to 697 hours).

### CPPopt yield

Two examples of CPPopt trends in TBI patients with long-term recordings are shown in appendix (SFig.1). In both cases the single window CPPopt trend (CPPopt_S) contains many missing values while the multi-window one (CPPopt_MA) is entirely free of those gaps. Table 3 shows the mean (±SE) yield per patient for each of the different methods for calculating CPPopt. The yield increased significantly from 51% ± 0.94% when using the single window method (CPPopt_S), to 94% ± 2.1% ( $p<0.05$) when using the multi-window average approach (CPPopt_MA). There was no significant difference in CPPopt yield between different variants of the multi-window approach ($p>0.05$).

### Stability of CPPopt

The standard deviation of sample-to-sample differences (SDD) in CPPopt is shown in Table 3. The stability of CPPopt was improved significantly by using the multi-window algorithm, with SDD of CPPopt_S was 0.83±0.015, while SDD of CPPopt_MA was 0.58±0.015 ($p<0.05$). There was no significant difference in SDD between different variants of the multi-window approach ($p>0.05$). CPPopt_MA was used as a representative of multi-window approach for the following study.

**Relationship between CPPopt_S and CPPopt_MA**

There was a linear relationship between CPPopt_MA and CPPot_S (Fig.2 A, R=0.89). The Bland-Altman plot demonstrates high agreement between the two methods (Fig. 2 B). The faint, parallel lines in the charts are associated with CPPopt values obtained from 'incomplete' U shape curves (i.e. only descending or ascending curves), and represent lowest/highest values of the CPP bins (central point) contained within the curve (thus explaining granularity of 5mmHg).

**Outcome analysis**

Fig.3 demonstrates the relationship between patient outcome and ΔCPP. Both CPPopt_S and CPPopt_MA showed similar performance in relation with patients' outcome, with CPP values below CPPopt more likely to result in fatal outcome (Fig.3 A).
For both approaches, the highest incidence of favorable outcome was associated with averaged median CPP around CPPopt (ΔCPP=0) (Fig.3 C). A nearly linear relationship between median CPP values above the optimal CPP threshold (ΔCPP >0) and severe disability rate can be observed (Fig.3 B). The lowest unfavorable outcome existed at the median CPP close to CPPopt (Fig.3 D). A ROC test showed that ΔCPP based on both the single window (CPPopt_S) or multi-window method (CPPopt_MA) can distinguish the mortality and survival outcome groups (p<0.001), where the AUC-ROC for ΔCPP based on CPPopt_S was 0.72, and the AUC-ROC for ΔCPP based on CPPopt_MA was 0.69.

## Discussion

Although continuous assessment of CPPopt seems to have prognostic value, its potential for clinical use is limited in part because of its apparent instability and frequent discontinuities. We have built on concepts presented by Depreitere *et al*[14] and implemented a new method of CPPopt calculation that improves the quality of the curve fit and yield as well as stability by taking advantage of multiple calculations from incrementally extended data windows.

Our method extended the number of windows that Depreitere *et al* [14] used from 7 to 36, varying from 2 hours to 8 hours, and took more factors into account. The results showed a marked increase in CPPopt yield (>90%), and a significant improvement in the stability of CPPopt, compared with traditional single-window based CPPopt.

This was of course not unexpected, given the methodology involved. It is easy to see that the algorithm should be able to fit an acceptable curve from windows of increasing sizes, all the way up to 8 hours. The averaging operation is also likely to have a stabilizing effect on the CPPopt trend. The question is, however, whether by increasing the window length up to 8 hours, we are calculating values that may perhaps be less relevant to the current patient state. The first factor in our weighting system, the window length penalty, which was applied such that shorter windows were given higher weights to gauge the curve fitting, should help to address this problem. As the algorithm then favors shorter windows, which were more related with most recent changes in CA, leading to more local curve fits.

An ideal U-shape curve with a clear minimum in the middle gives more confidence in identification of the best vasoreactivity (CPPopt), while strictly descending and ascending curves, might introduce some underestimation or overestimation, although they also carry information about vasoreactivity [19]. In our weighting approach, higher weight was given to a perfectly U-shape curve, and lower weights were given to strictly increasing or decreasing curves. In this way, we believe the CPP point with best autoregulation can be estimated more reasonably.

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Another criterion for the weighting approach was fit error. To take more data points into consideration, the full fit error was calculated between the individual PRx data points and the fitted curve, assigning larger weight to the curve with smaller fit error. Through this penalty, the curves which have better performance in curve fitting can have more influence on the final CPPopt calculation.

The comparison between current multi-window algorithm calculation and 4-hour window calculation already showed significant improvement in estimation of CPPopt using the new method. However, the weighting parameters of multi-window algorithm used in this study were decided roughly through a small sample study (appendix, SFig.2 ); further research and comparison need to be done to find out the best settings for these weighting factors. Moreover, in current weighting parameter settings, we did not find significant differences between various weighting average strategies (CPPopt_MA vs CPPopt_MW), further analysis needs to be done to explore the importance of different weighting parameters in the future.

Previous studies have indicated a relationship between patient outcome and ΔCPP [21–23]. We did not expect the relationship with outcome to change using the multi-window algorithm, as this is executed on patient-averaged values. What we did want to achieve is better stability and availability of the curve, without introducing errors that make the relation of c with outcome worse. Therefore, the fact that no difference was found between the relation of ΔCPP with outcome for the multi-window or the single-window approach is reassuring.

The previous study already confirmed that treating patients with individualized optimal CPP has a better discriminative value than a fixed threshold of 60 or 70 mm Hg[19]. This, larger, study of 526 TBI patients, showed CPPopt varying from 40 mmHg to 120 mmHg (Fig.2), sustaining the notion that one fixed CPP target for all patients may not be appropriate [2,24] , and that a dynamic CPP target based on CA is more likely to be recommended[25,26].

Lastly it must be stressed here that a fixed CPP threshold treatment approach is affected by the accuracy of measurement and the zeroing procedure of ABP. Overestimated or underestimated values of CPP introduced by an inappropriate zeroing level might result in inappropriate clinical decisions, when compared to the fixed, recommended by guidelines, CPP target. On the other hand, our CPPopt diagnosis-therapeutic method is immune to these effects as it effectively provides an individualized CPP target that has the same zero reference as the current CPP itself.



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**Conclusion**

The new CPPopt methodology increased availability of valid CPPopt values during most of the monitoring time, with markedly reduced short term variability. The technique has the potential to make 'optimal CPP' management widely applicable in most ICUs.

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**Tables**

Table 1. Abbreviations of labels for optimal cerebral perfusion pressure (CPPopt) calculation

| **Label** | **Calculation window** | **Use error bar weighting** | **Enforcing the curve to overlap a specific range of PRx values** | **Use multi-window weighting system** | **Description** |
|---|---|---|---|---|---|
| CPPopt_S | Single | NA | NA | NA | Using 4 hour window |
| CPPopt_SYE | Single | Y | Y | NA | Using 4 hour window, with error bar weighting and enforcing the curve to overlap the range of PRx values [-0.3,0.6] |
| CPPopt_MA | Multiple | NA | NA | NA | Calculate the average CPPopt based on multi-window approach |
| CPPopt_MAYE | Multiple | Y | Y | NA | Calculate the average CPPopt based on multi-window approach, with error bar weighting and enforcing the curve to overlap the range of PRx values [-0.3,0.6] |
| CPPopt_MW | Multiple | NA | NA | Y | Calculate the weighted average CPPopt based on multi-window approach; the weighting factors include window length, full fit error and parabolic minima value |
| CPPopt_MWYE | Multiple | Y | Y | Y | Calculate the weighted average CPPopt based on multi-window approach, with error bar weighting and enforcing the curve to |

| | | |
|---|---|---|
| | | overlap the range of PRx values [-0.3,0.6]; the weighting factors include window length, full fit error and parabolic minima value |

*Y: use this function, NA: not apply this function. S : single window calculation (a 4-hour window); M: multiple window calculation (36 windows); Y: enforcing the curve to overlap a specific range of PRx values (between -0.3 and 0.6; on the Y-axis); E: (standard) error bar weighting as part of curve fitting; W:using weighting algorithm; each plot was given a combined weight factor based on 3 rules (window length, full fit error and vertex presence; Equation 1); A: average.*



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Monitoring of optimal cerebral perfusion pressure in traumatic brain injured patients using a multi-window weighting algorithm (DOI: 10.1089/neu.2017.5003)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Table 2 Patient demographics, clinical variables, and outcome

| | N | Age | GCS | ABP | ICP | CPP | PRx |
|---|---|---|---|---|---|---|---|
| **Death** | 111 | 44.4 ±17.8 | 6.0 (IQR:3-8) | 94.2 ±14.0 | 20.4 ±12.3 | 75.0 ±13.6 | 0.16 ±0.20 |
| **Vegetative state** | 12 | 40.5 ±16.8 | 5.0 (IQR:3-9) | 90.3 ±11.6 | 16.1 ±8.3 | 72.9 ±9.5 | 0.06 ±0.20 |
| **Severe disability** | 165 | 39.0 ±15.4 | 6.0 (IQR:4-8) | 94.2 ±7.4 | 16.6 ±10.0 | 78.6 ±9.7 | 0.04 ± 0.16 |
| **Moderate disability** | 136 | 35.7 ±15.4 | 7.0 (IQR: 4-10) | 92.8 ±8.3 | 15.3 ±8.8 | 77.8 ± 8.2 | 0.04 ± 0.16 |
| **Good recovery** | 84 | 34.9 ±16.6 | 8 (IQR:4-10.5) | 93.3 ±7.8 | 14.7 ± 7.6 | 79.1 ± 7.0 | 0.01 ± 0.13 |
| **Total** | 526 (18 GOS missing) | 38.6 ± 16.5 | 7 (IQR: 4-9) | 93.6 ± 8.3 | 16.6 ± 9.9 | 77.7 ± 9.9 | 0.07 ± 0.18 |

*GOS, Glasgow Outcome Scale; M/F, males/females; GCS, Glasgow Coma Score; ABP, arterial blood pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; PRx, pressure reactivity index. wPRx: wavelet pressure reactivity index; Values are shown as mean ± SD or median and interquartile region. SD: standard deviation; IQR: interquartile range. ABP, ICP, CPP, PRx and wPRx were averaged in each patient over the whole monitoring period.*

Table 3. The yield and standard deviation of sample-to-sample differences (SDD) of optimal cerebral perfusion pressure (CPPopt) calculated using the single-window approach (CPPopt_S or CPPopt_SYE ) and using the multi-window algorithm (CPPopt_M*).

| Statistics | CPPopt_S | CPPopt_SYE | CPPopt_MA | CPPopt_MAYE | CPPopt_MW | CPPopt_MWYE |
|---|---|---|---|---|---|---|
| Yield (Mean ± S.E.) | 50.5% ± 0.94% | 46.1% ± 0.95% | 94.2% ±2.11% | 92.3% ± 2.09% | 94.2% ± 2.13% | 92.3% ± 2.08% |
| SDD (Mean ± S.E.) | 0.83 ±0.015 | 0.74 ±0.014 | 0.58 ±0.015 | 0.61 ±0.016 | 0.69 ±0.016 | 0.72 ±0.019 |

*PRx: pressure reactivity index. CPPopt: optimal cerebral perfusion pressure. For the abbreviations of CPPopt in this form, please refer to Table 1.*

## Figure Legends

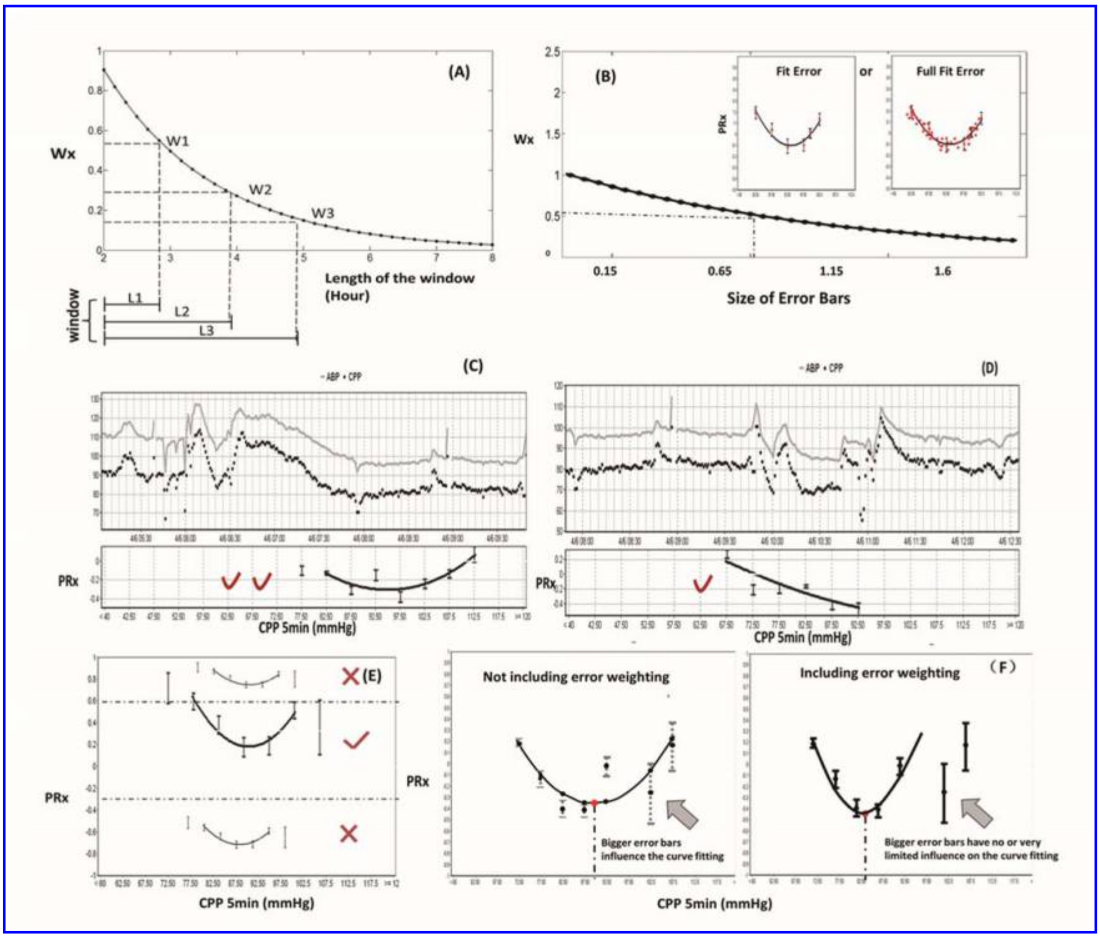



Figure.1 The three weighting rules (A-D) and two additional fit criteria (E-F) for optimal cerebral perfusion pressure (CPPopt) calculation using multi-window approach. A, Longer window duration lowers the weight factor; B, the smaller the curve ‘fit error’, the higher the weight factor; the fit error was calculated as the error between the original data points and the fitted curve (right panel), instead of between bin average data and the fitted curve (left panel) ; C-D: curve that includes the turning point of minimum value receives higher weight factor (C) than the one that does not (D). E, CPP bins were excluded for CPPopt calculation in the PRx regions of completely impaired (PRx > 0.6, upper panel) or completely working (PRx < -0.3, bottom panel) cerebral autoregulation. (F) inclusion of error weighting in the process of curve fitting (right panel) and exclusion of error weighting

in the process of curve fitting (left panel). PRx: pressure reactivity index; ABP: arterial blood pressure; CPP: cerebral perfusion pressure; CPP 5min: 5-minute mean value of CPP. Two red ticks implies higher weight, while one red tick means lower weight, red cross means the curve being excluded.

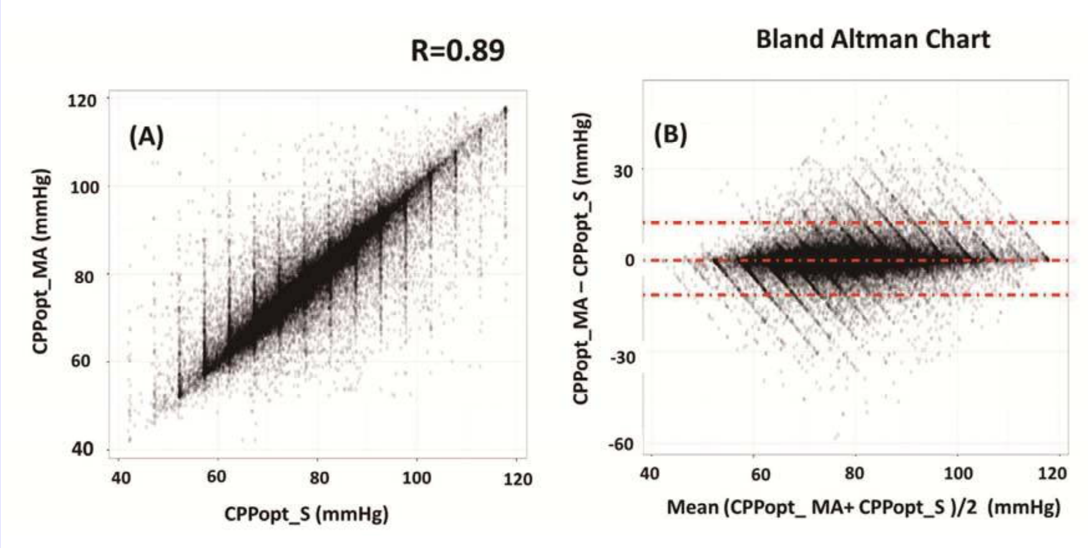



Figure 2. (A) Relationship between and (B) Bland Altman plot of CPPopt_S and CPPopt_MA. CPPopt_S refers to CPPopt calculated using a 4-hour window and CPPopt_MA refers to CPPopt calculated according to the multi-window approach (average CPPopt for window lengths varying from 2 to 8 hours, in steps of 10 minutes ). Dot line: 95%-confidence interval and mean.

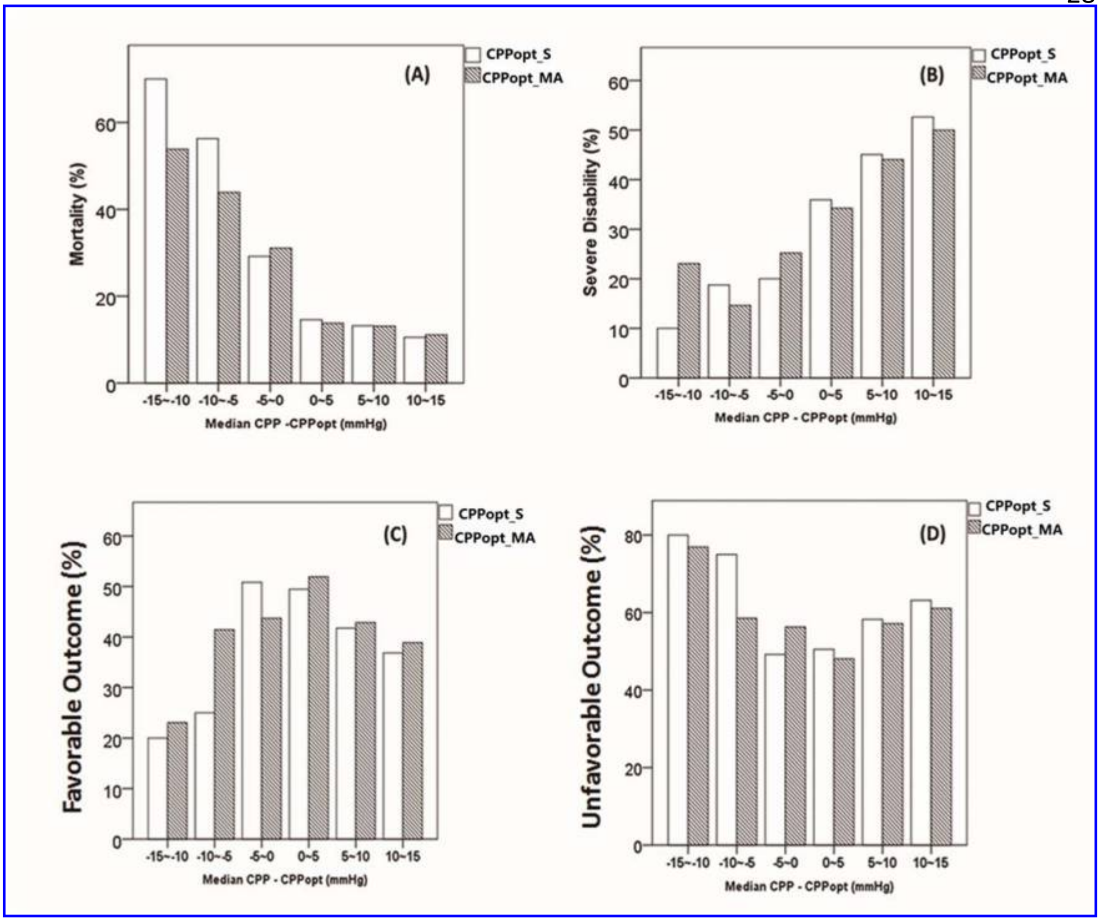
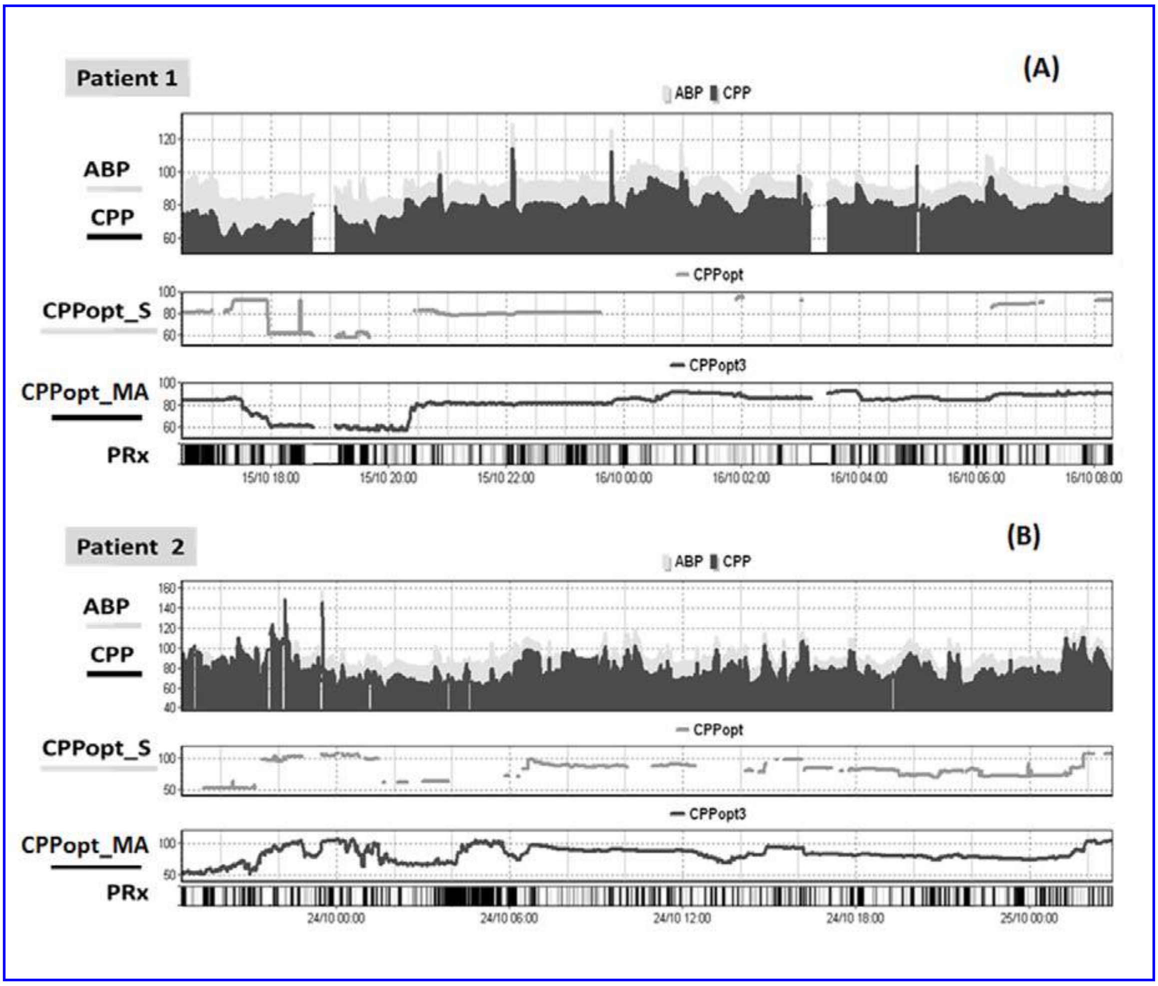



Figure 3. Relationship between ΔCPP and patient outcome: mortality(A), severe disability (B), favorable outcome(C), and unfavorable outcome (D). ΔCPP : the difference between averaged median cerebral perfusion pressure (CPP) and optimal cerebral perfusion pressure (CPP). The CPPopt was calculated using a single moving window of 4 hours (CPPopt_S, the white bar) and using a weighted multi-window average calculation (CPPopt_MA, the striped bar).

# A. **Appendix**

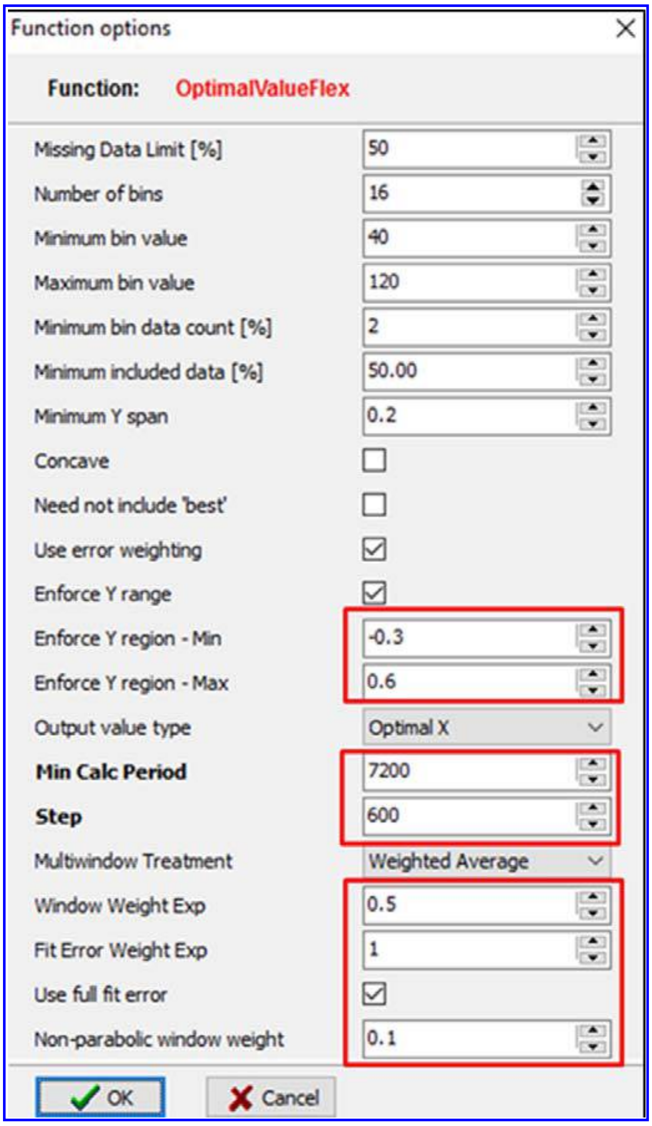
SFigure 1 shows two examples of optimal cerebral perfusion pressure (CPPopt) trends during monitoring.




B.

SFigure 1. Examples of optimal cerebral perfusion pressure (CPPopt) trends. ABP: arterial blood pressure; CPP: cerebral perfusion pressure; CPPopt_S: CPPopt calculated according to PRx using a 4-hour moving window; CPPopt_MA: CPPopt calculated according to the multi-window approach (average CPPopt for window lengths varying from 2 to 8 hours, in steps of 10 minutes).

SFigure 2 showed settings of weighting parameters used in this study for optimal cerebral perfusion pressure calculation.




SFigure 2. Settings of weighting parameters used in this study for CPPopt calculation based on a multi window system. The window weight was set at 0.5, the fit error weight was 1, the non-parabolic window weight was 0.1. The curve was forced to be (at least partially) included in the range of PRx values [-0.3,0.6]. The minimum length of calculation window was 7200 seconds, i.e. 2 hours. Increasing step was 600 seconds, i.e. 10 minutes.