Published in final edited form as:

Anesth Analg. 2015 July ; 121(1): 198–205. doi:10.1213/ANE.0000000000000790.

Monitoring Cerebral Autoregulation After Brain Injury: Multimodal Assessment of Cerebral Slow-Wave Oscillations Using Near-Infrared Spectroscopy

David Highton, MBChB, FRCA, FFICM*, Arnab Ghosh, MBChB, BSc, MRCS*, Ilias Tachtsidis, PhD†, Jasmina Panovska-Griffiths, PhD†, Clare E. Elwell, PhD†, and Martin Smith, MBBS, FRCA, FFICM*

*Department of Neurocritical Care, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust, London, United Kingdom

†Department of Medical Physics and Bioengineering, University College London, London, United Kingdom

Abstract

Background—Continuous monitoring of cerebral autoregulation might provide novel treatment targets and identify therapeutic windows after acute brain injury. Slow oscillations of cerebral hemodynamics (0.05–0.003 Hz) are visible in multimodal neuromonitoring and may be analyzed to provide novel, surrogate measures of autoregulation. Near-infrared spectroscopy (NIRS) is an

Address correspondence to David Highton, MBChB, FRCA, FFICM, Department of Neurocritical Care, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust, London WC1N 3BG, United Kingdom. Address e-mail to d.highton@ucl.ac.uk.

Jasmina Panovska-Griffiths, PhD, is currently affiliated with the Clinical and Operational Research Unit, Department of Mathematics, University College London, London, United Kingdom.

The authors declare no conflicts of interest.

This report was previously presented, in part, at the Society for Neuroscience in Anesthesiology and Critical Care Annual meeting, October 14–15, 2010, San Diego, CA.

Reprints will not be available from the authors.

Disclosures

Name: David Highton, MBChB, FRCA, FFICM.

Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

Attestation: David Highton has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

Name: Arnab Ghosh, MBChB, BSc, MRCS.

Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

Attestation: Arnab Ghosh has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Ilias Tachtsidis, PhD.

Contribution: This author helped design the study and write the manuscript.

Attestation: Ilias Tachtsidis reviewed the analysis of the data and approved the final manuscript.

Name: Jasmina Panovska-Griffiths, PhD.

Contribution: This author helped write the manuscript.

Attestation: Jasmina Panovska-Griffiths approved the final manuscript.

Name: Clare E. Elwell, PhD.

Contribution: This author helped design the study and write the manuscript.

Attestation: Clare E. Elwell approved the final manuscript.

Name: Martin Smith, MBBS, FRCA, FFICM.

Contribution: This author helped design the study and write the manuscript.

Attestation: Martin Smith approved the final manuscript.

This manuscript was handled by: Gregory J. Crosby, MD.

optical neuromonitoring technique, which shows promise for widespread clinical applicability because it is noninvasive and easily delivered across a wide range of clinical scenarios. The aim of this study is to identify the relationship between NIRS signal oscillations and multimodal neuromonitoring, examining the utility of near infrared derived indices of cerebrovascular reactivity.

Methods—Twenty-seven sedated, ventilated, brain-injured patients were included in this observational study. Intracranial pressure, transcranial Doppler–derived flow velocity in the middle cerebral artery, and ipsilateral cerebral NIRS variables were continuously monitored. Signals were compared using wavelet measures of phase and coherence to examine the spectral features involved in reactivity index calculations. Established indices of autoregulatory reserve such as the pressure reactivity index (PRx) and mean velocity index (Mx) and the NIRS indices such as total hemoglobin reactivity index (THx) and tissue oxygen reactivity index (TOx) were compared using correlation and Bland-Altman analysis.

Results—NIRS indices correlated significantly between PRx and THx ($r_s = 0.63$, $P < 0.001$), PRx and TOx ($r = 0.40$, $P = 0.04$), and Mx and TOx ($r = 0.61$, $P = 0.004$) but not between Mx and THx ($r_s = 0.26$, $P = 0.28$) and demonstrated wide limits between these variables: PRx and THx (bias, -0.06 ; 95% limits, -0.44 to 0.32) and Mx and TOx (bias, $+0.15$; 95% limits, -0.34 to 0.64). Analysis of slow-wave activity throughout the intracranial pressure, transcranial Doppler, and NIRS recordings revealed statistically significant interrelationships, which varied dynamically and were nonsignificant at frequencies <0.008 Hz.

Conclusions—Although slow-wave activity in intracranial pressure, transcranial Doppler, and NIRS is significantly similar, it varies dynamically in both time and frequency, and this manifests as incomplete agreement between reactivity indices. Analysis informed by a priori knowledge of physiology underpinning NIRS variables combined with sophisticated analysis techniques has the potential to deliver noninvasive surrogate measures of autoregulation, guiding therapy.

Cerebral autoregulation (CA) describes the ability of the brain to maintain stable blood flow despite changes in perfusion pressure, thereby protecting cerebral tissue from hypoperfusion and hyperperfusion. Impaired CA is a key mechanism of cerebral hemodynamic compromise after acute brain injury (ABI)^{1,2} and a contributor to poor outcome.³ It has been suggested that continuous monitoring of CA might help prognosticate and guide arterial blood pressure (ABP) and cerebral perfusion pressure targets to “optimal” levels, thereby minimizing secondary brain injury.⁴ Near-infrared spectroscopy (NIRS), a noninvasive optical technique, is emerging as a potential solution, because unlike other modalities that are invasive or intermittent, it can be delivered in all patient groups. Clinical NIRS devices that incorporate CA analysis are on the horizon,⁵ despite remaining questions regarding NIRS sensitivity to intracerebral physiology.

Myogenic, metabolic, and neuronal mechanisms influence cerebrovascular tone over different time scales, resulting in slow waves (0.05–0.003 Hz) in cerebral blood flow, cerebral blood volume (CBV), and oxygenation.⁶ Continuously monitored indices of cerebrovascular reactivity, based on the analysis of this slow-wave activity observed in intracranial pressure (ICP),^{3,7} transcranial Doppler (TCD) flow velocity in the middle

cerebral artery,⁸ brain tissue P_{O_2} ,⁹ and NIRS variables,^{10–13} have been described as surrogate measures of CA.

The pressure reactivity index (PRx) derived from correlation between ABP and ICP³ has been extensively investigated. When cerebrovascular reactivity is impaired, CBV and ICP increase and decrease passively with ABP. Thus, a negative value for PRx, when ICP is inversely correlated with ABP, indicates normal reactivity, and a positive value indicates a nonreactive cerebrovascular circulation. The mean velocity index (Mx) is similarly derived from ABP- and TCD-measured flow velocity.⁸ Impaired cerebrovascular reactivity is confirmed if these indices tend toward a positive value, usually 0.3–1.0, and “optimal” reactivity might be achieved by therapy or ABP levels that minimize the index value.

Light in the near-infrared spectrum penetrates through superficial cerebral tissues and is used by NIRS to measure oxyhemoglobin, deoxyhemoglobin, and total hemoglobin (HbT = oxyhemoglobin + deoxyhemoglobin) concentrations through their different absorption spectra.¹⁴ Regional cerebral tissue hemoglobin oxygen saturation (rSO_2), designated the tissue oxygenation index by the Hamamatsu NIRO™ devices (Hamamatsu Photonics, Hamamatsu City, Japan), is calculated and displayed ($rSO_2 = \text{oxyhemoglobin}/\text{HbT}$). NIRS slow-wave activity is apparent in HbT and rSO_2 , and these have been recently investigated as noninvasive measures of cerebrovascular reactivity in an analogous fashion to PRx and Mx. Crucially this translation of technique assumes that slow waves of CBV will be identified in HbT and ICP and cerebral blood flow waves in rSO_2 (assuming stable oxygen extraction). Thus, the total hemoglobin reactivity index (THx) is derived from HbT and ABP and tissue oxygen reactivity index (TOx) from rSO_2 and ABP.^{10,11} Limited agreement between THx and PRx (volume-based measures), TOx and Mx (flow-based measures),^{11,12} and their reported “optimal” values brings into question the clinical relevance of these indices. This argument can be reduced to analysis of the cerebral slow waves alone, because this determines the agreement between indices. Although this is examined in several validation studies, their analysis has used a variety of Fourier techniques, without significance testing, and may not give an accurate picture of dynamic slow-wave activity. Thus, there is a strong rationale to revisit the founding concepts of this technique before moving forward with further clinical studies. This may suggest further modifications required to optimize the technique.

We hypothesize that the relationship between slow waves in NIRS, ICP, and TCD is complex and dynamic and thus may have been overstaged or understated using Fourier-based techniques. The aim of this study is to investigate comprehensively the relationship between slow waves in NIRS, ICP, and TCD after ABI under ideal circumstances and the resultant manifestation in reactivity index calculation.

Methods

This study was approved by the Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Because all patients were unconscious at the time of the study, written consent was obtained from a personal representative. Clinically stable, ventilated, sedated patients with traumatic and nontraumatic

brain injury and intraparenchymal ICP monitoring as part of routine clinical care were eligible for inclusion in this study. All patients were managed using standardized protocol-based therapy specific to their brain injury type.^{15,16}

Monitoring

Multimodal monitoring was instituted including intraparenchymal ICP monitoring (Codman Microsensor, Johnson & Johnson, Raynham, MA) performed using a sensor placed through a frontal burr hole and cranial access device or at the time of surgery and TCD insonation of the middle cerebral artery performed with a 2-MHz probe (Doppler-Box, DWL, Singen, Germany) over the temporal window, ipsilateral to the ICP monitor. The Doppler probe was fixed in a stable position using a commercial fixation device (LAM-RAK, DWL, Singen, Germany).

NIRS data were collected with a NIRO 100 spectrometer (Hamamatsu Photonics) using a 4-cm source-detector separation centered in the midpupillary line ipsilateral to TCD and ICP monitoring. Spatially resolved spectroscopy (SRS) was used to measure scaled absolute concentrations of HbT (termed total hemoglobin index [THI]) and rSO₂. The use of two detectors in SRS allows measurement of light attenuation as a function of source-detector separation, and by combining these measures with an estimation of the wavelength dependency of light scattering, it is possible to derive scaled absolute hemoglobin concentrations, and therefore THI and rSO₂. Al-Rawi et al.¹⁷ examined SRS rSO₂ during internal and external carotid cross-clamping describing a 87.5% sensitivity to intracerebral and 0% sensitivity to extracerebral changes. Therefore, SRS-derived rSO₂ suffers from less (but not 0) extracerebral contamination compared with traditional NIRS-measured variables (such as concentration changes in oxyhemoglobin and deoxyhemoglobin) that are based on a single source-detector pair. It is for this reason that SRS-derived variables have been previously chosen to derive THx and TOx. ABP was measured invasively using a 20-G radial cannula and a transducer placed at the level of the tragus.

Data Capture

Data were gathered during a period of clinical stability to allow collection of 60 minutes of undisturbed recording. Patients were deeply sedated, ventilated, positioned with 30° head-up tilt, and did not undergo nursing intervention during the 60-minute study period. Physiological data were captured at 125 Hz using TrendFace data capture software (ixellence GmbH, Wildau, Germany) onto a PC, and NIRS data were downloaded simultaneously in a raw format through a PC serial connection at 18 Hz. Signals were synchronized and resampled to 0.5 Hz through cubic spline interpolation. Brief transient artifacts such as arterial line flushes were removed by interpolation.

Index Analyses

PRx, Mx, and NIRS indices (THx and TOx) were derived as described previously using a moving Pearson correlation coefficient of 10-second time-averaged data points over a 5-minute window.³ The autoregulation indices are typically determined from the average across at least a 30- to 60-minute monitoring period. Thus, the mean for the entire monitoring period for each patient was used for comparison. Variables were summarized

using median $\pm$ interquartile range or mean $\pm$ standard deviation as appropriate. SPSS 19 (IBM, New York, NY) was used to compare PRx, Mx, and TOx using Pearson correlation after testing for normality with the Shapiro-Wilk test (all $P > 0.06$). In view of an outlier, Spearman correlation was used in the THx comparisons. The differences between indices and residual from linear regression were normally distributed (Shapiro-Wilk test, $P > 0.11$).

Agreement between measures was assessed using Bland-Altman analysis between the mean autoregulation index for each patient. There is a wide variation in the reported Pearson correlation for autoregulation indices, from 0.8 for TOx and Mx10 to 0.50–0.54 for THx.¹¹ Inclusion of 27 patients has 80% power ($\alpha = 0.05$) based on the most conservative estimates from these previously published data.

Slow-Wave Analysis

Slow-wave analysis was conducted to compare similarity between NIRS slow waves of rSO₂ and THI with TCD and ICP, because this represents the validation for using these NIRS variables to monitor autoregulation¹⁸ and also to compare slow waves in rSO₂, THI, TCD, and ICP with ABP to assess agreement in both time and frequency content. Because these signals are highly dynamic, varying in both time and frequency, the preconditions for Fourier-based techniques are violated, and therefore, we applied wavelet-based methods to compare signal content. This advanced signal-processing technique offers excellent time-frequency resolution and is increasingly applied in this context.^{19–22} A detailed discussion of this methodology can be found in the Appendix, Supplemental Digital Content, <http://links.lww.com/AA/B144>. In brief, we used the continuous wavelet transform with the complex Morlet wavelet (MathWorks, Natick, MA) described by Grinsted et al.²³ and Torrence et al.²⁴ These techniques were applied to 0.5-Hz data and examined the spectrum surrounding in the calculation of PRx and Mx (i.e., between 0.05 and 0.003 Hz). Wavelet coherence, a measure of similarity between signals, was used to compare slow-wave activity in THI, rSO₂, ICP, and TCD with significance levels being calculated using Monte-Carlo modeling as described previously.²⁴

An alternative approach examining phase differences (semblance) was also used to compare ABP and neuromonitoring variables. In brief, wavelet semblance is the cosine of the instantaneous phase difference and varies toward unity when signals are closely aligned in phase and toward -1 when antiphase.²⁵ This bears close similarity to the identical changes in PRx and Mx, which vary between 0 and -1 , with intact autoregulation, and between 0 and $+1$, with progressively disturbed autoregulation, and is equivalent to similar wavelet phase-based approaches compared previously with PRx.²⁶

Results

Patient characteristics are shown in Table 1. Continuous 60-minute recordings from 27 patients were included in the analysis, but TCD monitoring was absent in 7 because of signal loss before study completion at 60 minutes or absent bone window.

Figure 1 demonstrates significant correlation between PRx and THx ($r_s = 0.63$, $P < 0.001$), PRx and TOx ($r = 0.40$, $P = 0.04$), Mx and TOx ($r = 0.61$, $P = 0.004$), but not between Mx

and THx ($r_s = 0.26$, $P = 0.28$). However, Bland-Altman analysis demonstrated wide limits of agreement between these variables; the bias (95% limits) for the PRx and THx comparison was -0.06 (-0.44 to 0.32), for the PRx and TOx was -0.03 (-0.57 to 0.51), for the Mx and THx was $+0.16$ (-0.38 to 0.69), and for the Mx and TOx was $+0.15$ (-0.34 to 0.64).

Figure 2 shows the group mean level of coherence between ICP and THI, and between TCD and rSo₂, across the range of frequencies selected for analysis for the entire group. The coherence is significant for all frequencies >0.008 Hz (which is equivalent to a period of <125 seconds). All wavelet analyses from all individual patients are available in the supplementary results, Supplemental Digital Content, <http://links.lww.com/AA/B144>.

However, the strength of this analysis technique is its ability to investigate in more detail data from individual patients. Figure 3 shows the data from a selected individual demonstrating intact reactivity (mean Mx = -0.59 , mean PRx = -0.02 , mean THx = 0.05 , mean TOx = -0.02). Pronounced slow-wave activity can be seen in THI and ICP time course traces, which are not passively entrained by ABP fluctuations (Fig. 3A). In this example, there is a strong coherence between THI and ICP within the wavelet coherence plot (Fig. 3B). Figure 3C shows the wavelet semblance between ABP/ICP and ABP/THI across time and frequency, indicating zones where these neuromonitoring variables move in an opposite direction from ABP, suggesting pressure reactive responses. Even in this patient, who is demonstrating high levels of coherence between ICP- and NIRS-measured signals, there still exists a significant degree of variability in coherence and semblance with time and frequency, as evidenced by the nonuniform patterns seen in Figure 3, B–D, indicating varying agreement and phase relationships between ICP and THI with ABP.

In contrast, Figure 4 demonstrates an example of impaired reactivity (Mx = 0.81 , PRx = 0.59 , THx = 0.40 , TOx = 0.35). In this example, there is a strong coherence between rSo₂ and TCD in low frequencies, indicated by the areas of grey in Figure 4B, but this does not hold true at higher frequencies. Pressure passive oscillations of TCD and rSo₂ are evident in Figure 4, C and D reflected by wavelet semblance that tends toward 1 (red) in the lower frequencies, indicating minimal phase difference. Again these relationships still show dynamic variation, most evident in the discrepancies between different semblance measures. ABP/TCD are much more closely related than ABP/rSo₂ in this situation of impaired reactivity and can be clearly seen by the more uniformly red appearance of ABP/TCD semblance across a broader spectrum of frequencies.

Thus, although mean coherence of all recordings was significant, it was not marked because there was a dynamic variation in the relationship between individual recordings (Figs. 3 and 4 and supplementary results, Supplemental Digital Content, <http://links.lww.com/AA/B144>), indicating varying agreement among NIRS, TCD, and ICP in both their time and frequency content. Highly coherent features are seen between 0.1 and 0.02 Hz in comparisons of ICP and THI and between TCD and rSo₂, highlighting a potential spectral area of clinical interest.

Discussion

We have demonstrated that although measurement of NIRS reactivity indices is feasible based on the significant agreement between slow waves of NIRS, ICP, and TCD within a portion of the slow-wave spectrum, this relationship is dynamic, inexact, and manifests as incomplete agreement among TOx, THx, PRx, and Mx. However, the relationship is statistically significant and similar to other reports^{10–12,27} under these ideal experimental conditions, but not clearly identifying either THx or TOx as a superior NIRS index.

Although our length of recording is insufficient to predict “optimal” cerebral perfusion pressure values, the level of agreement probably explains others’ inaccuracies demonstrating this.^{11,27} Longer recordings are possible and have been performed by others, but we instead focused on maintaining the highest fidelity of recording. Even in this situation, it was not possible to ensure a reliable 60-minute TCD recording in all patients, and this highlights the challenges of using this modality for this application. Unlike other studies, we have included a mixture of key conditions (traumatic brain injury, subarachnoid hemorrhage, and intracerebral hemorrhage) in which these autoregulation indices have been used previously.^{28–30} Impaired autoregulation is a component of physiology in all these situations, and measures of this process should be applicable across a broad range of diagnoses to be clinically relevant. Although we collected data from only 27 patients, our primary objective was to gather data from many patients with severely impaired CA, which we have achieved. In this study, 12 patients had Mx and/or PRx >0.3 . This seems to compare favorably with other investigations in ABI in which similar analyses have been performed (Zweifel et al.,¹² 2 of 27; mean Mx >0.3 and Zweifel et al.,¹¹ 7 of 120 recordings, PRx >0.3).

Our primary motivation to perform analysis of this complexity was to gain convincing evidence that slow waves in NIRS predominantly reflect the intracerebral physiology of interest rather than the limitations of the signal processing used in standard techniques. Because cerebral slow-wave activity is nonstationary and dynamic, it is a challenge for signal-processing techniques.^{31,32} We have applied wavelet techniques, suitable to this situation with measures of statistical significance, to define this. Previous evaluations have used a combination of Fourier techniques with windows approaching the length of low-frequency oscillations.^{10,11,33} Short windowing risks overestimating coherence in the low frequencies, whereas long windows will underestimate because of nonstationarity. This is a limitation of this type of technique. Zweifel et al.¹¹ approach this problem by reporting the average from the maximum coherence in each window (across all slow-wave frequencies), which again risks overstating the coherence. Importantly, we have computed significance thresholds, so despite reporting a group average coherence, we can define its significance as well as observe the behavior of individual data sets in the wavelet plots (see Supplemental Digital Content, <http://links.lww.com/AA/B144>).

Other more recent studies have taken the commendable and necessary step of comparing TOx with clinical outcomes (e.g., delayed cerebral ischemia in subarachnoid hemorrhage).¹³ Despite previously reported limited agreement between TOx and other autoregulatory indices,²⁷ TOx has been independently associated with delayed cerebral ischemia by clinical criteria. This is promising and may suggest that cortical physiology measured by

NIRS is relevant but different from other modalities because of its anatomical location. However, in the absence of other corroborating evidence, there are other possible explanations for the optical data. For example, cerebral oligoemia³⁴ associated with ischemia or blood load in cerebrospinal fluid³⁵ may cause the scalp signal to predominate, which will be strongly associated with ABP changes. These questions could be addressed by combining advanced optics with multimodal monitoring and imaging. Approaches integrating information from time-resolved spectroscopy, imaging, and multimodal neuromonitoring by optical and physiological modeling are feasible and may hold the key to predicting how cortical physiology manifests in NIRS optics.³⁶ NIRS reflects considerable physiological complexity, and model-based physiological interpretation^{37,38} of NIRS might therefore usefully be used to address influence of other confounding factors such as carbon dioxide tension,³⁹ oxygenation,⁴⁰ and cerebral metabolic rate.⁴¹ Such factors affect cerebral physiology over different time scales and lead to a complex pattern of slow waves in cerebral hemodynamics, metabolism, and oxygenation.¹⁹ A more complete interpretation of these signals requires incorporation of the key physiological processes with high fidelity. Because these are lacking in standard autoregulation indices, several different circumstances that influence both blood pressure and cerebral blood flow may masquerade as impaired CA when it is in fact normal. Important confounding situations may include changes in cerebral metabolic rate, carbon dioxide, seizures, and coughing. Although some elements of physiology such as CBF may be quantified by “gold standard” measurement techniques and could be used to validate autoregulation indices, such an approach neglects the full depth of the changing physiology. A useful concession might be to combine multiple imperfect techniques (such as NIRS) with advanced analysis strategies to elucidate the underlying physiological state.⁴²

Simpler approaches would be highly desirable in the clinical environment but should be ideally informed by physiology rather than postprocessing of signals. Our wavelet coherence results suggest that the frequency spectrum 0.1–0.02 Hz might reflect more reliable cortical information, and thus, restricting the index calculation window from 300 to 100 seconds might increase reliability. Attempts to optimize present reactivity indices by selecting high-power NIRS oscillations⁴³ could also be performed through wavelet coherence or power.

In conclusion, we have demonstrated significant agreement among PRx-, Mx-, and NIRS-derived indices of CA (THx and TOx) in patients with ABI. However, the strength of the interrelationship between ICP or TCD and NIRS signals (THI or rSo₂) limits the degree of agreement between these reactivity indices. Neither THI nor rSo₂ is clearly superior, and future studies may benefit from multimodal monitoring of CA combining analysis of THx and TOx. The clinical application of autoregulation indices requires the identification of robust markers and appropriate analysis techniques that consider the dynamic properties of the measured signals and the contribution of confounding features. NIRS is able to provide a clinically accessible, continuous, and noninvasive measure of cerebral hemodynamics and therefore has considerable potential as a noninvasive monitor of CA. However, a greater understanding of the origin of the NIRS signals and their dynamic properties is required before it could be used to inform autoregulation-directed therapy after ABI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Supported by MRC Clinical Research Training Fellowship G1000292 (to AG) and partially supported by the Department of Health's Institute for Health Research Centre's funding scheme via the UCLH/UCL Biomedical Research Centre (to MS) and National Institute for Health Research (to DH). This work was in part funded by a grant from the National Institute of Academic Anaesthesia and the Neuroanaesthesia Society of Great Britain and Ireland.

References

1. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990; 2:161–92. [PubMed: 2201348]
2. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA, Pickard JD. Clinical relevance of cerebral autoregulation following subarachnoid haemorrhage. *Nat Rev Neurol*. 2013; 9:152–63. [PubMed: 23419369]
3. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery*. 1997; 41:11–7. [PubMed: 9218290]
4. Lazaridis C, Smielewski P, Steiner LA, Brady KM, Hutchinson P, Pickard JD, Czosnyka M. Optimal cerebral perfusion pressure: are we ready for it? *Neurol Res*. 2013; 35:138–48. [PubMed: 23452576]
5. Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW. Validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. *Anesth Analg*. 2013; 116:198–204. [PubMed: 23223100]
6. Steinmeier R, Bauhuf C, Hubner U, Bauer RD. Slow rhythmic oscillations of blood pressure, intracranial pressure, microcirculation, and cerebral oxygenation dynamic interrelation and time course in humans. *Stroke*. 1996; 27:2236–43. [PubMed: 8969787]
7. Steiner LA, Coles JP, Johnston AJ, Chatfield DA, Smielewski P, Fryer TD, Aigbirhio FI, Clark JC, Pickard JD, Menon DK, Czosnyka M. Assessment of cerebrovascular autoregulation in head-injured patients: a validation study. *Stroke*. 2003; 34:2404–9. [PubMed: 12947157]
8. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke*. 1996; 27:1829–34. [PubMed: 8841340]
9. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. *Crit Care Med*. 2006; 34:1783–8. [PubMed: 16625135]
10. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocrit Care*. 2009; 10:122–8. [PubMed: 18807218]
11. Zweifel C, Castellani G, Czosnyka M, Helmy A, Manktelow A, Carrera E, Brady KM, Hutchinson PJ, Menon DK, Pickard JD, Smielewski P. Noninvasive monitoring of cerebrovascular reactivity with near infrared spectroscopy in head-injured patients. *J Neurotrauma*. 2010; 27:1951–8. [PubMed: 20812789]
12. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, Pickard JD, Smielewski P. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. *Stroke*. 2010; 41:1963–8. [PubMed: 20651272]
13. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, Pickard JD, Kirkpatrick PJ. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. *Stroke*. 2012; 43:3230–7. [PubMed: 23150652]

14. Wolf M, Ferrari M, Quaresima V. Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications. *J Biomed Opt.* 2007; 12:062104. [PubMed: 18163807]
15. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma.* 2007; 24(Suppl 1):S1–106.
16. Diring MN, Bleck TP, Claude Hemphill J III, Menon D, Shutter L, Vespa P, Bruder N, Connolly ES Jr, Citerio G, Gress D, Hänggi D, et al. Neurocritical Care Society. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care.* 2011; 15:211–40. [PubMed: 21773873]
17. Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke.* 2001; 32:2492–500. [PubMed: 11692006]
18. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke.* 2010; 41:1951–6. [PubMed: 20651274]
19. Latka M, Turalska M, Glaubic-Latka M, Kolodziej W, Latka D, West BJ. Phase dynamics in cerebral autoregulation. *Am J Physiol Heart Circ Physiol.* 2005; 289:H2272–9. [PubMed: 16024579]
20. Latka M, Kolodziej W, Turalska M, Latka D, Zub W, West BJ. Wavelet assessment of cerebrospinal compensatory reserve and cerebrovascular reactivity. *Physiol Meas.* 2007; 28:465–79. [PubMed: 17470981]
21. Rowley AB, Payne SJ, Tachtsidis I, Ebdon MJ, Whiteley JP, Gavaghan DJ, Tarassenko L, Smith M, Elwell CE, Delpy DT. Synchronization between arterial blood pressure and cerebral oxyhaemoglobin concentration investigated by wavelet crosscorrelation. *Physiol Meas.* 2007; 28:161–73. [PubMed: 17237588]
22. Caicedo A, Varon C, Thewissen L, Naulaers G, Lemmers P, Van Bel F, Van Huffel S. Influence of the maternal use of labetalol on the neurogenic mechanism for cerebral autoregulation assessed by means of NIRS. *Adv Exp Med Biol.* 2014; 812:173–9. [PubMed: 24729230]
23. Grinsted A, Moore JC, Jevrejeva S. Application of the cross wavelet transform and wavelet coherence to geophysical time series. *Nonlin Processes Geophys.* 2004; 11:561–6.
24. Torrence C, Compo GP. A practical guide to wavelet analysis. *Bull Am Meteorol Soc.* 1998; 79:61–78.
25. Cooper GRJ, Cowan DR. Comparing time series using wavelet-based semblance analysis. *Comput Geosci.* 2008; 34:95–102.
26. Kvandal P, Sheppard L, Landsverk SA, Stefanovska A, Kirkeboen KA. Impaired cerebrovascular reactivity after acute traumatic brain injury can be detected by wavelet phase coherence analysis of the intracranial and arterial blood pressure signals. *J Clin Monit Comput.* 2013; 27:375–83. [PubMed: 23748602]
27. Budohoski KP, Czosnyka M, Smielewski P, Varsos GV, Kasprówicz M, Brady KM, Pickard JD, Kirkpatrick PJ. Cerebral autoregulation after subarachnoid hemorrhage: comparison of three methods. *J Cereb Blood Flow Metab.* 2013; 33:449–56. [PubMed: 23232948]
28. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med.* 2002; 30:733–8. [PubMed: 11940737]
29. Diedler J, Sykora M, Rupp A, Poli S, Karpel-Massler G, Sakowitz O, Steiner T. Impaired cerebral vasomotor activity in spontaneous intracerebral hemorrhage. *Stroke.* 2009; 40:815–9. [PubMed: 19131652]
30. Bijlenga P, Czosnyka M, Budohoski KP, Soehle M, Pickard JD, Kirkpatrick PJ, Smielewski P. 'Optimal cerebral perfusion pressure' in poor grade patients after subarachnoid hemorrhage. *Neurocrit Care.* 2010; 13:17–23. [PubMed: 20405341]
31. Panerai RB. Complexity of the human cerebral circulation. *Philos Trans A Math Phys Eng Sci.* 2009; 367:1319–36. [PubMed: 19324711]

32. Mitsis GD, Zhang R, Levine BD, Marmarelis VZ. Modeling of nonlinear physiological systems with fast and slow dynamics. II. Application to cerebral autoregulation. *Ann Biomed Eng.* 2002; 30:555–65. [PubMed: 12086006]
33. Lee JK, Kibler KK, Benni PB, Easley RB, Czosnyka M, Smielewski P, Koehler RC, Shaffner DH, Brady KM. Cerebrovascular reactivity measured by near-infrared spectroscopy. *Stroke.* 2009; 40:1820–6. [PubMed: 19286593]
34. Yokose N, Sakatani K, Murata Y, Awano T, Igarashi T, Nakamura S, Hoshino T, Katayama Y. Bedside monitoring of cerebral blood oxygenation and hemodynamics after aneurysmal subarachnoid hemorrhage by quantitative time-resolved near-infrared spectroscopy. *World Neurosurg.* 2010; 73:508–13. [PubMed: 20920934]
35. Robertson JL, Ghosh A, Correia T, Highton D, Smith M, Elwell CE, Leung TS. Effect of blood in the cerebrospinal fluid on the accuracy of cerebral oxygenation measured by near infrared spectroscopy. *Adv Exp Med Biol.* 2014; 812:233–40. [PubMed: 24729238]
36. Hapuarachchi T, Moroz T, Bainbridge A, Price D, Cady E, Baer E, Broad K, Ezzati M, Thomas D, Golay X, Robertson NJ, et al. Modelling blood flow and metabolism in the piglet brain during hypoxia–ischaemia: simulating pH changes. *Adv Exp Med Biol.* 2013; 789:331–7. [PubMed: 23852512]
37. Banaji M, Mallet A, Elwell CE, Nicholls P, Cooper CE. A model of brain circulation and metabolism: NIRS signal changes during physiological challenges. *PLoS Comput Biol.* 2008; 4:e1000212. [PubMed: 18989392]
38. Highton D, Panovska-Griffiths J, Ghosh A, Tachtsidis I, Banaji M, Elwell C, Smith M. Modelling cerebrovascular reactivity: a novel near-infrared biomarker of cerebral autoregulation? *Adv Exp Med Biol.* 2013; 765:87–93. [PubMed: 22879019]
39. Leung TS, Tachtsidis I, Tisdall MM, Pritchard C, Smith M, Elwell CE. Estimating a modified Grubb's exponent in healthy human brains with near infrared spectroscopy and transcranial Doppler. *Physiol Meas.* 2009; 30:1–12. [PubMed: 19039165]
40. Tisdall MM, Tachtsidis I, Leung TS, Elwell CE, Smith M. Increase in cerebral aerobic metabolism by normobaric hyperoxia after traumatic brain injury. *J Neurosurg.* 2008; 109:424–32. [PubMed: 18759572]
41. Meng L, Gelb AW, McDonagh DL. Changes in cerebral tissue oxygen saturation during anaesthetic-induced hypotension: an interpretation based on neurovascular coupling and cerebral autoregulation. *Anaesthesia.* 2013; 68:736–41. [PubMed: 23614880]
42. Highton D, Panovska-Griffiths J, Smith M, Elwell CE. Mathematical modelling of near-infrared spectroscopy signals and intracranial pressure in brain-injured patients. *Adv Exp Med Biol.* 2013; 789:345–51. [PubMed: 23852514]
43. Diedler J, Zweifel C, Budohoski KP, Kaspruwicz M, Sorrentino E, Haubrich C, Brady KM, Czosnyka M, Pickard JD, Smielewski P. The limitations of near-infrared spectroscopy to assess cerebrovascular reactivity: the role of slow frequency oscillations. *Anesth Analg.* 2011; 113:849–57. [PubMed: 21821514]

Figure 1.

A–D, Correlation between autoregulation indices. Note the strong correlation between the total hemoglobin reactivity index (THx) and pressure reactivity index (PRx; volume-based measures) and tissue oxygen reactivity index (TOx) and mean velocity index (Mx; flow-based measures). A linear regression line of best fit and 95% confidence interval (dashed line) are shown. E–H, Bland-Altman plots for each of the index comparisons. The dashed line represents the 95% limits of agreement. Note the wide limits of agreement in contrast to the correlations in (A–D), suggesting limited interchangeability of near-infrared spectroscopy-derived autoregulatory indices and PRx and Mx.

Figure 2.

The mean coherence between intracranial pressure (ICP)/total hemoglobin index (THI) and transcranial Doppler (TCD)/regional cerebral tissue hemoglobin oxygen saturation (rSO₂), a measure of similarity of the oscillations between these modalities. Therefore, this relationship forms the foundations for applying a pressure reactivity index (PRx) style analysis using near-infrared spectroscopy. A particular spectral feature is seen in each of the comparisons with increased coherence <0.1 Hz. However, the mean coherence is not strong. The significance threshold has been calculated from Monte Carlo modeling, shown as a

dashed line. Below a frequency of 0.008 Hz, coherence in both comparisons is nonsignificant. The frequency across the x-axis is nonlinear because it reflects the nonlinear frequency scales of wavelets.

Figure 3.

Data set suggesting intact reactivity (mean velocity index, -0.59 ; pressure reactivity index, -0.02 ; total hemoglobin reactivity index, 0.05 ; tissue oxygen reactivity index, -0.02). Pronounced slow-wave activity can be seen in total hemoglobin index (THI) and intracranial pressure (ICP) traces, which are not passively entrained by arterial blood pressure (ABP) fluctuations. The wavelet plots describe this situation in more detail with time reflected on the x-axis and frequency on the y-axis. Wavelet semblance between both ABP/ICP and ABP/THI shows large blue areas (semblance, -1) across time and frequency indicating

zones where these neuromonitoring variables move in an opposite direction from ABP, suggesting pressure–reactive responses. In this example, there is a strong coherence between THI and ICP demonstrated by the large gray areas (coherence, 1) within the wavelet coherence plot. Despite this similarity, there remains a significant degree of variability with time and frequency in coherence and semblance, indicating varying agreement and phase relationships between ICP and THI with ABP.

Figure 4.

An example of impaired reactivity (mean velocity index, 0.81; pressure reactivity index, 0.59; total hemoglobin reactivity index, 0.40; tissue oxygen reactivity index, 0.35). Pressure passive oscillations of transcranial Doppler (TCD) and regional cerebral oxygen saturation (rSO₂) are evident and are reflected in wavelet semblance that tends toward 1 (red) in the lower frequencies indicating minimal phase difference. Coherent slow-wave oscillations are present between TCD and intracranial pressure—evident from the persistent areas of high coherence in the low-frequency zone of the wavelet coherence plot. Again these

relationships do still show dynamic variation—most evident in the discrepancies between different semblance measures—arterial blood pressure (ABP)/TCD are much more closely related than ABP/rSo₂ in this situation of impaired reactivity and can be clearly seen by the more uniformly red appearance of ABP/TCD semblance.

Table 1**Patient Characteristics**

Age (y)	50 (39–63)
Sex	
Male	13/27 (48%)
Female	14/27 (52%)
Brain injury	
TBI	11/27 (40%)
SAH	6/27 (22%)
ICH	10/27 (27%)
Time of data capture	
Days after injury	2 (2–5)
Indices of autoregulation	
PRx	0.05 (0.28)
Mx	0.14 (0.35)
THx	0.11 (0.22)
TOx	0.08 (0.22)

Values are presented as median (range), mean (standard deviation), or counts (percentage).

ICH = intracerebral hemorrhage; Mx = mean velocity index; PRx = pressure reactivity index; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; THx = total hemoglobin reactivity index; TOx = tissue oxygen reactivity index.