Continuous Time-Domain Analysis of Cerebrovascular Autoregulation Using Near-Infrared Spectroscopy

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Background and Purpose—Assessment of autoregulation in the time domain is a promising monitoring method for actively optimizing cerebral perfusion pressure (CPP) in critically ill patients. The ability to detect loss of autoregulatory vasoreactivity to spontaneous fluctuations in CPP was tested with a new time-domain method that used near-infrared spectroscopic measurements of tissue oxyhemoglobin saturation in an infant animal model.

Methods—Piglets were made progressively hypotensive over 4 to 5 hours by inflation of a balloon catheter in the inferior vena cava, and the breakpoint of autoregulation was determined using laser-Doppler flowmetry. The cerebral oximetry index (COx) was determined as a moving linear correlation coefficient between CPP and INVOS cerebral oximeter waveforms during 300-second periods. A laser-Doppler derived time-domain analysis of spontaneous autoregulation with the same parameters (LDx) was also determined.

Results—An increase in the correlation coefficient between cerebral oximetry values and dynamic CPP fluctuations, indicative of a pressure-passive relationship, occurred when CPP was below the steady state autoregulatory breakpoint. This COx had 92% sensitivity (73% to 99%) and 63% specificity (48% to 76%) for detecting loss of autoregulation attributable to hypotension when COx was above a threshold of 0.36. The area under the receiver-operator characteristics curve for the COx was 0.89. COx correlated with LDx when values were sorted and averaged according to the CPP at which they were obtained (r=0.67).

Conclusions—The COx is sensitive for loss of autoregulation attributable to hypotension and is a promising monitoring tool for determining optimal CPP for patients with acute brain injury. (Stroke. 2007;38:2818-2825.)

Key Words: autoregulation ■ cerebral blood flow ■ hypotension ■ neonate ■ oxygenation ■ piglet

Cerebral pressure autoregulation is defined as the maintenance of a constant cerebral blood flow (CBF) in the face of changing cerebral perfusion pressure (CPP). In health, this process protects the brain during transient changes in the arterial blood pressure (ABP) from diminished or excessive blood flow. Traumatic brain injury (TBI),1–3 stroke,4 meningeal,5,6 cardipulmonary bypass, and deep hypothermic circulatory arrest7 are examples of insults that have been shown to impair pressure autoregulation and have large-scale clinical impact. An impairment of autoregulation narrows the range of blood pressures at which flow is matched to metabolic needs. Optimal management of CPP for limiting tissue hypoxia at low CPP or edema at high CPP in these patients is critical but difficult to achieve because of limited monitoring capabilities. Despite the recent surge of multimodal neuromonitoring, optimal ABP and CPP have not been defined.

It has been postulated that continuous monitoring of autoregulatory vasoreactivity allows detection of an “optimal CPP” and titration of blood pressure into a range that maximizes vasoreactivity to perturbations in CPP.8 Autoregulation is measured by quantifying the consequence of changing blood pressure on CBF or its surrogate, and the methods have been extensively reviewed.9 Changes in ABP can be induced via drugs, tilt-table, or thigh cuff,10 or they can occur spontaneously. Using spontaneous changes in ABP is preferable to inducing ABP changes in an unstable patient with an acute intracranial process. However, relying on spontaneous and often subtle ABP fluctuations for this measurement results in an inferior signal-to-noise ratio.

Diverse surrogates of CBF are suitable for continuous monitoring of autoregulation and include flow velocity, measured by transcranial Doppler;11 red blood cell flux, measured by laser-Doppler;12 parenchymal oxygen tension, measured using a Licox monitor13,14; and cerebral tissue oxyhemoglobin saturation, measured by transcranial near-infrared spectroscopy (NIRS).15 Slow waves of intracranial pressure (ICP) reflecting vessel diameter changes in the autoregulatory process have also been correlated to ABP for an index describing autoregulation.16 An ideal CBF surrogate

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for an index of autoregulation would be noninvasive and require minimal caregiver attention. It would provide a continuous signal with time resolution sufficiently fine to discriminate changes in frequencies relevant to autoregulation, and that signal would be a close proxy for CBF. Transcranial monitors of cerebral oxygenation using NIRS have these attractive features. We present a novel index of autoregulatory vasoreactivity, the cerebral oximeter index (COx), which is derived from a time-domain analysis that correlates changes in ABP to the output of a commercially available, NIRS-based monitor of cerebral tissue oxyhemoglobin saturation. This correlation is performed continuously on overlapping epochs of 300 seconds, updated every 60 seconds, and does not require induced changes in ABP to detect autoregulatory failure.

We hypothesized that the COx would be sensitive for autoregulatory failure attributable to hypotension in a piglet model of the infant brain and measured the COx continuously in piglets, while slowly lowering their ABP below the breakpoint of autoregulation, as determined by laser-Doppler flowmetry. We determined the sensitivity and specificity of the COx for detecting the loss of autoregulation caused by hypotension. We also tested the COx against a similar, but invasive method, the laser-Doppler index (LDx), which uses a linear correlation coefficient between ABP and laser-Doppler flux measured in the frontoparietal cortex. We hypothesized that the COx and LDx would show agreement as measurements of autoregulatory vasoreactivity despite their distinct origins.

**Methods and Materials**

All procedures were approved by the Johns Hopkins University Animal Care and Use Committee and conformed to the standards of animal experimentation of the National Institutes of Health.

**Anesthesia**

Piglets (n=6), aged 3 to 8 days old and weighing 2.2 to 3.9 kg, were anesthetized with inhalation of 5% isoflurane, 50% nitrous oxide, and balance of oxygen. A tracheostomy was performed and mechanical ventilation was instituted. Peripheral intravenous access was obtained for the administration of vecuronium (5-mg bolus and 2-mg/h infusion) and fentanyl (25-µg bolus and 25-µg/h infusion). Isoflurane was decreased to 0.5% for the duration of the experiment, and the fentanyl was titrated between 10 to 50 µg/h for a target rate lower than 190 and normotension during surgery. During the recording period, when blood pressure was actively lowered, fentanyl was infused at 50 µg/h (20 µg/kg/h for most of the piglets) and tachycardia was permitted as a response to the preload reduction. Isoflurane remained at 0.5%, and the nitrous oxide remained at 50% of the inspired gas. Thus, the anesthetic for the recording period was primarily narcotic based, with a subanesthetic supplementation of inhalational agent. This combination was chosen to ensure the comfort of the animal and reduce the effect of inhaled anesthetic on cerebrovascular responsiveness. Piglets were kept on a warming pad to maintain brain and rectal temperature at 38.5°C to 39.5°C. Ventilation was adjusted to keep pH at 7.35 to 7.45 and PaO2 at 200 to 300 mm Hg.

**Surgery**

The femoral veins were cannulated bilaterally for placement of a central venous line for drug infusion and pressure monitoring and a 5 Fr esophageal balloon catheter (Cooper Surgical, Trundall, CT), which was used for interruption of venous return to the heart to produce hypotension. The femoral artery was cannulated for placement of a pressure and blood gas monitoring line. A craniotomy was performed 4 mm lateral and rostral to the bregma at midline for placement of an external ventricular drain catheter, which was transduced for ICP monitoring. An additional craniotomy was performed 4 mm lateral and rostral to the first craniotomy for placement of a laser-Doppler probe (Moor Instruments), which was advanced across the incised dura mater to contact the surface of the frontoparietal cortex. The probe was positioned to avoid high baseline flux values associated with placement over large vessels and was secured in place by a rubber washer cemented to the skull. A third craniotomy in the occipital skull lateral to the midline was used to place a brain temperature probe. After placement of each intracranial device, the respective craniotomies were glued with cyanoacrylate. Skin was reapplied to the skull, and the wound was sutured closed for heat retention and to create conditions for which the cerebral oximeter had been calibrated.

**Oximetry Probe Placement**

The INVOS pediatric cerebral oximeter probe (Somanetics) was placed above the eye, across the frontal and parietal cortex, opposite the side of craniotomies, with the emitting diode situated 1 cm lateral to midline to avoid the sagittal sinus. The cerebral specificity of the probe was then tested with a CO2 challenge: ventilation was increased to reduce end-tidal CO2 by at least 10 mm Hg. Cerebral oximetry was compared with oximetry obtained from a probe that was placed over the kidney. Cerebral oximetry values decreased (1.2±0.1%/mm Hg; ±SD), whereas the renal oximetry values were static (0.0±0.1%/mm Hg).

**Signal Sampling**

Waveforms from the pressure transducers (ABP, ICP), the laser-Doppler probe, and the INVOS cerebral oximeter were sampled from an analog-to-digital converter by ICM+ software (Cambridge University) at 60 Hz. The time resolution of INVOS oximetry is 4 seconds. These signals were then time-integrated as nonoverlapping 10-second mean values, which is equivalent to applying a moving average filter with a 10-second time window and resampling at 0.1 Hz. This operation eliminates high-frequency noise from the respiratory and pulse frequencies of the animals but, according to the Nyquist theorem, allows detection of oscillations and transients that occur below 0.05 Hz. CPP was calculated as the difference between the 10-second mean values of ABP and ICP.

**Calculation of the Laser-Doppler and Cerebral Oximeter Indices**

A continuous moving Pearson correlation coefficient was performed between the CPP and laser-Doppler to render the LDx or between the CPP and the cerebral oximeter output to render the COx. Consecutive, paired, 10-second averaged values from 300-second duration were used for each calculation, incorporating 30 data points for each index. These indices were calculated and recorded every 60 seconds from overlapping time periods.

**Blood Pressure Lowering and Construction of the Autoregulation Curve**

With the above-mentioned monitors in place, the balloon catheter in the inferior vena cava was gradually inflated by infusion of saline from a syringe pump to slowly lower ABP to ~10 mm Hg over 4 to 5 hours (Figure 1). Cerebral oximetry, laser-Doppler flux, COx, and LDx values were recorded every 60 seconds in real time and simultaneously sorted according to the CPP at which they were collected. Hypotension was induced over a prolonged period to permit sufficient time for spontaneous changes in CPP to occur over each range of quasi-steady state CPP and thus provide an adequate signal/noise ratio for calculating COx.

**Determination of the Steady-State Autoregulatory Breakpoint**

A scatter plot of laser-Doppler flow versus CPP was made for all of the data for each piglet using SigmaStat software (Systat). The CPP...
that demarcated 2 regression lines with the lowest combined residual squared error was determined and defined as the autoregulatory breakpoint. In addition, relative changes in cerebrovascular resistance (CVR) were calculated as a percent of the baseline CPP/laser-Doppler flux ratio. The effect of CPP lowering on laser-Doppler flux, CVR, and cerebral oximetry was assessed after averaging the mean values for the 6 piglets at each 5 mm Hg decrement of CPP with one way analysis of variance (ANOVA).

Receiver-Operator Characteristics
Prism software (GraphPad) was used to determine the receiver-operator characteristics (ROC) of the COx and LDx. To do so, the averaged index values at each CPP for each piglet were dichotomized above and below the CPP breakpoint, as derived from the laser-Doppler flow autoregulatory relationship for each piglet.

Comparison of the LDx and COx
Regression analysis and linear correlation of the COx against the LDx was performed with Prism software and with Bland-Altman plots, using LDx–COx and COx/LDx against the mean. This analysis was performed for all paired indices collected and again for averaged values collected on the same piglet at the same CPP.

Confirmation of the Spectral Range of Autoregulation in the Piglets
Using ICM Plus software, a cross-spectral analysis of coherence was performed, using ABP as input and either laser-Doppler flux or cerebral oximetry as output. Coherence at frequencies that ranged from 1 Hz to 0.001 Hz was compared between the hypotensive and normotensive states. These data are not presented formally but were used to structure the sampling and calculation parameters for the time-domain analysis presented (see Discussion).

Results
Arterial pH, PaCO2, and brain temperature were within the normal physiological range during normotension (CPP >50 mm Hg), moderate hypotension above the autoregulatory breakpoint (CPP 30 to 50 mm Hg), and severe hypotension below the autoregulatory breakpoint (CPP <30 mm Hg).

To prevent CO2 reactivity from affecting the oximeter readings, we sought to keep a constant PaCO2, but a small decrement was noted in each piglet as cardiac output fell to critical levels (from baseline 37.0±4.9 mm Hg to 33.0±1.6 mm Hg at CPP <30 mm Hg; ±SE). It is unlikely
that this small decrement introduced a bias into the autoregulatory indices, as they evaluate pressure passivity over discrete 300-second intervals that are relatively stationary with respect to the PaCO2. Mild metabolic acidosis was treated with NaHCO3 to keep arterial pH in the normal range (7.42 ± 0.02 at baseline and 7.39 ± 0.02 at CPP 30 mm Hg).

Brain temperature was unchanged during hypotension (38.7 ± 0.8°C at baseline and 38.6 ± 0.7°C at CPP 30 mm Hg).

An example of the autoregulatory assessment for a single piglet is shown in Figure 2. The lower limit of autoregulation of laser-Doppler flow was easily identified from the intersection of 2 regression lines that minimized the overall sum of the residual squared errors (Figure 2A). Interestingly, the plot of cerebral oximetry as a function of CPP was not as well characterized by an inflection point (Figure 2B). However, the laser-Doppler index (LDx, ± SE, C) and the cerebral oximetry index (COx, D) were concordant, showing low values above a CPP of 35 mm Hg and high values below a CPP of 35 mm Hg (arrows).

Data combined from 6 piglets for laser-Doppler flow, relative CVR, and cerebral oximetry are shown in Figure 3. The average breakpoint of laser-Doppler flow was 29.7 ± 5.5 mm Hg, which compares well with previous reports of piglet autoregulatory curves. Graded decreases in relative CVR and NIRS were evident during hypotension in the pooled data.

The average LDx and COx increased when CPP was below 30 mm Hg (Figure 4A and 4B). Knowing the steady-state autoregulatory breakpoint for each piglet permitted determination of the ROC for LDx and COx. Not surprisingly, because the LDx is a derivative of the laser-Doppler flow, the LDx performed better than the COx, but both accurately described the breakpoint well. The areas under the ROC curves were 0.95 for the LDx (Figure 4C) and 0.89 for the COx (Figure 4D). Summaries of the sensitivity, specificity, and likelihood ratios for cutoff values of the 2 indices are shown in Figure 4. In general, sensitivity was superior to specificity for both indices: all piglets showed abnormal autoregulatory vasoreactivity by both the COx and the LDx when hypotensive, but many also showed episodic disruptions of one or both indices in the normotensive or moderately hypotensive range.

The linear correlation and Bland-Altman comparison of the COx and LDx are shown in Figure 5. Agreement between the indices was limited when evaluated on a minute-to-minute basis (Pearson r = 0.36). Agreement improved greatly with averaging of the values stratified according to the 5-mm Hg incremental bins of CPP at which they were collected (Pearson r = 0.67). The Bland-Altman method showed no bias across the range of measurements (bias = -0.06 for all values measured, 0.03 for averaged values) and showed the improvement in agreement when values were averaged at the same CPP.

**Discussion**

The present results show that time-domain correlation of ABP and cerebral oximetry can quantify spontaneous aut-
regulatory vasoreactivity, and the resultant index is sensitive for loss of autoregulation caused by hypotension in a piglet model. This method has several features that are attractive for clinical application. The COx output is continuous and updated every 60 seconds, as configured in the animals presented. The COx can be displayed at the bedside as a function of clinical parameters, such as CPP, showing the effect of changes in management on the autoregulatory process. The COx requires no intracranial surgery for calculation and can use spontaneous changes in ABP, obviating the need to induce rapid changes in ABP in an unstable patient.

An important task in the development of the COx was the determination of relevant periods for waveform sampling. Our rationale for this determination, a discussion of the limitations of the COx, and a description of the potential clinical application of the COx are presented below.

Considerations of the Frequencies Chosen for Analysis in the COx

Associative relationships between ABP and CBF surrogates can be dynamically assessed by methods that fall into 2 broad categories: analysis in the frequency domain and analysis in the time domain. Frequency-domain analysis (based on coherence, transfer function, or phase shifts) is well suited for regular, periodic waves or induced changes in ABP in an otherwise static system. This analysis has assumptions of linearity and stationarity that are not always strictly present in a biologic system. Time-domain analysis can be performed as a linear correlation between low-pass filtered ABP and CBF waves, as presented here with the COx and LDx, but this filtering limits the spectral range of the test. For such an analysis to describe autoregulation, the clinically relevant wavelength periods that encompass CPP and oximetry correlations caused by autoregulatory failure must be known.

Our focus on frequencies between 0 and 0.04 Hz is based on 3 suppositions. First, and most important, is the work of Tsuji et al, who used a frequency-domain analysis of coherence between NIRS and ABP in premature infants. They identified a subgroup with a high coherence at frequencies lower than 0.01 Hz and found an increased incidence of intraventricular hemorrhage in this group, which was hypothesized to have been the result of impaired autoregulation. This finding suggests that these low frequencies are useful in describing correlations of ABP and CBF that can be clinically relevant. A second argument for the chosen frequencies comes from the ICP-derived index of autoregulation (PRx), which correlates slow “B” waves of ICP with ABP. The PRx has been shown to associate with outcome in head-injured patients and is thought to be a marker of the autoregulatory process. In our database, these slow ICP waves were too sporadic to appear with clarity in a Fourier transfer analysis, but they were identified in the raw waveforms obtained from the piglets and their duration range was measured to be 65 to 300 seconds, which would correspond to frequencies between 0.015 and 0.003 Hz. The final rationale comes from a coherence analysis of the ABP and NIRS waveforms in the piglets used in this study. In waveforms obtained at blood pressures below the lower limit of autoregulation, we found coherence at frequencies lower than 0.04 Hz, and especially at frequencies lower than 0.02 Hz. This coherence was absent from waveforms obtained during normotension.

Given the above findings, we desired to resolve waveform relationships that occurred at frequencies lower than 0.04 Hz (periods >25 seconds). At the same time, we wished to prevent the aliasing of noise from the high-frequency range, which included the respiratory and heart rate frequencies. The respiratory rate was 0.3 Hz (3-second periodicity). Thus, time averaging of 10-second periods suppressed this noise and preserved resolution at the chosen frequencies.

Limitations of the COx

Understanding the sources of error in the sensitivity and specificity of the COx can lead to strategies for improvement. Using transient and spontaneous changes in ABP decreases the signal-to-noise ratio, when compared with methods that induce large changes in blood pressure over brief periods of

Figure 3. Static autoregulation curves derived from 6 piglets (±SE). A, Laser-Doppler flux as a percent of baseline flux at 60 mm Hg. B, Cerebrovascular resistance (CVR), calculated as CPP/CBF from the same data set and expressed as a percentage of CVR at CPP of 60 mm Hg. C, Cerebral oximetry, measured by NIRS, shown as a percentage of baseline tissue oxyhemoglobin saturation. P<0.0001 by ANOVA for both laser-Doppler flux and oximetry curves. The average breakpoint of autoregulation, determined for individual piglets, was 29.7±5.5 mm Hg (vertical dashed line).
Two obvious solutions can be chosen for increasing the signal/noise ratio: (1) increasing the sampling time for calculating each index, or (2) averaging multiple discreet calculations of the indices together. We chose the second option because it has the same data smoothing effect but is more useful, as it allows for sorting according to clinically relevant variables (CPP, temperature, blood gases, sedation states, etc). These variables are likely to be more stationary over a 5-minute period than over 20- or 60-minute periods. Our experimental design sought to control these variables and thereby isolate the effect of changing CPP, but minor deviations in \( \text{PaCO}_2 \) did occur. Dynamic changes in cerebral \( \text{O}_2 \) consumption could affect \( \text{COx} \). We assume that the fentanyl, nitrous oxide, and isoflurane anesthesia provided a stable \( \text{O}_2 \) consumption over each 300-second period used to calculate \( \text{COx} \).

Deficiencies of sensitivity that occurred with either the LDx or the COx were largely limited to the extreme hypotensive state, just before the death of the animal, as can be seen with the increased variability at the CPP of 10 in Figure 4. The data set was incomplete in this range, consisting of a limited recording time and only 3 animals because of difficulties encountered in sustaining cardiac function. It is possible that ABP lower than the critical closing pressure caused low and static CBF and cerebral oxygenation that did not change with small ABP fluctuations. Others have dealt with the signal-to-noise ratio problem by incorporating exclusion rules in the index calculation that require a specific range of CPP. For instance, epochs of time with less than 10 mm Hg change in ABP could be excluded from analysis. The introduction of bias caused by excluding periods with stable blood pressure has not been determined, and this method was not practical for our experimental model because of the slow stable reduction in ABP that was achieved.
state could give the false appearance of intact autoregulation by the COx or LDx assessments. Dynamic decreases in cerebral O$_2$ consumption could also add to the variability of these indices. Blood pressure in this range is not important for the clinical questions targeted.

Clinical Implications of the COx
An important goal of clinical monitoring of autoregulation is the delineation of care parameters that improve autoregulation. Patients with intact autoregulation are more likely to survive neurologic injury, and commutative logic would suggest that improving autoregulation would improve neurologic recovery and survival.8,16,21 Tools that can quantify autoregulation at the clinical bedside will allow for testing of this hypothesis. Because the COx is not invasive, it can be used for patients with acute neurologic processes who do not or cannot undergo neurosurgical intervention, including patients with moderate head-trauma, stroke and meningitis, and patients undergoing cardiopulmonary bypass for corrective heart surgery or exchange transfusion for acute chest syndrome. In addition, the COx could be a valuable adjunct to the monitoring of pressure autoregulation in the setting of severe head injury when added to other indices derived from invasive monitoring.

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Figure 5. Linear regression (A, B) and Bland Altman plots (C, D) comparing LDx and COx for all data points (A, C) and averaged data points taken at the same CPP for each piglet (B, D). Agreement improves substantially by averaging, which implies a low signal-to-noise ratio for individual index measurements. Dashed lines are 95% CI (regression) and 95% limits of agreement (Bland-Altman).

Disclosures
One INVOS cerebral oximeter with analog output was donated by Somanetics for use in this research project. Drs Smielewski and Czosnyka have an ownership interest in ICM+ software, which was used to calculate the indices of autoregulation reported in this manuscript.
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