Cerebral autoregulation monitoring in acute traumatic brain injury: what's the evidence?

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Abstract:

Cerebral autoregulation is conceptualized as a vascular self-regulatory mechanism within the brain. Controlled by elusive relationships between various biophysical processes, it functions to protect the brain against potential damages caused by sudden changes in cerebral perfusion pressures and flow. Following events such as traumatic brain injuries (TBI), autoregulation may be compromised, potentially leading to an unfavorable outcome.

In spite of its complexity, autoregulation has been able to be quantified non-invasively within the neuro-critical care setting with the aid of transcranial Doppler. This information is interpreted particularly through calculated derived indices based on commonly-monitored input signals such as arterial blood pressure and intracranial pressure (i.e. Pressure reactivity index (PRx), mean flow index (Mx), etc.). For example, PRx values that trend towards positive numbers are correlated with

unfavorable outcome. These predictors are primarily surrogate markers of cerebral hemodynamic activity, although suggesting robust correlations between these indices and patient outcome.

This review of the literature seeks to explain the methodology behind the calculations of various measures of autoregulation in adult patients suffering from traumatic brain injuries, and how they can interact with one another to both create larger effects on patient outcome and general outcome prediction models. Insight into the driving forces behind cerebral autoregulation is imperative for guiding both clinical decision-making and global treatment protocols for neuro-critically ill patients. The evidence that autoregulation-oriented therapy may improve outcome after TBI is still oscillating around Level III.

Key Words: cerebral autoregulation, traumatic brain injury, pressure reactivity index, intracranial pressure, cerebral perfusion pressure, transcranial Doppler, near-infrared spectroscopy

Introduction:

Cerebral autoregulation is the inherent capability of the brain to regulate cerebral blood flow across a range of blood pressure within the cranial cavity. During certain pathological conditions, such as traumatic brain injury (TBI), it can be depleted. Autoregulation can often be a complicated concept both to define and to understand, as it is dependent upon biochemical and physiological interactions that have yet to be completely illustrated. Autoregulation has previously been described as a delicate balancing act between vasoconstriction and vasodilation as the resistance of the cerebrovascular bed adapts[1,2] to both sudden and slow dynamic changes in cerebral perfusion pressure (CPP), a product of the arterial blood pressure (ABP) and the intracranial pressure (ICP).

The mechanisms involved in autoregulation are not fully understood. Various theories have been suggested, including: metabolic, endothelial, myogenic, and neurogenic factors leading to the regulation of vessel caliber. To date, it is unclear which of these mechanisms predominate in the control of cerebral arterial vessel caliber[3]. The metabolic theory postulates that byproducts of cerebral metabolism lead to alterations in vessel diameter. However, the changes in extra-cellular metabolic byproducts is relatively slow in relation to the rapid response of the cerebral vasculature, thus it may not be integral in autoregulatory control[3]. Endothelial factors, such as nitric oxide synthase (NOS) and endothelin (ET), are expressed as a function of the flow-related stresses encountered by the endothelium. It is plausible to consider these endothelial mediators as a potential key player in preserved and deranged autoregulatory states[3]. Myogenic autoregulatory theories revolve around the concept of flow-related stress on the vascular smooth muscle, leading to reflexive changes in vessel diameter secondary to varied smooth muscle tone[3] Both myogenic and endothelial mechanisms probably overlap, forming one reflex, known as autoregulation: CBF remaining independent on changing cerebral perfusion pressure. Finally, the neurogenic hypothesis focuses on neurotransmitter-mediated changes in vascular tone, which are believe to stem from fluctuations in sympathetic/parasympathetic output to the tunica media[3]. One or more of these mechanisms may be the driver(s) of autoregulatory

control, and are likely subject to derangements depending on the individual host response to injury during various neuropathologic conditions[3].

Autoregulation can be disrupted following traumatic intra-cerebral hemorrhages and contusions, for example, and is theorized to be a multifactorial event process. Cerebral structural integrity can be compromised by injury, leading to the scrambled communication between metabolic demand and delivery pathways to the brain via blood vessels, or this can occur in the reverse order. However, the appearance of injury severity is not the decisive factor in determining the ability of the brain to recover its disposition towards this protective mechanism. Prediction of patient outcome in adult TBI is difficult; primarily correlational assessment methods of surrogate markers are relied upon for investigation into autoregulation (i.e., pressure reactivity index (PRx), mean flow velocity (Mx), oxygen pressure reactivity index (ORx), etc.). One tool that may play a more important role in the determination of autoregulatory status in the neurocritical care setting is the application of transcranial Doppler (TCD) following traumatic brain injury. TCD can detect irregularities in cerebral blood flow, providing diagnostic value for secondary insults like cerebral vasospasm. Residual autoregulatory capacity is then described by TCD as "either the speed or the direction of changes" of flow velocity in the face of fluctuations in arterial blood pressure[4]. Figures 1A and IB demonstrate the effects of variable ABP and ICP on blood flow velocity in animal models using TCD[5-7].

However, the management of autoregulation has not been standardized in neuro-critical care centers, primarily due to lack of "dedicated autoregulation monitors"[8]. As autoregulation seems to play a crucial role in patient treatment and outcome, countering these problems is in the best interest of both patients and supervising clinicians. Although forms of continuous monitoring are ideally preferred, there are no definitive methods to use or protocols to follow. Despite these limitations, there is a strong confirmation from multiple worldwide centers to calculate the pressure reactivity index (PRx) to gauge the level of autoregulatory impairment in patients suffering from traumatic brain injuries[9]. In compliance with the most recent Brain Trauma Foundation guidelines[10,11], reasserting control of cerebral autoregulation is an important goal of the early stages of treatment. The questions of how best to quantify measures of autoregulation and additionally, how to interpret this information for directing patient management return many, often conflicting, answers. The aim of this brief review is to explore some of the more popular derived indices of autoregulatory control mechanisms using TCD within the neuro-critical care setting, and to compare how these parameters interact with PRx to influence patient outcome after trauma. A comparison of relevant methods of the assessment of autoregulation and their respective relationships with outcome are listed in Table 1, with: PRx, mean flow index (Mx), NIRS-based spatially-resolved indices and brain tissue oxygenation ($PbtO_2$) -based oxygen reactivity index (ORx) highlighted. Finally, the advantages and disadvantages of each parent monitoring device are outlined in Table 2.

Pressure Reactivity Index (PRx)

PRx and Patient Outcomes

PRx, and subsequently, outcome, is affected by interrelationships between such parameters as mean arterial pressure (MAP), ICP, and CPP[12]. These components need to be controlled to drive minimal values of PRx, as appropriate vessel diameter modifications spurred by vascular smooth muscle cells ensure the protection of the brain [13,14]. However, emerging evidence indicates that PRx may be affected by many other factors including red blood cell transfusion[15], alterations in temperature[16], or arterial glucose concentration[17].

The PRx is calculated as the moving linear correlation coefficient between MAP and ICP, from 30 consecutive samples binned into 10-second data windows[18]. PRx values at or below 0 reflect intact autoregulatory reserves. PRx values above 0 indicate the increasing passivity of the cerebrovascular bed, in which variations in arterial blood pressure directly influence increases or decreases in ICP. This inability of the brain to discriminate the ABP and ICP input, and to mediate vasoconstriction or vasodilation accordingly is a predictor of poor outcome. Ideally, in the attempt to preserve cerebral autoregulation, these indices should not be co-dependent, as cerebrovascular passivity intimates a global autoregulatory disturbance. The utilization of computerized ABP and ICP monitoring to produce the PRx as a correlation coefficient has shown to be a robust predictor of outcome following rises in intracranial pressure (ICP). Sorrentino et al.[19] described critical values of PRx that maximized the difference between patients who died (PRx = 0.25) and those with a more favorable outcome (PRx = 0.05).

The inherent capacity for this neuroprotective mechanism deteriorates with age[20], but is especially compounded by TBI[18]. The age of patients may serve as a predisposition to secondary insults, with natural aging processes affecting the reactivity of the cerebrovascular bed[20]. The impaired state of the brain after injury makes it even more vulnerable to and uncompromising with sudden changes in ICP and CPP[21]. For example, large reductions in CPP lead to arteriolar dilations, which in turn decrease cerebovascular resistance, and vice versa[22]. Therefore, the elderly TBI population may be more vulnerable to secondary brain injuries caused by reductions in CPP.

Interactions of PRx with Cerebral Metabolic Factors

In combination with CPP, brain tissue oxygenation ($PbtO_2$) is theorized to act as a surrogate marker of cerebral blood flow, taking tissue oxygenation pressure into account[23]. Disturbances in cerebral blood flow after severe head injury directly contribute to the brain's inability to adjust vessel diameter in response to transmural pressure demands. Microdialysis can aid in the detection of TBI-mediated cerebral metabolic changes. Common markers include glucose, lactate, pyruvate, glutamate, glycerol, and the lactate/pyruvate ratio. The relative concentrations of these parameters are associated with outcome. For instance, Timofeev et al.[24] quantified the lactate/pyruvate ratio as a surrogate marker of cerebral metabolism, showing that higher values (>25) reflect an independent association with patient mortality attributable to either mitochondrial dysfunction or a lack of oxygen supply in the brain.

Further assessment of these additional factors' effects on PRx can be useful in outcome prediction. Steiner et al.[25]questioned the role of cerebral metabolic dysfunction in suboptimal PRx, and

subsequently, outcome. The global cerebral metabolic rate of oxygen ($CMRO_2$) was hypothesized to play a role in the incidence of dysautoregulation explained by PRx that could prime patients for secondary insults to the brain (i.e. ischemia, hyperemia, etc.). Ang et al.[26], posited similar oxygen disturbances in lesioned tissue as evidence of autoregulatory failure. An inverse relationship between $CMRO_2$ and PRx was determined, but the effects of the two could not pinpoint the underlying causes of poor outcome, or the dynamics and concentrations of blood in the lesioned part of the brain. Autoregulatory status is important for neuro-intensive care management. Autoregulation depends on CPP to balance cerebral blood flow and cerebral metabolism[25]. Elevated CPP can predispose patients to cerebral metabolic failure (demonstrated by decreased $CMRO_2$), and thus can potentially drive autoregulatory failure. However, there is currently no data available to firmly suggest that changing local metabolics would lead to improved autoregulation, although support for the theory that metabolic derangements are associated with unfavorable PRx is leant by the work of Timofeev et al.[24]. It remains to be proven that cerebral metabolic alterations will influence patient outcome; for example, $CMRO_2$ signal decreases may be a downstream consequence of autoregulatory failure[25].

Application of PRx to Optimize Cerebral Perfusion Pressure (CPP_{OPT})

The autoregulatory response to CPP changes has been demonstrated within the physiological boundaries of 50-100 mmHg, with some studies showing evidence of CPP values above this upper bound[27,28]. Drastic CPP variations after TBI can greatly affect a patient's chances of survival, and additionally, functional outcome[1]. The progressive failure of autoregulation with falling CPP can predict the incidence of secondary, potentially intractable insults to the brain such as delayed cerebral ischemia, vasospasm, etc. However, increasing CPP past a "safe" range could lead to hyperperfusion (current guidelines stipulate that CPP should rest between 60-70 mm Hg) which has been associated with risk of edema or leakages through the blood-brain barrier, as well as potential cardiac or respiratory distress[10].

To simplify cerebral vasoreactivity as a direct measure of pressure and flow, it is perhaps best to explain it by its relationship with CPP[29]. PRx is the regression between ICP and blood pressure, and CPP is the difference between blood pressure and ICP. PRx has been used to derive an optimal CPP (CPP_{OPT}) in traumatic brain-injured patients[1]. CPP_{OPT} is determined from the lowest PRx value plotted against all of the CPP values within a recorded period (usually 4 hours). This often results in a simple to comprehend U-shaped curve in which CPP_{OPT} is the minimum value found at the base of the curve (Figure 2). On the further suggestion of Steiner et al.[30] with CPP_{OPT} determined as the lowest-measured plotted average of PRx trends, it may be sensible to continually direct patient management towards 0 or negative values in accordance with CPP_{OPT} treatment protocols based on pressure autoregulatory capacity to protect the patient's autoregulatory mechanism[22,31,32].

Yet, individualized CPP_{OPT} values may not be contained within the boundaries of 60-70 mm Hg, as evidenced by Figure 2, which features a CPP_{OPT} value at 91.14 mm Hg. Some patients may achieve a more stable PRx at CPP_{OPT} above or below the advised "safe" range, an observation which has led research to examine the benefits of CPP_{OPT} therapies that are separately tailored to each patient, to reduce incidences of secondary injuries across the board[4,22,25,33]. A recent systematic review conducted by Needham et al.[1] reaffirms the importance of safeguarding against mortality by treating each patient in accordance with his or her individually-determined target CPP_{OPT} to maximize cerebrovascular reactivity.

Criticisms of PRx

The original definition of PRx functions as a descriptor of "graded loss of autoregulation"[30], raising the question of whether it is possible to incorporate PRx into CPP management protocols, yielding an autoregulatory therapy (perhaps indexed as PRx_{OPT}). Steiner et al.[30] assessed the effect of time on PRx and posited that disturbed PRx (reported as PRx >0.2) for a period of six hours was a strong predictor of patient mortality. Corresponding CPP values during these observations were analyzed for deviations from calculated CPP_{OPT}, however, CPP_{OPT} was unable to be defined in some cases, demonstrating that autoregulation-oriented therapy is difficult to implement because it is nearly impossible to guarantee the consistency of curve-fitting between surrogate measures of autoregulation. CPP_{OPT} fundamentally requires an index of vascular reactivity for its calculation, in addition to high-frequency data examined every four hours to create time points[34]. Table 2 at the end of this manuscript provides an in-depth description of the strengths and limitations of PRx and other continuous autoregulatory indices.

Aries et al.[35] similarly found an obstacle to the design of PRx-guided therapy, stating that the fundamental calculation of PRx as a function of arterial blood pressure and intracranial pressure assumes that the vacillations of cerebrovascular resistance are coupled with those of cerebral blood volume, inducing the direction of ICP towards higher values when intracranial compliance is low, and vice versa. The necessity of this pairing is problematic for independent models of PRx-guided therapy protocols, as PRx is a "noisy" derived index requiring a higher signal-to-noise ratio and time-domain analysis[35]. To counter this, Aries et al.[35] put forth the proposition of PAx (the index of the intracranial pressure waveform amplitude) as a modification of PRx that is "potentially independent" of ICP fluxes that could affect the validity of PRx as a true measure of autoregulation[36].

Finally, the plot showing the distribution of PRx along various CPP values, contains lot of intrinsic calculations. It is PRx: correlation of ABP and ICP, versus difference: ABP minus ICP. It may be possible that the U-shape of this relationship may be derived from the nature of mathematical transformations, rather than a physiological relationship.

Mean Blood Flow Velocity Index (Mx)

The first two days after admission constitute a critical period of autoregulatory equilibration[18, 37]. TCD recordings can judge the ability of these patients to autoregulate despite random fluctuations of cerebral perfusion pressure. In this same report by Czosnyka et al[38]., the Mx was derived from the correlation coefficient between mean flow velocity (mFV) within the middle cerebral artery (MCA) and cerebral perfusion pressure (an example of this is presented in Figure 3). The MCA is assumed to have a constant diameter, although this has yet to be truly validated[39,40]. Overall patient outcome (dichotomized into "favorable" and "unfavorable" outcome) appeared to be largely affected by positive values of Mx within this timeframe, regardless of whether Mx "recovered" to negative values during the patient's course of stay.

PRx and Mx have been suggested to describe different components of the autoregulatory mechanism and it has been suggested that Mx is a better predictor of functional outcome than of mortality,[13,41] (PRx is more discriminatory for survival versus mortality); however, both demonstrate U-shaped curves when plotted against CPP and additionally are directly responsive to alterations of ICP[12]. High values of Mx and PRx insinuate the inability of the cerebral vasculature to regulate cerebral blood flow as measured by either of these parameters[14]. The utility of TCD was further affirmed by Panerai et al.[42], who compared the quality of the measurement to the sensitivity of gradient-echo magnetic resonance imaging (MRI) sequences as a marker of blood flow velocity changes attributable to injury and pathology in patients suffering from acute ischemic stroke. However, TCD recordings are generally short (< 1 hour), and only able to provide a snapshot of activity within the brain. Additionally, there are technical concerns with the device itself, as variable TCD probe placement and non-guaranteed inter-operator validity cast some doubts on the acceptance of the technique[43]. The relative strengths and limitations of TCD-based assessments are detailed further in Table 2.

Lang et al. (2003)[44] used Mx with TCD to gauge autoregulation in a cohort of TBI patients. Recalling that Mx is a continuous measure of slow, spontaneous changes in CPP and cerebral blood flow volume (CBFV) applied for the examination of MCA blood flow regularity[45], this research group attempted to produce the same results with Mx values derived from each of the separate input signals of ABP and CPP. Despite revealing a non-significant difference between the discriminatory powers of these two input signals, Lang et al. (2003)[44] cautioned that Mx as a function of CPP necessitates invasive ICP data collection to produce CPP calculations, whereas Mx as a function of ABP does not. As non-invasive measures of autoregulatory status are prioritized, it seems much more likely for Mx derived from ABP as the input to become a routine TCD index than would its counterpart when invasive monitoring is undesirable. However, in a more recent study in a larger cohort of patients (n=288), Liu et al., 2015[46] compared Mx derived from both ABP and CPP in outcome prediction, finding CPP to be the superior input signal.

Budohoski et al.[47] compared the effects of various components of flow velocity (FV) on transcranial Doppler analysis. Citing the calculation of autoregulatory markers as dissociable correlations between systolic, diastolic, and mean blood flow parameters, the authors hypothesized that autoregulatory information is primarily disseminated by examination of the FV waveform rather than the ABP or CPP waveforms. The former may instead serve as "triggers" for autoregulation[47]. The FV waveform was resolved into its constituents systolic (Sx) and diastolic (Dx), and compared with mean flow velocity (Mx) in separate analyses using the input signals of ABP and CPP. CPP was determined to be the better input signal, with systolic flow indices (Sx) most significantly predicting both outcome and mortality (followed by Mx and then Dx), suggesting that relative values of dynamic components of FV should be used when assessing autoregulation in TBI patients with TCD[47].

Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) provides a continuous, dynamic measure of cerebral autoregulation through the calculation of the tissue oxygenation index TOx (used interchangeably with the cerebral oximetry index, COx), the moving correlation coefficient between invasive ABP and regional oxygen saturation (rSO_2) over 30 consecutive samples averaged over 10 seconds[48]. Cerebral oxygenation is obtained non-invasively by affixing optodes to a patient's forehead, which capture the light emitted

from a single laser diode in the near-infrared spectrum that penetrates the superficial cerebral tissues. rSO_2 is displayed by NIRS as the tissue oxygenation index, a compilation of the concentrations of oxygenated, deoxygenated, and total hemoglobin in region, parameters which can be further dissociated by their absorption spectra[49,50,51]. NIRS has been verified as an alternative technique through which to describe autoregulation in TBI patients when ICP monitors are declared unfeasible by the nature of pathology. Additionally, NIRS is not operator-dependent like TCD, which makes it more accessible to clinicians. However, NIRS can be confounded by factors such as the presence of frontal contusions, which can complicate optode placement[49].

TOx is invasive, requiring an arterial catheter for the ABP input signal[48]. Similar to the acquisition of CPP_{OPT} by PRx, recorded ABP values can be plotted against TOx, producing a curve-fitted "ABP_{OPT}" as the lowest-associated TOx[48,49]. Highton et al.[50] applied ICP, TCD, and NIRS to compare the agreements between PRx, Mx, and TOx in predicting autoregulatory failure. They found that both PRx and Mx were significantly correlated with TOx, although there was incomplete agreement between the reactivity indices[50]. The NIRS-derived total hemoglobin reactivity index (THx), the correlation coefficient between the total hemoglobin index (THI =oxygenation + deoxygenated) and ABP, has been suggested as analogous to PRx[52]. THI used in this calculation is described by Diedler et al.[52] as "a normalized measure of [total] hemoglobin concentration and thereby provides a tracer of cerebral blood volume". NIRS-based THx has been suggested as a non-invasive substitute for PRx, supporting the PRx-THx association reported by Zweifel et al.[49], who posited that ABP can provide a "reasonable approximation" of CPP. Later work by Dias et al.[53] examined the calculation of CPP_{OPT} with TOx instead of PRx, although the results of that single-center study have yet to be confirmed as evidence of the influence of NIRS for CPP_{OPT} determination. Further details on the relative strengths and limitations of the application of NIRS for autoregulatory assessment are available in Table 2.

Oxygen Reactivity Index (ORx)

Collating analog MAP, ICP, CPP, and brain tissue oxygen ($PbtO_2$) data from double-lumen skull bolts (Licox IM2, Integra NeuroSciences Inc.) inserted in the right frontal region of the brain, Jaeger et al.[31] calculated the oxygen pressure reactivity index (ORx) as a moving correlation coefficient between CPP and the invasively-quantified $PbtO_2$. They discovered parallels between the scoring of ORx and that of PRx to measure whether a patient is capable of autoregulating. (Table 2 compares ORx to PRx as has been documented within the existing body literature). Similar to PRx, ORx values range between -1 and 1, with a positive, passive relationship between $PbtO_2$ and CPP indicating impaired autoregulation. Figure 4 describes this relationship.

Conclusion:

Cerebral autoregulation is not fully elucidated, but it is widely agreed-upon that disturbed autoregulation directly influences outcome following TBI. This selective review of the existing body of literature confirms that the concept of autoregulation is difficult to model, and even more so to mediate. Intricate relationships between blood flow and blood pressure govern calculations of derived indices of autoregulation, such as that of PRx and Mx, which are suitable for continuous monitoring.

Assessments of autoregulation, heavily reliant on non-invasive transcranial Doppler analysis of blood flow within the middle cerebral artery, can provide deeper insight into autoregulation available, although this notion is challenged by both mechanical and data-driven criticism of TCD monitoring. Near-infrared spectroscopy can be considered as promising technology, but is still awaiting strong proofs. Despite the absence of a true marker of autoregulatory capacity, the control of this mechanism is a central feature of neuro-critical care management plans, whether treating patients in accordance with either ICP- or CPP-oriented protocols.

Key Messages:

- Cerebral autoregulation regulates cerebral blood flow, and is vulnerable to TBI. Residual autoregulatory capacity can be affected by combinations of structural and metabolic imbalances, which influence outcome prediction following TBI.
- Non-invasive determinations of autoregulatory status through the application of TCD and NIRS can direct ICP- or individual CPP_{OPT} - based therapies. These techniques carry very little risk of patient disturbance or of infection.
- Cerebral autoregulation cannot yet be directly measured, but can be quantified through such surrogate markers as PRx, CPP_{OPT}, Mx, etc. in neuro-critical care settings. Favorable outcome, for example, has been associated with low or negative values of PRx, Mx, and ORx.

References:

1. Needham E, McFadyen C, Newcombe V, Synnot AJ, Czosnyka M, and Menon D. Cerebral Perfusion Pressure Targets Individualized to Pressure-Reactivity Index in Moderate to Severe Traumatic Brain Injury: A Systematic Review. J. Neurotrauma 2017;34:963-970.
2. Willie CK, Tzeng Y, Fisher JA, and Ainslie PN. Integrative Regulation of Human Brain Blood Flow. J. Physiol. 2014;592:841-859.
3. Youmans JR, Winn HR. Youmans Neurological Surgery. 6th ed. Vol. 4. Ch.343. Philadelphia, PA: Elsevier/Saunders;2011.
4. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA, and Pickard JD. Clinical Relevance of Cerebral Autoregulation Following Subarachnoid Hemorrhage. Nat. Rev. Neurol. 2013;9:152–163.

5. Brady K, Lee J, Kibler K, Easley RB, Koehler RC, and Shaffner DH. Continuous Measurement of Autoregulation by Spontaneous Fluctuations in Cerebral Perfusion Pressure: Comparison of 3 Methods. Stroke 2008;39:2531-2537.
6. Donnelly J, Czosnyka M, Harland S, Varsos GV, Cardim D, Robba C, et al. Cerebral Haemodynamics During Experimental Intracranial Hypertension. J. Cereb. Blood Flow Metab. 2016;37:694-705.
7. Brady KM, Easley RB, Kibler K, Kaczka DW, Andropoulos D, Fraser CD, et al. Positive End-Expiratory Pressure Oscillation Facilitates Brain Vascular Reactivity Monitoring. J. Appl. Physiol. 2012;113:1362–8.
8. Czosnyka M and Miller C. Monitoring of Cerebral Autoregulation. Neurocrit. Care 2014;21: S95-S102.
9. Lazaridis C, DeSantis S, Smielewski P, Menon DK, Hutchinson P, Pickard JD et al. Patient-Specific Thresholds of Intracranial Pressure in Severe Traumatic Brain Injury. J. Neurosurg. 2014;120:893-900.
10. Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury: 4th Edition [Internet]. Guidelines for the Management of Severe Traumatic Brain Injury. Brain Trauma Foundation; 2016 [cited 2017Feb16]. Available from: https://www.braintrauma.org/uploads/13/06/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf.
11. Carney N, Totten AM, O'Reilly C, Chesnut RM, Coplin W, Ghajar J, et al. Guidelines for the Management of Severe Traumatic Brain Injury. Neurosurgery 2016.
12. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, et al. Impairment of Cerebral Autoregulation Predicts Delayed Cerebral Ischemia After Subarachnoid Hemorrhage: A Prospective Observational Study. Stroke 2012;43:3230-3237.

13. Sánchez-Porras R, Santos E, Czosnyka M, Zheng Z, Unterberg AW, and Sakowitz OW. 'Long' Pressure Reactivity Index (L-PRx) as a Measure of Autoregulation Correlates with Outcome in Traumatic Brain Injury Patients. Acta Neurochirurgica 2012;154:1575-1581.
14. Budohoski KP, Czosnyka M, de Riva N, Smielewski P, Pickard JD, Menon DK, et al. The Relationship Between Cerebral Blood Flow Autoregulation and Cerebrovascular Pressure Reactivity After Traumatic Brain Injury. Neurosurgery;71:652–661.
15. Sekhon MS, Griesdale DE, Czosnyka M, Donnelly J, Liu X, Aries MJ, et al. The Effect of Red Blood Cell Transfusion on Cerebral Autoregulation in Patients with Severe Traumatic Brain Injury. Neurocrit. Care 2015;23:210–216.
16. Lavinio A, Timofeev I, Nortje J, Outtrim J, Smielewski P, Gupta A, et al. Cerebrovascular Reactivity During Hypothermia and Rewarming. Br. J. Anaesth. 2007;99:237–44.
17. Donnelly J, Czosnyka M, Sudhan N, Varsos GV, Nasr N, Jalloh I, et al. Increased Blood Glucose is Related to Disturbed Cerebrovascular Pressure Reactivity After Traumatic Brain Injury. Neurocrit. Care 2014;22:20–5.
18. Czosnyka M, Smielewski P, Kirkpatrick, PJ, Laing RJ, Menon D, and Pickard JD. Continuous Assessment of the Cerebral Vasomotor Reactivity in Head Injury. Neurosurgery 1997;41: 11-19.
19. Sorrentino E, Diedler J, Kasprowicz M, Budohoski KP, Haubrich C, Smielewski P, et al. Critical Thresholds for Cerebrovascular Reactivity After Traumatic Brain Injury. Neurocrit. Care 2012;16:258-266.
20. Czosnyka M, Balestreri M, Steiner LA, Smielewski P, Hutchinson PJ, Matta B, et al. Age, Intracranial Pressure, Autoregulation, and Outcome After Brain Trauma. J. Neurosurg. 2005;102:450-454.

21. Sykora M, Czosnyka M, Liu X, Donnelly J, Nasr N, Diedler J, et al. Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuroimaging Study. Crit. Care Medicine 2016;44:1173-1181.
22. Schmidt JM and Kummer BR. Clinical Decision Support for Cerebral Perfusion Optimization After Traumatic Brain Injury. Crit. Care Medicine 2016;44: 1958-1960.
23. Jaeger M, Dengl M, Meixensberger J, and Schuhmann MU. Effects of Cerebrovascular Pressure Reactivity-Guided Optimization of Cerebral Perfusion Pressure on Brain Tissue Oxygenation after Traumatic Brain Injury. Crit. Care Medicine 2010;38:1343-1347.
24. Timofeev I, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, et al. Cerebral Extracellular Chemistry and Outcome Following Traumatic Brain Injury: A Microdialysis Study of 223 Patients. Brain 2011;134:484-494.
25. Steiner LA, Coles JP, Czosnyka M, Minhas PS, Fryer TD, Aigbirhio FI, et al. Cerebrovascular Pressure Reactivity is Related to Global Cerebral Oxygen Metabolism After Head Injury. J. Neurol., Neurosurg., Psychiatry 2003;74:765-770.
26. Ang BT, Wong J, Lee KK, Wang E, and Ng I. Temporal Changes in Cerebral Tissue Oxygenation with Cerebrovascular Pressure Reactivity in Severe Traumatic Brain Injury. J. Neurol., Neurosurg., Psychiatry 2007;78:298-302.
27. Len TK and Neary JP. Cerebrovascular Pathophysiology Following Mild Traumatic Brain Injury. Clinical Physiology and Functional Imaging 2011;31:85-93.
28. Cecil S, Chen PM, Callaway SE, Rowland SM, Adler DE, and Chen JW. Traumatic Brain Injury: Advanced Multimodal Neuromonitoring From Theory to Clinical Practice. Critical Care Nurse 2011;31:25-37.
29. Rosenthal G, Sanchez-Mejia RO, Phan N, Hemphill JC, Martin C, and Manley GT. Incorporating a Parenchymal Thermal Diffusion Cerebral Blood Flow Probe in Bedside Assessment of

Cerebral Autoregulation and Vasoreactivity in Patients with Severe Traumatic Brain Injury: Clinical Article. J. Neurosurg. 2011;114:62-70.

30. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, et al. Continuous Monitoring of Cerebrovascular Pressure Reactivity Allows Determination of Optimal Cerebral Perfusion Pressure in Patients with Traumatic Brain Injury. Crit. Care Medicine 2002;30:733-738.
31. Jaeger M, Schuhmann M, Soehle M, and Meixensberger J. Continuous Assessment of Cerebrovascular Autoregulation After Traumatic Brain Injury Using Brain Tissue Oxygenation Pressure Reactivity. Crit. Care Medicine 2006;34:1783-1788.
32. Depreitere B, Güiza F, Van Den Berghe G, Schuhmann MU, Maier G, Piper I, et al. Pressure Autoregulation Monitoring and Cerebral Perfusion Pressure Target Recommendation in Patients with Severe Traumatic Brain Injury Based on Minute-by-Minute Monitoring Data. J. Neurosurg. 2014;120:1451-1457.
33. Donnelly J, Aries MJ, and Czosnyka M. Further Understanding of Cerebral Autoregulation at the Bedside: Possible Implications for Future Therapy. Expert Rev. Neurother. 2015;15: 169-185.
34. Guiza F, Depreitere B, Schuhmann M, Van Den Berghe G, and Meyfroidt G. Development of a Low-Frequency Autoregulation Index for Calculation of Optimal CPP in Severe Traumatic Brain Injury. J. Crit. Care 2012;28: e8.
35. Aries MJ, Czosnyka M, Budohoski KP, Kolias AG, Radolovich DK, Lavinio A, et al. Continuous Monitoring of Cerebrovascular Reactivity Using Pulse Waveform of Intracranial Pressure. Neurocrit. Care 2012;17: 67-76.
36. Tan CO and Taylor JA. Integrative Physiological and Computational Approaches to Understand Autonomic Control of Cerebral Autoregulation. Exp. Physiol. 2014;99:3-15.

37. Hlatky R, Furuya Y, Valadka, AB, Gonzalez J, Chacko A, Mizutani Y, et al. Dynamic Autoregulatory Response After Severe Head Injury. J. Neurosurg. 2002;97:1054-1061.

38. Czosnyka M, Smielewski P, Kirkpatrick PJ, Menon DK, and Pickard JD. Monitoring of Cerebral Autoregulation in Head-Injured Patients. Stroke;27:1829-1834.

39. Verbree J, Bronzwaer A-SGT, Ghariq E, Versluis MJ, Daemen AP, van Buchem MA, et al. Assessment of Middle Cerebral Artery Diameter During Hypocapnia and Hypercapnia in Humans Using Ultra-High-Field MRI. J. Appl. Physiol. 2014;117:1084-1089.

40. Wilson MH, Edsell MEG, Davagnanam I, Hirani SP, Martin DS, Levett DZ, et al. Cerebral Artery Dilatation Maintains Cerebral Oxygenation at Extreme Altitude and in Acute Hypoxia--an Ultrasound and MRI Study. J. Cereb. Blood Flow Metab. 2011;31:2019–2029.

41. Schmidt B, Reinhard M, Lezaic V, McLeod DD, Weinhold M, Mattes H, et al. Autoregulation Monitoring and Outcome Prediction in Neurocritical Care Patients: Does One Index Fit All? J. Clin. Monit. Comput. 2016;30:367-375.

42. Panerai RB, Jara JL, Saeed NP, Horsfield MA, and Robinson TG . Dynamic Cerebral Autoregulation Following Acute Ischemic Stroke: Comparison of Transcranial Doppler and Magnetic Resonance Imaging Techniques. J. Cereb Blood Flow Metab. 2015;1-9.

43. Minciotti P, Ceravolo MG, and Provinciali L. Inter-Examiner Variability of Transcranial Doppler Procedure and Reports: A Multicenter Survey. The Italian Journal of Neurological Sciences 1997;18:21-30.

44. Lang EW, Lagopoulos J, Griffith J, Yip K, Mudaliar Y, Mehdorn HM, et al. Noninvasive Cerebrovascular Autoregulation Assessment in TBI: Validation and Utility. J. Neurotrauma 2003;20:69-75.

45. Lang EW, Mehdorn HM, Dorsch NWC, and Czosnyka, M. Continuous Monitoring of Cerebrovascular Autoregulation: A Validation Study. J. Neurol., Neurosurg., Psychiatry 2002;72:583-586.

46. Liu X, Czosnyka M, Donnelly JD, Budohoski KP, Varsos GV, Nasr N, et al. Comparison of Frequency and Time-Domain Methods of Assessment of Cerebral Autoregulation in Traumatic Brain Injury. J. Cereb. Blood Flow Metab. 2015;35:248-256.

47. Budohoski KP, Reinhard M, Aries MJ, Czosnyka Z, Smielewski P, Pickard JD, et al. Monitoring Cerebral Autoregulation After Head Injury. Which Component of Transcranial Doppler Flow Velocity is Optimal? Neurocrit. Care 2012;17:211-218.

48. Bindra J, Pham P, Aneman A, Chuan A, and Jaeger M. Non-invasive Monitoring of Dynamic Cerebrovascular Autoregulation Using Near Infrared Spectroscopy and the Finometer Photoplethysmograph. Neurocrit. Care 2016;24:442-447.

49. Zweifel C, Castellani G, Czosnyka M, Helmy A, Manktelow A, Carrera E, et al. Noninvasive Monitoring of Cerebrovascular Reactivity with Near Infrared Spectroscopy in Head-Injured Patients. J. Neurotrauma 2010; 27:1951-1958.

50. Highton D, Ghosh A, Tachtsidis I, Panovska-Griffiths J, Elwell CE, and Smith, M. Monitoring Cerebral Autoregulation After Brain Injury: Multimodal Assessment of Cerebral Slow-Wave Oscillations Using Near-Infrared Spectroscopy. Anesthesia and Analgesia 2015;121:198-205.

51. Weigl W, Milej D, Janusek D, Wojtkiewicz S, Sawosz P, Kacprzak M, et al. Application of Optical Methods in the Monitoring of Traumatic Brain Injury: A Review. J. Cereb. Blood Flow Metab 2016;36:1825-1843.

52. Diedler J, Zweifel C, Budohoski KP, Kasprowicz M, Sorrentino Enrico, Haubrich C, et al. The Limitations of Near-Infrared Spectroscopy to Assess Cerebrovascular Reactivity: The Role of Slow Frequency Oscillations. Anesthesia & Analgesia 2011;113:849-857.

53. Dias C, Silva MJ, Pereira E, Monteiro E, Maia I, Silvina B, et al. Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. Neurocrit. Care 2015;23:92-102.

54. Adams H, Donnelly J, Kolias A, Liu X, Newcombe V, Menon D, et al. Characterising the Temporal Evolution of ICP and Cerebrovascular Reactivity after Severe Traumatic Brain Injury: Best International Abstract Award. J Neurosurg. 2016;124:A1195-1196.

55. Zweifel C, Lavinio A, Steiner LA, Radolovich D, Smielewski P, Timofeev I, et al. Continuous Monitoring of Cerebrovascular Pressure Reactivity in Patients with Head Injury. Neurosurg. Focus 2008;25:E2.

56. Highton D, Ghosh A, Tachtsidis I, Kolyva C, Panovska J, Elwell C, et al. Deoxyhaemoglobin as a Biomarker of Cerebral Autoregulation. Crit. Care 2012;16:S106-107.

57. Lang EW, Kasprowicz M, Smielewski P, Pickard J, and Czosnyka M. Changes in Cerebral Partial Oxygen Pressure and Cerebrovascular Reactivity During Intracranial Pressure Plateau Waves. Neurocrit. Care 2015;23:85-91.

58. Soehle M, Jaeger M, and Meixensberger J. Online Assessment of Brain Tissue Oxygen Autoregulation in Traumatic Brain Injury and Subarachnoid Hemorrhage. Neurol. Res. 2003;25:411-417.

59. Dias C, Silva MJ, Pereira E, Silva S, Cerejo A, Smielewski P, et al. Post-Traumatic Multimodal Brain Monitoring: Response to Hypertonic Saline. J Neurotrauma 2014;31:1872-1880.

60. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, et al. Real-Time Continuous Monitoring of Cerebral Blood Flow Autoregulation Using Near-Infrared Spectroscopy in Patients Undergoing Cardiopulmonary Bypass. Stroke 2010; 41:1951–1956.

61. Sorrentino E, Budohoski KP, Kasprowicz M, Smielewski P, Matta B, Pickard JD, et al. Critical Thresholds for Transcranial Doppler Indices of Cerebral Autoregulation in Traumatic Brain Injury. Neurocrit. Care 2011;14:188-193.

Figure Legends:

Figure 1. Graphs over time highlighting (top to bottom) pressure-passivity of the cerebrovascular bed in animal models. Panel A: FVx, ABP, ICP and CPP over a 20-minute recording period in New Zealand white rabbits being subjected to intracranial hypertension. There is a robust correlation (R=0.96) between FVx and CPP below lower limit of autoregulation[6]. Panel B: Doppler flow, ABP, ICP, and CPP during a 2-hour recording period in piglets with induced arterial hypotension. ICP and ABP are strongly-correlated below the lower limit of autoregulation (R=0.70), again demonstrating pressure-passivity with decreasing ABP accompanied by decreasing ICP[7]. [FVx = middle cerebral arterial flow velocity, ABP = arterial blood pressure, ICP = intracranial pressure, CPP = cerebral perfusion pressure, mm Hg = millimeters of Mercury].

Figure 2. An example of CPP derived from PRx obtained from a single patient over a monitoring period of approximately 4 hours. The green, yellow, orange, and red bars of PRx respectively represent a spectrum of favorable to unfavorable PRx during the observation. These values of PRx are plotted against CPP, with the minimum value of the curve declared $CPP_{OPT.}$ In this particular patient, CPP_{OPT} is equivalent to 91.14 mm Hg. [PRx = pressure reactivity index, CPP = cerebral perfusion pressure, mm Hg = millimeters of Mercury].

Figure 3. Dynamic changes in flow velocity and cerebral perfusion pressure as captured during a transcranial Doppler recording for a single TBI patient over 5 minutes. Cerebral autoregulation can be approximated by a calculation of Mx from the correlation coefficient between mean FV and CPP, here Mx valuie is positive (0.73), denoting disturbed autoregulation). [MCA = middle cerebral artery, FV = flow velocity, CPP = cerebral perfusion pressure, Mx = mean flow velocity, mm Hg = millimeters of Mercury].

Figure 4. Panel A: An example of a 50-minute time-trend of ORx derived from $PbtO_2$ plotted against PRx obtained from a single patient to demonstrate the similarities in scoring between the indices. Panel B: Although this ORx-PRx plot suggests a robust correlation between ORx and PRx (R=0.68), it should be noted that $PbtO_2$ can be mechanically altered, whereas ICP is only subject to natural fluctuations within the brain – therefore, PRx values cannot change while ABP or ICP remain the same [ORx = oxygen pressure reactivity index, $PbtO_2$ = brain tissue oxygenation, PRx = pressure reactivity index, CPP = cerebral perfusion pressure, ICP = intracranial pressure, mm Hg = millimeters of Mercury].

Conflicts of Interest:

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