Optical Detection of Intracranial Pressure and Perfusion Changes in Neonates With Hydrocephalus

Tracy M. Flanders, MD[1,2], Shih-Shan Lang, MD[1], Tiffany S. Ko, PhD[3], Kristen N. Andersen, BA[3], Jharna Jahnavi, BA[3], John J. Flibotte, MD[4], Daniel J. Licht, MD[3], Gregory E. Tasian, MD, MSc, MSCE[2,5], Susan T. Sotardi, MD[6], Arjun G. Yodh, PhD[7], Jennifer M. Lynch, MD, PhD[8], Benjamin C. Kennedy, MD[1], Phillip B. Storm, MD[1], Brian R. White, MD, PhD[9], Gregory G. Heuer, MD, PhD[1], and Wesley B. Baker, PhD[3]

Objective To demonstrate that a novel noninvasive index of intracranial pressure (ICP) derived from diffuse optics-based techniques is associated with intracranial hypertension.

Study design We compared noninvasive and invasive ICP measurements in infants with hydrocephalus. Infants born term and preterm were eligible for inclusion if clinically determined to require cerebrospinal fluid (CSF) diversion. Ventricular size was assessed preoperatively via ultrasound measurement of the fronto-occipital (FOR) and frontotemporal (FTHR) horn ratios. Invasive ICP was obtained at the time of surgical intervention with a manometer. Intracranial hypertension was defined as invasive ICP ≥15 mmHg. Diffuse optical measurements of cerebral perfusion, oxygen extraction, and noninvasive ICP were performed preoperatively, intraoperatively, and postoperatively. Optical and ultrasound measures were compared with invasive ICP measurements, and their change in values after CSF diversion were obtained.

Results We included 39 infants, 23 with intracranial hypertension. No group difference in ventricular size was found by FOR (P = .93) or FTHR (P = .76). Infants with intracranial hypertension had significantly higher noninvasive ICP (P = .02) and oxygen extraction fraction (OEF) (P = .01) compared with infants without intracranial hypertension. Increased cerebral blood flow (P = .005) and improved OEF (P < .001) after CSF diversion were observed only in infants with intracranial hypertension.

Conclusions Noninvasive diffuse optical measures (including a noninvasive ICP index) were associated with intracranial hypertension. The findings suggest that impaired perfusion from intracranial hypertension was independent of ventricular size. Hemodynamic evidence of the benefits of CSF diversion was seen in infants with intracranial hypertension. Noninvasive optical techniques hold promise for aiding the assessment of CSF diversion timing. *(J Pediatr 2021;236:54-61)*.

Hydrocephalus, the most common neuropathology treated in pediatric neurosurgery,[1] is commonly associated with impaired cognitive outcomes.[2-5] Among the causes of these deficits are periventricular white matter insult and hypoxic-ischemic injury to brain parenchyma that arise from intracranial hypertension.[4,6,7] Therefore, the timing of neurosurgical intervention for CSF diversion to relieve intracranial hypertension is important. This timing is currently highly variable among pediatric neurosurgeons, however,[7,8] and bedside noninvasive detection of intracranial hypertension could aid clinical decision making.

Numerous techniques for such detection have been proposed,[9-12] and although promising, they are not yet reliable enough for clinical use. Recent

BP	Blood pressure	ICP	Intracranial pressure
CBF	Cerebral blood flow	MAP	Mean arterial pressure
$CMRO_2$	Cerebral metabolic rate of oxygen consumption	nICP	Noninvasive intracranial pressure index
CSF	Cerebrospinal fluid	NICU	Neonatal intensive care unit
DCS	Diffuse correlation spectroscopy	OEF	Oxygen extraction fraction
FD-DOS	Frequency-domain diffuse optical spectroscopy	PI	Pulsatility index
FOR	Fronto-occipital horn ratio	StO_2	Tissue oxygen saturation
FTHR	Frontotemporal horn ratio	THC	Total hemoglobin concentration

From the [1]Division of Neurosurgery, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania; [2]Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania; [3]Division of Neurology, Department of Neurology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania; Divisions of [4]Neonatology and [5]Urology, Children's Hospital of Philadelphia; [6]Department of Radiology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania; [7]Department of Physics and Astronomy, University of Pennsylvania; [8]Department of Anesthesiology and Critical Care Medicine; and [9]Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Funded by the National Institutes of Health (Grants R01 NS113945, to W.B., S.L., G.H., J.F., and D.L.; K08 NS117897, to B.W.; R01 NS060653, to A.Y. and W.B.; P41 EB015893, to A.Y.; and T32-HL007915, to T.K.) and the Pediatric Hydrocephalus Foundation (T.F.). The authors declare no conflicts of interest.

Portions of this study were presented at the 47th Annual Meeting of the International Society of Pediatric Neurosurgery, October 2019, Birmingham, UK; the American Association of Neurological Surgeons/Congress of Neurological Surgeons Section on Pediatric Neurological Surgery Annual Meeting, December 2019, Scottsdale, AZ; and the Optical Society of America Biophotonics Conference, April 2020, Fort Lauderdale, FL.

https://doi.org/10.1016/j.jpeds.2021.05.024

proof-of-concept studies have further used machine learning to model the relationship between optical measurements of cerebral blood flow (CBF) waveform morphology and intracranial pressure (ICP).[13,14] Here we present a pilot study of noninvasive optical methods for detection of intracranial hypertension in neonatal hydrocephalus.

We combined 2 optical techniques, frequency-domain diffuse optical spectroscopy (FD-DOS) and diffuse correlation spectroscopy (DCS), to derive noninvasive indices of CBF, oxygen extraction fraction (OEF), and ICP.[15-19] We assessed these methods in infants receiving CSF diversion. We hypothesized that (1) FD-DOS/DCS measurements can detect intracranial hypertension in neonatal hydrocephalus; (2) intracranial hypertension is associated with impaired cerebral oxygen delivery (ie, diminished CBF and elevated OEF as measured by FD-DOS/DCS); and (3) intracranial hypertension is associated with a favorable metabolic response to CSF diversion (ie, increased CBF and decreased OEF). Ultimately, successful implementation of bedside FD-DOS/DCS monitoring of ICP may facilitate individualized patient-specific management of infant hydrocephalus.

Methods

The Children's Hospital of Philadelphia's Institutional Review Board approved this study, and written informed consent was obtained from the guardians of all participants. We screened all patients admitted to the neonatal intensive care unit (NICU) between September 1, 2018, and March 15, 2020. Patients were eligible for inclusion if they (1) were age <2 months, (2) had a diagnosis of hydrocephalus, and (3) met local surgical criteria[20,21] for CSF diversion to manage hydrocephalus. Infants were excluded if an invasive ICP measurement was not performed. CSF diversion and shunt timing were based on weight, brain ultrasound measurements of ventriculomegaly, and clinical exam criteria.[20,21] Demographic information, including sex, weight and age at surgery, race, diagnosis, and head circumference, were abstracted from the clinical chart.

Enrolled subjects underwent a preoperative FD-DOS/DCS measurement over the frontal lobe (**Figure 1**; available at www.jpeds.com) within 7 days of surgery. We also examined the closest preoperative brain ultrasound to surgery; the timing of this ultrasound was based on routine clinical care, but to be eligible for use in the study, it had to have been obtained within 10 days of surgery. At the time of surgery, after induction of anesthesia, an intraoperative optical measurement was obtained. During surgical CSF diversion, a brain cannula was used to create the tract to the ventricle, and the attending neurosurgeon immediately acquired an invasive ICP measurement with a manometer attached to the end of the cannula; the 0-point level was the foramen of Monro. A postoperative optical measurement was obtained within 7 days of surgery. Accompanying each optical measurement, a single blood pressure was acquired with a clinical oscillometric cuff. Calculation of CBF, cerebral tissue oxygen saturation (StO_2), and total hemoglobin concentration (THC) was performed.[16] The optical instrument and methods are further described in the **Appendix** (available at www.jpeds.com).

Our primary study measurement parameter was a noninvasive ICP index (nICP) calculated from FD-DOS/DCS. In brief, ICP was estimated based on the relationship between microvascular CBF and blood pressure. (ICP is the extrapolated arterial blood pressure at which CBF reaches 0.) This value, which is also known as the critical closing pressure, can be calculated using the pulsatility indices (PIs) of both CBF and blood pressure (BP) (PI_{CBF} and PI_{BP}).[17] The PI of a measurement is its value in systole minus its value in diastole divided by its mean. Then, as described elsewhere,[17] we defined $nICP = 0.6 \cdot MAP(1 - PI_{BP}/PI_{CBF})$, where MAP is the mean arterial blood pressure. MAP and PI_{BP} were calculated from the oscillometric arterial blood pressure measurement, and PI_{CBF} was calculated from the DCS data using Fourier analysis.[17]

First, we compared intraoperatively measured nICP to invasively measured ICP (the gold standard); the optical measurement was made several minutes before the invasive ICP measurement under similar anesthetic conditions (**Figure 1**, B). We hypothesized that nICP would be significantly correlated with invasively measured ICP, and that elevated nICP would be associated with intracranial hypertension; intracranial hypertension was defined as an invasive ICP measurement of ≥15 mm Hg. This threshold for dichotomization is consistent with the current literature[11] and was chosen based on extrapolation of adult traumatic brain injury data.

We also investigated whether other optical biomarkers, obtained intraoperatively, were associated with intracranial hypertension. Namely, we measured StO_2, THC, and CBF and derived OEF and the cerebral metabolic rate of oxygen consumption ($CMRO_2$) using standard calculations[16,22] (**Appendix**). We compared invasively measured ICP with brain ultrasound measurements of the fronto-occipital horn ratio (FOR) and frontotemporal horn ratio (FTHR).[23,24] FOR and FTHR, standard metrics of ventricular size, were measured post hoc by an experienced neuroradiologist blinded to the clinical status of the patient. Finally, we investigated whether the average rate of change in head circumference over the week before surgery was associated with intracranial hypertension.

Statistical Analyses

For the main analyses, mean optical measures across both hemispheres were used. Statistical calculations were performed with MATLAB R2018a (MathWorks). All statistical tests were 2-sided, and $P < .05$ was considered to indicate significance.

We assessed whether infants with and infants without intracranial hypertension differed in intraoperative optical biomarkers (nICP, StO_2, THC, CBF, OEF, and $CMRO_2$) or ultrasound biomarkers (FOR and FTHR, measured preoperatively) using the *t* test. We also used linear regression and

Table I. Demographics of patients with and without intracranial hypertension

Demographics	No intracranial hypertension (ICP <15 mmHg)	Intracranial hypertension (ICP ≥15 mmHg)	*P* value
Number of patients	16	23	
Female sex, n (%)	7 (44)	8 (35)	.74
Gestational age, wk, median (IQR)	32.4 (26.5-35.9)	32.6 (24.9-37.1)	.89
Weight at time of CSF diversion surgery, g, median (IQR)	2525 (2130-2900)	3080 (2358-3600)	.06
Race, n (%)			
White	9 (56)	15 (65)	.74
Black	7 (44)	8 (35)	.74
Born preterm, n (%)	13 (81)	16 (70)	.48
Age at time of CSF diversion surgery, d, median (IQR)			
Preterm infants	27 (22-25)	64 (29-112)	.12
Term infants	5 (2-8)	6 (5-10)	.72
Etiology of hydrocephalus, n (%)			
Posthemorrhagic	8 (50)	8 (35)	.51
Congenital	1 (6)	4 (17)	.63
Myelomeningocele (postnatal repair)	4 (25)	8 (35)	.73
Myelomeningocele (prenatal repair)	1 (6)	2 (9)	>.99
Other	2 (13)	1 (4)	.56
CSF diversion type, n (%)			
Ventriculoperitoneal shunt	11 (69)	22 (96)	.03
Ommaya reservoir	4 (25)	0 (0)	.02
External ventricular drain	0 (0)	1 (4)	>.99
Endoscopic third ventriculostomy	1 (6)	0 (0)	.41
Inhalational volatile anesthetic used for CSF diversion surgery, n (%)	12 (75)	23 (100)	.02
Serial drainage before CSF diversion surgery, n (%)	2 (13)	5 (22)	.68
Intraoperative head circumference percentile, median (IQR)	77 (24-94)	92 (46-97)	.44
Rate of change in head circumference over the week before CSF diversion surgery, cm/d, median (IQR)	0.17 (0.02-0.24)	0.21 (0.10-0.28)	.33
Intraoperative MAP, mmHg, median (IQR)	40 (34-42)	44 (38-46)	.22
Intraoperative cerebral perfusion pressure, mmHg, median (IQR)	28 (23-31)	24 (17-28)	.04

P values were computed using the Fisher exact test and Wilcoxon rank-sum test, as appropriate. Intraoperative MAP is the mean cuff blood pressure between anesthesia induction and surgical incision. Intraoperative cerebral perfusion pressure is the difference between MAP and ICP.

Bland–Altman analyses to investigate agreement between intraoperative nICP and invasive ICP. Finally, we used linear regression analyses to estimate the associations between preoperative ultrasound metrics (FOR and FTHR) and invasive ICP.

For our secondary analysis, we examined preoperative to postoperative changes in optically measured nICP, StO_2, THC, CBF, OEF, and $CMRO_2$. Of note, because the intraoperative optical measurement occurred immediately before CSF diversion, we used the measured intraoperative to postoperative changes for this analysis to best isolate the hemodynamic effects associated with CSF diversion. Specifically, the relative postoperative/intraoperative ratios were computed for OEF, CBF, THC, and $CMRO_2$, and the relative postoperative-to-intraoperative differences were computed for nICP and StO_2. Paired *t* tests were used to determine whether mean changes in these variables were different from 0 for both infants with intracranial hypertension and infants without intracranial hypertension. Finally, we assessed agreement between intraoperative and preoperative FD-DOS/DCS measurements with intraclass correlation coefficients (**Appendix**).[25]

Results

During the study period, 52 patients were eligible for enrollment (**Figure 2**; available at www.jpeds.com). Of these, 5 parents refused consent, 1 parent was not approached for consent due to staff availability, and 7 patients did not have invasive ICP measurements performed. Thus, 39 patients were included in the analyses. There were 26 deviations from the intended study protocol requiring some patients to be excluded from some analyses. Namely, 5 patients did not have a preoperative optical measurement, 11 did not have an intraoperative optical measurement, and 10 did not have a postoperative optical measurement. The reasons for missed measurements were FD-DOS/DCS machine availability (1 preoperative, 4 intraoperative, and 2 postoperative), staff availability (4 preoperative, 7 intraoperative, and 3 postoperative), NICU discharge (4 postoperative), and clinical instability (1 postoperative). In 9 patients, brain ultrasound was not performed within 10 days of the operation. The preoperative optical measurement occurred at a median of 2.5 days (IQR, 2-4 days) before surgery. Similarly, the postoperative optical measurement occurred at a median of 2.5 days (IQR, 2-4 days) after surgery. Finally, the brain ultrasound scans occurred at a median of 4.5 days (IQR, 3-8 days) before surgery.

There was a wide variation in invasively measured ICP at the time of CSF diversion, ranging from 5 to 30 mmHg; 23 patients (59%) met the study definition of intracranial hypertension (**Table I**). Compared with infants without intracranial hypertension, a higher proportion of infants with intracranial hypertension underwent the ventriculoperitoneal shunting

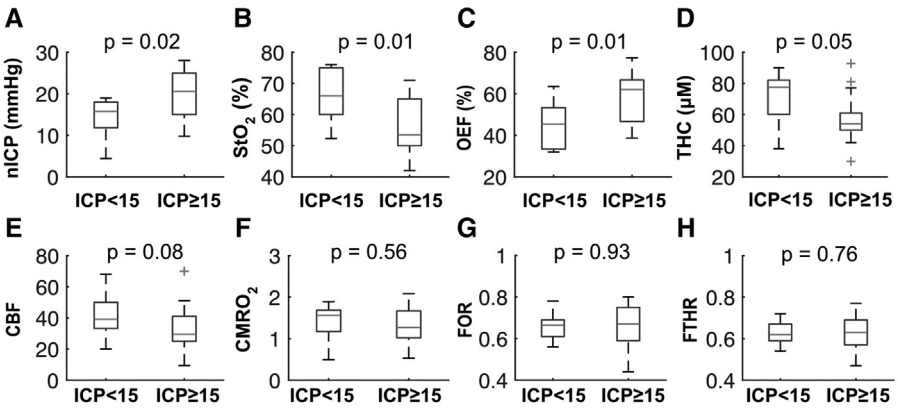

Figure 3. Association of noninvasive optical and ultrasound biomarkers with intracranial hypertension defined as an invasive ICP measurement ≥15 mmHg. Units for CBF and $CMRO_2$ indices are 10^{-9} cm^2/s and 10^{-4} μM cm^2/s, respectively. All boxplots show the median and IQR.

method of CSF diversion (P = .03). The use of general anesthesia during CSF diversion also differed between the groups (P = .02). Infant weight at the time of CSF diversion was lower in the non-intracranial hypertension group, but this difference was not significant (P = .06). Cerebral perfusion pressure at the time of surgery was lower in the intracranial hypertension group (P = .04). No other differences between groups were identified.

Primary Outcome: Association of Noninvasive Biomarkers with Intracranial Hypertension

The primary outcome analysis involved 28 patients with both intraoperative FD-DOS/DCS and invasive ICP data. Of these patients, 18 (64%) had intracranial hypertension. Noninvasive ICP was significantly higher in the infants with intracranial hypertension (P = .02; **Figure 3**, A). Patients with intracranial hypertension also had significantly lower StO_2 (P = .01; **Figure 3**, B) and higher OEF (P = .01; **Figure 3**, C). THC and CBF were lower in the intracranial hypertension group, although these differences were not significant (**Figure 3**, D and E). No between-group difference in $CMRO_2$ was observed (P = .56; **Figure 3**, F).

Thirty patients had invasive ICP data and preoperative FOR and FTHR measurements for analysis; 20 of these patients were in the primary outcome analysis. Of these patients, 16 (53%) had intracranial hypertension. In contrast to optical biomarkers, there were no differences in preoperative ultrasound metrics (median FOR, P = .93; and FTHR, P = .76) between the groups with and without intracranial hypertension (**Figure 3**, G and H).

Secondary Analyses

Linear regression analysis showed nICP to be significantly correlated with ICP (P = .01; **Figure 4**, A), although the correlation was moderate (R = 0.48), and the slope of the line of best fit between nICP and ICP was 0.50 (95% CI, 0.13-0.87). In Bland–Altman analysis, the mean difference of nICP and ICP was 1.0 mmHg (95% CI, −10.5 to 12.4), not significantly different from 0 (P = .39). Conversely, increased FOR and FTHR measured by brain ultrasound were not associated with increasing invasively measured ICP (FOR: slope, −0.0005; 95% CI, −0.0075 to 0.0065; R = −0.03; P = .89 and FTHR: slope, −0.0001; 95% CI, −0.0056 to 0.0054; R = −0.01; P = .97; **Figure 4**, C and D). Although head circumference was not associated with intracranial hypertension (**Table I**), it did increase modestly between the time of ultrasound and surgery by a median of 0.9 cm (IQR, 0.1-1.5 cm).

Eighteen patients had both intraoperative and postoperative FD-DOS/DCS data for analysis of changes in optical

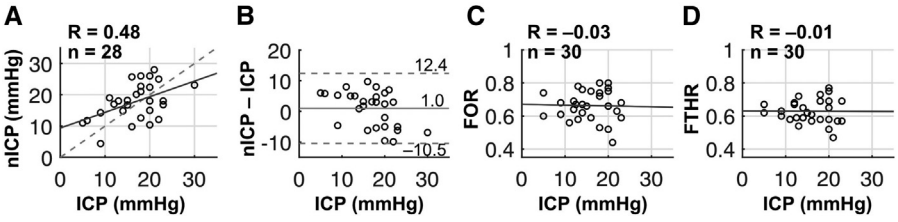

Figure 4. **A,** Intraoperative nICP was correlated with ICP acquired during CSF diversion surgery (solid line, linear best fit; dashed line, line of unity). **B,** Bland–Altman plot of the difference between nICP and ICP (solid line, mean difference; dashed lines, 95% limits of agreement, ie, the mean ± 1.96 times the SD of the difference). **C** and **D,** Preoperative FOR (**C**) and FTHR (**D**) as measured on brain ultrasound were not correlated with ICP (solid lines, linear best fit).

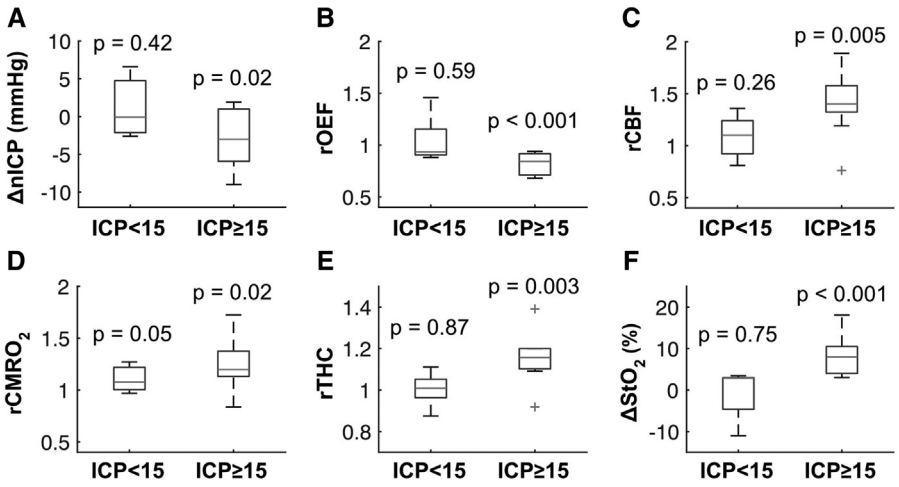

Figure 5. Changes in optical biomarkers from before to after CSF diversion surgery, dichotomized by our definition of intracranial hypertension as an ICP ≥15 mmHg. ΔnICP is the difference between postoperatively and intraoperatively measured nICP. Relative OEF (rOEF), relative CBF (rCBF), relative $CMRO_2$ ($rCMRO_2$), and relative THC (rTHC) are expressed as postoperative-to-intraoperative ratios. ΔStO_2 is the difference between postoperatively and intraoperatively measured StO_2. *P* values indicate whether the mean change was different from 0. All boxplots show the median and IQR values.

biomarkers; 10 had intracranial hypertension (56%). Patients who had intracranial hypertension demonstrated postoperative decreases in nICP ($P = .02$) and OEF ($P < .001$) and postoperative increases in CBF ($P = .005$), $CMRO_2$ ($P = .02$), THC ($P = .003$), and StO_2 ($P < .001$). In contrast, patients without intracranial hypertension showed smaller physiologic effects of surgery with no statistically significant changes in FD-DOS/DCS measures; $CMRO_2$ was increased after surgery in these patients ($P = .05$; **Figure 5**). Finally, although MAP was not associated with intracranial hypertension (**Table I**), the median intraoperative MAP of 41 mmHg (IQR, 37-45 mmHg) was lower than both the median postoperative MAP of 55 mmHg (IQR, 49-63 mmHg) and the median preoperative MAP of 48 mmHg (IQR, 43-60 mmHg).

The repeatability of the optical measures was assessed with intraclass correlation coefficients. For all optical biomarkers, good agreement was noted between measurements in each hemisphere and between preoperative and intraoperative measures (**Table II**; available at www.jpeds.com).

Discussion

In this pilot study, we have demonstrated the feasibility of noninvasive, bedside FD-DOS/DCS measurements in infants with hydrocephalus. Moreover, we have shown that these measurements can provide important information not attainable with current clinical proxies for elevated ICP. Notably, our noninvasive ICP index, nICP, was significantly associated with intracranial hypertension, whereas the current clinical standards of FOR and FTHR, calculated from brain ultrasound, were not associated with intracranial hypertension. These results suggest that ventricular size alone is inadequate as a predictor of intracranial hypertension in neonatal hydrocephalus.

In the present investigation, we found that intracranial hypertension was associated with evidence of impaired cerebral oxygen delivery; OEF was higher in patients with intracranial hypertension. A higher OEF indicates that more oxygen is extracted from the delivered blood. Direct evidence of decreased oxygen delivery was not found; that is, CBF and THC were not significantly lower in patients with intracranial hypertension. However, both CBF and THC showed a trend toward a statistically significant decrease, with *P* values affected by a single patient with intracranial hypertension with high CBF and THC. Although one might expect that increases in MAP can compensate for intracranial hypertension to maintain cerebral perfusion pressure, cerebral perfusion pressure was lower in the group with intracranial hypertension. In an extreme case, decreased oxygen delivery would result in ischemia and lower oxygen metabolism. On average, decreased oxygen delivery was compensated for by increased oxygen extraction (ie, elevated OEF); consequently, there was no measured difference in intraoperative $CMRO_2$ index between the groups with and without intracranial hypertension. However, this overall assessment may miss individual patients with critically diminished oxygen delivery.

FD-DOS/DCS measurements also supported our hypothesis that CSF diversion in patients with intracranial hypertension is associated with improved biomarkers of cerebrovascular function. CSF diversion resulted in a decrease in nICP, as would be expected for a successful surgical result. These patients experienced an increase in CBF, an increase in blood volume, and a decrease in OEF. Thus, CSF diversion resulted in improved oxygen delivery and a return toward more normative metabolism.

Our finding that patients without intracranial hypertension did not show a physiologic response to CSF diversion is interesting and has implications for clinical care. Patients with ICP <15 mmHg had no change in nICP, CBF, or other measures of oxygen delivery after CSF diversion. When selecting patients for invasive surgery to relieve intracranial hypertension, we desire tools that are both sensitive (to avoid delaying surgery beyond the point at which increased ICP impairs oxygen delivery) and specific (to avoid surgery in patients in whom conservative management may be appropriate). The variance in ICP observed at the invasive management time point indicates that there is significant variability in current clinical practice. Future work with longitudinal FD-DOS/DCS measurements holds the potential to provide a more complete picture of neonatal hydrocephalus pathophysiology, thereby enabling improved prognostication and determination of patient-specific risks and benefits of surgical intervention.

Our results expand on previous studies of optical neuromonitoring in this population, which commonly relied on detection of diminished cerebral oxygenation using near-infrared spectroscopy.[26-30] Whereas cerebral oxygenation has been associated with ventricular dilation[30] and has been demonstrated to improve after CSF diversion,[26-29] near-infrared spectroscopy measurements have limited reproducibility and reliability.[31,32] FD-DOS uses a more quantitative measurement of StO_2 that accounts for tissue scattering.[15] The success of this approach is demonstrated by the high intermeasurement reliability.

Our study has several limitations. In a significant number of patients, optical measurements were not available at all time points. Similarly, owing to variations in clinical care (outside of the research protocol), brain ultrasounds were not always available for analysis. Thus, the sample size was below that initially anticipated, and the various analyses were performed on slightly different populations. Although certain analyses may be underpowered, we would not expect these deviations to result in fundamental changes in interpretation. We note that there was a near-significant difference in weight at the time of surgery between the groups with and without intracranial hypertension, which is likely why more Ommaya reservoirs were used in the group without intracranial hypertension. Differences in physiologic responses between Ommaya reservoirs and ventriculoperitoneal shunts need to be investigated in future work. Larger studies in the future are also needed to facilitate multivariate modeling for the prediction of intracranial hypertension based on FD-DOS/DCS measurements and other covariates, such as etiology of hydrocephalus, age, head circumference percentile, rate of change of head circumference, apneic spells, bradycardia episodes, and other clinical markers.

We were limited in the timing of ultrasound measures based on routine clinical care, and we did not assess for longitudinal changes in ultrasound metrics. It is possible that preoperative FOR and FTHR measurements obtained immediately before surgery would be more predictive of ICP. However, the minor changes observed in head circumference before surgery suggest that interval changes in ultrasound would be small as well. Thus, although day-of-surgery ultrasounds likely would have slightly higher FOR and FTHR, this likely would not impact the lack of association between ultrasound and ICP that we observed.

Our measurement of nICP has some methodological limitations. We relied on a single noninvasive cuff blood pressure measurement to determine systolic, diastolic, and mean arterial pressure. Calculation of nICP would be improved by continuous arterial blood pressure monitoring; however, because invasive blood pressure monitoring is not standard of care at our institution, such data were unavailable to us. In the future, the use of continuous noninvasive blood pressure measurements[33] has the potential to substantially improve the accuracy of nICP measurements. We note that the use of the average across cuff blood pressure readings from anesthesia induction to incision to calculate nICP did not improve accuracy; the Pearson correlation with invasive ICP decreased from 0.48 to 0.44. There is also scope to improve nICP measurement accuracy through the development of improved tissue models that account for the effects of superficial tissue contamination in the FD-DOS/DCS optical signals (which likely are more pronounced in older patients).[34,35] A third direction for future research is the use of machine learning strategies.[13,14]

Anesthesia is a potential confound for our secondary analysis of intraoperative to postoperative changes. We did observe that patients with intracranial hypertension were more likely than patients without intracranial hypertension to receive general anesthesia with an inhalational volatile anesthetic. Inhalational volatile anesthetics can potentially alter intraoperative cerebral hemodynamics, for example, by decreasing cerebrovascular resistance; however, our observed agreement between preoperative and intraoperative CBF measurements (**Table II**) suggests that the influence of general anesthesia on cerebrovascular resistance is modest. Furthermore, the higher postoperative MAP observed when a patient is awake would most likely elevate ICP and would not impact our observation of decreased nICP after CSF diversion in the intracranial hypertension group.

Finally, we defined intracranial hypertension as an invasive ICP ≥15 mmHg. We arrived at this definition based on previous results in adults and children[11,36-38]; however, we acknowledge that no standard definition of intracranial hypertension exists. The gold standard would be a reliable way to predict long-term neurodevelopmental outcomes based on data available preoperatively or intraoperatively. In the absence of such a gold standard, we believe that our dichotomization of patients using 15 mmHg was a reasonable definition. We aspire to conduct larger cohort studies to compare optical biomarkers with long-term neurodevelopmental testing.

We have shown that a novel noninvasive diffuse optical index of ICP was significantly associated with intracranial hypertension in neonatal hydrocephalus. In contrast, ventricular size near the time of CSF diversion surgery was not associated with ICP. Furthermore, the diffuse optical

measurements illuminated the effect of intracranial hypertension on cerebral metabolism; the measurements demonstrated that diminished cerebral oxygen delivery and a positive response to CSF diversion were observed only in infants with elevated ICP. Our findings suggest that the use of noninvasive optical biomarkers may potentially improve on current clinical practice by offering better ways to classify patients such that the risks and benefits of surgery can be individualized. ■

We thank Alexander Tucker, MD; Cameron Briley, MD; and Yourong Su, MD, all affiliated with the Department of Neurosurgery at the Children's Hospital of Philadelphia, for their work obtaining the FD-DOS/DCS measurements. We also thank Kristina Heye, MD, affiliated with the Department of Neurology at the Children's Hospital of Philadelphia, for her work with the Institutional Review Board for this study.

Submitted for publication Jan 12, 2021; last revision received Apr 30, 2021; accepted May 10, 2021.

Reprint requests: Wesley B. Baker, PhD, Childrens Hospital of Philadelphia, Department of Neurology, 3501 Civic Center Boulevard, Philadelphia, PA 19104. E-mail: bakerw@chop.edu

References

1. Simon TD, Riva-Cambrin J, Srivastava R, Bratton SL, Dean JM, Kestle JRW. Hospital care for children with hydrocephalus in the United States: utilization, charges, comorbidities, and deaths. J Neurosurg Pediatr 2008;1:131-7.
2. Dalen K, Bruarøy S, Wentzel-Larsen T, Laegreid LM. Intelligence in children with hydrocephalus, aged 4-15 years: a population-based, controlled study. Neuropediatrics 2008;39:146-50.
3. Lindquist B, Persson EK, Uvebrant P, Carlsson G. Learning, memory and executive functions in children with hydrocephalus. Acta Paediatr 2008;97:596-601.
4. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:e1167-77.
5. Vinchon M, Rekate H, Kulkarni AV. Pediatric hydrocephalus outcomes: a review. Fluids Barriers CNS 2012;9:18.
6. Cherian S, Whitelaw A, Thoresen M, Love S. The pathogenesis of neonatal post-hemorrhagic hydrocephalus. Brain Pathol 2004;14:305-11.
7. El-Dib M, Limbrick DD Jr, Inder T, Whitelaw A, Kulkarni AV, Warf B, et al. Management of post-hemorrhagic ventricular dilatation in the infant born preterm. *J Pediatr* 2020. [Epub ahead of print], https://doi.org/10.1016/j.jpeds.2020.07.079
8. Kahle KT, Kulkarni AV, Limbrick DD Jr, Warf BC. Hydrocephalus in children. Lancet 2016;387:788-99.
9. Zhang X, Medow JE, Iskandar BJ, Wang F, Shokoueinejad M, Koueik J, et al. Invasive and noninvasive means of measuring intracranial pressure: a review. Physiol Meas 2017;38:R143-82.
10. Padayachy LC. Non-invasive intracranial pressure assessment. Childs Nerv Syst 2016;32:1587-97.
11. Swanson JW, Aleman TS, Xu W, Ying GS, Pan W, Liu GT, et al. Evaluation of optical coherence tomography to detect elevated intracranial pressure in children. JAMA Ophthalmol 2017;135:320-8.
12. Cardim D, Robba C, Bohdanowicz M, Donnelly J, Cabella B, Liu X, et al. Non-invasive monitoring of intracranial pressure using transcranial Doppler ultrasonography: is it possible? Neurocrit Care 2016;25:473-91.
13. Fischer JB, Ghouse A, Tagliabue S, Maruccia F, Rey-Perez A, Báguena M, et al. Non-invasive estimation of intracranial pressure by diffuse optics: a proof-of-concept study. J Neurotrauma 2020;37:2569-79.
14. Ruesch A, Yang J, Schmitt S, Acharya D, Smith MA, Kainerstorfer JM. Estimating intracranial pressure using pulsatile cerebral blood flow measured with diffuse correlation spectroscopy. Biomed Opt Express 2020;11:1462-76.
15. Durduran T, Choe R, Baker WB, Yodh AG. Diffuse optics for tissue monitoring and tomography. Rep Prog Phys 2010;73:076701.
16. Ko TS, Mavroudis CD, Baker WB, Morano VC, Mensah-Brown K, Boorady TW, et al. Non-invasive optical neuromonitoring of the temperature-dependence of cerebral oxygen metabolism during deep hypothermic cardiopulmonary bypass in neonatal swine. J Cereb Blood Flow Metab 2020;40:187-203.
17. Baker WB, Parthasarathy AB, Gannon KP, Kavuri VC, Busch DR, Abramson K, et al. Noninvasive optical monitoring of critical closing pressure and arteriole compliance in human subjects. J Cereb Blood Flow Metab 2017;37:2691-705.
18. Farzam P, Sutin J, Wu KC, Zimmermann BB, Tamborini D, Dubb J, et al. Fast diffuse correlation spectroscopy (DCS) for non-invasive measurement of intracranial pressure (ICP) (Conference Presentation). Proceedings Volume 10050 SPIE BIOS. San Francisco, California: Clinical and Translational Neurophotonics; April 19, 2017.
19. Wu KC, Sunwoo J, Sheriff F, Farzam P, Farzam PY, Orihuela-Espina F, et al. Validation of diffuse correlation spectroscopy measures of critical closing pressure against transcranial Doppler ultrasound in stroke patients. J Biomed Opt 2021;26:036008.
20. Flanders TM, Kimmel AC, Lang SS, Bellah R, Chuo J, Wellons JC 3rd, et al. Standardizing treatment of preterm infants with post-hemorrhagic hydrocephalus at a single institution with a multidisciplinary team. Childs Nerv Syst 2020;36:1737-44.
21. Flibotte J, Heuer G, Heimall L, Giaccone A, Munson D, Moyer-Fuchs T, et al. N/IICU clinical pathway for the treatment of preterm infants with post-hemorrhagic hydrocephalus. Accessed April 29, 2021. Available at: https://www.chop.edu/clinical-pathway/post-hemorrhagic-hydrocephalus-clinical-pathway
22. Verdecchia K, Diop M, Lee TY, St Lawrence K. Quantifying the cerebral metabolic rate of oxygen by combining diffuse correlation spectroscopy and time-resolved near-infrared spectroscopy. J Biomed Opt 2013;18:27007.
23. O'Hayon BB, Drake JM, Ossip MG, Tuli S, Clarke M. Frontal and occipital horn ratio: a linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. Pediatr Neurosurg 1998;29:245-9.
24. Radhakrishnan R, Brown BP, Kralik SF, Bain D, Persohn S, Territo PR, et al. Frontal occipital and frontal temporal horn ratios: comparison and validation of head ultrasound-derived indexes with MRI and ventricular volumes in infantile ventriculomegaly. AJR Am J Roentgenol 2019;213:925-31.
25. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15:155-63.
26. Abramo TJ, Zhou C, Estrada C, Meredith M, Miller R, Pearson M, et al. Innovative application of cerebral rSO_2 monitoring during shunt tap in pediatric ventricular malfunctioning shunts. Pediatr Emerg Care 2015;31:479-86.
27. Shojima M, Watanabe E, Mayanagi Y. Cerebral blood oxygenation after cerebrospinal fluid removal in hydrocephalus measured by near-infrared spectroscopy. Surg Neurol 2004;62:312-8. discussion 318.
28. Lang SS, Khanna O, Atkin NJ, Palma JE, Yuan I, Storm PB, et al. Perioperative near-infrared spectroscopy cerebral oxygen saturation in symptomatic pediatric hydrocephalus patients at risk for intracranial hypertension. *J Neurosurg Pediatr* 2019. [Epub ahead of print], https://doi.org/10.3171/2019.9.PEDS19457
29. Norooz F, Urlesberger B, Giordano V, Klebermasz-Schrehof K, Weninger M, Berger A, et al. Decompressing posthaemorrhagic ventricular dilatation significantly improves regional cerebral oxygen saturation in preterm infants. Acta Paediatr 2015;104:663-9.
30. Kochan M, McPadden J, Bass WT, Shah T, Brown WT, Tye GW, et al. Changes in cerebral oxygenation in preterm infants with progressive posthemorrhagic ventricular dilatation. Pediatr Neurol 2017;73:57-63.
31. Schneider A, Minnich B, Hofstätter E, Weisser C, Hattinger-Jürgenssen E, Wald M. Comparison of four near-infrared spectroscopy

devices shows that they are only suitable for monitoring cerebral oxygenation trends in preterm infants. Acta Paediatr 2014;103:934-8.
32. da Costa CS, Greisen G, Austin T. Is near-infrared spectroscopy clinically useful in the preterm infant? Arch Dis Child Fetal Neonatal Ed 2015;100:F558-61.
33. Heeney ND, Habib F, Brar GK, Krahn G, Campbell DA, Sanatani S, et al. Validation of finger blood pressure monitoring in children. Blood Press Monit 2019;24:137-45.
34. Wu MM, Chan ST, Mazumder D, Tamborini D, Stephens KA, Deng B, et al. Improved accuracy of cerebral blood flow quantification in the presence of systemic physiology cross-talk using multi-layer Monte Carlo modeling. Neurophotonics 2021;8:015001.
35. Milej D, Abdalmalak A, Rajaram A, St Lawrence K. Direct assessment of extracerebral signal contamination on optical measurements of cerebral blood flow, oxygenation, and metabolism. Neurophotonics 2020;7:045002.
36. Wiegand C, Richards P. Measurement of intracranial pressure in children: a critical review of current methods. Dev Med Child Neurol 2007;49:935-41.
37. Gambardella G, Zaccone C, Cardia E, Tomasello F. Intracranial pressure monitoring in children: comparison of external ventricular device with the fiberoptic system. Childs Nerv Syst 1993;9:470-3.
38. Pople IK, Muhlbauer MS, Sanford RA, Kirk E. Results and complications of intracranial pressure monitoring in 303 children. Pediatr Neurosurg 1995;23:64-7.

50 Years Ago in *The Journal of Pediatrics*

Neonatal Herpes Virus Infection in the Preacyclovir Era

Catalano LW, Safley GH, Museles M, Jarzynski DJ. Disseminated herpesvirus infection in a newborn infant. Virologic, serologic, coagulation and interferon studies. J Pediatr 1971;79:393-400.

Catalano et al presented in *The Journal* 50 years ago a 6-day-old infant diagnosed with disseminated herpes virus (HSV) type 1 infection. The mother had had herpetic vulvovaginitis 1 week before vaginal delivery. The virus was detected in the throat, skin vesicles, and blood. The infant died owing to disseminated intravascular coagulation and shock at 11 days of age.

Acyclovir was discovered in 1974[1] and was available to physicians in topical form in 1982. Thus, in 1971, there was no effective treatment for HSV disease. The outcome of a neonatal infection was, more often than not, fatal. In the US, the incidence in 1971 and today is similar, 5-33 per 100 000 live births; however, in 1971 the mortality rate was much higher. For disseminated HSV infection it was 85% vs 29% today, and in central nervous system disease 50% vs 4%.[2] The morbidity after central nervous system disease has sadly not improved much with treatment, and still only 31% of infants develop normally after central nervous system infection. For disseminated and skin, eye, mouth disease, the morbidity has improved vastly; for survivors of disseminated disease normal development is now seen in 83% vs 50%, and for skin, eye, mouth disease the numbers are >98% vs 75% 50 years ago.[2]

Catalano et al's case of neonatal HSV infection in the preacyclovir era, ended fatally, as was often the case. Researchers found a way to treat HSV infections, a race that started at the Burroughs Welcome in the 1960s. We are fortunate to live in an era when, despite being a disease we still fear, we have the opportunity to treat neonatal HSV. Hopefully, with time, we will also find effective treatments for other viruses that pose a threat to the neonatal population.

Jannicke H. Andresen, MD, PhD
Department of Neonatology
Oslo University Hospital
Oslo, Norway

Ola Didrik Saugstad, MD, PhD
Department of Pediatric Research
University of Oslo
Oslo, Norway
Ann and Robert H. Lurie Children's Hospital of Chicago
Northwestern University Feinberg School of Medicine
Chicago, Illinois

References

1. King DH. History, pharmacokinetics, and pharmacology of acyclovir. J Am Acad Dermatol 1988;18:176-9.
2. Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. Semin Perinatol 2018;42:168-75.

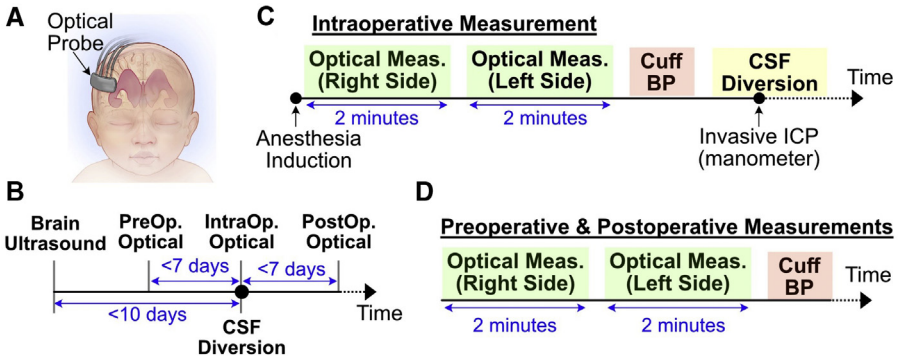

Figure 1. **A,** Schematic of optical probe placement as it was manually held against the forehead during data acquisition. **B,** Timeline of the study's preoperative, intraoperative, and postoperative measurements encompassing CSF diversion surgery. **C,** Study design for intraoperative measurements, which include right and left hemisphere optical measurements, a cuff BP measurement, and an invasive ICP measurement obtained during CSF diversion surgery. **D,** Study design for preoperative and postoperative measurements.

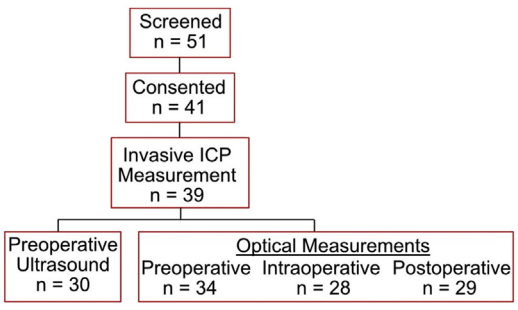

Figure 2. Patient flow chart.

Table II. Intraclass correlation coefficients for optical biomarkers within and across measurements

Markers	Left and right hemispheres (n = 90)	Preoperative and intraoperative (n = 23)
nICP	0.86 (0.80-0.91)	0.72 (0.44-0.87)
StO_2	0.74 (0.62-0.82)	0.80 (0.56-0.91)
THC	0.88 (0.82-0.92)	0.89 (0.73-0.95)
CBF	0.87 (0.80-0.91)	0.84 (0.59-0.94)
OEF	0.74 (0.62-0.82)	0.80 (0.57-0.92)
$CMRO_2$	0.72 (0.60-0.81)	0.81 (0.55-0.92)

Intraclass correlation coefficients (ICCs) for noninvasive intracranial pressure index (nICP), tissue oxygen saturation (StO_2), total hemoglobin concentration (THC), cerebral blood flow (CBF), oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen consumption ($CMRO_2$) were all good to excellent. Data are presented as ICC and 95% CI.