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Diagnosis Influences Response of Cerebral NIRS to Intracranial Hypertension in Children

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Abstract

Objective—To describe cerebral regional oxygen saturation (rSO₂) measured by near infrared spectroscopy (NIRS) in the setting of normal and increased intracranial pressure (ICP) in children in order to evaluate the association between cerebral rSO₂ and ICP in comparison with other clinical variables.

Design—Prospective observational cohort study.

Setting—Two academic tertiary care centers' pediatric intensive care units (PICU).

Patients—Thirty patients with ICP and NIRS monitoring (median age 11.5 years; interquartile range 5.2–13 years) for a range of neurologic diagnoses including brain tumor, trauma, intracerebral hemorrhage and hydrocephalus.

Interventions—None.

Measurements—Temporally correlated cerebral rSO₂ with hematologic (hematocrit), biochemical (pH) and physiologic (intracranial pressure, mean arterial pressure, cerebral perfusion pressure, temperature, heart rate, pulse oximetry and end-tidal carbon dioxide) variables.

Main Results—Cerebral rSO₂ during episodes of increased ICP was lower than with normal ICP (mean±SD % ICP > 20 = 71±13%, vs. ICP < 20 = 75±10%), although the mean difference (–4%) is small compared to variability in the measurement. Neither isolated values, nor change (Δ) in cerebral rSO₂ were significantly associated with ICP or cerebral perfusion pressure (CPP) in the overall population. Isolated values and change in end-tidal CO₂ were significantly correlated with cerebral rSO₂ and Δ cerebral rSO₂ (all P<0.01). In exploratory analyses diagnostic group significantly modified the effect of intracranial hypertension on rSO₂: rSO₂ decreased during intracranial hypertension in patients with brain tumors (P=0.05) and hydrocephalus (P<0.001), but increased during intracranial hypertension in those with intracranial hemorrhage (P<0.001).

Conclusions—These data suggest that cerebral rSO₂ is lower with intracranial hypertension. However, the relationship between cerebral rSO₂ and ICP is strongly influenced by diagnosis.

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Keywords

Near-Infrared Spectroscopy; Pediatric Intensive Care Unit; Intracranial Pressure; Brain

Introduction

Elevation of intracranial pressure (ICP) may compromise cerebral blood flow, resulting in secondary neurologic morbidity. Treatment of intracranial hypertension is focused on minimizing the volume of intracranial compartments, while preserving brain tissue viability through manipulation of cerebral oxygen delivery and consumption. Measurement of increased ICP is difficult without invasive monitors that carry significant risks of bleeding [1] and infection [2, 3]. Currently no method exists for non-invasively measuring ICP. Venous oxygen hemoglobin saturation can be used to monitor changes in cerebral blood flow under conditions of constant arterial oxygen content and brain metabolic rate [4]. Cerebral oxygen saturation therefore, might be useful to infer changes in intracranial pressure through effects on cerebral blood flow provided similar assumptions are met and other clinical variables known to affect cerebral blood flow (e.g. arterial carbon dioxide tension) are not changed.

Near-infrared spectroscopy (NIRS) is a noninvasive method to measure changes in regional tissue oxygen saturation [5]. Cerebral oxygen saturation measured by NIRS has been shown to be a reliable surrogate marker of changes in cerebral blood flow in experimental models [6] and cerebral oxygenation improves following drainage of cerebral spinal fluid in neonates with post hemorrhagic hydrocephalus [7]. Cerebral NIRS monitoring is used to monitor and adjust regional cerebral perfusion during cardiopulmonary bypass for aortic arch reconstruction [8] and is used extensively in Pediatric Cardiac [9, 10] and Neonatal Intensive Care Units [11, 12]. However, current NIRS technology has been criticized for a variety of methodological issues that have limited widespread clinical use of the technique [13, 14].

This objective of this study was to determine the relationship between cerebral NIRS and ICP in comparison with other physiologic, hematologic and biochemical variables in children with intracranial hypertension, with the hypothesis that cerebral oxygen saturation should decrease during periods of intracranial hypertension.

Methods

Patients

Thirty pediatric patients admitted to the pediatric intensive care units (PICU), 16 at University of California, San Francisco Children's Hospital and 14 at Children's Hospital Oakland, from August 2006 to March 2008 were prospectively enrolled. Patients were included if they required placement of an intracranial pressure monitor for the suspicion of increased ICP and if a clinical decision was made to monitor cerebral oxygen saturation with NIRS. Voluntary parental consent was waived because the study involved no intervention, no more than minimal risk to the patient and all data were stripped of identifiers that might compromise confidentiality of private healthcare information. The Committee on Human Research at the University of California, San Francisco and the Children's Hospital and Research Center Oakland approved the study protocol.

Only one patient meeting inclusion criteria was excluded from the analysis. A single patient (Table 1 – patient #28) with systemic lupus erythematosus (SLE) received an external ventricular drain for enlarged cerebral ventricles and altered mental status during a

hospitalization for exacerbation of SLE that included multiple thromboses, renal failure and progressive neurologic decompensation. This patient was found to have a normal intracranial pressure and the ventricular dilatation was interpreted as hydrocephalus ex vacuo. Subsequent neuroimaging studies showed diffuse attenuation of the anterior and posterior arterial circulation consistent with central nervous system vasculitis. This patient had the lowest cerebral rSO₂ values recorded in the study (42.9+/-3.1% mean +/- standard deviation). As these values were almost 3 standard deviations below the average cerebral rSO₂ defined by the study population (74.1+/-11.0%), the patient was not included in the subsequent analysis.

Regional Oxygen Saturation Monitoring

Regional oxygen saturation was monitored with an INVOS 5100C Cerebral Oximeter (Somanetics, Troy, MI), which affords single or dual-site monitoring with an adult (>40 kg) or pediatric (<40 kg) disposable sensor. The INVOS 5100C emits near-infrared light at two wavelengths (730 and 805 nm) and employs two detectors and spatially resolved spectroscopy to measure light absorption by oxy- and deoxy-hemoglobin in the brain. Using a proprietary calculation, the ratio of oxy-hemoglobin to deoxy-hemoglobin is expressed as regional oxygen percent saturation (rSO₂).

Data Collection

Demographic variables, laboratory results and physiologic variables were collected from the patient's medical record using a data sampling algorithm and database structure developed for a prior study of cerebral NIRS monitoring in a Pediatric Cardiac Intensive Care Unit (PICU) [9]. A set of variables was then selected for extraction from the PICU nursing flow sheet: vital signs (including temperature, heart rate, peripheral oxygen saturation (SaO₂), end-tidal carbon dioxide (etCO₂), mean arterial pressure, ICP and cerebral perfusion pressure (CPP)), hematocrit and arterial blood gas values (pH, bicarbonate (HCO₃)). End-tidal CO₂ was analyzed in place of PaCO₂ because more values of etCO₂ were available for analysis and these two measurements correlate closely (Spearman's rho = 0.5, P<0.0001, N=487). Data were extracted in response to the following prespecified events: 1. Regular sampling every 4 hours; 2. Change in: etCO₂ >5 torr, peripheral oxygen saturation > 5%, temperature > 1°C, mean arterial blood pressure >10 mmHg, ICP >10 mmHg, cerebral perfusion pressure >10 mmHg, or change in regional oxygen saturation > 10%; or 3. In response to laboratory test results. For each event, the correspondent rSO₂ was extracted from the continuous NIRS recording or the nursing flow sheet and were compared for agreement. All events were paired chronologically and used to determine change (Δ) values. Examples of measurement pairs for an event of ICP change are shown in Figure 1B.

Data Analysis

All the clinical variables were entered into a relational database (Filemaker Pro 7) and exported for statistical calculations with Stata 8 software (Stata Corporation, College Station, TX). ICP was dichotomized to normal (ICP < 20 mmHg) or elevated (ICP $\geq$ 20 mmHg). Bilateral cerebral rSO₂ measurements were coded by side (left vs. right) or by relationship to the ICP monitor (ipsilateral vs. contralateral). Variability among the bilateral NIRS measurements was explored with Bland-Altman analysis of the difference between measurements compared with the average of measurements. Linear regression for repeated measures, generalized estimating equation with robust within-subjects correlation estimation, was used to determine associations between the isolated values and change in rSO₂ and clinical variables with an independent correlation structure. Exploratory analysis tested the effect of diagnostic group on the relationship of ICP with rSO₂ by adding an interaction term to the linear regression.

Results

Patient Characteristics and Clinical Measurements

Thirty patients with a median age of 11.5 years (range 0.3–17 years) admitted to one of two pediatric intensive care units were studied from August 2006 to March 2008. The patients' demographics, diagnoses and imaging findings are summarized in Table 1. Patients who were monitored for ICP and either unilateral or bilateral cerebral NIRS monitoring were enrolled. Diagnoses causing intracranial hypertension included brain tumors, traumatic brain injury, intracranial bleeding, hydrocephalus and other pathologies including encephalitis and vasculitis. Three patients who presented with spontaneous intracranial hemorrhage (ICH) had arteriovenous malformations (AVM); two presented with a primary ICH while one had bleeding due to recurrence of AVM more than one year after surgical resection. The final patient had spontaneous intracranial hemorrhage in the setting of a new diagnosis of acute myelogenous leukemia. A single patient with recurrent headache and vomiting due to pseudotumor cerebri was included within the hydrocephalus category. Decisions to institute or terminate monitoring were made by the clinical team. No interventions were specified based upon cerebral rSO₂ values. There were no complications attributable to cerebral oxygen saturation monitoring or data collection.

Recordings were analyzed for up to the first 48 hrs after NIRS monitor was placed. Recording duration lasted for a median of 26.5 hours/patient (interquartile range (IQR) 21–30.7 hrs) and a median of 28 events (IQR 19–34 events) per patient were extracted according to the prespecified sampling protocol (see methods). Data were extracted in measurement pairs in order to analyze both isolated values and changes in clinical variables. The median values and interquartile range of clinical variables are summarized in Table 2. Data were extracted in the setting of both normal (ICP < 20 mmHg) and increased ICP (ICP ≥ 20 mmHg). The median ICP was 16 mmHg (IQR 9–24). Other clinical variables were age-appropriate for a pediatric population, but included hypertensive blood pressure values and hypothermic body temperatures owing to treatment interventions for increased ICP. The clinical team made all decisions regarding treatment of increased ICP. A majority of patients (93%) received some therapy for intracranial hypertension, or therapy that may affect ICP including: CSF drainage (80%), sedation (63%), mechanical ventilation (93%), cerebral perfusion pressure management (40%), osmotherapy (43%), barbiturate coma (17%) or hypothermia (27%).

Examples of the raw cerebral rSO₂ recordings are shown in Figure 1 for a patient with hydrocephalus (Figure 1A) and a patient with closed head trauma (Figure 1B). Low cerebral rSO₂ in the patient with hydrocephalus and ventriculoperitoneal shunt malfunction improved following placement of an external ventricular drain and cerebral spinal fluid drainage (Figure 1A). Cerebral rSO₂ recordings from patients with other diagnosis showed a range of variability, with frequent changes in some patients (Figure 1B) and flat tracings in others (data not shown). Isolated examples of changes in ICP can be observed that are associated with no change (Figure 1B, event 1), discordant change (Figure 1B, event 2) or concordant change (Figure 1B, event 3).

Cerebral Regional Oxygen Saturation Trends to Lower Values with Increased ICP

To determine if rSO₂ differs during normal and increased ICP, we dichotomized measurements into two categories: normal (< 20 mmHg) and hypertensive (≥ 20 mmHg). Cerebral rSO₂ values in patients during periods without intracranial hypertension show a normal population distribution (Figure 2A fitted normal-density plot) with a mean of 75.2% and standard deviation of 10.1% (N=961). Cerebral rSO₂ values during intracranial hypertension show a bimodal distribution, with a lower population mean (Figure 2B). rSO₂

is lower during episodes of intracranial hypertension (mean $\pm$ S.D., 70.8% $\pm$ 12.5%, N=660), although the difference is small (mean difference = -4.4%, 95% confidence interval -5.6% - -3.2%). Accounting for the multiple repeated measurements in each patient, this difference is not significant ($P=0.3$, N=1432).

Evaluation of Bilateral Cerebral rSO₂ Measurements

To examine the agreement of simultaneous left and right-sided measurements we performed Bland-Altman analysis for all cases monitored with bilateral NIRS sensors (Figure 2C, N=9 patients, N=307 measurements). The mean difference was small (2.1%, 95% confidence interval 1.5 - 2.8%). However the 95% limits of agreement were wide (-9.9 - 14.1%) indicating significant variability between sides. To explore the possibility that asymmetric cerebral pathology accounted for this variability, we repeated the Bland-Altman analysis comparing measurements made ipsilateral or contralateral to the ICP monitor, noting that the ICP monitor was placed on the side opposite to the pathology in 4 of 5 cases with asymmetric pathology. The mean difference between ipsilateral and contralateral measurements was similar to that of left and right pairs (3.1%, 95% confidence interval 2.6 - 3.7%). The limits of agreement were slightly narrower (-6.1 - 12.3%). At low values of cerebral rSO₂ (< 70%), ipsilateral measurements tend to be significantly lower than contralateral measurements ($P < 0.001$, $r = 0.16$, Pitman's test of difference in variance). This relationship is reversed at high values of cerebral rSO₂ (> 80%). However, the limits of agreement at low and high values of cerebral rSO₂ are not different from those calculated for the entire range of measurements.

Association of Cerebral rSO₂ with other Clinical Variables

To understand the association between other clinical variables, including CPP, and individual values of cerebral rSO₂, we performed linear regression between ipsilateral cerebral rSO₂ and isolated clinical variables accounting for repeated measurements in each patient (Table 3). The table includes the regression coefficient (β) and 95% confidence intervals for the coefficient, as well as the P value for the analysis. Significant associations are identified for cerebral rSO₂ and end-tidal carbon dioxide (etCO₂, $\beta=0.58$, $P=0.01$, N=1265, linear regression for repeated measures), indicating that for each change in etCO₂ of 1 torr, cerebral rSO₂ increases by 0.58 percent saturation. Temperature also affects cerebral rSO₂ ($\beta=2.2$, $P=0.01$, N=1191), but in a paradoxical direction. Finally, as with ICP, CPP is not significantly associated with cerebral rSO₂ ($P=0.59$, N=1430). Placing the significant variables etCO₂ and temperature into a multivariable model, both remain significantly associated with cerebral rSO₂ (all $P < 0.01$). Finally, repeating the regression analyses with left rSO₂, rather than ipsilateral rSO₂ does not substantially alter the results.

Trends in Cerebral Oxygen Saturation are Associated with Changes in etCO₂, Hematocrit and Heart rate, not ICP or CPP

Cerebral blood flow is dynamically autoregulated by changes in perfusion pressure, metabolism and carbon dioxide [15]. To determine whether trends in the change of rSO₂ and clinical variables were more closely associated than the isolated values, we identified all measurement pairs of rSO₂ and clinical variables and compared the changes (Δ) between measurements. Δ cerebral rSO₂ is associated with Δ etCO₂ ($\beta=0.42$, $P < 0.001$, N=736), Δ heart rate ($\beta=0.10$, $P=0.004$, N=904) and change in hematocrit ($\beta=0.57$, $P=0.004$, N=38), but not change in ICP or CPP. Δ ICP was not significantly associated with Δ cerebral rSO₂, even when the analysis was limited to large changes in ICP ($> \pm 10$ mmHg). Examining all variables with significance in their association with Δ cerebral rSO₂ (Δ etCO₂, Δ heart rate, Δ hematocrit) in a multivariable model, Δ etCO₂ and Δ hematocrit remain significantly associated with Δ cerebral rSO₂ (Δ etCO₂: $\beta=0.82$, $P<0.001$; Δ hematocrit: $\beta=0.49$, $P=0.04$).

Changes in ICP are Not Preceded, nor Followed by Decrease in rSO₂

To examine the temporal aspects of the relationship between cerebral rSO₂ and ICP, we examined all possible correlations between NIRS and ICP data, computing the correlation coefficient between the two at multiple temporal offsets in a subset of patients (N=11). Recordings were selected with multiple episodes (N>5) of intracranial hypertension and included patients from all diagnostic groups. First, the NIRS data was shifted by a series of lags (–120 min to 120 min at 15 min intervals). Next, the ICP data was linearly interpolated to match the sample time points of the shifted NIRS measurements, and the correlation coefficient between each of the shifted NIRS traces and the interpolated ICP trace was calculated, giving a correlation coefficient as a function of time lag. The average correlation coefficient across patients (Fig 3A, mean $\pm$ SEM) shows no significant correlation at any temporal offset.

Diagnostic Group Influences the Response of Cerebral rSO₂ to Intracranial Hypertension

The hypothesis for this study did not include an effect of patient diagnosis. To explore the possibility that changes in cerebral rSO₂ during periods of intracranial hypertension might vary depending upon specific cerebral pathologies, we plotted cerebral rSO₂ during periods of normal (< 20 mmHg) and elevated (> 20 mmHg) ICP for each of the major diagnostic categories (brain tumor, trauma, intracerebral hemorrhage and hydrocephalus) (Figure 3B). In patients with brain tumors (N=11), trauma (N=10) and hydrocephalus (N=3), cerebral rSO₂ falls during intracranial hypertension. Paradoxically, in patients with intracerebral hemorrhage (N=4), cerebral rSO₂ rises during intracranial hypertension. To test the significance this observation for the purpose of generating hypotheses for future studies, we performed an exploratory analysis adding diagnostic group as an interaction term to the linear regression for ICP. This analysis indicates strong effect modification of diagnosis ($P < 0.0001$) on the relationship between cerebral rSO₂ and ICP. Stratifying the regression analyses by diagnostic group indicates a significant association between cerebral rSO₂ and ICP for patients with brain tumor ($\beta = -0.31$, 95% confidence interval $-0.63 - 0.004$, $P = 0.05$), intracerebral hemorrhage ($\beta = 0.61$, 95% confidence interval $0.50 - 0.74$, $P < 0.001$) and hydrocephalus ($\beta = -0.91$, 95% confidence interval $-1.0 - -0.79$, $P < 0.001$). Patients with brain trauma do not show a significant association between cerebral rSO₂ and ICP ($P = 0.3$). Considering the effect of diagnostic group on the relationship between Δ cerebral rSO₂ and Δ ICP, a smaller but significant interaction effect ($P = 0.01$) is also observed. Limited patient numbers for each diagnostic group precludes further subgroup analysis.

Discussion

This study was motivated by observations of a relationship between cerebral NIRS values and cerebral spinal fluid (CSF) removal in animal models [6] and in human neonates [7, 16]. These reports indicated that hydrocephalus compromised cerebral blood flow and oxygenation through alterations in ICP. We reasoned that this relationship might allow non-invasive cerebral NIRS monitoring to predict intracranial hypertension and act as a surrogate for direct ICP monitoring, if important assumptions regarding constant arterial oxygen content and brain metabolic rate are taken into account. Our results demonstrate that although cerebral rSO₂ tends to be lower when ICP is greater than 20 mmHg, the mean difference is small in comparison with overall NIRS measurement variability, limiting the predictive value of cerebral rSO₂ for intracranial hypertension. Our study was designed to test for a relationship between cerebral oxygen saturation and intracranial pressure in a heterogeneous patient population. Nonetheless, subgroup analysis suggests divergence in the response of cerebral rSO₂ *by diagnostic group*. Firm conclusions based upon this exploratory analysis must be tempered by consideration of the small numbers within each subgroup.

The mean difference between cerebral rSO₂ during normal and increased ICP in the overall population was small (−4.1%) in comparison with the variability of cerebral rSO₂ measurements (standard deviation = 10%). Considering each diagnostic group separately, the differences are larger (summarized in Figure 3B; e.g. brain tumor mean difference (95% confidence interval), −8.0% (−6.1% – −9.9%)) suggesting that for specific diagnostic categories, cerebral rSO₂ may be a more useful predictor of intracranial hypertension. However, the magnitude of these differences within subgroups remains similar to the variability in the cerebral rSO₂ measurement. Further studies of larger sample size within each of the groups presented here are warranted.

Variability in cerebral rSO₂ arises from numerous sources including technical issues with current generation NIRS monitors[13, 17, 18], but also the influence of changes in important physiologic variables. In a prior study of cerebral NIRS monitoring in neonatal patients after cardiac surgery [9], we found that end-tidal carbon dioxide was the clinical variable most strongly associated with cerebral rSO₂. Notably this relationship appeared to be brain-specific, as etCO₂ was not associated with flank rSO₂. Results presented here confirm this relationship between isolated values of cerebral rSO₂ and etCO₂. Change in etCO₂ was also associated with change in cerebral rSO₂, as were change in heart rate and hematocrit. In a multivariable model, only change in etCO₂ and hematocrit remain significantly associated with change in cerebral rSO₂. Hematocrit strongly affects arterial oxygen content, one of the variables that must remain constant in order to use change in venous saturation to estimate change in blood flow. For cerebral rSO₂ to be a useful predictor of intracranial hypertension, potent effects of other physiologic variables, most notably carbon dioxide levels, must be considered.

The majority of current generation NIRS monitors, including the Invos 5100c used in the present study, utilize a continuous wave NIRS method that relies upon change in absorbance of near infrared light by endogenous chromophores (e.g. oxy- and deoxyhemoglobin) across a series of light pulses[19]. This method has been criticized for high intra- and interpatient variability [20]. Technical issues identified that contribute to measurement variability include failure to measure light diffusion path length[19], contamination by extra-cranial signal [21] and variation according to sensor position[17, 18]. We examined the variability between simultaneous bilateral NIRS measurements by performing Bland-Altman analysis on measurements from left vs. right sensors. As expected, there is minimal detectable bias between measurements from the right and left forehead. However, there is substantial variability in the simultaneous measurements (95% limits of agreement, −9.9% – 14.1%), which is larger than the overall effect size of intracranial hypertension on cerebral rSO₂. Some of this variability reflects asymmetry of intracranial pathology, as the Bland-Altman limits of agreement were smaller (−6.1 – 12.3%) when considering simultaneous measurements coded by side in relation to the ICP monitor. Again, these limits of agreement remain larger than the overall effect size of intracranial hypertension. Considering the relative contributions of technical issues related NIRS methodology versus variability in patient physiology, it is important to note that variability of similar magnitude has been described for measurement of jugular [22] and central venous saturations [23] by blood gas analyzer.

An unexpected observation in the present study was the increase in cerebral rSO₂ in a small group of patients with spontaneous ICH (three of four patients in this group had AVMs). AVMs are known to induce alterations in cerebral blood flow to surrounding brain tissue that have been described in terms of preoperative ‘steal’ and are associated with postoperative hyperemic complications (perilesional hemorrhage or edema) [24]. Two competing theories have been considered to account for these changes, ‘normal perfusion pressure breakthrough’ [25] relating to loss of autoregulation in surrounding vessels and

'occlusive hyperemia' [26] secondary to stagnant arterial flow and obstruction of venous outflow. Studies employing intraoperative cortical NIRS measurements have noted an increase in cerebral saturation following resection of AVM, with the magnitude of increase associated with the risk of developing postoperative complications [27]. These studies have generally supported the normal perfusion pressure breakthrough theory, although autoregulation was intact in surrounding vessels[28]. Neither study examined the response of cerebral rSO₂ to intracranial hypertension and in fact, preoperative cerebral saturations in patients with AVMs were the same or lower than comparison patients without AVMs.

Cerebral vascular pressure autoregulation is impaired following intracerebral hemorrhage in adults [29]. This may result from either direct tissue injury surrounding the hematoma or from a sudden increase in ICP with a secondary loss of autoregulation. Intracranial hypertension resulting from increases in systemic arterial blood pressure in the presence of impaired pressure autoregulation would be expected to increase cerebral blood volume and potentially lead to a rise in cerebral rSO₂. Finally, cerebral NIRS measures a mixed hemoglobin sample estimated to be approximately 25% arterial, 5% capillary and 70% venous blood [22]. Any change in this distribution favoring the arterial component would tend to increase the regional saturation.

In addition to the effect of diagnostic group on the behavior of cerebral rSO₂, we also considered whether cerebral rSO₂ and ICP do not change concurrently. In other words, we considered whether changes in cerebral rSO₂ precede or follow changes in ICP. These possibilities might arise if decreased cerebral oxygenation leads to autoregulatory changes in cerebral blood volume and subsequent increases in ICP. A second possibility is that intracranial hypertension leads to increased cerebral vascular resistance and ischemia, resulting in a fall in cerebral rSO₂. In a subset of patients, we analyzed the correlation between rSO₂ and ICP in 15-minute intervals at temporal offsets ranging from two hours before to two hours after an episode of intracranial hypertension. No significant correlations are found for cerebral rSO₂ preceding or following intracranial hypertension. Inspection of individual plots of cerebral rSO₂ and ICP over time (Figure 1) confirms that variability occurs in both cerebral rSO₂ and ICP with complex temporal frequency and examples can be found of changes that occur simultaneously or independently.

A majority of patients in the present study received treatment known to affect cerebral blood flow and oxygen delivery (CPP management, osmotherapy), as well as cerebral metabolic rate (sedation) and these factors may have improved cerebral rSO₂ during intracranial hypertension, tending to minimize the effect of ICP on cerebral rSO₂. The clinical variables measured share complex physiologic interrelationships that are affected by clinical interventions, perhaps leading to spurious observations. An example of this is the relationship between patient temperature and cerebral rSO₂, where the regression coefficient is positive implying that as temperature increased, so did cerebral rSO₂. This relationship is unexpected as increasing temperature increases brain metabolic rate and oxygen consumption[30] and thus would lower cerebral rSO₂. The effect may be explained by confounding associations between diagnosis, illness severity and treatments affecting both body temperature and cerebral rSO₂ (e.g. hypothermia). A stronger relationship between cerebral rSO₂ and ICP might have been detected using a study design with carefully controlled, sequential manipulation of blood pressure and carbon dioxide that has been used to evaluate brain tissue oxygen probes [31] and measure cerebral autoregulation in children following traumatic brain injury [32]. Future studies would benefit from continuous acquisition and analysis of all physiologic variables and enrollment of larger patient groups controlled for type of diagnosis, age and treatment. However, this study was designed to understand information provided by the monitor under conditions of current clinical practice and therefore clinical interventions were not controlled. Finally the utility of cerebral NIRS

monitoring for optimizing long-term neurodevelopmental outcome remains to be determined. Unresolved issues include the determination of critical cerebral NIRS values below which there is an increased risk of ischemic brain injury. A critical value of 45% was identified as a risk for newly acquired postoperative white matter injury in neonates receiving the Norwood procedure for hypoplastic left heart disease [33].

Although the observational study design and heterogeneity of the patient population limit this study, it does reflect current practice utilizing cerebral NIRS monitoring in the setting of the varied neurologic pathology encountered in an academic PICU. The present results do not strongly support the use of cerebral NIRS measurements to predict increased ICP or to monitor clinical interventions that may alter ICP. The surprising behavior of cerebral rSO₂ in the setting of cerebral hemorrhage should also be confirmed, as this observation may have therapeutic implications. These rSO₂ measurements suggest that more complex physiologic changes are occurring that require further clarification with more detailed monitoring. These data provide a population estimate for expected cerebral rSO₂ values in pediatric patients with neuropathology and a description of both population and intra-patient variability. Cerebral NIRS values well below this normal range should be investigated with sensitive neuroimaging modalities.

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Figure 1. Representative plots of the continuous recordings of cerebral rSO₂ in a patient with hydrocephalus and ventriculoperitoneal shunt malfunction (A) and closed head trauma (B). Placement of external ventricular drain is noted in (A). ICP values are plotted in (B, solid black squares). Three events of ICP change > 10 mmHg are identified by rectangular boxes.

Figure 2.

Histogram summarizing the range of values for cerebral rSO₂ during normal ICP (A). The population fits a normal distribution (fitted curve). Cerebral rSO₂ values during intracranial hypertension are summarized by histogram in (B). Cerebral rSO₂ during increased ICP is shifted to lower values compared with those observed during normal ICP (fitted curve from panel A). Bland-Altman plots (average vs. difference) of simultaneous right and left cerebral rSO₂ (C) compared with cerebral rSO₂ ipsilateral and contralateral to the ICP monitor (D).

Figure 3.

Summary of the mean $\pm$ standard error of the mean correlation coefficients between cerebral rSO₂ and ICP shifted by a series of time lags (–120 minutes to 120 minutes at 15 minute intervals) (A). Box plots (median, quartiles and outliers) of cerebral rSO₂ during periods of normal ICP (< 20 mmHg) and intracranial hypertension by diagnostic group. Measurement number is summarized above the box plots. Patient number is summarized below the X-axis category labels.

Table 1**Patient Demographics and Diagnosis**

Pt.#	Sex	Age	Diagnosis/mechanism	Initial CT findings
26	M	0.5	Choroid plexus papilloma	Right temporoparietal mass, IVH, transtentorial herniation
18	F	1	Atypical Teratoid Tumor	Bilateral suboccipital craniotomy, resection of fourth ventricle mass, hydrocephalus
25	M	6	Medulloblastoma	Suboccipital craniotomy IVH, hydrocephalus
2	F	7	Ependymoma	Left lateral ventricle mass
20	F	8	Medulloblastoma	Midline cerebellar mass
27	F	9	Medulloblastoma	Left temporoparietal craniotomy, left frontal lobe parenchymal hemorrhage
19	M	11	Glioblastoma multiforme	Subtotal resection of left pontine mass, hydrocephalus
21	M	12	Mixed germ cell tumor	Pineal mass, hydrocephalus
24	M	13	Germinoma	Pineal mass, hydrocephalus
14	M	15	Astrocytoma	Occipital craniotomy, resection astrocytoma, transtentorial herniation
8	M	17	Ependymoma	Occipital craniotomy, transtentorial herniation, hydrocephalus,
Trauma				
36	M	0.3	Motor vehicle accident	Bilateral parietal fracture, subarachnoid hemorrhage, biconvexity extraaxial collections
34	M	0.9	Fall vs. non-accidental trauma	Right occipital fracture, parietal fracture, left cerebral, right subfrontal and right cerebellum hypodensity, left subdural evacuation
29	M	1	Auto vs. pedestrian	Multiple skull base fractures, depressed right parietal fracture with underlying extraaxial hematoma, bilateral depressed occipital fracture
31	F	2	Gunshot wound	Hemorrhagic tract from the right to left parietal lobe
23	M	3	Fall vs. non-accidental trauma	Left subdural hematoma, left hemispheric infarction
32	M	12	Fall	Left temporal subdural, left frontal extraaxial hemorrhage
17	M	13	Assault (baseball bat)	Left posterior temporal/occipital fracture, left parietal and temporal hemorrhagic contusions
35	M	14	Skateboard accident	Left temporal and frontal hemorrhagic contusions, bilateral temporoparietal extraaxial hemorrhage, diminute ventricles and basal cisterns
1	M	16	Skateboard accident	Bilateral frontal and right temporal lobe hemorrhagic contusions
13	M	16	Motor vehicle accident	Right occipital fracture, right occipital and cerebellar extraaxial hemorrhage, bilateral frontal intraparenchymal contusions and extraaxial hemorrhages
Hemorrhage				
5	F	8	AVM rupture	Right parietal intraparenchymal hemorrhage, right parietal AVM
6	F	9	AVM rupture	Bilateral IVH, choroid plexus AVM
16	M	12	Acute myelogenous leukemia	Midbrain and thalamic bleed
37	F	14	AVM rupture	Left basal ganglia and thalamic hemorrhage
Hydrocephalus				
22	M	5	Ventriculoperitoneal shunt malfunction	Ventriculomegaly
33	M	13	Ventriculoperitoneal shunt malfunction	Ventriculomegaly
11	M	12	Pseudotumor cerebri	Remote foramen magnum decompression

Pt.#	Sex	Age	Diagnosis/mechanism	Initial CT findings
Other				
28	F	17	Hydrocephalus ex vacuo, SLE vasculitis	Ventriculomegaly, volume loss
30	M	13	Encephalitis	Left hemispherectomy with external herniation frontal, parietal and temporal lobes

Summary of abbreviations: Pt. – patient, M – male, F – female, IVH – intraventricular hemorrhage, vs. – versus, AVM – arteriovenous malformations, SLE – systemic lupus erythematosus.

Table 2

Summary of Clinical Variables.

Variable	Units	Median (Interquartile Range) or % (number)	N
Age	years	11.5 (5.2–13)	
Weight	kg	38.2 (16.4–55.8)	
Sex	male	70% (21)	
Etiology			
Trauma	%	33 (10)	
Tumor	%	37 (11)	
Hemorrhage	%	13 (4)	
Other	%	17 (5)	
rSO2 left	%	73 (64–82)	1493
rSO2 right	%	72 (65–85)	609
rSO2 ipsilateral	%	73 (64–82)	1460
MAP	mmHg	80 (72–91)	1688
ICP	mmHG	16 (9–24)	1682
CPP	mmHg	65 (52–75)	1669
Heart Rate	bpm	102 (82–127)	1697
ETCO2	mmHg	34 (30–38)	1484
SaO2	%	100 (n.a.)	1692
pH		7.38 (7.35 –7.41)	497
Temperature	°C	36.5 (35.2– 37.5)	1379
Hematocrit	%	31.4 (7.9– 36)	238

Table 3

Summary of clinical variables

	rSO2			ArSO2			
	β	95% CI	P	β	95% CI	P	
ICP	-0.15	-0.43 - 0.13	0.29	Δ ICP	-0.04	-0.17 - 0.09	0.53
CPP	-0.06	-0.29 - 0.16	0.59	Δ CPP	0.01	-0.08 - 0.10	0.78
MAP	-0.15	-0.38 - 0.08	0.21	Δ MAP	-0.004	-0.14 - 0.14	0.95
HR	0.07	-0.06 - 0.21	0.32	Δ HR	0.10	0.03 - 0.17	0.004
Temp	2.2	0.79 - 3.7	0.002	Δ Temp	0.51	-0.19 - 1.2	0.16
etCO2	0.58	0.17 - 0.99	0.01	Δ etCO2	0.42	0.25 - 0.58	< 0.001
O2 sat	-0.94	-3.0 - 1.1	0.36	Δ O2 sat	0.12	-0.75 - 0.99	0.79
pH	19	-27 - 65	0.42	Δ pH	-20	-99 - 59	0.62
Hct	0.33	-0.18 - 0.83	0.21	Δ Hct	0.57	0.19 - 0.97	0.004