Applications of Transcranial Doppler Ultrasonography in Sickle Cell Disease, Stroke, and Critical Illness in Children

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Background

Since the 1980s, TCD has remained the gold standard stroke risk prediction tool in children with sickle cell disease (SCD) by identifying those who benefit from blood transfusion [1–5]. The rigor of this prior research and impact of TCD on the health of children with SCD has remained unmatched to date in other pediatric populations. Results largely from single center, small pediatric studies, and precedent from adult neurocritical care, however, suggest that use of TCD in critically ill children may have promise. According to a survey of 27 centers in the United States with an expert interest in pediatric neurocritical care (PNCC), TCD was

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being applied in the PICU for a variety of conditions including: traumatic brain injury (TBI), hypoxic-ischemic encephalopathy (HIE) following cardiac arrest, arterial ischemic stroke, subarachnoid hemorrhage, cerebral vascular malformation, hepatic encephalopathy, sepsis, and diabetic ketoacidosis (DKA). Importantly, TCD seemed to direct clinical care in 75% of the contributing PICUs in this survey [6]. In acute care settings like the PICU and pediatric emergency department (ED), TCD has several potential roles: as a point of care ultrasound (POCUS) study to rapidly diagnose disorders of cerebral perfusion and incorporate findings into clinical decisions in an aim to improve clinical care and outcomes; and as a continuous non-invasive neuromonitoring tool alone or integrated with multi-modal monitoring systems.

There are a number of barriers that must be overcome, however, before TCD can be used in a safe, meaningful, and effective way in pediatric acute care. First and foremost, normal values with a clear understanding of variability due to age, gender, type of critical illness, and associated therapies are needed [7, 8]. Although there is a reasonable starting point for normative values in healthy children and in those sedated and mechanically ventilated, the main limitation of these prior studies is the small sample size for each age category [8, 9]. Normative data for healthy children are available in Table 1 [8]. In the absence of reliable normative data, abnormal TCD findings in critically ill children should be treated as hypothesis-generating. Secondly, large cohort studies are needed to validate TCD findings in children against an acceptable gold standard (e.g. imaging studies, measurements of absolute intracranial pressure [ICP] from invasive ICP monitors), to determine the appropriate clinical indications for the performance of TCD, and to quantify the impact of TCD findings on clinical care and outcomes. Finally, there are several technical challenges to overcome in order to achieve consistent results in children including: properly fitting, safe, and comfortable headgear for uninterrupted signal acquisition; standardized performance of the TCD examination in the PICU for reproducible and verifiable waveforms; and examiner expertise in the care of criti-

Table 1 Normative transcranial doppler ultrasound values by age (mean (SD) [8]

Age	MCA	ICA	ACA	PCA	BA
Systolic peak velocity:					
0–10 days	*46 (10)*	47 (9)	35 (8)	–	–
11–90 days	*75 (15)*	77 (19)	58 (15)	–	–
3–11.9 months	*114 (20)*	104 (12)	77 (15)	–	–
1–2.9 years	*124 (10)*	118 (24)	81 (19)	69 (9)	71 (6)
3–5.9 years	*147 (17)*	144 (19)	104 (22)	81 (16)	88 (9)
6–9.9 years	*143 (13)*	140 (14)	100 (20)	75 (10)	85 (17)
10–18 years	*129 (17)*	125 (18)	92 (19)	66 (10)	68 (11)
Mean flow velocity[a]:					
0–10 days	*24 (7)*	25 (6)	19 (6)	–	–
11–90 days	*42 (10)*	43 (12)	33 (11)	–	–
3–11.9 months	*74 (14)*	67 (10)	50 (11)	–	–
1–2.9 years	*85 (10)*	81 (8)	55 (13)	50 (12)	51 (6)
3–5.9 years	*94 (10)*	93 (9)	71 (15)	48 (11)	58 (6)
6–9.9 years	*97 (9)*	93 (9)	65 (13)	51 (9)	58 (9)
10–18 years	*81 (11)*	79 (12)	56 (14)	45 (9)	46 (8)
End diastolic peak velocity:					
0–10 days	*12 (7)*	12 (6)	10 (6)	–	–
11–90 days	*24 (8)*	24 (8)	19 (9)	–	–
3–11.9 months	*46 (9)*	40 (8)	33 (7)	–	–
1–2.9 years	*65 (11)*	58 (5)	40 (11)	35 (7)	35 (6)
3–5.9 years	*65 (9)*	66 (8)	48 (9)	35 (9)	41 (5)
6–9.9 years	*72 (9)*	68 (10)	51 (10)	38 (7)	44 (8)
10–18 years	*60 (8)*	59 (9)	46 (11)	33 (7)	36 (7)

MCA Middle Cerebral Artery, *ICA* Internal Carotid Artery, *ACA* Anterior Cerebral Artery, *PCA* Posterior Cerebral Artery, *BA* Basilar Artery
[a]Mean Flow Velocity = time mean of the maximal velocity envelope curve

cally ill children for appropriate interpretation and integration of the waveforms into clinical decision making.

In this chapter we will review some potential emerging clinical applications for TCD in children recognizing that these limitations must be resolved before TCD can be put into clinical practice. We will focus on: first, childhood stroke and arteriopathies; and

second, those applications that may be well suited for children in the critical care setting including traumatic brain injury (TBI), cerebral vasospasm, monitoring during extracorporeal membrane oxygenation (ECMO), and brain death. The content of this chapter is relevant not only for providers in PNCC (e.g. intensivists, neurologists, anesthesiologists), but also for radiologists who have an interest in this predominantly non-sickle cell population.

Childhood Stroke and Arteriopathies

Sickle Cell Disease (SCD) in Children

SCD is a group of genetic disorders that result in production of hemoglobin S. Under conditions of cellular stress, hemoglobin S polymerizes, distorts the shape of red blood cells, and leads to irreversible sickling. Sickled cells have a reduced life span, which leads to an intravascular hemolytic anemia, and can cause occlusion of the microvasculature, which is believed to be the major cause of the wide range of clinical symptoms. The largest inception cohort study demonstrated an alarming stroke rate of nearly 12% by age 18 years [10]. Stroke mechanisms in children with SCD are likely multifactorial and include: microvascular occlusion as occurs in the systemic circulation; endothelial injury from a potential cell-mediated inflammatory vasculopathy and/or a potential role for platelet and/or monocyte dysfunction; and reduced nitric oxide bioavailability from chronic hemolysis and excess plasma free hemoglobin (nitric oxide has anti-inflammatory and anti-thrombotic properties) [11, 12]. Angiographic series and pathologic studies support a large artery occlusive vasculopathy as the major contributor to ischemic stroke in children with SCD [13–17].

In the 1980s, Dr. Robert J Adams used a vessel-based approach with TCD to stratify stroke risk in children with SCD. The key findings from his series of studies were: (1) TCD could distinguish children with SCD from those without SCD [18]; (2) TCD could detect stenotic lesions as seen on angiography and distinguish children with SCD with stenosis from those without steno-

sis [19]; and (3) stroke risk could be stratified by the time averaged mean of the maximum flow velocity (TAMMX) in the middle cerebral artery (MCA) or internal carotid artery (ICA) such that children with TAMMX in either artery ≥200 cm/s had a 40% risk of a first ever stroke within 3 years [1, 20].

In the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study, 1934 children with SCD from age 2 to 16 years old were screened with TCD at 14 clinic sites in the United States. Children with mean flow velocity ≥200 cm/s in the MCA or ICA were randomized into two groups. Sixty-three children received regular blood transfusions every 3–4 weeks to maintain their hemoglobin S level ≤30% (intervention arm). Sixty-seven children received standard care with periodic blood transfusions (control group). The main finding was a 10% yearly stroke rate in the control group compared to a <1% stroke rate in the intervention arm, indicating a 92% relative risk reduction for a first ever stroke ($p < 0.001$) [2]. Based on the results of this study, current guidelines recommend that children between ages 2 years and 16 years with sickle cell disease should be screened with TCD annually if the study is normal (TAMMX in the MCA or ICA <170 cm/s), and quarterly if conditional (TAMMX 170–199 cm/s). Regular blood transfusions should be initiated for an abnormal TCD (TAMMX in least one artery ≥200 cm/s) [21].

Other Childhood Arteriopathies

Children with moyamoya syndrome present with ischemic stroke or transient ischemic attack due to chronic and progressive stenoses involving the arteries in the anterior cerebral circulation. Based on adult data, there may be a role for TCD as an adjunct to angiography in children with moya-moya syndrome [22]. However, validation of cerebral blood flow velocity (CBFV) thresholds in moyamoya in children that suggests clinically relevant stenoses do not exist. Rather, in children with angiographic evidence of vascular occlusion or stenosis, CBFVs may be followed over time once baseline data are procured to monitor for worsening of disease.

Children with focal cerebral arteriopathy (FCA) may be differentiated from moyamoya or cerebral vasculitis by a clinical course of improvement or stabilization over time, occasionally after a period of initial worsening. Acute central nervous system (CNS) infections from bacterial infections and herpesvirus can be associated with the development of FCA and arterial ischemic stroke in children [23–25]. While stroke mechanisms in FCA remain unclear, vessel diameter narrowing (stenosis and/or vasospasm) from contact of exudate with the vessel wall may play a role. While vascular changes are best characterized by angiography, this diagnostic study often has to be repeated frequently over weeks to months after the acute illness and may require repeated sedation and/or endotracheal intubation in young children. TCD may have a preferred role in long-term monitoring of this disease if a correlation with angiography is found.

Pediatric Critical Care Applications

Moderate to Severe TBI

In adults, TCD criteria for hypoperfusion following severe TBI have been used to guide early resuscitation [26, 27]. Similar criteria for children, however, remain unclear. In a study by Trabold et al. of 36 children with moderate to severe TBI, end diastolic cerebral blood flow velocity (Vd) <25 cm/second and pulsatility index (PI) >1.31 after the first resuscitation in the ED was associated with poor outcome, defined as Glasgow Outcome Scale 3–5 at hospital discharge (Vd: AUROC 0.91 ± 0.02, $p = 0.03$; PI: AUROC 0.89 ± 0.02, $p = 0.04$) [28]. It is important to note that in this study, mortality rate was high at 11%, and the study was not powered to perform multivariate analyses on variables besides TCD measurements, such as the Glasgow Coma Scale and other injury severity scores, that may be independent factors of poor prognosis. Other investigators have attempted to discover relationships between CBFVs and outcome, but these studies are limited by small sample sizes, retrospective study design, and

lack of rigorous, serial protocol-driven TCD measurements [29–31]. More individual level and rigorous data collection and analyses are needed.

In children with moderate to severe TBI, there has also been some work on the use of TCD for non-invasive ICP and cerebral perfusion pressure (CPP) estimation. TCD is an attractive alternative to invasive monitoring in children for 2 reasons: (1) the recommendation in the 2019 updated guidelines for management of severe TBI in children can only support class III evidence for ICP monitoring [32, 33]; and (2) there is low utilization of gold standard invasive ICP monitoring in children [34–39]. Similar to the adult literature, Vd and PI are not reliable indicators of increased ICP in children when compared to gold standard invasive ICP measurements [28, 40–42]. The main limitations in these studies are that PI measurements were often made as single, point source measurements at different timepoints following the injury in small numbers of children. A continuous, fully automated, real-time engineering approach using synchronized systemic arterial blood pressure and MCA waveforms has been recently shown to estimate ICP with similar accuracy and precision as routinely used invasive ICP monitors [43]. Validation in larger cohorts is needed. Regarding the use of TCD to estimate CPP (CPPe) in children with severe TBI, use of the formula CPPe = ABPmean*FVd (diastolic flow velocity)/Fvm (mean flow velocity) +14 as a regression equation gives limits of agreement of −17 to +25 mmHg, which is not clinically acceptable [44].

Cerebral Vasospasm

Cerebral vasospasm is a reversible reduction in the caliber of an arterial lumen of a vessel in the subarachnoid space. Arterial narrowing leads to an increase in TCD derived CBFVs and a decrease in PI with worsening spasm. If severe, vasospasm can lead to a critical reduction in cerebral blood flow and cerebral ischemia. Cerebral vasospasm has been reported following resection of brain tumors, ruptured cerebral aneurysms and arteriovenous malformations, CNS infections, and moderate to severe TBI in chil-

dren [29, 45–51]. The diagnostic accuracy of TCD for angiographic proven vasospasm when adult criteria are used in children is low, with a positive likelihood ratio of only 2.0 [52]. Using adult criteria in pediatrics has such a low positive likelihood ratio because CBFVs are higher in children compared to adults across all age groups [53]. The pediatric literature to date on this topic is limited by the use of adult criteria, lack of radiographic confirmation of elevated CBFVs and Lindegaard ratios, and small sample sizes. Thus, validated TCD thresholds for vasospasm do not exist for children. Prospective studies comparing age-related CBFV measurements and Lindegaard ratios to angiographic data in children with symptomatic vasospasm are needed. In the absence of robust pediatric data, TCD should be used as a precursor to definitive imaging when there is a suspicion for vasospasm (e.g. persistent increase in CBFVs over time, or significant day to day changes in CBFVs). Figure 1 is an example of a representative case where TCD was used to assist in the diagnosis and management of a child with cerebral vasospasm.

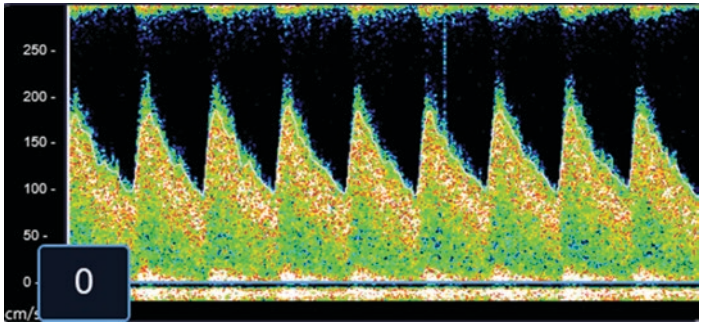

Fig. 1 24-month-old female involved in a motor vehicle accident. Transcranial Doppler ultrasound (TCD) was normal on days 1–3, but on post-injury day 4, right middle cerebral artery flow increased to 220 cm/sec with an LR of 6.9. Neurologic status declined with new left sided hemiparesis. Based on results of the TCD, angiogram was ordered and confirmed the diagnosis of cerebral vasospasm. Therapeutic interventions were undertaken, and neurologic examination improved. TCD was repeated daily with no further worsening of vasospasm and normalization of flow by post-injury day 7. Therapies were weaned with no worsening of TCD flow velocities

Monitoring During ECMO

Detection of acute brain injury that is clinically recognizable or in the subclinical phase during ECMO in a sedated and/or paralyzed child is difficult. To date, what is known about the relevance of CBFV measurements in children is that similar to adults, CBFVs and PI are lower in children supported on ECMO during the first 5 days of therapy in those who do not have acute brain injury [54]. Serial TCD monitoring has not, however, shown a reliable correlation between changes in velocity and brain ischemia or hemorrhage [54, 55]. Larger studies in this population are needed. At present, the only reliable way to detect acute brain injury during ECMO is "after the fact" by serial neurologic exams with confirmation of focal neurologic deficits by neuroimaging.

ECMO is a life-saving treatment for heart and/or lung failure, as a bridge to transplant, or as an aid to cardiopulmonary resuscitation for in hospital cardiac arrest. The use of ECMO has quadrupled in children in the last 15 years to >2500 cases in 2016 [56]. ECMO technology has improved so that avoiding acute brain injury during the course of ECMO is now key to survival and better long-term outcomes [57–61]. Acute brain injury occurs in the form of hypoxic ischemic injury, intracranial hemorrhage, and arterial ischemic stroke. Data supporting the use and effectiveness of current neuromonitoring methods on ECMO to detect acute brain injury is limited. The majority of the evidence for monitoring using neuroimaging, electroencephalography (EEG), cerebral oximetry, serum biomarkers and Doppler ultrasound is limited to mainly level 3B (case-control) and 4 (case series).

Cerebral emboli, representing air or solid matter, are one potential cause of acute brain injury during ECMO. Emboli may occur as a result of low cardiac output, or direct passage of emboli in the systemic circulation from the ECMO circuit or left heart chambers [62–64]. TCD can detect emboli as distinct high intensity signals (HITS) or microembolic signals (MES) in the Doppler spectrum. Although consensus on their signature exists in the Doppler spectrum [65], emboli monitoring has not transitioned into routine clinical care in children for the following reasons: (1) sparse pediatric literature; (2) commercial TCD software seems to generate excess false positive events and better event separation is needed

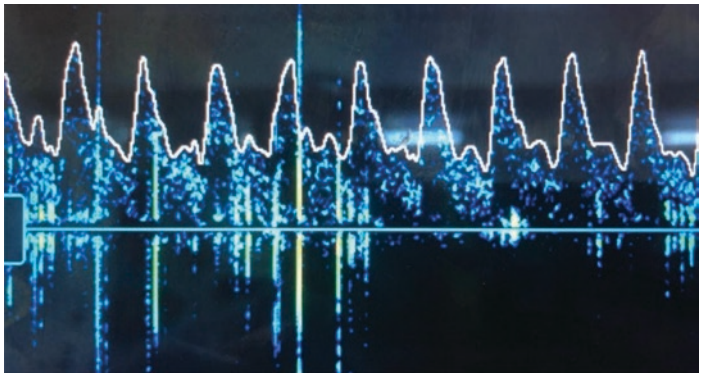

Fig. 2 7-month-old male undergoing TCD monitoring during cardiopulmonary bypass for complex congenital heart disease repair. Multiple high-intensity signals were noted throughout the case. The events were of unknown clinical significance as patient did not have any gross neurologic deficits on hospital discharge

[66]; (3) manual review is laborious and time consuming; and (4) uninterrupted signal acquisition remains a challenge due to the lack of appropriately sized headgear for infants and young children. Further technical improvements are needed to distinguish the true embolic count, size, and composition of embolic events. As a starting point to generate further data, emboli monitoring may be appropriate for infants and children on cardiopulmonary bypass while undergoing cardiac surgery [67]. Figure 2 represents embolic phenomenon identified by TCD in a child on cardiopulmonary bypass for repair of congenital heart disease.

Brain Death

Unlike adults, standards and guidelines for the TCD diagnosis of cerebral circulatory arrest do not exist for children. There are >10 cases reported in the literature of children from birth to 11 months who met clinical (loss of brainstem reflexes) and EEG criteria for brain death, but cerebral blood flow by angiography and/or TCD was detected [68, 69]. One reason for these findings may be that the elastic infant skull with open fontanelles can oppose rising ICP, allowing

for significant increases in cranial volume without a reduction in CPP (risk of false negative). False positives, on the other hand, may occur due to operator inexperience and misinterpretation of "absent" flow in infants who normally have a low diastolic flow velocity (12 ± 7 cm/sec). Accordingly, TCD is not currently recommended as an ancillary test to aid in brain death determination in children <18 years. TCD may, however, indicate the optimal timing for a perfusion study if there is clinical diagnostic uncertainty of brain death [70]. Figure 3 represents the use of TCD in a child suffering traumatic brain injury to direct timing of confirmatory brain death testing.

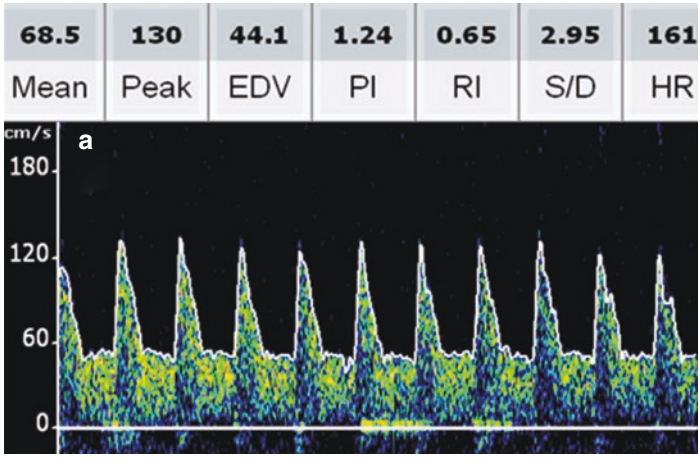

Fig. 3 8-year-old male suffering severe traumatic brain injury following a motor vehicle collision. Panel A represents his admission TCD with near normal peak systolic velocities but with flattened diastolic flow and a modestly high pulsatility index. Intracranial pressure (ICP) was 29 mmHg during the TCD examination. Despite maximal medical and surgical management, ICP continued to increase to 60 mmHg by hospital day 3. Clinical examination was concerning for brain death, but apnea testing could not be performed due to hypoxia secondary to bilateral pulmonary contusions and lacerations. Panel B represents TCD images of the middle cerebral artery acquired on hospital day 3. Trace diastolic flow was noted. Thus, given the uncertain diagnostic certainty of a confirmatory perfusion study at that time in a patient who was not clinically stable, it was deferred. Panel C represents TCD images of the middle cerebral artery acquired on hospital day 4. Systolic spikes with complete lack of diastolic flow were noted and brain death was confirmed with perfusion study following the TCD examination

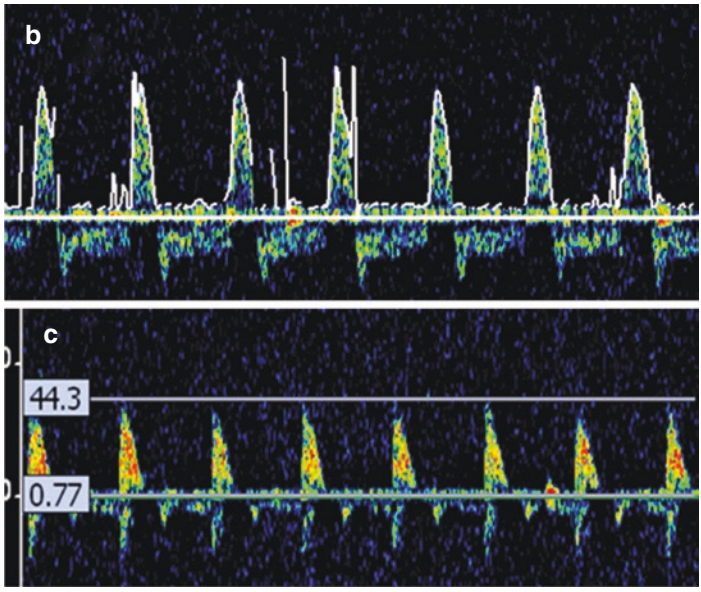

Fig. 3 (continued)

Other Conditions

One last potential unique application of TCD may be as a screening tool to aid in clinical decisions and guide therapy in children in low income countries with cerebral malaria (CM). Malaria is a global health problem resulting in >400,000 deaths annually, two-thirds of which occur in children under age 5 years [71]. CM is a severe manifestation of malaria and can be diagnosed when the child presents in coma with Plasmodium parasitemia and no other identifiable cause for coma (such as hypoglycemia, seizures, or meningitis). Severe neurologic disability (e.g. weakness/paralysis, hypotonia, spasticity, speech and language disorders, movement and gait disorders, vision impairment, epilepsy, and behavioral problems) is present in about one half of survivors [72]. Even with excellent clinical care, the mortality rate from CM is approximately 15% [73].

In a prospective observational study performed at 3 clinical sites in the Democratic Republic of the Congo between 2015 and 2017, O'Brien et al. found 5 different TCD "phenotypes" in 160 children with CM during the first 8 days of hospital admission. Interestingly, a total of 151/160 patients remained in one of the following phenotypic categories until normalization or death: hyperemia was seen in 42 cases (26%), low flow state in 46 cases (28%), microvascular obstruction in 35 cases (22%), and cerebral vasospasm in 21 cases (13%) [50]. Validation of pathophysiologic mechanisms associated with each TCD phenotype may aid in the development of individual targeted adjunctive therapies that may improve outcomes for children with CM.

Conclusions

TCD has an established clinical role in reducing a first ever stroke in children with SCD by identifying those who are high risk and benefit from blood transfusion. Beyond sickle cell disease, other potential roles for TCD are as a point of care ultrasound or neuromonitoring strategy in the PICU setting. TCD data in critically ill children should be treated as hypothesis-generating. TCD may serve as a precursor or adjunct to definitive imaging or invasive techniques. Collaboration and research is needed to advance the TCD field in pediatrics.

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