Continuous Measurement of Autoregulation by Spontaneous Fluctuations in Cerebral Perfusion Pressure
Comparison of 3 Methods

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Background and Purpose—Clinical application of continuous autoregulation monitoring would benefit from a comparison of curves generated by online monitoring with standard autoregulation curves in animal models. We characterized the accuracy of 3 continuous monitors of autoregulation in a piglet model of hypotension.

Methods—Piglets 5 to 10 days old with intracranial pressure (ICP) at naive or elevated (20 mm Hg) levels had gradual arterial hypotension induced by a balloon catheter in the inferior vena cava. Elevated ICP was maintained by a continuous infusion of artificial cerebrospinal fluid. Three indices of autoregulation were simultaneously and continuously calculated. A moving, linear Pearson’s coefficient between spontaneous slow waves of cerebral perfusion pressure and slow waves of laser-Doppler flux or cortical oxygenation rendered the laser-Doppler index and cerebral-oximetry index, respectively. Similar correlation between slow waves of arterial blood pressure and ICP rendered the pressure-reactivity index. The lower limit of autoregulation was determined directly for each animal by plotting laser-Doppler cortical red blood cell flux as a function of cerebral perfusion pressure. Receiver-operator characteristics were determined for the 3 indices.

Results—The areas under the receiver-operator characteristics curves for discriminating the individual lower limit of autoregulation at low and high ICP were 0.89 and 0.85 for the laser-Doppler index, 0.89 and 0.84 for the cerebral-oximetry index, and 0.79 and 0.79 for the pressure-reactivity index. The pressure-reactivity index performed equally well at low and high ICPs.

Conclusions—Continuous monitoring of autoregulation by spontaneous slow waves of cerebral perfusion pressure can accurately detect loss of autoregulation due to hypotension in piglets by all 3 modalities. (Stroke. 2008;39:2531-2537.)

Key Words: autoregulation ■ cerebral blood flow ■ hypotension ■ neonates ■ oxygenation ■ piglets

Cerebrovascular autoregulation maintains a relatively constant level of cerebral blood flow (CBF) across a range of arterial blood pressure (ABP).1 The orthodox model of autoregulation is conceptualized as dynamic changes in vascular resistance (pressure reactivity) that protect the brain from low or high microvascular pressure and perfusion caused by changes in cerebral perfusion pressure (CPP). Traditionally, this concept is presented in the medical literature as an all-or-none phenomenon, where pressure reactivity is fully operational within a range of ABP, and complete pressure passivity is observed outside that range. A heterodox model of autoregulation has emerged in the last decade owing to an increase in the resolution of quantitative autoregulatory monitoring techniques. Online monitoring of dynamic autoregulation suggests that autoregulation fails in a graded fashion as ABP deviates from an optimal range. More important, a strong association was found between poor neurologic outcomes and deviation from optimal CPP, defined by online monitoring of pressure reactivity as the CPP at which pressure reactivity is strongest.2 These findings were included in the updated “Guidelines for the management of severe traumatic brain injury” published by the Brain Trauma Foundation,3 in which a level III recommendation suggests ancillary neuromonitoring to fine-tune CPP goals, including an option to monitor the state of autoregulation.

The Cambridge method of monitoring autoregulation is a frequency-specific linear correlation between CPP and surrogates of CBF4 or cerebral blood volume5 that can detect pressure-passive vasculature from only spontaneous slow waves of ABP for a signal.4 Diverse neuromonitoring modalities have been applied to this moving linear correlation technique, yielding monitors of autoregulation with different theoretical assumptions and practical limitations (Table 1).6,7 Supportive clinical data from observational human studies of these modalities abound, including validation by positron emission tomographic determination of the state of autoreg-
ulation as a “gold standard.” However, data from animal models that definitively determine the relation of these measurements to the full autoregulation curve are limited. The objective of the present study was to perform a validation study of 3 separate, continuous monitors of autoregulation: the laser-Doppler index (LDx),9 the cerebral-oximetry index (COx),7 and the pressure-reactivity index (PRx). We hypothesized that these 3 indices would accurately detect loss of autoregulation in an infant swine model, in which the lower limit of autoregulation (LLA) was crossed by slowly inducing arterial hypotension without severe hemodilution.

An assumption unique to the PRx measurement is that intracranial volume changes caused by dynamic vascular resistance are transmitted to intracranial pressure (ICP) as slow waves. Because of the assumed relation between vascular volume and ICP used to measure the PRx, we hypothesized that the accuracy of the PRx would be dependent on the compliance of the intracranial compartment. This hypothesis was tested by comparing the PRx to standard autoregulation curves generated by laser-Doppler flow (LDF) measurement in 2 sets of piglets with naïve or elevated ICP levels.

Materials and Methods

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

Anesthesia and surgical preparation were similar to those previously described.7 Piglets 5 to 10 days old and weighing 2.2 to 3.9 kg, were anesthetized by inhalation of 5% isoflurane, 50% nitrous oxide, and 45% O2. Mechanical ventilation by tracheostomy was adjusted to keep pH at 7.35 to 7.45 and PaO2 at 200 to 300 mm Hg. Anesthesia was maintained with vecuronium (5-mg bolus and 2-mg/h infusion), fentanyl (25-µg bolus and 25-µg/h infusion), and 0.8% isoflurane vaporized with 50% nitrous oxide and 50% O2. Fentanyl was titrated between 10 and 50 µg/h for a target heart rate <200 and normotension during surgery. During the recording period, when BP was actively lowered, fentanyl was infused at approximately 20 µg/kg per hour, and tachycardia was permitted as a response to the preload reduction. Thus, the anesthetic for the recording period was primarily narcotic based, with a modest supplementation of inhalational agent. This combination ensures the comfort of the animal and reduces 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.

Surgery

The femoral veins were cannulated for placement of a central venous line and a 5F esophageal balloon catheter (Cooper Surgical, Trundall, Conn). The balloon catheter was advanced to the inferior vena cava and was used to slow systemic venous return to produce hypotension. The femoral artery was cannulated for placement of a pressure and blood gas monitoring line. To measure ICP, a craniotomy was performed 4 mm lateral and 4 mm rostral to the bregma at the midline for placement of an external ventricular drain catheter. For piglets in the elevated ICP group, an additional contralateral craniotomy was performed for placement of a second ventricular catheter for artificial cerebrospinal fluid infusion. Another craniotomy was performed 4 mm lateral and 4 mm rostral to the ICP monitoring catheter for placement of an LDF probe (Moor Instruments, Devon, UK). The probe was advanced across the incised dura mater to contact the surface of the frontoparietal cortex, positioned to avoid high baseline flux values associated with placement over large vessels, and secured in place by rubber washers cemented to the skull. A final craniotomy in the occipital skull lateral to the midline was used to place a brain temperature probe. To preserve a competent intracranial compartment, all craniotomies were sealed with dental cement. Skin was reapplied to the skull, and the wound was sutured closed for heat retention and to create conditions for which the cerebral oximeter was calibrated.

Oximetry Probe Placement

The INVOS pediatric cerebral oximeter probe (Somanetics, Troy, Mich) was placed above the eye, across the frontal and parietal cortex, with the emitting diode situated 1 cm lateral to the midline to avoid the sagittal sinus. Probe placement was then tested with a CO2 challenge as previously described.7

Signal Sampling and Calculation of the LDx, COx, and PRx

ABP, ICP, LDF, and cerebral oximetry analog waveforms were sampled from an analog-to-digital converter by ICM+ software (Cambridge University, Cambridge, UK) at 60 Hz.10 INVOS cerebral oximetry has a 4-second refresh rate. These signals were then time-integrated as nonoverlapping 10-second mean values to eliminate high-frequency waves at the pulse and respiratory frequency and their harmonics. This low-pass filtering still permits 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. A continuous, moving Pearson’s correlation coeffi-
cient was performed between the CPP and LDF values to render the LDx, between the CPP and the cerebral oximeter values to render the COx, and between the ABP and ICP values to render the PRx. Consecutive, paired, 10-second averaged values from 300-second durations were used for each calculation, thereby incorporating 30 data points for each index calculation. These indices were calculated and recorded every 60 seconds from overlapping time periods.

**Elevated ICP**
For piglets in the elevated ICP group, artificial cerebrospinal fluid (KCl 3.0 mmol/L, MgCl₂ 0.6 mmol/L, CaCl₂ 1.3 mmol/L, NaCl 131.8 mmol/L, NaHCO₃ 24.6 mmol/L, urea 6.7 mmol/L, and glucose 3.6 mmol/L) was infused in the external ventricular drain catheter at varying rates to achieve and maintain a steady-state ICP of ~20 mm Hg throughout the experiment. Piglets with elevated ICP exhibited a spontaneous compensatory increase in ABP, which restored CPP to near baseline values.

**Determining the LLA**
The balloon catheter in the inferior vena cava was gradually inflated by infusion of saline from a syringe pump to slowly lower CPP to ~10 mm Hg in both the naïve ICP group (n=8) and the elevated ICP group (n=6) after achieving a steady state of mean ICP. Our goal was to reduce the ABP over ~3 hours to have a quasi–steady-state CPP and encompass a sufficient number of spontaneous slow fluctuations for analysis. Durations of recording during ABP lowering were 3.25±1.25 hours and 3.17±0.98 hours for the naïve and elevated ICP groups, respectively. A scatterplot of 1-minute averaged LDF versus CPP was made for each piglet. The CPP at the intersection of 2 regression lines having the lowest combined residual squared error was defined as the autoregulatory breakpoint.

**Receiver-Operator Characteristics**
Cerebral oximetry, LDF, LDx, COx, and PRx values were recorded every 60 seconds in real time and simultaneously sorted into 5-mm Hg bins according to the CPP at which they were collected. For each piglet, 1 average value of each parameter at each CPP was reported. Using the LLA determined from the breakpoint analysis as described, we then separated the index values into 2 data sets, 1 above and 1 below the LLA. Prism software (GraphPad, San Diego, Calif) was used to determine the receiver-operator characteristics (ROCs) of the LDx, COx, and PRx.

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Determining the LLA for each subject. A, Construction of an autoregulation curve for a piglet with naïve ICP. ABP (mm Hg), ICP (mm Hg), LD flux (LDOPPLER, AU), and cerebral oximetry (CEREBROX, % saturation) were recorded while a balloon catheter in the inferior vena cava was gradually inflated over 2 to 4 hours. LD measurements of flux were then plotted as a function of CPP. This plot is demarcated into 2 sets of data having best-fit lines with the lowest combined residual squared error. Solving for the intersection of the 2 lines yields the LLA. Notice the spontaneous slow increase in ICP with decreasing ABP and the increase in frequency and amplitude of spontaneous B waves, also with decreasing ABP. B, Example for a piglet with an ICP of 20 mm Hg. Before a reduction in ABP, the ICP was increased to 20 mm Hg by a steady-state infusion of artificial cerebrospinal fluid, which was maintained throughout the experiment.
**Results**

Examples of recordings for the entire protocol are shown on a compressed time scale in Figure 1. As ABP was gradually lowered during a 2- to 4-hour period, spontaneous fluctuations in ABP and ICP permitted dynamic autoregulatory indices to be calculated. Quasi–steady-state autoregulatory curves of LDF versus CPP were generated, and distinct lower limit breakpoints could be calculated in individual piglets from 2 regression lines that minimized the overall residual squared error (Figure 1). The LDF data from 8 piglets in the naïve group and from 6 piglets in the elevated ICP group were pooled in 5-mm Hg CPP bins to generate overall autoregulation curves (Figure 2). The LLA was at a CPP of $30 \pm 5.1$ mm Hg in the naïve piglets and $38 \pm 7.7$ mm Hg in piglets with an ICP of 20 mm Hg (mean ± SD). This difference was not statistically significant ($P=0.08$ by Mann-Whitney test).

Arterial pH, blood gas tensions, hemoglobin concentrations, and brain temperatures were not significantly different between the naïve and high ICP groups (Table 2). Average values in Table 2 are shown in a dichotomous stratification to illustrate the effect of lowering CPP on these potentially confounding variables. Prolonged arterial hypotension was associated with moderate metabolic acidosis without a change in arterial blood gases or brain temperatures.

The purpose of determining the LLA for each piglet was to have a standard against which to compare the autoregulation curves generated by the continuous analysis. By analyzing individual subjects, one can assess the confidence that can be attributed to an autoregulation curve at a patient’s bedside when it is derived from linear-correlation functions of the ICP, cerebral oximetry, or LD flux with the spontaneous waves of CPP. For the ROCs of each modality, we used the final curves generated during the entire experimental recording period for each animal after averaging the measurements at each 5-mm Hg bin, which is the result displayed on the monitor in its usual configuration with ICM+ software. We have shown that individual measurements of COx and LDx are subject to noise, limiting their usefulness in determining the state of autoregulation. Although discrete values of the PRx, COx, or LDx have limited utility, the power of the method is derived from averaging the continuous observations sorted by CPP. Therefore, our assessment of accuracy uses the output of the monitoring system as it appears in the clinical setting.

Data for the 3 autoregulatory indices in the 2 groups of animals are shown in Figure 3. The abscissa was normalized to have the origin at the LLA for each animal. This normalization allows for a visual inspection of the overall ability of the index to indicate (1) pressure reactivity with low correlation coefficient values above the LLA and (2) pressure passivity with high correlation coefficient values below the LLA. In general, the 3 indices showed increasing trends with lowering of the CPP at or below the LLA. The ROCs from this same data set are shown in Figure 4. These data show that all of the indices were reasonably accurate at normal and elevated ICP, with the best performance found in the naïve ICP group with both the LDx and COx, where the area under the curve was 0.89 in both cases. The performance of the PRx favored specificity over sensitivity, but the area under the curve for both the normal and high ICP groups was the same, 0.79.

<p>| Table 2. Physiologic Parameters (±SD) of the Piglets at Normal and Low CPP |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>pH</th>
<th>(P_a CO_2), mm Hg</th>
<th>(P_a O_2), mm Hg</th>
<th>Hemoglobin, g/dL</th>
<th>Brain Temperature, °C</th>
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<td><strong>Naive ICP</strong></td>
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<td>CPP &gt;40 mm Hg</td>
<td>7.41±0.03</td>
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<tr>
<td>CPP &lt;40 mm Hg</td>
<td>7.33±0.05</td>
<td>36.0±2.3</td>
<td>212±31</td>
<td>6.5±1.9</td>
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<tr>
<td><strong>ICP 20 mm Hg</strong></td>
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<tr>
<td>CPP &gt;40 mm Hg</td>
<td>7.44±0.05</td>
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<tr>
<td>CPP &lt;40 mm Hg</td>
<td>7.33±0.05</td>
<td>37.3±4.8</td>
<td>225±70</td>
<td>6.1±0.4</td>
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Discussion

Validity of Continuous Monitoring of Autoregulation

Our results support the hypothesis that pressure passivity can be accurately detected with linear correlation of low-frequency spontaneous waves of CPP and surrogates of CBF. Given the published associations between the PRx and outcomes of patients with traumatic brain injury,²¹ these findings are not unexpected. However, the present
study demonstrates the relation between a static, invasive, gold standard autoregulation curve and an autoregulation curve generated by the continuous linear-correlation method.

The PRx-derived autoregulation curve has been well described in patients with traumatic brain injury. In most of these patients, a U-shaped curve is seen, wherein the lowest correlation scores between ABP and ICP occur in a restricted range of CPP (called CPP_opt). Deviation from CPP_opt by even 10 to 20 mm Hg is often met with pressure passivity and has been shown to be associated with worse outcome. A precise definition of CPP_opt was not obtained in the present study because arterial hypertension was not studied. However, in all 3 indices studied and under both conditions of ICP, the values obtained above the LLA were similar, suggesting that in the uninjured brain, the autoregulatory mechanism is not improved by driving the CPP in excess of the LLA.

Comparing the PRx and COx
The PRx has an inherently different set of assumptions when compared with the LDx and COx. The PRx uses ICP as a surrogate of cerebral blood volume, whereas the LDx and COx use flux and cortical oxygenation as surrogates of CBF. Whereas vascular diameter (and volume) changes are the presumed mechanism of pressure autoregulation, the relation between vascular radius and cerebrovascular resistance is nonlinear. Autoregulation defined as regulation of flow can theoretically fail before failure of vessel reactivity, as was demonstrated in adult cats in which the LLA was documented by the hydrogen clearance method at an ABP of 60 mm Hg, whereas pial arteries continued to increase in size down to an ABP of 35 mm Hg. Pressure reactivity, as measured by the PRx, is therefore linked but is not synonymous with pressure-induced autoregulation of CBF, as measured by the LDx and COx.

In comparison with the LDx and COx, the PRx curves indicated more pressure reactivity at CPP values around the LLA. This curve shape may explain the difference in sensitivity between the PRx and the other 2 indices. In the animals studied, at CPP 10 to 15 mm Hg lower than the LLA, the PRx was noted to trend upward. In comparison, the COx and LDx were trending upward at or 5 mm Hg below the LLA (see Figure 3) in most animals. A possible explanation is that cerebral arteoli continue to dilate below the lower limit of blood flow autoregulation and will result in active increases in blood volume sensed by the PRx. The nonlinear relation between blood flow and blood volume may explain the lack of a substantial increase in PRx until CPP is below the lower limit of blood flow autoregulation. Despite the closed fontanelles in the piglets, it is possible that other factors, such as compressibility, related to the developing brain, spinal cord, skull, and circulation limit the sensitivity of the PRx in the normal range of CPP.

Does the PRx Have Compliance-Dependent Accuracy?
The PRx was equally accurate for detecting loss of autoregulation in both the naïve and elevated ICP groups. Therefore, we must reject the hypothesis that the PRx accuracy is dependent on intracranial compliance. We can propose 2 reasons for this. First, as the naïve piglets became progressively hypotensive, ICP was seen to rise, presumably due to increased vascular volume associated with intact pressure reactivity. At the point of vasoreactivity failure, when the ICP of the animal became passive to ABP, the ICP reached a zenith between 15 and 20 mm Hg. One would therefore expect that the ICP waveform would have robust signals transmitted from vascular volume changes, and pressure reactivity would be accurately quantified by a linear correlation between ABP and ICP at low CPP. We also observed an increase in the frequency and amplitude of B waves, slow waves of vascular origin that last 50 to 200 seconds in the piglets when they became hypotensive. These B waves may have served to improve the signal-to-noise ratio of the ICP waveform for detecting vascular activity. This result is also interesting because the initial concept of the PRx was to use B waves as a spontaneous signal to replace the need for BP manipulations in autoregulatory assessment. If either of these theoretical explanations is true, then compliance dependence in the PRx may not be clinically relevant with an intact skull because hypotension in a naïve brain surrounded by an intact skull will produce enough vasogenic activity to improve the signal-to-noise ratio, and pressure passivity due to hypotension will be detectable. This model fits the observations in our piglets, but our data cannot determine the reliability of the PRx in patients who have had a decompressive craniectomy.

We conclude that using spontaneous waves of CPP and ABP to monitor autoregulation is accurate for the detection of loss of autoregulation due to hypotension with all 3 of the modalities tested. CPP below the LLA caused progressive pressure passivity as assessed by the COx and LDx in these piglets. The shape of the PRx-derived autoregulation curve has an apparent blunted response at CPP around the LLA when compared with the COx- and LDx-derived curves. Increasing ICP did not change the overall performance of the PRx in neonatal piglets, and the PRx was very specific for loss of autoregulation at either naïve or elevated ICP.

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Disclosures
None.

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