Cerebrovascular Reactivity Measured by Near-Infrared Spectroscopy

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Background and Purpose—The pressure reactivity index (PRx) describes cerebral vessel reactivity by correlation of slow waves of intracranial pressure (ICP) and arterial blood pressure. In theory, slow changes in the relative total hemoglobin (rTHb) measured by near-infrared spectroscopy are caused by the same blood volume changes that cause slow waves of ICP. Our objective was to develop a new index of vascular reactivity, the hemoglobin volume index (HVx), which is a low-frequency correlation of arterial blood pressure and rTHb measured with near-infrared spectroscopy.

Methods—Gradual hypotension was induced in piglets while cortical laser-Doppler flux was monitored. ICP was monitored, and rTHb was measured continuously using reflectance near-infrared spectroscopy. The HVx was recorded as a moving linear correlation between slow waves (20 to 300 seconds) of arterial blood pressure and rTHb. Autoregulation curves were constructed by averaging values of the PRx or HVx in 5-mm Hg bins of cerebral perfusion pressure.

Results—The laser-Doppler flux-determined lower limit of autoregulation was 29.4±6.7 mm Hg (±SD). Coherence between rTHb and ICP was high at low frequencies. HVx was linearly correlated with PRx. The PRx and HVx both showed higher values below the lower limit of autoregulation and lower values above the lower limit of autoregulation. Areas under the receiver operator characteristic curves were 0.88 and 0.85 for the PRx and HVx, respectively.

Conclusions—Coherence between the rTHb and ICP waveforms at the frequency of slow waves suggests that slow waves of ICP are related to blood volume changes. The HVx has potential for further development as a noninvasive alternative to the PRx. (Stroke. 2009;40:1820-1826.)

Key Words: autoregulation ▪ cerebral blood flow ▪ hemoglobin ▪ hypotension ▪ near-infrared spectroscopy ▪ neonate ▪ piglet
The prototypical monitor of vascular reactivity is the pressure reactivity index (PRx). Intracranial pressure (ICP) is used as the surrogate of CBV to derive the PRx, which is a moving linear correlation between slow waves of ABP and ICP. A positive PRx, indicating pressure passivity, is associated with death in adults with traumatic brain injury. A negative PRx, indicating pressure reactivity, is associated with survival in adults with traumatic brain injury. The PRx can delineate a range of perfusion pressure with maximal vascular reactivity in most patients with traumatic brain injury, and deviation from this optimal perfusion pressure is associated with death and persistent vegetative state. The strength of these data led to a citation in the guidelines for the management of severe traumatic brain injury from The Brain Trauma Foundation with a new option for autoregulation monitoring to fine-tune CPP goals.

Clinical application of the PRx is limited by the requirement for invasive ICP monitoring. Many patients at risk of devastating atraumatic neurological injuries do not or cannot have ICP monitors. Examples include patients on cardiopulmonary bypass and premature infants at risk for developing intraventricular hemorrhage and periventricular leukomalacia. It is reasonable to hypothesize that these patients would benefit from clarification of optimal blood pressure goals by a nonintracranially invasive form of monitoring vascular reactivity. We have previously reported the use of noninvasive cerebral oximetry as a surrogate of CBF in a monitor of autoregulation—the cerebral oximetry index. Our objective with the present work is to use near-infrared reflectance spectroscopy (NIRS) to trend changes in CBV (relative total hemoglobin in the reflectance arc) to create a near-infrared-based monitor of vascular reactivity—the hemoglobin volume index (HVx).

We hypothesized that slow waves of relative total hemoglobin (rTHb) measured with NIRS would be coherent with slow waves of ICP. Predicated on demonstrating this low-frequency coherence, we further hypothesized that the HVx, a moving linear correlation between slow waves of rTHb and ABP, would have a strong correlation to the PRx, thereby providing a relatively noninvasive method by which to quantify vascular reactivity in patients without ICP monitors. Finally, we hypothesized that the HVx, like the PRx, would accurately detect the lower limit of cerebrovascular autoregulation in a swine model of induced hypotension. We tested these hypotheses by continuously measuring rTHb with NIRS while synchronously measuring ICP and ABP in piglets as ABP was lowered below the lower limit of autoregulation (LLA).

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

Anesthesia
Methods of anesthesia and surgical preparation have been previously described and published. Eight piglets, 5 to 10 days old and weighing 2.34±0.47 kg (mean±SD), were anesthetized with inhaled 5% isoflurane, 50% nitrous oxide, and 50% oxygen. Tracheostomy was performed and mechanical ventilation initiated and adjusted to maintain arterial pH between 7.35 and 7.45 and PaO\textsubscript{2} between 200 and 300 mm Hg. Maintenance anesthesia consisted of 0.8% isoflurane, 50% nitrous oxide, 50% oxygen, fentanyl (25-μg bolus followed by 25-μg/h infusion), and vecuronium (5-mg bolus followed by 2-mg/h infusion). The fentanyl infusion was adjusted to remain between 10 and 50 μg/h to keep the heart rate less than 200 beats per minute and to maintain normal blood pressure. When the blood pressure was actively lowered by inflating a balloon catheter in the inferior vena cava, tachycardia was permitted as an expected response to the induced reduction in preload. The primarily narcotic-based anesthetic technique, supplemented with a relatively low concentration of isoflurane, ensured the animals’ comfort while minimizing the cerebrovascular response to the volatile anesthetic agent. Piglets were placed on a warming pad to keep their brain and rectal temperatures at 38.5° to 39.5°C.

Surgery
A femoral central venous catheter for drug infusion and a femoral arterial catheter for blood pressure monitoring and blood sampling were placed. A 5-Fr esophageal balloon catheter (Cooper Surgical, Trundall, Conn) was placed in the contralateral groin and threaded into the inferior vena cava. Slow, controlled systemic hypotension was induced by slowly inflating the balloon catheter in the inferior vena cava.

A craniotomy was performed 4 mm rostral and 4 mm lateral to the bregma at midline for placement of an external ventricular drain catheter to monitor ICP. A second craniotomy was performed 4 mm lateral to the ventricular drain for placement of a laser-Doppler flux (LDF) probe (Moor Instruments, Devon, UK). The dura mater was incised, and the LDF probe was advanced to contact the surface of the frontoparietal cortex and secured in place with rubber washers cemented to the cranium. A third small craniotomy in the occipital cranium just lateral to midline was performed for a brain temperature probe. All craniotomy sites were sealed with dental cement to preserve the integrity of the intracranial compartment. The skin was reapplied to the skull and sutured closed for heat retention.

Neonatal optodes for the FORE-SIGHT near-infrared spectroscopic monitor (CASMED, Inc, Branford, Conn) were placed contralateral to the craniotomy sites, lying across the frontal and parietal lobes, sutured in place, and shielded with opaque black nylon until the neonate left the room. A 0.5-mm tungsten wire for the plethysmographic monitor (CASMED, Inc, Branford, Conn) was placed in the contralateral groin and threaded into the inferior vena cava for mechanical ventilation. The wire was shielded with opaque black nylon until the neonate left the room.

Signal Sampling
ABP, ICP, and LDF measurements were sampled from an analog-to-digital converter at 100 Hz using ICM+ software (Cambridge University, Cambridge, UK, www.neurosurg.cam.ac.uk/icmplus). CPP was calculated as (ABP−ICP) and recorded every 10 seconds.

rTHb Measurement
We used the FORE-SIGHT monitor to record rTHb using an algorithm developed at the University College of London and used in the Hamamatsu NIRO-500/1000 series NIRS systems. We used a multivariate form of this algorithm with 3 wavelengths (780, 805, 850 nm) to solve 2 unknowns (\text{Hb} and \text{HbO}_2), which when added yielded rTHb.

An alternative method of determining rTHb was much simpler. We used transmittance from a nearly isobestic wavelength (805 nm) of infrared light as an approximation of rTHb. The index of autoregulation derived from this approximation was indistinguishable from that obtained with the more complicated University College of London rTHb algorithm. Although neither of these measurements of rTHb concentration are calibrated and an artificial nonlinearity is introduced by using simple transmittance (instead of its logarithm in the modified Beer-Lambert equation) to trend blood
volume, both measures of rTHb had the same accuracy when used to describe vascular reactivity. Because the rTHb change during autoregulation is a small fraction of the absolute hemoglobin, a logarithmic transformation may not be necessary. Moreover, the phase of the blood volume waveform is more important than the power when describing vascular reactivity. Results in this article are reported using the University College of London algorithm, but it should be noted that receiver operating characteristics (ROC) of the derived indices using the University College of London method versus transmittance of 805 nm light for rTHb were identical (data not shown).

Determining the LLA

The balloon catheter in the inferior vena cava was inflated with saline through a syringe pump infusion to slowly lower ABP. The goal was to decrease ABP over approximately 3 hours to achieve a quasisteady-state CPP and capture an adequate sample of spontaneous slow wave fluctuations (Figure 1A). The recording period during which ABP was lowered was 3 hours 39 minutes ± 48 minutes (mean ± SD). A scatterplot of 1-minute averaged LDF versus CPP was generated for each piglet. The CPP at the intersection of the 2 regression lines with the lowest combined residual squared error was defined as the LLA (Figure 1B). The slope of the line describing the range of intact autoregulation was not required to be zero.

Low-Pass Filtering and Calculation of the PRx and HVx

The signals were time-integrated and resampled as nonoverlapping 10-second mean values to eliminate high-frequency waves and, specifically, harmonics from pulse and respiration. Oscillatory changes that occur <0.05 Hz are still detected with this low-pass filtering method.

The vascular reactivity indices were calculated as follows. A continuous moving Pearson correlation was performed between slow waves (20 to 300 seconds) of ICP and ABP to calculate PRx and between slow waves of rTHb and ABP to calculate HVx. Consecutive paired 10-second averaged values from 300-second epochs generated 30 data points for inclusion in each Pearson coefficient used to determine the PRx and HVx. As explained at the beginning of this article, positive values of PRx or HVx indicate impaired vascular reactivity, and negative values indicate intact vascular reactivity.
Statistical Analysis

Comparison of rTHb and ICP Waveforms

The waveforms of ICP and rTHb were collected from each animal during a 60-minute period of rest without manipulation of ABP. Coherence between the 2 waveforms was assessed using the Welsh method with 40 overlapping segments (at 10% overlap) with a spectral range from 0.004 to 0.05 Hz having total hemoglobin as the input and ICP as the output (Figure 2).

Correlation of the PRx and HVx

All paired values of the PRx and HVx from the entire duration of the 8 experiments were included in a linear (Spearman) correlation and Bland-Altman analysis using Prism software (GraphPad, San Diego, Calif).

Receiver Operating Characteristics

PRx and HVx were calculated every 10 seconds from overlapping 300-second analysis periods and sorted into 5-mm Hg bins according to the CPP at which they were recorded. For each piglet, average values for PRx and HVx were reported at each CPP bin. After calculating the LLA from the LDF data as described, the PRx and HVx were divided into data sets above and below the LLA. Prism software was used to generate the ROC of the PRx and HVx from this dichotomized data set, in which values obtained below the LLA are labeled measurements in the lost autoregulatory state and values obtained above the LLA are labeled measurements in the intact autoregulatory state.

Results

Arterial pH, blood gas tensions, hemoglobin concentration, and brain temperatures were similar among all piglets (Table). The piglets had an average ICP of 7.8±2.8 mm Hg (±SD). On average, the LLA occurred at a CPP of 29.4±6.7 mm Hg (±SD) for the 8 animals studied, a result that is consistent with our prior study of piglets.10

Spontaneous low-frequency (0.004 to 0.05 Hz) changes in rTHb were usually in phase with ICP (Figure 2). Harmonics in this spectral range had periodicity ranging from 20 seconds to 250 seconds, the period of slow waves. Coherence scores between rTHb and ICP were divided into frequency bins and reported using box whiskerplots. The result of this cross-spectral analysis, averaging the data from all 8 animals, is shown in Figure 3. Slow waves of ICP in these piglets occurred with longer periods (often ≥50 seconds) than those seen in humans with ICP monitoring. This period corresponds to a frequency of <0.02 Hz, and it can be seen from our data that the coherence scores between the ICP and rTHb are higher in this range. This demonstration is a sine qua non for our study design: slow waves of ICP are the signal used for the PRx, and finding coherence between ICP and rTHb slow waves raises the possibility that rTHb can be used in place of ICP to quantify vascular reactivity.

The relationship of HVx with PRx was examined using all 2242 measurements from the 8 experiments (Figure 4). Plotting these paired measurements of HVx and PRx yielded a robust correlation with a Spearman rank r value of 0.73. Increases in PRx are sensitive for detecting the LLA in piglets.11 To determine if HVx is equally sensitive, results

| Table. Physiological Parameters of the Piglets at Normal and Low CPP |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CPP            | pH              | PdCO2, mm Hg    | PdO2, mm Hg     | Hemoglobin, g/dL | Brain Temperature, °C |
| >40 mm Hg      | 7.39±0.08       | 38±3            | 279±47          | 8.5±1.4          | 38.5±1.0         |
| <40 mm Hg      | 7.35±0.08       | 41±4            | 267±32          | 7.9±1.5          | 38.3±1.1         |

Figure 2. Analysis of coherence between rTHb and ICP. A, A 1-hour resting period was recorded for each animal with monitoring of ICP (mm Hg), rTHb (AU), and ABP (mm Hg). Slow waves (0.004 to 0.05 Hz) of ICP occurred in each animal and are shown with waves of rTHb for comparison. B, Coherence between the ICP and rTHb waves was assessed using a cross-spectral analysis. In this animal, coherence was high in the frequency of the slow waves observed in A, which corresponds to a period of 50 seconds. The relationship observed here suggests that slow waves of ICP are the result of intracerebral vascular volume changes.
Discussion

The results of the experiments presented here have 2 important implications. First, the results imply that the nonintracranially invasive HVx has a potential clinical role in the care of patients at risk of neurological injury. Second, the conceptual model used to derive the PRx is now better supported by the close agreement between the HVx and PRx.

Given the amount and quality of patient data linking a positive PRx to poor outcome, it is perhaps academic to validate the conceptual model that was used to create the PRx 10 years ago. However, the lack of a continuous and convenient metric for CBV, other than the ICP itself, has precluded such a validation. The PRx is, in theory, a measure of the responses of cerebral resistance arterioles to slow waves of ABP that are commonly seen in monitored patients. The assumption inherent in this model is that slow waves of ICP, specifically waves with a period of between 20 and 300 seconds, are the result of CBV changes, which are in turn caused by changes in the collective arteriolar diameter. Our finding of coherence between rTHb and ICP at the slow-wave frequency in these animals links these slow ICP waves to slow blood volume waves. The finding of a reactive relationship between blood volume and ABP above the LLA and a passive relationship between blood volume and ABP below the LLA at the frequency of slow waves specifically implicates resistance arterioles as the vascular compartment responsible for the slow waves seen in both the blood volume and ICP. Taken together, these results defend the assumptions made when using the PRx.

We have shown, in the naïve animal, that the HVx is an excellent nonintracranially invasive alternative to the PRx. One difference between the PRx and HVx that should be considered is the regional specificity of the HVx, which only describes vasculature in the reflective path of infrared light between the optodes of the NIRS-based monitor. The PRx uses a global measurement of ICP, potentially influenced by the collective activity of all cerebral vessels. The implications of this difference have not been determined and are probably situationally specific. For instance, after trauma, is the HVx of this difference have not been determined and are probably situationally specific. For instance, after trauma, is the HVx
Success has previously been reported in quantifying relative CBV noninvasively with an ultrasound time-of-flight measurement. This measurement was then used to measure vascular reactivity as a phase shift between the relative blood volume and the ABP changes at the respiratory frequency as opposed to analyzing at the frequency of slow waves as is done with the PRx and the HVx. The theoretical advantage of using respiratory frequency waveform analysis is the regular periodicity when compared with the sporadic nature of slow waves. However, the phase shift between CBV and ABP resulting from vascular reactivity is “incomplete” at this frequency (that is to say that the high-pass filter used to describe the effect of autoregulation on ABP–CBV transmission has its transition band around this frequency). Furthermore, the pediatric range of respiratory frequency is higher and more variable than the adult range. Therefore, the phase shift of blood volume to blood pressure variation at the pediatric respiratory frequency is likely smaller and more variable than that reported in adults. Until the effect of autoregulation on ABP–CBV transmission has its transition band around this frequency. Furthermore, in the present study, we have demonstrated slow waves in piglets at rest without intracranial or hemodynamic manipulation (Figures 2 and 3).

PRx and HVx were observed to increase in grades as CPP was reduced below the LLA. This finding implies that the vasculature is not completely passive at the breakpoint of CBF autoregulation and is consistent with the concept that additional vasodilation occurs below the LLA. However, this additional vasodilation is insufficient to maintain CBF.

Clinical considerations for the HVx are prompted by the convenient and relatively noninvasive nature of the measurement. The HVx could possibly be rendered completely noninvasive by the use of noninvasive ABP monitoring with the Finapres device. Furthermore, the HVx has long been the only continuous assessment of vascular reactivity, and it requires an ICP monitor. Our objective in rendering a near-infrared-based vascular reactivity index was to develop a tool that can be used to define the bounds of autoregulatory reserve when the ICP monitor is unavailable. In particular, we seek to meet the pressing need to define autoregulation boundaries in infants and children that have yet to be satisfactorily explored. The pediatric population has an elevated incidence of, and mortality from, traumatic brain injury and is a subset of patients for whom we lack data to formulate even basic perfusion pressure goals. Premature infants have a risk of germinal matrix hemorrhage and periventricular ischemia, but there is no standard practice of neuromonitoring to guide the hemodynamic management of these unstable patients. It is possible that monitoring and optimizing vascular reactivity within ischemically sensitive regions of the premature brain might afford neuroprotection. With the HVx, this hypothesis can be tested without an ICP monitor.
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Disclosures

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