

# Fast Doppler as a novel bedside measure of cerebral perfusion in preterm infants

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**BACKGROUND:** Altered cerebral perfusion from impaired autoregulation may contribute to the morbidity and mortality associated with premature birth. We hypothesized that fast Doppler imaging could provide a reproducible bedside estimation of cerebral perfusion and autoregulation in preterm infants.

**METHODS:** This is a prospective pilot study using fast Doppler ultrasound to assess blood flow velocity in the basal ganglia of 19 subjects born at 26–32 wk gestation. Intraclass correlation provided a measure of test–retest reliability, and linear regression of cerebral blood flow velocity and heart rate or blood pressure allowed for estimations of autoregulatory ability.

**RESULTS:** The intraclass correlation when imaging in the first 48 h of life was 0.634. We found significant and independent correlations between the systolic blood flow velocity and both systolic blood pressure and heart rate ( $P = 0.015$  and  $0.012$  respectively) only in the 26–28 wk gestational age infants in the first 48 h of life.

**CONCLUSION:** Our results suggest that fast Doppler provides reliable bedside measurements of cerebral blood flow velocity at the tissue level in premature infants, acting as a proxy for cerebral tissue perfusion. Additionally, autoregulation appears to be impaired in the extremely preterm infants, even within a normal range of blood pressures.

Pretermaturity is associated with one-third of all infant deaths in the United States and accounts for over 25 percent of children with cerebral palsy and vision, cognitive or hearing impairment (1). One potential contributing factor is systemic hypotension resulting in impairment of cerebral perfusion and increased risk for cerebral hemorrhage. In healthy term infants, cerebral autoregulation limits the variation in cerebral blood flow by altering the diameter of the cerebral arteries in response to changes in blood pressure over a certain range. At low blood pressures or when autoregulation is impaired, the vessels are unable to adequately compensate, resulting in compromise of perfusion and oxygenation. Impaired cerebral autoregulation has been associated with the development of ischemic brain injury and poor long-term clinical outcomes (2–5). There is great variability in the management of systemic

hypotension in premature infants, as currently there are no adequate clinical methods of determining the limits of autoregulation at which perfusion begins to be compromised. In addition, the autoregulatory threshold appears to vary based on gestational age, postnatal age, and level of illness (6).

Available noninvasive methods of evaluating cerebral perfusion include near infrared spectroscopy and large vessel color or power Doppler sonography of the superior vena cava or middle cerebral, carotid, and vertebral arteries. Standard color or power Doppler ultrasonography is limited to measuring the velocities in large vessels; so, it is unable to directly assess the vascular regulation that is thought to primarily occur at the level of the capillaries and precapillary arterioles (7). Near infrared spectroscopy monitoring is a promising imaging modality that provides a continuous measure of the regional oxygenation of superficial aspects of the brain (8,9); however, it is unable to directly measure cerebral blood flow. Invasive methods of assessing cerebral perfusion, including <sup>133</sup>xenon clearance measurements, positron emission tomography, single-photon emission computed tomography, and arterial spin labeled perfusion magnetic resonance imaging, are able to better define true cerebral blood flow values, but their clinical value is limited due to the need for sedation and/or radiation.

Fast Doppler plane-wave imaging is able to capture sufficiently fast and spatially dense Doppler maps to quantify net blood flow in tissue. Osmanski *et al.* (10) successfully utilized fast Doppler to measure cardiac tissue perfusion in the context of myocardial infarction. A research version of this technology was recently used in the neonatal population to provide functional whole brain imaging, resulting in spatiotemporal resolution that was superior to other noninvasive modalities (11). We expected similar success in quantifying small vessel velocities in the neonatal brain with a clinical version of this technology and hypothesized that commercial fast Doppler (simply fast Doppler going forward) could be a reproducible method to measure cerebral blood flow velocity at the tissue level in preterm infants as a proxy for cerebral perfusion. By correlating those values to measurements of systemic blood pressure and heart rate, we also hoped to assess autoregulatory status in this preterm population.

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## RESULTS

From May 2014 to March 2015, this pilot study enrolled a total of 30 subjects, as demonstrated in the recruitment flow chart in **Figure 1**. Three of the subjects enrolled early in the study had imaging performed that was inadequate to obtain the measurements needed, and another three received treatment for hypotension during the study period, so will be analyzed separately from the normotensive group discussed in this paper. No treatment threshold for hypotension was defined by our study protocol, due to the lack of a clear definition for hypotension in this population. The most common definition used by practitioners in our institution is a mean blood pressure less than the gestational age with associated signs of decreased perfusion. Nineteen subjects were included in the final analyses. **Table 1** lists the descriptive statistics for the study population. Routine cranial ultrasonography was ordered by the attending physician caring for the infant, based on the unit guidelines, but was not performed in three of the subjects. All three were greater than 31 wk gestation, and two of them were greater than 1,500 g at birth.

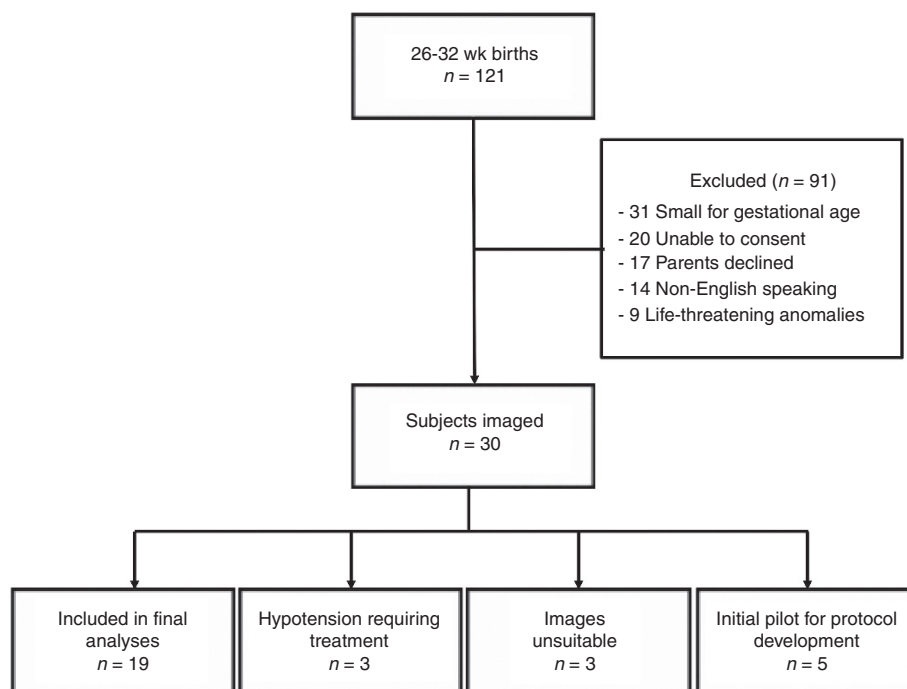
Forty of the 260 imaging sequences obtained (15%) did not contain measureable Doppler data, due to perfusion values below the measurable range of the device. Of the remaining sequences, the mean systolic velocity in the basal ganglia was  $1.055 \pm 0.119$  cm/s in the early imaging group vs.  $1.120 \pm 0.063$  cm/s in the late imaging group. The difference in means was 0.066 cm/s lower in the early imaging group (two-sided  $P$  value of 0.630). The difference in variances, when paired by subject, was 0.126 higher in the early imaging group (0.207 for early group, 0.081 for late group,  $P = 0.604$ ). As a measure of relative reliability, we calculated the intraclass correlation coefficient (ICC), which was 0.634 (95% confidence interval (CI): 0.414, 0.809) for the early

group, and 0.327 (95% CI: 0.136, 0.600) for the late group. Five subjects had fewer than three valid measurements so were not included in the ICC analysis. Absolute reliability was measured using the standard error of measurement, which was 0.427 cm/s in the early group and 0.275 cm/s in the late group.

**Table 2** and **Figure 2** demonstrate the correlation of cerebral systolic blood flow velocity with heart rate and systolic blood pressure. Data extracted from early imaging sessions of the 26–28-wk gestation group yielded statistically significant correlations between blood flow velocity and heart rate when heart rate (adjusted slope = 0.019,  $P = 0.036$ ) and blood pressure (adjusted slope 0.012,  $P = 0.252$ ) were simultaneously adjusted for in the regression model. Moreover, heart rate and blood pressure had a statistically significant correlation with each other in only the early imaging group ( $P = 0.003$ ), however with a significant spread in the data ( $R^2 = 0.072$ ).

## DISCUSSION

Fast Doppler demonstrates good reliability when measuring blood flow velocity in the small vessels of the basal ganglia (ICC of 0.634 when imaging within the first 48 h), and meets the previously described cut-off for clinical utility (12). Our findings are comparable to the correlation coefficients of 0.72–0.83 previously observed in color Doppler imaging of the internal carotid and anterior cerebral arteries (13), taking into account an expected decrease in the ICC due to higher physiologic variability at the level of the small vessels than larger ones. As this is a relative measure of reliability, the difference in the ICC for the late imaging session vs. the early session likely reflects both greater within-subject and decreased between-subject variability. The increasing activity level of infants over the first week of life produces an increased risk for motion



**Figure 1.** Study subject recruitment flow diagram.

artifact as well as difficulty in obtaining measurements at consistent angles of insonation, resulting in higher within-subject variability. This is compounded by an increased physiologic stability of the blood flow velocities, decreasing the between-subject variability. The latter observation is supported by an increase in the absolute reliability (standard error of measurement of 0.420 cm/s in the early images vs. 0.286 cm/sec in the late images), due to a decrease in variability of the blood flow velocity with increasing postnatal age.

A significant statistical correlation between cerebral blood flow systolic velocity and systemic blood pressure can provide information regarding the status of autoregulatory

mechanisms within the cerebral vasculature. Previous studies assessing cerebral autoregulation have suggested that sick preterm infants frequently have impaired autoregulation primarily during periods of hypotension (4,14–16). Whereas, normotensive preterm infants maintain autoregulation (17). This has supported the idea of an autoregulatory plateau where, over a certain range of blood pressures, the cerebral blood flow changes very little. The plateau causes the correlation between blood pressure and cerebral blood flow, as demonstrated by the slope of the association, to approach zero.

Within the blood pressure range seen in our subjects (interquartile range of systolic values 47–61), we observed a significant correlation between blood pressure and cerebral systolic velocity in the 26–28 wk gestation subgroup early imaging sessions but not the late imaging sessions. Overall cerebral pressure autoregulation appeared intact in the subjects with gestational age between 28 and 32 completed weeks, as the correlation was not statistically different from zero for either the early or late imaging sessions (Figure 2). These findings suggest that cerebral autoregulation may be impaired in the most premature infants, but matures with both increasing gestational and postnatal age.

A previous report by Boylan *et al.* (18) also demonstrated impaired autoregulation in both high- and low-risk preterm infants that resolved with increasing gestational age. This is consistent with previous reports of impairment of cerebral autoregulation in extremely preterm infants and correlates with the timing of greatest vulnerability to intraventricular hemorrhage (19). The findings observed in our study are of particular interest because the range of systemic blood pressure that demonstrated pressure passivity in the 26–28-wk gestation group is generally thought to be within the plateau of the autoregulatory curve. This may demonstrate an increased sensitivity for determining autoregulation by fast Doppler when imaging smaller cerebral blood vessels.

A recent study by Rhee *et al.* (20) demonstrated that Doppler diastolic cerebral blood flow velocity is nearly absent in preterm infants, suggesting that cerebral blood flow may be primarily dependent on systolic, not mean or diastolic velocities. Our experience was similar, as many of the measured diastolic blood flow velocities were near or below the lower limits of the

**Table 1.** Subject characteristics

	Gestational age (weeks)		All subjects (n = 19)
	26–28 (n = 11)	28–32 (n = 8)	
Imaging time (hours of life) <sup>a</sup>			
Early images	28.0 ± 10.8	24.7 ± 9.4	26.8 ± 10.5
Late images	203.3 ± 24.1	200.8 ± 14.8	202.3 ± 20.9
Gestational age (weeks) <sup>a</sup>	27.0 ± 0.5	29.8 ± 1.3	28.2 ± 1.7
Birth weight (grams) <sup>a</sup>	990 ± 185	1,310 ± 221	1,124 ± 254
Male, n (%)	7 (63.6)	7 (87.5)	14 (73.7)
Mode of ventilation, n (%) <sup>b</sup>			
None	1 (9.10)	4 (50.0)	4 (22.2)
Nasal cannula	1 (9.10)	2 (25.0)	3 (16.6)
High-flow nasal cannula	3 (27.3)	5 (62.5)	8 (44.4)
Nasal CPAP	1 (9.10)	1 (12.5)	1 (5.6)
Noninvasive ventilation	4 (36.4)	1 (12.5)	5 (27.8)
Conventional ventilator	6 (54.5)	1 (12.5)	7 (38.9)
High-frequency oscillator	1 (9.10)	0 (0)	1 (5.6)
Intraventricular hemorrhage, n (%) <sup>c</sup>	1 (9.10)	2 (40.0)	3 (20.0)
Death, n (%)	1 (9.10)	0 (0)	1 (5.6)

CPAP, continuous positive airway pressure.

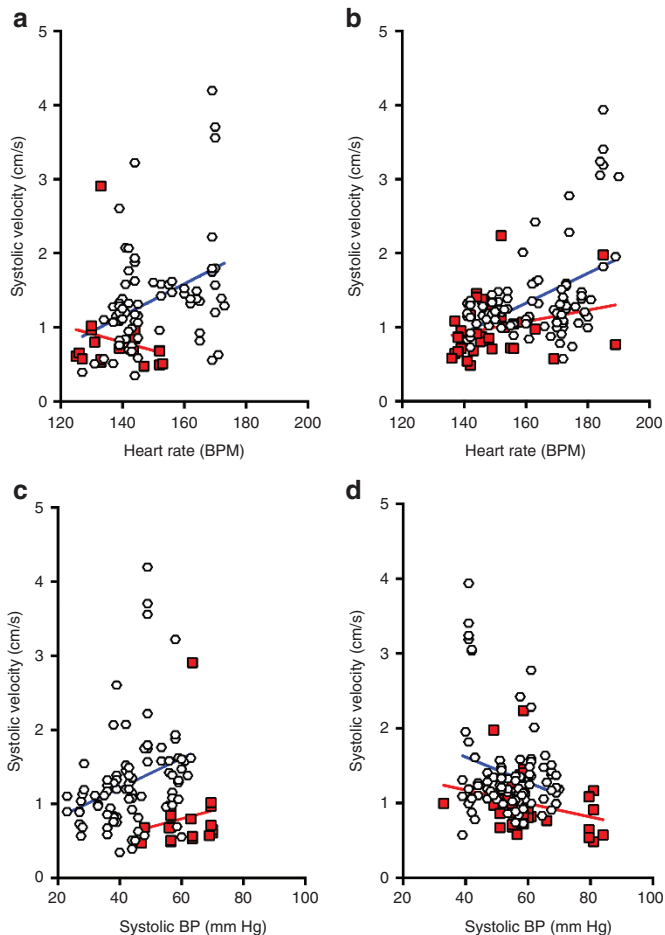
<sup>a</sup>Continuous variables described as mean ± SD. <sup>b</sup>At the time of imaging—note that some subjects were on more than one mode of ventilation during the study period.

<sup>c</sup>Three infants did not have standard cranial ultrasounds performed.

**Table 2.** Correlation values derived from linear regression models

	Early slope (95% CI)	P value	Late slope (95% CI)	P value
SBP to SV				
All subjects (n = 19)	−0.002 (−0.015, 0.011)	0.799	−0.001 (−0.007, 0.005)	0.758
26–28 wk GA (n = 11)	0.022 (0.004, 0.039)	0.015	0.004 (−0.003, 0.012)	0.244
28–32 wk GA (n = 8)	0.007 (−0.011, 0.026)	0.416	−0.009 (−0.018, 0.001)	0.078
HR to SV				
All subjects (n = 19)	0.021 (0.007, 0.034)	0.003	0.004 (0.000, 0.009)	0.060
26–28 wk GA (n = 11)	0.022 (0.005, 0.038)	0.012	0.002 (−0.003, 0.006)	0.415
28–32 wk GA (n = 8)	−0.045 (−0.162, 0.072)	0.348	−0.001 (−0.016, 0.015)	0.941
SBP to HR	−0.204 (−0.336, −0.073)	0.003	−0.070 (−0.213, 0.073)	0.335

GA, gestational age at birth; HR, heart rate; SBP, systolic blood pressure; SV, systolic blood flow velocity.



**Figure 2.** Correlation of systolic cerebral blood flow velocity with systolic blood pressure and heart rate, stratified by gestational age and imaging time. Graphs demonstrating the association between systolic velocity and heart rate in (a) the first 48 h of life and (b) 7–10 d of life, as well as systolic blood pressure in (c) the first 48 h of life and (d) 7–10 d of life. Data are stratified by gestational age, with 26–28 wk gestation represented as open circles with blue lines for the linear regression model, and 28–32 wk gestation represented as red-filled squares with red lines for the linear regression model. Statistically significant associations are seen in the first 48 h of life between cerebral systolic blood flow velocity and both heart rate (a) and systolic blood pressure (c) in the 26–28-wk gestation group only (blue line).

device's measurement capabilities. The exact etiology is of this phenomenon is unclear. The presence of a patent ductus arteriosus could play a role by causing diastolic steal, however most of the infants in our study did not have echocardiographic evaluation of the ductus, so we cannot comment on any correlation within this study population. As such, we considered the diastolic velocities to be unreliable and only evaluated the systolic phase of the cerebral blood flow velocities in our analyses.

To further examine potential causes for cerebral blood flow variation, the correlation between the cerebral blood flow velocity and heart rate was assessed. Infants are limited in their ability to alter their stroke volume, thus primarily regulating their cardiac output by varying their heart rate, making heart rate a surrogate marker for cardiac output. As with systemic blood pressure, heart rate showed a significant correlation with systolic cerebral blood flow in the most preterm group,

and only in the early imaging. Interestingly, the correlation remained significant when both heart rate and blood pressure were simultaneously adjusted in the regression model, demonstrating an effect of heart rate on cerebral blood flow independent from that of blood pressure. A recent study also demonstrated dynamic heart rate passivity in preterm neonates in the first few days of life using near infrared spectroscopy monitoring (21). Using heart rate as an indicator of cardiac status may be confounded by other factors that separately affect heart rate, including pain, agitation, temperature, medications, and hypoxia. It may be important to adjust for the presence of these and possibly other factors when modeling an association between heart rate and cerebral perfusion.

There are several limitations to this pilot study. Currently, this technology is unable to allow for continuous monitoring due to the need for an inactive period between images to optimize probe function, and therefore is limited to measuring static autoregulation (i.e., data collected over a period of minutes) as opposed to dynamic (i.e., over a period of seconds). This was further complicated by the lack of invasive arterial blood pressure monitoring in some of our subjects, as intermittent blood pressure cuff monitoring provides only an estimate of the blood pressure at the time of imaging. The physiology of sick preterm infants is likely to change rapidly over short periods of time, so we must interpret these intermittent measures of blood pressure and perfusion with caution. We have not yet compared our values to a standard measure, such as  $^{133}\text{Xe}$  measurements or superior vena cava flow, so are unable to determine agreement of our values with other previous studies. In addition, we did not control for variables that are likely to affect cerebral blood flow velocity, such as the serum  $\text{PaCO}_2$  or  $\text{PaO}_2$ .

When attempting to understand the complicated hemodynamic physiology of preterm infants, no single monitoring method is going to provide all of the data necessary to allow for truly informed clinical decisions regarding hemodynamic support at the bedside. As such, it is vital that we find safe and complimentary modes of continuous bedside monitoring (22). This pilot study demonstrates that fast Doppler embodied within a commercial ultrasound device provides reliable bedside measures of blood flow velocity in the small arteries within the basal ganglia in premature infants. Moreover, the data derived from this study suggest that autoregulation may be impaired in extremely premature infants within the first 48 h, even within a normal range of blood pressure. Finally, our observations suggest that heart rate has an independent effect on the cerebral blood flow velocity. These findings will need to be confirmed in a larger group of subjects, ideally correlating them with short- and long-term outcomes, and evaluating agreement with previously established methods of measuring cerebral blood flow such as superior vena cava flow.

## METHODS

### Participants

This prospective observational study was approved by the University of Washington Institutional Review Board (Human Subjects Division). Written consent was obtained from the parents of all subjects prior to enrollment. Eligible neonates between 26 0/7 wk and 31



6/7 wk gestation admitted to the neonatal intensive care unit at the University of Washington Medical Center were enrolled within the first 48 h of life as part of a pilot study to assess the feasibility and reliability of cerebral perfusion measures obtained by fast Doppler (23). Infants with intrauterine growth restriction have been found to have significantly altered cerebral perfusion measures (24,25), so growth restricted infants were excluded from this study. Additional exclusion criteria were known chromosomal abnormality or central nervous system anomaly, life-threatening congenital malformations, and non-English speaking families. Demographics and outcome data were obtained from the electronic medical record, including sex, gestational age at birth, birth weight, presence of intraventricular hemorrhage on routine cranial ultrasonography, and death.

As the study group had not previously used this device clinically, the first five subjects enrolled were part of the imaging protocol development and were not included in the final data analysis. This group of subjects provided an opportunity for the study ultrasonographers to alter the initial imaging protocol as necessary to ensure feasibility and optimize imaging results prior to the continuation of enrollment.

### Ultrasound Imaging Protocol

First, transfontanellar color Doppler ultrasound images were assessed at the bedside using the Aixplorer ultrasound system (Supersonic Imagine, Aix-en-Provence, France) equipped with an SL 10–2 linear array probe. With this information, we established the anatomical location for our subsequent fast Doppler imaging sequences. We then obtained fast-Doppler image sequences (described below) of the basal ganglia through the anterior fontanel. The basal ganglia were chosen as the primary region of interest because neuronal and axonal injury to the basal ganglia is a common feature of brain injury in preterm infants.

All images were obtained at two time points on all subjects. The first was within 48 h of birth (“early”), with the second between 7 and 10 d of life (“late”). To assess test–retest reliability, we obtained up to nine image sequences at each time point, performed consecutively to minimize physiologic variability between measures. Doppler velocity measures are sensitive to the precise angle of insonation of a blood vessel, so in the postimaging analysis of test–retest reliability, we attempted to correct for this source of error by grouping the images by similar orientation and brightness of the gray scale portions of the images, as well as shape of key landmarks such as the ventricles

and skull. The fast Doppler device allows for corrections to the velocity measures based on the angle of the blood vessel being imaged, however imaging at the tissue level is complicated by having multiple small blood vessels angled in different directions, rendering the angle correction tool ineffective.

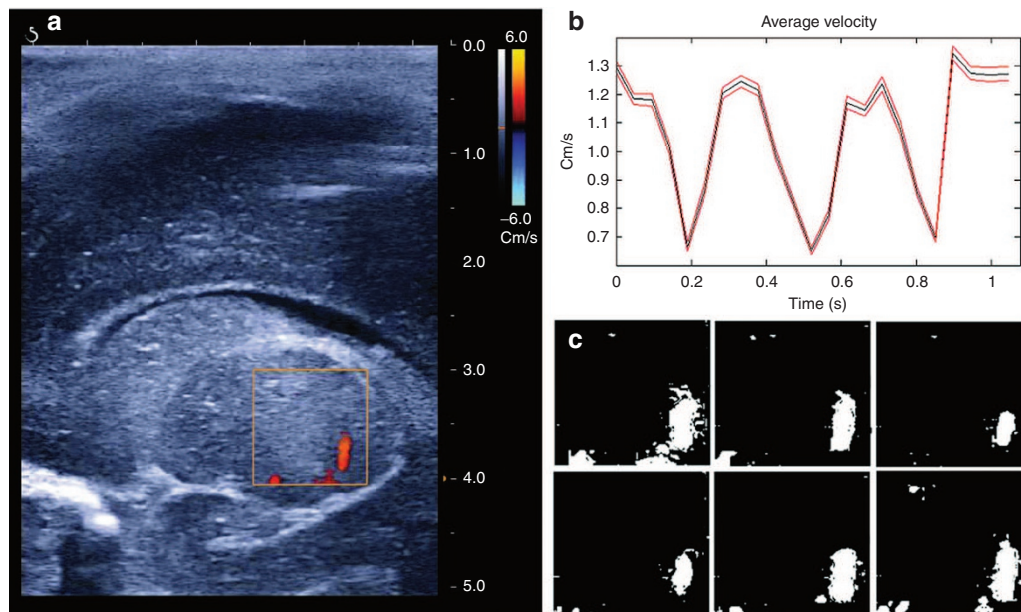
Blood flow velocities at the smallest vessels were expected to measure below 6 cm/s, thus a range of  $-4$  to  $+4$  cm/s was set for an initial survey with standard color Doppler before turning on fast Doppler, which had a corresponding range of  $-6$  to  $+6$  cm/s. The basal ganglia images were obtained at an average depth of 4 cm, allowing for a 22 Hz compounded frame rate. Each fast Doppler video clip lasted for 2 s and consisted of 44 frames of Doppler data. The device required 10–20 s between fast Doppler images to maintain ideal function of the probe, thus the three to nine consecutive clips at each region of interest were obtained over an average time frame of 1 to 5 min, depending on the number of clips and the activity level of the infant.

### Postimaging Processing and Analysis

Fast Doppler video clips were extracted from the device and post-processed using code created in Matlab (Mathworks, Natick, MA) to calculate average systolic, diastolic, and mean velocity over the video clip (Figure 3).

Each of the 44 frames over 2 s of Doppler data was converted into an image file for processing in Matlab. The fast Doppler data was extracted from each pixel within the images by translating red, green, and blue values from the images into blood-flow velocity using the velocity vs. color scale within each image. Application of a Matlab-based thresholding function then eliminated all gray background noise, leaving only the blood flow velocity data within the region of interest.

Systolic and diastolic values were obtained across the duration of the clip using a peak and trough detection algorithm based on the mean values of velocity across all pixels for one image. In order to avoid aliasing, the peak and trough detection compared every data point along the cardiac cycle to two adjacent points on either side. As neonates frequently have upwards of three cardiac cycles per second, attempting to compare more than two points on either side would have exceeded the temporal resolution of the compounding rate. Mean systolic, diastolic, and mean velocity were calculated from data collected across the entire time span of the 44 frames.



**Figure 3.** Postimaging data extraction process. (a) Single B-mode image frame in the sagittal plane, with fast Doppler color box over the basal ganglia. (b) Graph demonstrating the average fast Doppler blood flow velocity over one second of the captured video clip (black line signifies mean, with red lines demonstrating upper and lower bounds of the 95% confidence interval). (c) Matlab-derived masks demonstrating the identified portions of color Doppler data (white) over the time course between two systolic peaks. From left to right, the masks show a gradual decrease in perfusion area in the top row, followed by a gradual increase in the bottom row.

### Physiologic Measurements

Blood pressure, heart rate, and oxygen saturation were measured throughout each ultrasound session. Heart rate and oxygen saturation levels were recorded in 1-min interval. Arterial blood pressure tracings were also recorded in 1-min interval if available. If not, a blood pressure cuff was placed on the right upper extremity, and recordings were obtained every 5 min. Blood pressures obtained by cuff readings are reported as the average over the 5-min interval.

### Statistical Analysis

Data were analyzed using STATA (version 12.1, Statacorp, College Station, TX). Measured descriptive covariates are listed in **Table 1**, stratified by gestational age groups: 26 0/7 to 27 6/7, and 28 0/7 to 31 6/7 wk completed gestation at birth. Continuous variables were described as mean  $\pm$  1 SD. The difference in mean between early and late imaging values was calculated using a paired *t*-test. Categorical variables were described as the number and percent in each study population.

The relative test-retest reliability was quantified by an ICC of single measures using a mixed-effects model (26), which takes into account both systematic and random errors in the data. All images included in the final test-retest analysis were obtained by the same investigator (E.P.) in order to avoid inter-observer variability. The interpretation of the ICC is not universal. It has been suggested that an ICC < 0.4 indicates poor,  $0.4 \leq$  ICC < 0.75 indicates fair to good, and  $\geq$  0.75 indicates excellent reliability (27). Alternatively, a single cut-off of  $\geq$  0.6 has been used to indicate clinically useful measures (12). Absolute test-retest reliability was calculated using the standard error of measurement (28). The Wilcoxon signed-rank test was used to test for a difference in the measurement variance between groups defined by imaging time points (early vs. late).

For measures of test-retest reliability, imaging sessions within each subject that were obtained at different time points (i.e., early vs. late) were treated as independent samples due to an expected change in physiology between time points. Only imaging sessions with at least three valid measurements were included in the test-retest analysis. Images without enough Doppler data to perform calculations of velocity were treated as missing values, were reported as such, and were not included in the final analyses.

Correlations between systolic velocities and systemic blood pressure or heart rate were assessed using classic linear regression with robust standard errors. A regression slope statistically different from zero suggested impaired autoregulation. The independence of each of the correlations was tested by simultaneously placing both covariates into a multivariate linear regression model and testing whether each slope remained different from zero. The R-squared values provided an estimate of goodness-of-fit. *P* values and 95% CI were evaluated when appropriate, using an  $\alpha$  level of 0.05 to test for statistical significance.

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### REFERENCES

- Gargus RA, Vohr BR, Tyson JE, et al. Unimpaired outcomes for extremely low birth weight infants at 18 to 22 months. *Pediatrics* 2009;124:112–21.
- Perlman JM. The relationship between systemic hemodynamic perturbations and periventricular-intraventricular hemorrhage—a historical perspective. *Semin Pediatr Neurol* 2009;16:191–9.
- Caicedo A, De Smet D, Vanderhaegen J, et al. Impaired cerebral autoregulation using near-infrared spectroscopy and its relation to clinical outcomes in premature infants. *Adv Exp Med Biol* 2011;701:233–9.
- Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000;106:625–32.
- O’Leary H, Gregas MC, Limperopoulos C, et al. Elevated cerebral pressure passivity is associated with prematurity-related intracranial hemorrhage. *Pediatrics* 2009;124:302–9.
- Greisen G. Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;81:423–8.
- Fernández-Klett F, Priller J. Diverse functions of pericytes in cerebral blood flow regulation and ischemia. *J Cereb Blood Flow Metab* 2015;35:883–7.
- Greisen G, Leung T, Wolf M. Has the time come to use near-infrared spectroscopy as a routine clinical tool in preterm infants undergoing intensive care? *Philos Trans A Math Phys Eng Sci* 2011;369:4440–51.
- Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ* 2015;350:g7635.
- Osmanski BF, Pernot M, Montaldo G, Bel A, Messas E, Tanter M. Ultrafast Doppler imaging of blood flow dynamics in the myocardium. *IEEE Trans Med Imaging* 2012;31:1661–8.
- Demené C, Pernot M, Biran V, et al. Ultrafast Doppler reveals the mapping of cerebral vascular resistivity in neonates. *J Cereb Blood Flow Metab* 2014;34:1009–17.
- Chinn S. Statistics in respiratory medicine. 2. Repeatability and method comparison. *Thorax* 1991;46:454–6.
- Greisen G, Johansen K, Ellison PH, Fredriksen PS, Mali J, Friis-Hansen B. Cerebral blood flow in the newborn infant: comparison of Doppler ultrasound and 133xenon clearance. *J Pediatr* 1984;104:411–8.
- Lou HC, Lassen NA, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 1979;94:118–21.
- Soul JS, Hammer PE, Tsuji M, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res* 2007;61:467–73.
- Wong FY, Silas R, Hew S, Samarasinghe T, Walker AM. Cerebral oxygenation is highly sensitive to blood pressure variability in sick preterm infants. *PLoS One* 2012;7:e43165.
- Tyszczyk L, Meek J, Elwell C, Wyatt JS. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. *Pediatrics* 1998;102(2 Pt 1):337–41.
- Boylan GB, Young K, Panerai RB, Rennie JM, Evans DH. Dynamic cerebral autoregulation in sick newborn infants. *Pediatr Res* 2000;48:12–7.
- Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000;82:F188–94.
- Rhee CJ, Fraser CD 3rd, Kibler K, et al. The ontogeny of cerebrovascular pressure autoregulation in premature infants. *J Perinatol* 2014;34:926–31.
- Mitra S, Czosnyka M, Smielewski P, O’Reilly H, Brady K, Austin T. Heart rate passivity of cerebral tissue oxygenation is associated with predictors of poor outcome in preterm infants. *Acta Paediatr* 2014;103:e374–82.
- Azhibekov T, Soleymani S, Lee BH, Noori S, Seri I. Hemodynamic monitoring of the critically ill neonate: An eye on the future. *Semin Fetal Neonatal Med* 2015;20:246–54.
- Bercoff J, Montaldo G, Loupas T, et al. Ultrafast compound Doppler imaging: providing full blood flow characterization. *IEEE Trans Ultrason Ferroelectr Freq Control* 2011;58:134–47.
- Basu S, Dewangan S, Barman S, Shukla RC, Kumar A. Postnatal changes in cerebral blood flow velocity in term intra-uterine growth-restricted neonates. *Paediatr Int Child Health* 2014;34:189–93.
- Bozzetti V, Paterlini G, Bel F, van V, et al. Cerebral and somatic NIRS-determined oxygenation in IUGR preterm infants during transition. *J Matern Fetal Neonatal Med* 2015; e-pub ahead of print 21 January 2015.
- Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963–74.
- Rosner B. *Fundamentals of Biostatistics*. 6th edn. Duxbury Press; 2006.
- Stratford PW. Getting more from the literature: estimating the standard error of measurement from reliability studies. *Physiotherapy Canada* 2004;56:27–30.