Comparison of frequency and time domain methods of assessment of cerebral autoregulation in traumatic brain injury

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Abstract

The impulse response based autoregulation index (ARI) allows for continuous monitoring of cerebral autoregulation using spontaneous fluctuations of arterial blood pressure and cerebral flow velocity (FV). We compared three methods of autoregulation assessment in 288 TBI patients managed in the Neurocritical Care Unit: 1) Impulse Response-based ARI; 2) Transfer Function phase, gain and coherence; and 3) Mean flow index (Mx). ARI was calculated using the transfer function estimation (Welch method) and classified according to the original Tiecks' model. Mx was calculated as a correlation-coefficient between 10s averages of ABP and FV using a moving 300s data window. Transfer function phase, gain and coherence were extracted in the very low frequency (VLF, 0~0.05 HZ) and low frequency (LF, 0.05~0.15HZ) bandwidths. We studied the relationship between these parameters and also compared them with patients' Glasgow outcome score. The calculations were performed using both cerebral perfusion pressure (CPP; suffix 'c') as input and ABP (suffix 'a').

The result showed a significant relationship between ARI and Mx when using either ABP ($r = -0.38$, $p<0.001$) or CPP ($r = -0.404$, $p<0.001$) as input. Transfer function phase and coherence_a were significantly correlated with ARI_a and ARI_c ($p<0.05$). Only ARI_a, ARI_c, Mx_a, Mx_c and phase_c were significantly correlated with patients' outcome, with Mx_c showing strongest association.

Key Words

Cerebral Autoregulation Index, Mean Flow Index, Transcranial Doppler, Transfer Function Analysis

Introduction

Cerebral pressure autoregulation (CA) refers to the ability of cerebral arterial blood vessels to keep cerebral blood flow (CBF) constant in spite of changes in cerebral perfusion pressure (CPP) [1, 2]. CA is thought to be a fundamental physiologic mechanism that protects the brain from ischaemic or hyperemic

insults following a decrease or increase in CPP. Impaired CA in patients with a traumatic brain injury (TBI) [3] can lead to an increased vulnerability of vessels to protect against the secondary ischemic insults caused by elevated ICP [4,5] and, ultimately, poor outcome [6,7]. Several different methods to assess CA exist (see Appendix I) but how they relate to each other, how they relate to patient outcome, and which signals should be used for their calculation is still not fully investigated, especially in TBI.

Various time-domain and frequency-domain algorithms have been proposed for investigation of CA using measurements of the middle cerebral artery blood flow velocity (FV) and arterial blood pressure (ABP) or CPP. One popular method that takes advantage of spontaneous fluctuations in ABP and FV is transfer function (TF) analysis. It is based on the assumption that cerebral autoregulation can be modelled as a linear high-pass filter, freely passing rapid changes in ABP to FV but attenuating low-frequency perturbations[1,8-12]. This attenuation of low frequency oscillations (defined usually as frequencies <0.15 Hz) is related to the strength of autoregulation. Numerically, the properties of such a filter can be expressed by three parameters (frequency dependent): TF phase, gain and coherence.

The TF gain reflects how much the input signal variation is transmitted to the output signal, and is expressed as a ratio of amplitude of the output (FV) to the amplitude of the input (ABP). With intact autoregulation, the low frequency fluctuations in FV related to fluctuations in ABP are largely suppressed, resulting in low TF gain, whereas a high gain represents impaired CA.

TF Phase, in simple terms, describes the 'inertia' of the autoregulation filter, which manifests itself as a shift (delay) in degrees between sinusoidal (Fourier) components of the input signal (ABP) and the output signal (FV) [10]. High pass filter nature of the cerebral autoregulation means that intact autoregulation is associated with highly positive phase values (90 degree and more) for low frequency decreasing down to zero for high frequencies (of heart rate and above) [13,14]. Impaired autoregulation on the other hand elicits no active response and thus no 'inertia' effects, manifested as 0 phase shift at all frequencies.

Coherence is the most elusive parameter of the three and reflects the degree of linear correlation between the input and output amplitudes of the Fourier components at each frequency point. If the two signals are purely linearly related with absence of any extraneous noise contribution then the coherence is 1 for all frequencies. However, if there is a significant degree of non-linearity in the character of association between the two signals, the coherence will be reduced, making also the estimated values of gain and phase largely invalid. On the other hand even if the system is linear but has low gain (high attenuation) and this is accompanied with a significant extraneous 'noise' present at the corresponding frequencies (due to measurement errors or contribution from other, unrelated, sources of variation), the coherence values at those frequencies will also be reduced [15]. The latter effect has, rather controversially, led to the use of coherence as an indicator of CA [15].

Panerai's impulse response (IR) autoregulation index (ARI) is based on the parametric model of autoregulation developed by Tiecks for analysis of 'thigh-cuff' tests [1,16]. In this method, a response of FV to a hypothetical impulse change in ABP is estimated, using transfer function analysis of spontaneous fluctuations in ABP and FV, and, compared to the theoretical impulse responses of original Tiecks' model (graded as ARI 0 – ARI 9, higher ARI indicating better autoregulation).

Finally, the mean flow index (Mx), is a purely time domain measure of autoregulation which is based on analysis of strength of correlation between spontaneous slow fluctuations in mean CPP and FV. Since it was introduced in the mid 90's, Mx has been applied to various experimental and clinical scenarios and, importantly, has been shown to be associated with outcome in TBI patients [17,18,19].

All those methods describe cerebral autoregulation, but perhaps reflect its slightly different aspects (Appendix I) and their mutual relationship is still unclear. In addition, their properties will be affected by issues related to their estimation from the measurement data, as well as by the degree of misfit of the data to the underlying physiology models used.

The primary aim of this study was to analyze the relationship between Mx, ARI, TF phase, gain and coherence in a population of TBI patients. Our secondary aim was to analyze the effect of different inputs (ABP or CPP) on CA assessment. The third aim was to explore the relationship between all these parameters and patients' outcome after injury.

Materials and Methods

Patients

Transcranial Doppler ultrasound (TCD) was used to monitor FV from the middle cerebral arteries in 288 traumatic brain injury (TBI) patients admitted to the Neurocritical Care Unit (NCCU), Addenbrooke's Hospital in the United Kingdom between the year of 1992 to 2013 (822 data recording sessions in total). The mean age of this population was 33 (mean) ± 16 (standard deviation, SD) and the mean Glasgow Coma Scale (GCS) at the scene was 6 ± 3 (mean ± SD). Daily TCD monitoring was retrospective analyzed anonymously performed and analyzed anonymously as a part of standard audit approved by Neurocritical Care Users Group Committee.

Patients were managed according to current institutional traumatic brain injury guidelines (adapted from Menon, 1999) [21]. In brief, patients were sedated, intubated, ventilated and paralyzed with CPP managed according to ICP/CPP management protocol for NCCU. Interventions were aimed at keeping ICP < 20 mm Hg using positioning, sedation, muscle paralysis, moderate hyperventilation, ventriculostomy, osmotic agents, and induced hypothermia. CPP was maintained > 60 - 70 mm Hg using vasopressors, inotropes and intravenous fluids. Autoregulation parameters analyzed in this study were not included in the protocol and therefore analysis of their association with outcome was valid.

Monitoring and Data Analysis

ABP was measured with an arterial line zero calibrated at the level of the right atrium (Baxter Healthcare CA, USA), intracranial pressure was measured using intraparenchymal probe inserted in the right frontal

lobe zero calibrated at the level of the foramen of munro (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA). Cerebral blood flow velocity (FV) was monitored from the middle cerebral arteries (MCA) via the transtemporal windows bilaterally using Doppler Box (DWL Compumedics, Germany) or Neuroguard (Medasonic, CA) [22]. The insonation depth was from 4 to 6 cm and the examinations were performed during the first 3 days after head injury [23]. We obtained a total of 822 monitoring sessions from 288 patients with each recording lasting around for 20 minutes to 1 hour.

Data from the bed-side monitors were digitized using A/D converters (DT 2814, DT9801 and DT9803, Data Translation, Marlboro, USA) and sampled at 50Hz (2001- 2008) and 100Hz (2008-2013) using data acquisition software ICM+® (Cambridge Enterprise Ltd, Cambridge, UK,

http://www.neurosurg.cam.ac.uk/icmplus) or, in the early years (before 2001), using waveform recorder WREC for DOS (W Zabolotny, Warsaw University of Technology). Artefacts introduced by tracheal suctioning, arterial line flushing or transducer malfunction were removed before data analysis.

Calculation of Autoregulation Indices

ARI was calculated by comparing an impulse response estimated from the ABP and FV recordings with the impulse response (IR) derived from Tiecks' model (see Appendix II). FV and ABP were first normalized into z scores (mean subtracted, and divided by the standard deviation), then divided into 4 data segments of 120 seconds duration (amounting to 50% segment overlap) and transformed with the FFT algorithm (Welch method). The cross-spectra and auto-spectra of ABP and FV, the transfer function squared coherence were estimated using the average value of the 4 segments [24,25]. The time domain impulse response was computed from the inverse FFT of transfer function with a cut-off frequency of 0.5 Hz. After comparing the estimated IR with the ten curves of IR of Tiecks' model the best fit one, selected using the minimum squared error criterion, was chosen as the ARI value for the segment, labelled here as ARIa. This 300 s calculation was applied sequentially every 10 s across the whole recording session. The same calculation has also been conducted using CPP instead of ABP, giving a parameter labelled here as

ARIc. An example of the comparison between the estimated IR (dot line) from one patient and the IR of Tiecks' model (solid lines) is shown in the figure attached in Appendix II (Fig.4).

Transfer function phase, gain and squared coherence in two main frequency ranges which are normally used in CA field: 0~0.05 HZ (very low frequency domain, VLF) and 0.05~0.15 HZ (low frequency domain, LF) were calculated [25,27]. Both ABP and CPP were used as input respectively and we use 'a' or 'c' for abbreviation, for example gain_a_VLF referred to the gain between ABP and FV at the very low frequency range (Appendix III). All the calculations were performed using a 300s moving window and updated every 10 seconds [25]. Here the coherence refers to the squared modulus of coherence between input and output.

Mean flow index (Mx) was calculated following the method described in our previous publications [3]. A moving Pearson's correlation coefficient was calculated between 10s averages of CPP and FV. The calculations were performed using a 300s data window and the results were averaged for each recording session. Mx metrics using CPP are labelled Mxc, whereas Mx metrics using ABP are labelled Mxa.

In order to analyze the relationship between ARI, Mx and TF parameters, the averaged values of each parameter during each monitoring session were compared with each other giving a total of 822 samples of time-averaged CA parameters.

We also evaluated the performance of these parameters in relation to patients' outcome. In this case, the mean values of each monitoring session were calculated first and then averaged for each patient across all his/her recordings, giving one value for each patient. These averaged values were then compared with patient's outcome as assessed using the Glasgow outcome scale (GOS) at 6 months after injury (GOS obtained at rehabilitation clinic or by phone interview). For the purpose of the statistical analysis the patients' outcomes were dichotomized into favorable group (good outcome and moderate disability) and unfavorable group (severe disability, vegetative state and death).

One potential problem with TF analysis approach to analysis of autoregulation is that its estimation of gain and phase should be treated with caution if the coherence between the FV and ABP (or CPP) is low (as describe in the introduction). Therefore, we re-evaluated the relationship between ARI and gain/phase while squared coherence was above 0.36. The relationship between TF parameters and patients' outcome was also analyzed.

Statistical Analysis

Statistical analyzes were performed using the IBM SPSS Statistics (version 19, Armonk, NY USA) software. The cross-relationship between these autoregulation indices was studied using a regression curve estimation method. As these parameters had different quantities with different resolutions (i.e. 0.01 for Mx, and 1 for ARI) and different value ranges, the Pearson's correlation coefficient r was calculated to test the relationship between them. Independent-samples T test was used to analyze differences in autoregulatory indices in two outcome groups (favorable and unfavorable). Results were considered significant at $p < 0.05$.

In addition, Chi-squared tests were employed to describe the "degree of equivalence" of examined CA parameters with patients' outcome groups dichotomized by receiver operating characteristic (ROC) curve analysis. The degree of inter-rater agreement was described by Cohen's kappa (κ) value, where κ value of zero indicates no agreement; value 1 implies perfect agreement; κ value lower than 0.2 represents slight agreement, and κ value between 0.21 and 0.6 means fair to moderate agreement; κ between 0.61 to 1 implies substantial to perfect agreement.

Results

Patients' mean ABP was 91.24 ± 11.93 mmHg and mean ICP was 17.99 mmHg ± 9.78 mmHg (mean ± SD). The mean FV was 62.50 ± 27.22 cm/s and mean CPP was 73.2 ± 12.8 mmHg (mean ± SD). The Glasgow outcome scale scores at 6 months were distributed as follows: good outcome, n = 75 (26%);

moderate disability, n = 69 (24%); severe disability, n = 74 (26%); persistent vegetative state, n = 9 (3%); and death, n = 61 (21%). 50% patients achieved favorable outcome. An ARI values of 9 (both ARIa and ARIc) indicates hyper-responsive autoregulation, which is rarely seen even in healthy subjects. In this study, 7 measurements of ARI=9 were observed. As this group was disproportionally smaller than other groups, they were excluded from further outcome analysis.

The relationship between parameters using CPP as input

The relationship between Mx and ARI using CPP as input is presented in Fig 1A, Table 1. ARI was significantly related to Mx, though non-linearly ($r = -0.404$, $p<0.001$). From ARI = 0 to 2, Mx was constant, whereas from ARI 2-8 the relationship was strongly negative: $Mxc = 0.401 - 0.081 \times ARIc$ ($p<0.001$, Fig. 1A).

Of the transfer functions, only phase was correlated with ARI in the VLF range ($r=0.230$, $p<0.001$, Fig. 2B), and the LF range ($r = 0.111$, $p=0.001$, Fig.2E). The relationship between ARIc and phase_c_VLF from ARIc=1 to ARIc=8, can be described by the linear model: $Phase\_c\_VLF = 35.64 + 3.108 \times ARIc$ ($p<0.001$, Fig. 2B). For the LF range, $Phase\_c\_LF = 27.5 + 3.13 \times ARIc$ ($p<0.001$, Fig.2E). There was no significant relationship between ARIc and gain_c in either of the frequency ranges ($p>0.05$, Fig.2A and Fig.2D). No significant relationship was found between ARIc and squared coherence_c ($p>0.05$, Fig.2C and Fig.2F).

The relationship between parameters using ABP as input

Using ABP as the input signal, the ARIa and Mxa were strongly correlated, presenting a significant negative, non-linear, relationship between them ($r = -0.38$, $p<0.001$, Fig. 1B, Table 1).

A significant negative relationship between ARIa and Mxc is shown in Fig.1C ($r=-0.382$, $p<0.001$). From ARIa = 1 to 8, the relationship can be described by a linear function: $Mxc = 0.321 - 0.077 \times ARIa$ ($p<0.001$,).

For transfer function parameters, ARI correlated significantly with phase_a in both VLF ($r=0.345$, $p<0.001$, Fig. 3B) and LF ranges ($r=0.254$, $p<0.001$, Fig. 3E). Phase_a_VLF and ARIa were linearly related from ARIa=1 to ARIa =8, which can be described as: $Phase\_a = 26.25 + 3.11 \times ARIa$ ($p<0.05$, Fig.

3E). The squared coherence_a was negatively related to ARIa at both frequencies (r=-0.178, p<0.001 for VLF, Fig.3C; r=-0.079, p = 0.024 for LF, Fig.3F). No obvious relationship between ARIa and gain_a was found (Fig.3A and Fig.3D).

Outcome analysis

Significant differences could be found both in ARI and Mx (p<0.05, Table 2) for two groups of patients with dichotomized Glasgow outcome scores (1-2: favorable; or 3-5: unfavorable). Patients with favorable outcome attained higher ARI value and lower Mx value, the result is shown in Table 2. ARIa showed a lower p value and higher AUC than ARIc, demonstrating a better distinction between the two outcome groups than ARIc. By contrast, Mxc showed much better performance in differing the two groups than Mxa. Of transfer function parameters, only phase_c at the VLF showed a significant difference (F=5.82, p=0.016, AUC = 0.582). Neither the gain nor coherence showed any relationship with outcome in this cohort.

For the agreement analysis between the CA parameters, Chi-squared tests showed that there was fair agreement between ARI and Mx (κ value between ARIa and Mxa is 0.135, between ARIc and Mxc equals 0.332), with ARIa and Mxc demonstrated the best agreement (κ value was 0.347). Moreover, phase agreed well with Mx and ARI. No agreements were found between other TF parameters.

Re-evaluation of the relationship between TF parameters and ARI/ Mx while high coherence

To the relationship between CA parameters (while squared coherence is above 0.36), the result showed that besides phase, gain_a_VLF (p=0.033) and gain_c_VLF (p=0.022) also showed significant relationship with ARI. There was also significant relationship between gain_a_VLF (p<0.001) and Mx as well as gain_c_VLF (p<0.001) and Mx. The outcome analysis result hasn't been changed.

Discussion

Several methods for CA assessment using spontaneous fluctuations in ABP and FV (such as ARI, Mx, transfer function phase and gain) have been applied to patients with stroke, carotid stenosis and subarachnoid hemorrhage [26,27]. However their application for TBI has not been fully validated. This

paper compared the results of three important autoregulation monitoring methods in a cohort of TBI patients. Significant relationships were found between Mx, ARI and TF phase. A negative relationship between Mx and ARI existed, with both of them performed well in distinguishing patients' outcome (favorable and unfavorable). There was a negative relationship between phase and ARI. Except phase_c_VLF, other TF parameters did not show significant differences between patients' outcome.

Mx and ARI as cerebral autoregulation indicators

Theoretical considerations as well as our own unpublished modelling data indicate that Mx index loses its sensitivity at both ends of the measurement range (i.e. for fully intact and fully impaired autoregulation), and ARI seems to lose its sensitivity for low values (Fig.4). The linear relationship between ARI and Mx from ARI=2 to ARI=7 agrees with the results in our previous study, conducted in a smaller group of patients [23]. The finding that within ARI range of 0 to 2, Mx remained at ~ 0.3 seems to add support to the recommendations given by Sorrentino et al [28] that Mx value of 0.3 should be treated as a threshold for disturbed autoregulation.

Mx describes stability of cerebral blood flow in the face of CPP or ABP changes with values ranging from -1 to 1 (resolution was 0.01). It is a non-parametric, i.e. model-free method and only assesses whether, and to what extent, variation in one parameter (pressure) is significantly associated with variations in the other (flow). It reflects the shape of Lassen's curve, with stable CBF within, and pressure-passive CBF outside the limits of autoregulation. On the other hand ARI explains how fast FV can recover from any changes in ABP or CPP, but its performance will depend on how accurately the model reflects the physiology of the cerebral blood flow autoregulation in the individual circumstances. Theoretically, if the assumptions are met, parametric methods are more sensitive to changes in physiology than non-parametric ones. In this respect, as long as the Tiecks' model describes CA system well enough, ARI should perform with greater precision and sensitivity than Mx. On the other hand if the model assumptions are not entirely met, a non-parametric method like Mx should give more reliable results. In the present study, the quality of fit of the estimated impulse response to the model, though satisfactory in

most cases, was sometimes poor, suggesting assumptions violation. Perhaps some sort of combination of those two approaches might yield more satisfactory results in the future.

Transfer function indices as cerebral autoregulation indicators

Many factors can cause rhythmic fluctuations in both ABP and ICP, such as pulse wave, respiratory wave and slow waves. However, the pulse wave and even the respiratory wave are too fast to engage cerebral autoregulation effectively [29]. According to the 'high-pass filter' model, the variation in cerebral blood flow due to changes in ABP would be effectively damped only in the low frequency range, and therefore low frequency waves are considered to be most relevant for testing/monitoring CA [15]. These slow waves can be generally classified further as A-waves (or plateau waves), B-waves and C-waves [30]. A-waves, known also as 'plateau waves', are characterized by a steep increase in ICP reaching a plateau lasting for more than 5 minutes. B-waves, described originally by Lundberg, refer to the spontaneous fluctuations occurring in the frequency range of 0.008~0.05 HZ [30,31]. C-waves refer to oscillations with a frequency of 4-8 waves/min, often termed the Mayer (M) waves [30,32]. In this study, we chose two frequency ranges that include A/B waves (around 0~0.05 HZ) and M waves (0.05~015 HZ) to be our main targets for TF analysis.

Transfer function analysis allows us to look at the character of transmission from input to output of a linear system at different frequencies. Theoretically, increases in steady-state cerebrovascular resistance or decreases in vascular compliance during cerebral vasoconstriction should be directly reflected in changes in gain and phase of the transfer function [33]. In this study, however, we found that only phase and coherence_a was consistently related to strength of autoregulation as measured by ARI. A linear relationship existed between ARI (in the range of 1 to 8) and phase at both frequencies. On the contrary, as demonstrated in Fig.2 and Fig.3, there was no relationship between gain and ARI. This might potentially be explained by the nature of transfer function characteristics of Tiecks' model (Fig.4). In Tiecks' model, phase increases along with the increase of ARI across the frequencies of interest. In

contrast, gain does not have a uniform relationship with ARI; at lower frequencies lower gain corresponded with higher ARI, whereas at higher frequencies, higher gain corresponded with higher ARI.

In order to ensure the TF analysis under the linear condition, we used high squared coherence (above 0.36) as criterion. The result showed correlations of TF gain with ARI (and Mx) did have been improved, but the remaining results did not change significantly (including the outcome analysis).

Relationship between CA indices and patients' outcome

Our results confirmed the previous findings [3, 35] of a significant reduction in ARI and an increase in Mx from favorable to unfavorable outcome in TBI patients. No significant relationships between TF parameters and outcome were detected however, which seems to suggest that they might not perform very well in distinguishing TBI patients' outcome, and perhaps other indices, like ARI and Mx should be used instead. Of those two measures, Mx(c) performed better than ARI(a), indicating that its simple qualitative, non-parametric, nature may be on average more robust than the more complex linear modelling for CA assessment in traumatic brain injury.

Moreover, the actual 'driving force' of the cerebral blood flow is cerebral perfusion pressure, not arterial blood pressure alone. In patient populations where no pathology of increased intracranial pressure is expected, changes in CPP and ABP practically amount to the same thing. However this cannot be said for traumatic brain injury where intracranial hypertension induced high amplitude ICP waves are common. In those patients neglecting ICP effects will lead to increased estimation errors, illustrated by the fact that Mxc showed better correlation with outcome than Mxa. This is in agreement with a previous study of Lewis et al [20]. However, ARI showed better relationship with outcome when using arterial blood pressure alone. This effect is a little puzzling but it could perhaps be a consequence of the additional non-linear component introduced by the ICP-moderated feedback. However, if this was true one would expect the coherence in CPP-FV model to be lower than in the ABP-FV, which was generally not the case.

Limitations

In this study, we used Transcranial Doppler technology to monitor FV for CA assessment. Due to issues with probe repositioning and fixation, it is currently only practical to make intermittent (e.g. daily) short recordings of FV and prolonged monitoring over hours and days is unfeasible. In TBI patients, with their highly dynamic course of pathology over the first few days post injury, such intermittent measurements are likely to miss development of transient pathological processes, e.g. plateau waves, that are likely to affect the final outcome, thus weakening the associations to outcome measures. More frequent TCD examinations or development of self-focusing/adjusting ultrasound probes seem to be the only ways these problems can be overcome.

Finally, we used blood flow velocity of middle cerebral artery (MCA) as a surrogate for cerebral blood flow on the basis that the diameter of MCA remains constant during the monitoring period. However, there are still some ongoing discussions about the influences of diameter changes of MCA affecting the pressure-flow relationship. Many researchers have demonstrated that cerebral blood flow velocity measurements correlated closely with changes in cerebral blood flow in healthy volunteers and patients with extracranial or intracranial artery stenosis [39,40], but whether this is also the case in severe TBI is not entirely certain.

Conclusion

This study confirms that the IR-based ARI correlates significantly with the time correlation based index Mx in TBI patients. Both parameters are significantly related to patients' outcome although Mx correlates stronger than ARI. There is also a strong relationship between ARI and phase. However, the transfer function parameters have a poor relationship with patients' outcome; we cannot therefore recommend them for autoregulation measurements in acute TBI patiemts.

Disclosure/Conflict of Interest

ICM+ Software is licensed by Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/. MC and PS have a financial interest in a fraction of the licensing fee.

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Titles and Legends to figures

Fig.1 The relationship between autoregulation index (ARI) and mean flow index (Mx). (A) ARIc and Mxc (B) ARIa and Mxa (C) ARIa and Mxc. Error bar: standard deviation. ARIa and Mxa refer ARI and Mx using arterial blood pressure (ABP) as input, ARIc and Mxc indicate ARI and Mx using cerebral perfusion pressure (CPP) as input.

Fig.2 The relationship between autoregulation index (ARI) and transfer function (TF) parameters at very low frequency (VLF) and low frequency range (LF) using cerebral perfusion pressure (CPP) as input. ARIc: ARI using CPP as input. Gain_c, phase_c and coh_c refer to the gain, phase and squared coherence between CPP and flow velocity FV. The graphs show the relationship between ARIc and gain_c at VLF (A) and LF (D); The relationship between ARIc and phase_c at VLF (B) and LF (E); The relationship between ARIc and coh_c at VLF (C) and LF (F). VLF: very low frequency, 0~0.05 HZ; LF: low frequency, 0.05~0.15 HZ. The unit for phase is degree. Error bar: standard deviation.

Fig.3 The relationship between autoregulation index (ARI) and transfer function (TF) parameters at very low frequency (VLF) and low frequency range (LF) using arterial blood pressure (ABP). ARIa: ARI using ABP as input. Gain_a, phase_a and coh_a refer to the gain, phase andsquared coherence between ABP and flow velocity FV. The graphs show the relationship between ARIa and gain_a at VLF (A) and LF (D); The relationship between ARIa and phase_a at VLF (B) and LF (E); The relationship between ARIa and coh_a at VLF (C) and LF (F). VLF: very low frequency, 0~0.05 HZ; LF: low frequency, 0.05~0.15 HZ. The unit for phase is degree. Error bar: standard deviation.

Fig.4 The upper panel shows the step response (A) and impulse response of original Tiecks' model. The lower panel shows the transfer function (TF) characteristics of Tiecks' model (C and D). (A) From bottom to top, each line represents autoregulation index (ARI) value of 0 to 9 respectively. (B) From bottom to top, the solid lines stand for ARI 9 to ARI 0. The dot line was a sample of the IR between real ABP and real FV of one patient. (C) The TF gain of Tiecks' model; (D) The TF phase of Tiecks' model.

Tables

Table 1 The result of the correlation analysis between cerebral autoregulation parameters.

Index	**Mxa**	**Phase_a**	**Phase_a**	**Gain_a**	**Gain_a**	**Coh_a**	**Coh_a**
		VLF	**LF**	**VLF**	**LF**	**VLF**	**LF**
ARIa	r =-0.38	r=0.345	r=0.254,	p>0.05	p>0.05	r=-0.178,	r=-0.079,
	p<0.00	p<0.001	p<0.001			p<0.001	p = 0.024
Index	**Mxc**	**Phase_c**	**Phase_c**	**Gain_c**	**Gain_c**	**Coh_c**	**Coh_c**
		VLF	**LF**	**VLF**	**LF**	**VLF**	**LF**
ARIc	r =-0.404,	r=0.230,	r =0.111,	p>0.05	p>0.05	p>0.05	p>0.05
	p<0.001	p<0.001,	p=0.001				

R: correlation coefficient, p <0.05 was considered to be significant relationship. Mx: mean flow index. ARI: autoregulation index. Mxa: Mx using arterial blood pressure (ABP) as input. ARIa: ARI using ABP as input. Mxc: Mx using cerebral perfusion pressure (CPP) as input; ARIc: ARI using CPP as input. VLF: very low frequency (0~0.05 HZ); LF: low frequency (0.05~0.15 HZ). Phase_a, gain_a, coh_a refer to transfer function phase/gain/squared coherence using ABP as input. Phase_c, gain_c, coh_c refer to transfer function phase/gain/squared coherence using CPP as input.

Table 2 The mean value of cerebral autoregulatio parameters of favorable and unfavorable group

Index	**Mean value of favorable outcome**	**Mean value of unfavorable outcome**	**P Value**	**F value**	**AUC**
Mxa	0.18 ± 0.24	0.26 ± 0.21	0.002	10.08	0.627
Mxc	-0.04 ± 0.29	0.09 ± 0.28	P<0.0001	15.38	0.647
ARIa	4.09 ± 1.63,	3.48 ± 1.64	0.002	9.56	0.614
ARIc	4.89 ± 1.91	4.42 ± 1.97	0.043	4.14	0.56
Phase_c VLF(degree)	52.2 ± 16.6	47.4 ± 15.4	0.016	5.82	0.582

Value format: Mean ± SD; SD.: standard deviation. p <0.05 was considered to be statistically significant. AUC : area under the curve (receiver operating characteristic analysis). Mx: mean flow index. ARI: autoregulation index. Mxa: Mx using arterial blood pressure (ABP) as input. ARIa: ARI using ABP as input. Mxc: Mx using cerebral perfusion pressure (CPP) as input; ARIc: ARI using CPP as input. Phase_c_VLF: transfer fucntion phase at very low frequency (0~0.05 HZ) using CPP as input.

Appendix

Appendix I: Characterization of cerebral autoregulation indices[15-18]

Index	Calculation	General Interpretation	AR Assessment Considerations
ARI	Compares the measured impulse response of cerebral blood flow velocity (FV) using a second order high pass filter model.	Reflects how fast the blood flow can respond to changes in blood pressure.	Traditionally requires a step change in arterial blood pressure (ABP). Can be adapted for continuous use with spontaneous ABP changes. Higher ARI indicates robust dynamic autoregulation.
TF Gain	Magnitude of the complex transfer function (between ABP and FV), averaged over a selected frequency range (slow waves)	Shows how effectively the influence of fluctuations of ABP on blood flow (or FV) is attenuated by cerebral autoregulation	Autoregulation is represented by diminished magnitude of the FV changes relative to ABP changes (low gain of transfer).
TF Phase	Phase of the complex transfer function (between ABP and FV), averaged over a selected frequency range (slow waves)	Tells us about the delay of reaction of cerebral resistive vessels to changes in transmural pressure.	Autoregulation is represented by a large phase lead from FV changes to ABP changes. Dysautoregulation is represented by a zero phase shift.
TF	Ratio between the absolute	It is a measurement of	It could potentially be used directly,

Coherence	value of cross-spectrum of ABP and FV and product of their power spectrums	linear association between input and output as a function of frequency.	with values close to 1 denoting completely absent autoregulation and values close to 0 indicating fully functional autoregulation. Alternatively coherence could be used as a quality control tool for phase and gain estimation.
Mx	A moving, linear correlation coefficient between ABP and FV.	Performed in the time domain, describes the stability of cerebral blood flow during changes in cerebral perfusion pressure in the low frequency bandwidth (below 0.05 Hz). It reflects the shape of Lassen's curve.	Functional autoregulation is represented by a lack or negative correlation between ABP and FV.

Mx: mean flow index. ARI: autoregulation index. TF: transfer function.

Appendix II : Impulse response of Tiecks' Model

The ten reference step responses of Tiecks' model are calculated using a second-order-equation (E1-E4) by providing 10 carefully selected sets of 4 parameters: time constant T, damping factor D, autoregulatory dynamic gain K [1]. ARI 0 means that the changes in FV follow entirely the changes in ABP and thus

reflect completely abolished autoregulation. ARI 9, on the other hand, means that FV returns to the baseline value rapidly and therefore indicates highly effective autoregulation. In the original Tiecks' model, p(n) is the normalized change in ABP from its baseline value (the value before ABP drop). However, here impulse signal is the input and the baseline signal is assumed to be 0, so p(n) equals to the impulse ABP signal. V (n) in Equation 4 presents the flow velocity, and in this study, it means impulse response of Tiecks' model. f represents the sampling frequency. x1 and x2 are just intermediate variables, which were assumed to be equal to 0 at the beginning. Fig.4 shows the step response (A) and impulse response of original Tiecks' model (B). An example of the comparison between the estimated IR (dot line) from one patient and the IR of Tiecks' model (solid lines) is shown in the Fig.4B. The squared error between the real IR and the modelled curve of ARI 3 was smallest. Therefore, we defined the ARI value of this patient as 3.

$$p(n) = \begin{cases} 0, & n \neq 1; \\ 1, & n = 1; \end{cases} \quad \text{(E1)}$$

$$x_1(n) = x_1(n-1) + \frac{P(n) - x_2(n-1)}{f \cdot T} \quad \text{(E2)}$$

$$x_2(n) = x_2(n-1) + \frac{x_1(n) - 2D \cdot x_2(n-1)}{f \cdot T} \quad \text{(E3)}$$

$$V(n) = 1 + P(n) - K \cdot x_2(n) \quad \text{(E4)}$$

Appendix III Abbreviations used in this study

1. ABP: Arterial Blood Pressure
2. ICP: Intracranial Pressure
3. FV: Flow Velocity
4. CA: Cerebral Autoregulation
5. CPP: Cerebral Perfusion Pressure
6. ARI: Autoregulation Index
7. Mx: Mean flow index
8. TF: Transfer function

9. TBI: Traumatic Brain Injury Patient 10. ROC: receiver operating characteristic analysis

11. AUC : area under the curve 12. SD: standard deviation

13. VLF: Very Low Frequency, 0~0.05 HZ 14. LF: Low Frequency range, 0.05~0.15 HZ

15. Phase_a_VLF: Phase between ABP and FV at very low frequency

16. Phase_a_LF: Phase between ABP and FV at low frequency

17. Phase_c_VLF: Phase between CPP and FV at very low frequency

18. Phase_c_LF: Phase between CPP and FV at low frequency

19.Gain_a_VLF: Gain between ABP and FV at very low frequency

20.Gain_a_LF: Gain between ABP and FV at low frequency

21.Gain_c_VLF： Gain between CPP and FV at very low frequency

22. Gain_c_LF： Gain between CPP and FV at low frequency

23. Coh_a_VLF：Squared Coherence between ABP and FV at very low frequency

24. Coh_a_LF：Squared Coherence between ABP and FV at low frequency

25.Coh_c_VLF：Squared Coherence between CPP and FV at very low frequency

26.Coh_c_LF：Squared Coherence between CPP and FV at low frequency