

Reference values for cerebral blood flow velocities in critically ill, sedated children

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Abstract

Objective Transcranial Doppler ultrasound (TCD) is increasingly being used in the pediatric intensive care unit to assess cerebral hemodynamics during critical illness. However, no normative data in this patient population have been published to date. Therefore, we aimed to describe the anterior and posterior cerebral blood flow velocities in critically ill children undergoing mechanical ventilation and sedation.

Design A prospective, observational cohort study was performed. Children with known or suspected acute or chronic neurologic conditions were excluded. Participants underwent TCD measurement of middle cerebral and basilar artery flow velocities.

Results One hundred and forty children newborn to 17 years of age were enrolled. Measured values were lower in this cohort of children than the previously published cerebral flow velocities of normal, healthy children.

Conclusions Cerebral blood flow velocities of the basal cerebral arteries in critically ill, mechanically ventilated, sedated children are lower than in healthy children of the same age and gender published in previous studies. As such, the cerebral blood flow velocity (CBFV) values reported here may serve as a more accurate reference point when using TCD as a

clinical tool to diagnose CBFV abnormalities and guide therapy in this patient population.

Keywords Transcranial Doppler ultrasound · Cerebral blood flow · Critical illness · Infant · Children

Introduction

Doppler ultrasound was first described as a principle by Christian Johann Doppler in 1843. Utilization of ultrasound for evaluating the cerebral circulation outside infancy was initially limited due to the inability of ultrasound to penetrate the skull. However, in 1982, Rune Aaslid and colleagues successfully used low-frequency ultrasound (1–2 MHz) to traverse the skull and measure cerebral blood flow velocities (CBFVs) in the cerebral vessels around the circle of Willis [1]. This technique became known as transcranial Doppler ultrasound (TCD). TCD is non-invasive and portable, does not expose the patient to radiation, and can be used for repeated assessments in real time. Thus, it is an ideal tool to obtain diagnostic information about cerebral hemodynamics and to follow the response to treatment of various acute neurologic conditions in children in the intensive care unit. In fact, recent publications report using TCD as a clinical tool in children with traumatic brain injury, intracranial hypertension, stroke, cerebrovascular disorders, hydrocephalus, and central nervous system infection [2–15].

To date, measured CBFVs in these scenarios have typically been compared to well-established normal CBFVs for healthy children of similar age and gender [16–18]. However, TCD-derived cerebral blood flow velocities may be altered during critical illness, mechanical ventilation, or sedation independent of the child's neurologic illness or injury [19–24]. Therefore, when using TCD as a clinical tool in critically ill

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children with acute neurologic illness or injury, comparing cerebral blood flow velocities to those of normal healthy children may be inappropriate and lead to misdiagnosis and mismanagement.

Developing appropriate reference values for TCD-derived cerebral blood flow velocities in critically ill children is paramount to the future use of TCD as a tool in the pediatric intensive care unit. Thus, we designed this prospective, observational study to describe the anterior and posterior cerebral blood flow velocities in critically ill children undergoing mechanical ventilation and sedation without known neurologic illness or injury.

Patients and methods

Study participants and setting

This study was approved by Nationwide Children's Hospital institutional review board. Informed consent for participation was obtained from the parent or guardian. Critically ill children 0–17 years of age admitted to the pediatric intensive care unit requiring invasive mechanical ventilation and sedation were eligible to participate. Children with an acute diagnosis of status epilepticus, meningitis, encephalitis, traumatic brain injury, stroke, central nervous system vascular malformation, central nervous system malignancy, hypoxic ischemic encephalopathy, cardiopulmonary arrest, intoxication, and altered mental status were excluded. Children with an oxygen saturation <90 % or a mean arterial blood pressure (MABP) <5 % for age documented at any point in the pre-hospital setting, emergency room, or intensive care unit were excluded. Children undergoing extracorporeal membrane oxygenation were excluded. Children with a chronic diagnosis of seizure disorder, cerebral palsy, developmental delay, moya-moya, sickle cell disease, and congenital heart disease were also excluded. Additionally, children requiring dexmedetomidine for sedation were excluded. These criteria were selected in order to eliminate those children with known or suspected acute neurologic illness or injury that could impact cerebral blood flow velocity measurements.

Study design and protocol

Each subject was positioned supine with the head of the bed elevated to 30°. Transcranial Doppler ultrasonography (TCD) was performed at a single time point for each participant at the bedside by a single experienced sonographer using a 2-MHz pulsed probe and commercially available TCD ultrasonography unit (Sonara Digital TCD, CareFusion, Middleton, WI). Middle cerebral arteries (MCAs) and basilar arteries (BAs) were insonated at 1-mm intervals using the method described by Aaslid [1]. Peak systolic flow velocity (Vs), mean flow

velocity (Vm) (time-mean of the maximum velocity envelope curve) and end diastolic flow velocity (Vd) were recorded for each vessel. The pulsatility index (PI) was calculated according to the formula $PI = (Vs - Vd)/Vs$ and was also recorded.

Three previously published manuscripts describe reference values for CBFV in normal, healthy children [16–18]. Bode et al. evaluated children across a variety of age ranges from the neonatal period through age 18 (9–20 children/group) and found that expected flow velocities are lowest in the first 90 days of life then increase thereafter until maximal flow velocities are reached at an age of 5 years. Beyond this time, flow velocities decreased until age 18 where they approached normative adult values [16]. Subsequently to this, Tontisirin et al. evaluated the CBFVs of 24 girls and 24 boys age 5–10 years and Vavilala et al. evaluated 13 girls and 13 boys 11–16 years of age [17, 18]. While the CBFV reference values of these two studies described are similar to those of Bode, they did find that in both of these age groups girls had higher middle cerebral and basilar artery flow velocities than age-matched boys. Measured CBFVs in our cohort were compared to these previously published reference values in normal, healthy children. Age range categories were set in our cohort to match those studies [16–18]. For comparison, we used the values published by Bode et al. for children aged 4 and under. Given gender variability beyond this age, we compared our measured CBFVs to those described by Tontisirin et al. for girls and boys aged 5–10 years and to those described by Vavilala et al. for girls and boys >10 years.

TCD examinations were only performed when no changes to the ventilator had occurred within the previous 4 h. Positive end expiratory pressure (PEEP) was set at ≤ 10 cm H₂O during each evaluation. Partial pressure of carbon dioxide (PaCO₂) was between 35 and 45 mmHg at the time of each study and hematocrit was in the normal range of 30–41 %. All patients were hemodynamically stable with mean arterial blood pressures between the 25 and 75 % for age. If on vasopressor support, no changes in the dosage of these agents were made in the 4 h prior to TCD evaluation. Additionally, patients were normothermic and sodium levels were 135–145 mEq/L during TCD studies.

All children were sedated with fentanyl and versed infusions. These were titrated according to the Face, Legs, Activity, Cry, Consolability (FLACC) score. The FLACC score is a standardized, validated measure of pain, agitation, and sedation for children in the PICU [25, 26]. The FLACC score is measured by 5 min of observation of the patient with the legs and body uncovered. Five categories (face, legs, activity, cry, consolability) are evaluated and each category is scored from 0 to 2 points with higher numbers indicating tenseness, increased tone, and agitation. In interpreting the FLACC scale, a score of 0 indicates a relaxed/comfortable patient. Scores of 1–3 indicate mild discomfort or pain, scores

of 4–6 indicate moderate discomfort or pain, and scores of 7–10 indicate severe discomfort or pain. In our PICU, target FLACC score is less than 3. Sedation infusions were increased by 10 % every 10 min if FLACC scores were above that goal. All TCD examinations were done when FLACC scores were in goal range.

Statistical analysis

Means and standard deviations of the study parameters were calculated. Flow velocities in critically ill children were compared to published values for healthy controls using independent sample *t* tests, assuming unequal group variances. The Holm-Bonferroni step-down procedure with a familywise error rate of 0.05 was used to determine which comparisons would remain statistically significant after accounting for multiple comparisons. SPSS statistical software (version 21.2; IBM Corporation, Armonk, NY) was used to perform statistical analysis.

Results

One hundred sixty-seven consecutive eligible children's parents or guardians were approached for consent to participate. Thirty-seven declined. One hundred forty children were enrolled and completed the study. The number of children enrolled in each age category was variable (age <90 days $n = 31$, 3–12 months $n = 25$, 13–35 months $n = 19$, 3–4 years $n = 13$, 5–10-year females $n = 12$, 5–10-year males $n = 13$, 11–17-year females $n = 12$, 11–17-year males $n = 15$). Admission diagnosis for each participant varied by age and gender (Fig. 1). Younger age groups were most often admitted for respiratory failure. Older age groups had more diverse diagnosis on admission. All children were intubated and undergoing mechanical ventilation at the time of the TCD examination. For the entire group, the mean PEEP on the mechanical ventilator at the time each study was 6 (± 2) cm H₂O with a range of 4–10 cm H₂O. Thirteen children were admitted with

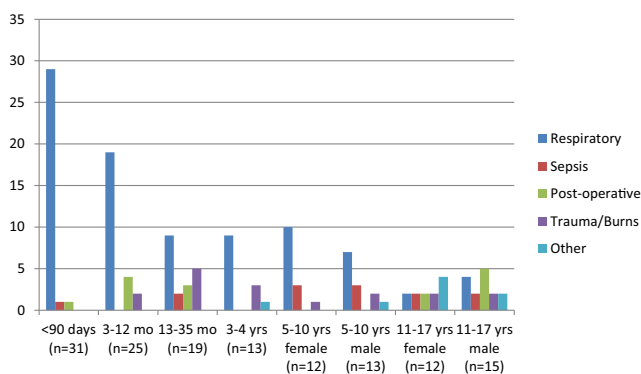


Fig. 1 Admission diagnosis of 140 critically ill, intubated, sedated children. Y axis represents absolute number

sepsis. Of those children, four were undergoing hemodynamic support with epinephrine and two with norepinephrine. Mean dose of epinephrine was 0.05 mcg/kg/min (range 0.03–0.2 mcg/kg/min) and mean dose of norepinephrine was 0.08 /kg/min (range 0.06–0.1 mcg/kg/min). Flow velocities in these children were not significantly different than in children with sepsis without the need for vasopressor support or from other participants of similar age or gender without sepsis (results not shown). For the entire cohort of patients, the mean fentanyl dosage was 1.4 (± 0.7) mcg/kg/h and the mean versed dosage was 0.1 (± 0.08) mg/kg/h at the time of the TCD examinations. Infants <90 days of age were receiving the lowest fentanyl dosage (1.1 ± 0.6 mcg/kg/h) as well as the lowest versed dosage (0.07 ± 0.02 mg/kg/h) during TCD studies. Children in the 13–35-month and in the 3–4-year-age ranges received the highest dosages of analgesics and sedatives (mean fentanyl dosage 1.7 ± 0.6 mcg/kg/h, mean versed dosage 0.15 ± 0.1 mg/kg/h for both age groups).

Systolic, mean, and diastolic flow velocities and pulsatility indices in the middle cerebral and basilar arteries across age ranges and genders were determined as per the methods described above and are noted in Table 1. Specific recorded CBFVs for each participant are available as [supplemental material](#). Measured CBFVs in our cohort were, in general, lowest in the neonatal age group and then increased through age 4 after which point they decreased to near adult values. Figure 2 depicts measured CBFV values in each age and gender group of our cohort compared to CBFV in previously reported healthy children [16–18]. In children ≥ 3 years of age of both genders, MCA Vs, Vm, and Vd were significantly lower in our mechanically ventilated, sedated children when compared to historical controls. On average, Vs was reduced by 24 % (range 17–40 %), Vm was reduced by 26 % (range 21–47 %), and Vd was reduced by 38 % (range 31–55 %) (all values statistically significant with *p* value ranging 0.02 to <0.001). In sedated, mechanically ventilated children 3–35 months of age, MCA systolic flow velocities were 10 % lower (non-significant (ns)) and mean and diastolic flow velocities were 22 and 37.5 % lower than published controls ($p = 0.0003$ for Vm, $p = <0.0001$ for Vd). In infants <90 days, Vs was reduced by 3 % (ns), Vm by 10 % (ns), and Vd by 21 % ($p = 0.01$) (Fig. 2).

In the basilar artery, across all age and gender groups, Vs was reduced on average by 9 % (range 2–13 %) in sedated, mechanically ventilated children compared to controls. None of these systolic flow reductions were found to be significantly different than basilar artery systolic flow velocities in normal healthy children in any age group. Average BA Vm was reduced by 17 % (range 11–22 %) in children ≥ 35 months ($p = 0.08$ in 3–4 years, $p = 0.002$ in females and males 5–10 years, $p = 0.06$ in females 11–17 years, and $p = 0.15$ in males 11–17 years) and by 4 % in children 13–35 months ($p = 0.56$). BA Vd was significantly lower in sedated, mechanically ventilated children ≥ 3 years of

Table 1 Systolic, mean, and diastolic flow velocities and pulsatility indices in the middle cerebral and basilar arteries across age ranges and genders

Age	Number	MCA in mechanically ventilated, sedated children	BA in mechanically ventilated, sedated children
Systolic flow velocity			
< 90 days	31	73 (21)	59 (14)
3–12 months	25	103 (24)	71 (15)
13–35 months	19	113 (32)	77 (15)
3–4 years	13	125 (28)	80 (21)
5–10 years (female)	12	87 (28)	80 (11)
5–10 years (male)	13	106 (26)	74 (18)
11–17 years (female)	12	115 (45)	70 (20)
11–17 years (male)	15	96 (25)	67 (15)
Mean flow velocity			
< 90 days	31	38 (14)	31 (8)
3–12 months	25	58 (15)	41 (11)
13–35 months	19	66 (21)	49 (12)
3–4 years	13	75 (25)	48 (18)
5–10 years (female)	12	52 (18)	46 (6)
5–10 years (male)	13	62 (13)	45 (7)
11–17 years (female)	12	61 (21)	40 (7)
11–17 years (male)	15	58 (14)	41 (10)
Diastolic flow velocity			
< 90 days	31	19 (7)	16 (6)
3–12 months	25	30 (10)	24 (7)
13–35 months	19	39 (14)	32 (9)
3–4 years	13	45 (21)	31 (16)
5–10 years (female)	12	33 (14)	30 (6)
5–10 years (male)	13	38 (9)	30 (6)
11–17 years (female)	12	35 (13)	25 (5)
11–17 years (male)	15	38 (11)	29 (8)
Pulsatility index			
< 90 days	31	1.47 (0.42)	1.41 (0.39)
3–12 months	25	1.25 (0.23)	1.12 (0.29)
13–35 months	19	1.11 (0.19)	0.94 (0.24)
3–4 years	13	1.11 (0.26)	1.07 (0.25)
5–10 years (female)	12	1.04 (0.15)	1.05 (0.24)
5–10 years (male)	13	1.04 (0.29)	1.03 (0.37)
11–17 years (female)	12	1.22 (0.33)	1.07 (0.35)
11–17 years (male)	15	0.96 (0.18)	0.92 (0.2)

MCA middle cerebral artery, BA basilar artery

age (average 28 % reduction, range 19–32 %, $p = 0.05$ in 3–4 years, $p < 0.001$ in females and males 5–10 years and females 11–17 years, $p = 0.02$ in males 11–17 years), but not in children 13–35 months (9 %, $p = 0.31$) compared to controls (Fig. 2). There are no published normal values for basilar artery flow velocity in children less than one year of age, so measured values in these children were not compared to controls. Additionally, specific values for pulsatility index in healthy control children of different age ranges have not been published, so we also did not compare our measured PIs to controls.

Discussion

Transcranial Doppler ultrasound is increasingly being utilized as an important clinical tool to aid in the diagnosis of and to guide therapy in critically ill children with acute neurologic illness or injury [2–15]. Cerebral blood flow velocities in these children have traditionally been compared to published normative CBFVs in healthy, ambulatory children. However, due to mechanical ventilation and sedation, CBFVs in critically ill children may be different than in normal healthy controls.

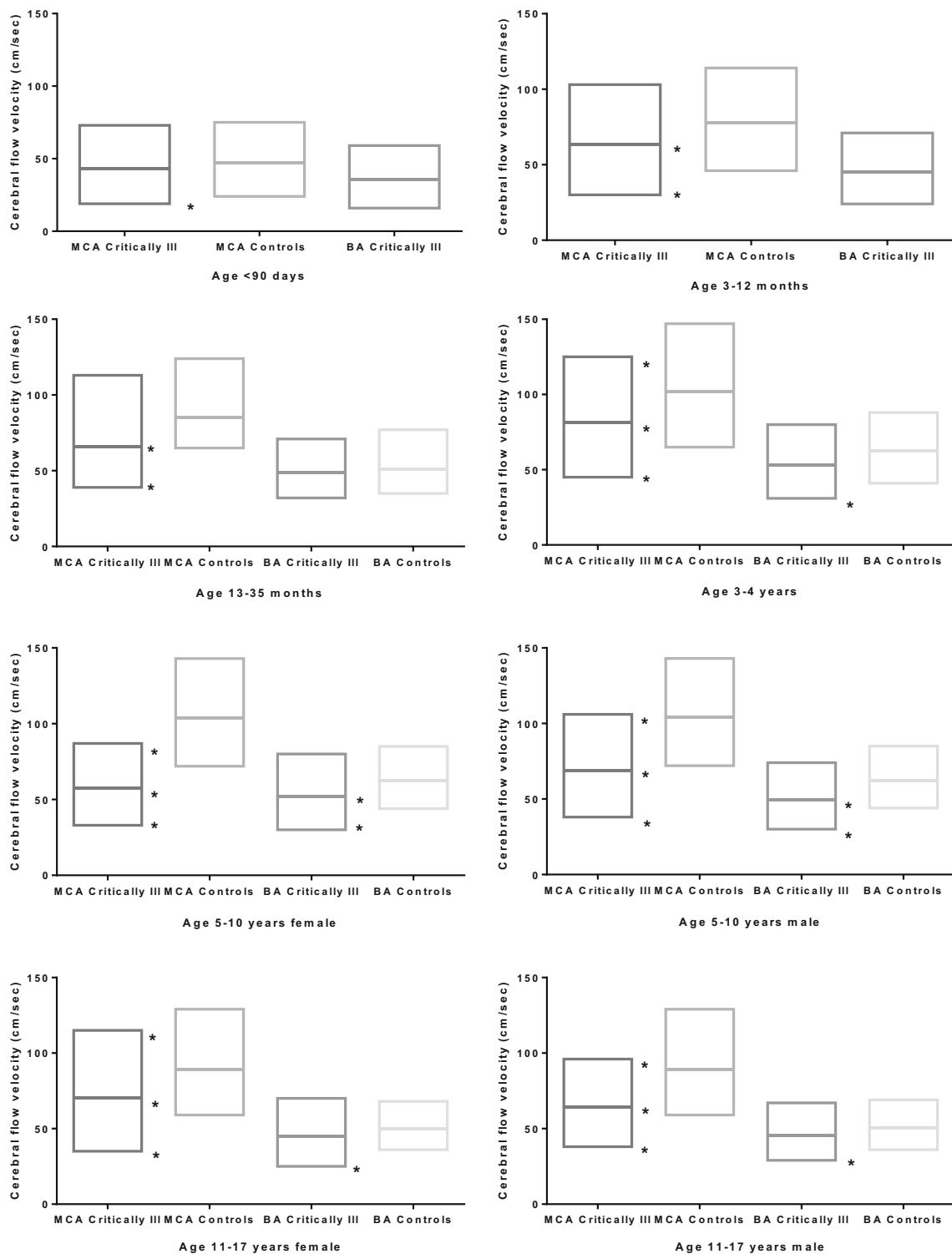


Fig. 2 Cerebral blood flow velocities in the middle cerebral artery (MCA) and basilar artery (BA) in a cross-sectional study of critically ill, intubated, sedated children without neurologic illness or injury ($n = 140$). These values are compared with previously published cerebral blood flow velocities in healthy children (references [16–18]).

The lines comprising each bar represent, respectively, the systolic, mean, and diastolic flow velocities for each vessel. The asterisk (*) notes flow velocities that are significantly different between groups ($p < 0.05$) after accounting for multiple comparisons using a Bonferroni-Holm step-down procedure

Therefore, to avoid misdiagnosis and mismanagement in children with acute, severe neurologic conditions, it is imperative

to compare their CBFVs to those of other children who are also undergoing mechanical ventilation and sedation but who

do not have a neurologic condition. We present flow velocities and pulsatility indices for the basal cerebral arteries recorded by transcranial Doppler ultrasound in critically ill, mechanically ventilated, sedated children 0–17 years of age without known neurologic illness or injury.

In our cohort of 140 children, systolic, mean, and diastolic flow velocities in the middle cerebral and basilar arteries were lowest in the neonatal period and then increased through age 4 after which point they decreased to near adult values. These findings are consistent with the general trends in flow velocities in healthy children [16]. This pattern of flow velocities can be attributed to the fact that beyond infancy, there is a sharp rise in neuronal activity with higher cerebral metabolic demand and subsequent increased cerebral flow that peaks around age 4–5 years [16].

The most important finding in this study is that, across every age group, MCA flow velocities in our cohort were, in fact, lower than reported flow velocities in healthy children. In children ≥ 3 years of age, V_s was reduced by 24 % (range 17–40 %), V_m was reduced by 26 % (range 21–47 %), and V_d was reduced by 38 % (range 31–55 %). In children 3–35 months of age, MCA systolic flow velocities were 10 % lower and mean and diastolic flow velocities were 22 and 37.5 % lower than published controls. In infants < 90 days, V_s was reduced by 3 %, V_m by 10 %, and V_d by 21 % (Fig. 2). Basilar artery flow velocities were more variably reduced in our cohort compared to historical controls. These findings are largely consistent with the expected changes associated with the physiological state of our cohort compared to that of healthy children. During sedation, the brain's resting metabolic rate is significantly reduced and cerebral blood flow falls to match this lowered demand. This effect is most pronounced in the frontal/parietal/temporal cortex which is supplied by the middle cerebral arteries [19–22]. Also, the positive end expiratory pressure (PEEP) applied during mechanical ventilation increases intrathoracic pressure and decreases cerebral venous outflow which causes subsequent reductions in cerebral blood flow velocities [23, 24].

While the majority of the CBFVs in our cohort were significantly lower than previously reported values in healthy children, even those not reaching statistical significance may be considered clinically relevant when using TCD as a tool to diagnose abnormalities and guide therapy in critically ill children. As such, we believe the values reported here can serve as a reference point for V_s , V_m , and V_d in children who are critically ill and undergoing sedation and mechanical ventilation in the pediatric intensive care unit instead of comparing their measured values to previously published CBFVs in healthy children.

Several important limitations to this study should be noted. Most importantly, some of the age ranges included a relatively small sample size. Future studies should focus on larger numbers of patients in each age and gender category to further

confirm the findings of this study. Furthermore, sample size may have impacted our ability to detect a statistically significant difference in some of the measured flow velocities in our cohort compared to normal, healthy controls. While each group size was sufficiently powered to detect a 20 % difference in measured cerebral flow velocity (with an alpha value of 0.05), children in the younger age ranges typically had reductions in measured flow velocities but that were less than this 20 % difference. Future studies including larger numbers of children in these younger age ranges will be required to determine if sedation and mechanical ventilation result in significant reductions in expected CBFV in these children or not.

In each age group, there was also a significant amount of heterogeneity in terms of admission diagnosis. Even when the above physiological parameters are met, it is possible that other factors associated with the actual disease process itself could affect expected TCD flow profiles. Future studies should focus on validating this normative data in groups of very homogenous patients that are specifically grouped by not only age and gender but also admission diagnosis.

It is also important to note that various physiological variables will affect CBFVs measured by TCD. For example, hypercapnea will increase and hypocapnea will decrease CBFVs. Hematocrit is inversely related to measured CBFVs [27, 28]. Hyponatremia has been shown to increase CBFVs [29]. At the time of TCD examination in this study, all patients had carbon dioxide levels, mean arterial blood pressures, hematocrit, and sodium levels in the normal range. In clinical practice, TCD parameters should always be carefully correlated with these important physiological parameters. In children in whom these variables are outside the normal range, TCD may be more useful as a tool to trend CBFV over time rather than to classify a child's cerebral flow as normal or abnormal at a single point in time.

It should be noted that the CBFVs reported in this study should not be applied to children spontaneously breathing and undergoing continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP). Previous studies in adults suggest that this form of respiratory support may actually increase, not decrease measured CBFVs [30, 31]. Future studies should be performed to determine normative TCD CBFV values in these children.

Additionally, children undergoing sedation with dexmedetomidine alone or in combination with other agents were not included in this study. This was done because animal and human studies suggest that, through stimulation of central postsynaptic α_2 -receptors, dexmedetomidine increases cerebral vascular resistance and reduces cerebral blood flow directly and more significantly than other sedative agents [32, 33]. Therefore, future studies should also be performed to further evaluate normative CBFVs in critically ill children undergoing dexmedetomidine sedation, as these flow velocities are likely reduced even further than those reported here.

Conclusion

Cerebral blood flow velocities of the basal cerebral arteries in critically ill, mechanically ventilated, sedated children are lowest in the neonatal period, increase through age 4, and then decrease to near adult values thereafter. CBFVs in these children are lower than in healthy children of the same age and gender published in previous studies. As such, the CBFV values reported here may serve as a more accurate reference point when using TCD as a clinical tool to diagnose CBFV abnormalities and guide therapy in mechanically ventilated, sedated children in the intensive care unit.

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Conflict of interest The author has no conflict of interest to disclose.

Compliance with Ethical Standards This study met all ethical requirements of the IRB at Nationwide Children's Hospital.

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