Research article

Transcranial doppler velocities in a large healthy population of African children

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A R T I C L E   I N F O

A B S T R A C T

Background and purpose: Transcranial doppler ultrasound (TCD) is a tool that diagnoses and monitors pathophysiological changes to the cerebrovasculature. As cerebral blood flow velocities (CBFVs) increase throughout childhood, interpretation of TCD examinations in pediatrics requires comparison to age matched normative data. Large cohorts of healthy children have not been examined to develop these reference values in any population. There is a complete absence of normative values in African children where, due to lack of alternate neuroimaging techniques, utilization of TCD is rapidly emerging.
Materials and methods: A prospective study of 710 healthy African children 3 months-15 years was performed. Demographics, vital signs, and hemoglobin values were recorded. Participants underwent a complete, non-imaging TCD examination. Systolic (Vs), diastolic (Vd), and mean (Vm) flow velocities and pulsatility index (PI) were calculated by the instrument for each measurement.
Results: Vs, Vd, and Vm increased through early childhood in all vessels, with the highest CBFVs identified in children 5–5.9 years. There were few significant gender differences in CBFVs in any

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vessels in any age group. No correlations between blood pressure or hemoglobin and CBFVs were identified. Children in the youngest age groups had CBFVs similar to those previously published, whereas nearly every vessel in children ≥ 3 years had significantly lower Vs, Vd, and Vm.

Conclusions: For the first time, reference TCD values for African children are established. Utilization of these CBFVs in the interpretation of TCD examinations in this population will improve the overall accuracy of TCD as a clinical tool on the continent.

1. Introduction

Transcranial doppler ultrasound (TCD) is a portable, non-invasive tool that readily evaluates cerebral blood flow velocities (CBFVs) and cerebrovascular hemodynamics in all the major vessels of the Circle of Willis [1]. The technique is repeatable, with interpretation available in real time, making it an ideal "stethoscope into the brain" that can be used for point of care assessments, monitoring, and to guide decision making in a variety of clinical scenarios [2]. However, one major limitation to the utilization of TCD in pediatrics is the lack of normative data derived from large populations of healthy children [3].

To meet the metabolic demand of rapid brain growth in early childhood, cerebral blood flow increases significantly from birth through approximately age 6 years, and then declines to adult levels by adolescence. Interpretation of TCD examinations as normal or abnormal must occur in this context, with comparison of measured CBFVs to age matched healthy children. Recent multidisciplinary expert consensus guidelines for the performance of TCD in critically ill children recommend the comparison of TCD study results to those published by Bode et al., in 1988 that included a cohort of only 112 healthy, European children divided between 6 different age groups [3,4]. The small number of participations in this report is a significant limitation to the field.

Furthermore, as a result of its favorable attributes and the lack of alternate, available neuroimaging techniques, TCD is increasingly being used in the management of African children with sickle cell disease, obstructive hydrocephalus, sinus venous thrombosis, meningitis and cerebral malaria [5–10]. The interpretation of TCD examinations in this context is particularly problematic given the complete absence of normative data in African children. We therefore performed this prospective, observational study to determine TCD normative values in a large, healthy population of Congolese, Zambian, and Malawian children.

2. Materials and Methods

This was a prospective, observational study performed at six centers across three countries in sub-Saharan Africa (SSA) including: 1) Kinshasa, Democratic Republic of the Congo (DRC); 2) Lodja, DRC; 3) Bunia, DRC; 4) Lusaka, Zambia; 5) Chipata, Zambia; and 6) Blantyre, Malawi from September 2021–June 2022. Children 3 months to 15 years of age were eligible to participate and were recruited from areas immediately surrounding the previously established TCD Center of Excellence at each site. Children with a history of any known cerebrovascular pathophysiology (stroke, meningitis, cerebral malaria, cerebral palsy, obstructive hydrocephalus) or systemic disorders with cerebrovascular effects (sickle cell disease) were excluded. Ethics approval was obtained in each country (DRC CES ID 279/CNES/BN/PMMF/2021, Zambia ERES ID 00005948, Malawi COMREC ID P.02/21/3270) and guardians gave informed consent prior to participation.

Age and sex of participants were determined by evaluation of the patient's written medical record or by verbal report from the parent or guardian. Participants underwent assessment of vital signs including temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation. Mid upper arm circumference (MUAC) was also measured to assess for malnutrition. Following the World Health Organization recommendations, MUAC <12.5 cm was considered to represent moderate malnutrition and MUAC <11.5 severe malnutrition (for children 6–59 months). All children underwent point of care Sickle SCAN (Biomedomics, North Carolina, USA) screening to ensure the absence of sickle cell disease. Given the potential impact of anemia on measured TCD flow velocities, hemoglobin values were determined using point of care testing (HemoCue, Angelhom, Sweden).

TCD examinations were performed by individuals who had successfully completed the sub-Saharan African TCD Academy course content which includes: 1) 12 online didactic lectures designed to teach basic concepts of TCD science including neuroanatomy, scan techniques, doppler waveform characteristics, diagnostic criteria, and clinical applications in children 2) 100 case studies aimed to develop interpretation skills 3) a hands-on introduction to TCD training session to develop TCD scanning proficiency and 4) a written examination. The course was considered successfully finished when didactics and case studies were reviewed, the participant demonstrated proficiency in TCD scanning (each study measurement for a complete TCD examination has a coefficient of variation <10% from that of the trainer ((NO)), and the written examination was passed.

TCD examinations were acquired at each site using a commercially available non-imaging TCD device (Lucid TCD, NovaSignal, Los Angeles, CA). A TCD study interrogating 12 arterial segments and 5 venous segments was performed following a standardized protocol, based on accepted TCD practice. These segments were: the bilateral middle cerebral arteries (MCA), bilateral anterior cerebral arteries (ACA), bilateral posterior cerebral arteries ((PCA)); P1), bilateral extra-cranial internal carotid arteries (Ex-ICA), bilateral vertebral arteries (VA), the basilar artery (BA), one ophthalmic artery (OA), bilateral middle cerebral veins, bilateral internal jugular veins, and one ophthalmic vein. Vessel depths varied based on participant age. Correct depths for insonation were identified utilizing the M mode. The length of the entire vessel was interrogated in 2 mm increments. A sweep speed of 5 s per screen was used to yield 5–7 quality waveforms per page. Systolic, diastolic, and mean flow velocities (Vs, Vd, Vm) and pulsatility index (PI) values were calculated using the instrument's automated waveform tracking function. Non-pulsatile venous flow was measured by hand on the device. All studies

were reviewed by one of two study team members (NO, HJ) to assure the quality of the study.

2.1. Statistical analysis

Not all arterial segments were able to be insonated in each individual; thus, analyses were based on available TCD measurements for each vessel. Right-left differences in bilateral vessels (MCA, ACA, PCA, VA) were examined by fitting vessel specific mixed effects linear models with subject as a random effect and side as a fixed effect using maximum likelihood estimation under data missing at random assumptions for each of the two dependent variables, mean flow velocity, and PI. Because few of the right-left differences were statistically significant, the observed measurements were averaged from the right and left sides for subsequent analyses. Descriptive values were expressed as frequencies and percentages for dichotomous variables and as mean $\pm$ SD for normally distributed or median [interquartile range (IQR)] for non-normally distributed continuous variables. For comparison of continuous variables, independent sample t-test was used. All examined vessel segments were examined by age group with Pearson or Spearman correlation coefficient evaluation of association with continuous variables (hemoglobin, mean arterial blood pressure, MUAC). Simple logistic regression was performed to assess the association between measured flow velocities and categorical variables (sickle cell trait status ((AA vs AS)). All analysis were completed with GraphPad version 9.0 (San Diego, CA). A $p < 0.05$ was considered statistically significant.

3. Results

A total of 734 potential participants were screened and 710 were enrolled (Fig. 1). Of participants, 49% (n = 348) were female and 51% (n = 362) were male. Blood pressure ranged, across the cohort, from the 10th-90th percentile for age. Mean MUAC was 15 ($\pm$2) cm with 10 children (1.4%) meeting criteria for severe acute malnutrition and 15 children (2.1%) meeting criteria for moderate malnutrition. On screening, 82% (n = 582) were found to have hemoglobin AA and 18% (n = 128) hemoglobin AS. The mean hemoglobin was 11.2 ($\pm$2.2) g/dL with a range of 4.2 to 14.3 g/dL. Forty-five total hemoglobin measurements were <7 g/dL and an additional 155 were between 7 and 10 g/dL.

Measured TCD values for each insonated vessel by age are in Table 1. For the entire cohort, the MCA side to side differences were 11% ($\pm$10%) with no significant differences noted between age groups (p > 0.5, data not shown). There were few statistically significant differences in any measured flow velocities in any vessel between females and males in any age group (Fig. 2, A-P). Regarding mean arterial blood pressure (MABP), the only significant correlation between any TCD measurements in any age group and MABP was between the OA and the middle cerebral vein in 14-year-olds (r = 0.87, 95% CI 0.04–0.99 for the OA and r = 0.84, 95% CI 0.4–0.96 for the middle cerebral vein). No significant correlations were identified between any TCD measurements and MUAC or measured hemoglobin concentration (r < 0.7 for all measurements). There was no interaction between hemoglobin AA or AS status and any measured flow velocities (p = 0.78).

Current guidelines recommend utilization of normative values published by Bode et al. for comparison to determine if an acquired TCD examination is normal or abnormal (more than 2SD above or below these published values) [3,4]. Following grouping of our data into the same age groups presented by Bode et al. (3 months–11.9 months, 1–2.9 years, 3–5.9 years, 6–9.9 years, >10 years), multiple significant differences in measured flow velocities were identified (Table 2). Most notably, MCA, ACA, and PCA flow velocities were significantly lower in our cohort in most age groups (>3 years) than previously reported, whereas BA flow was similar.

Eligible patients
(n=734)

Not included: n= 24

·No insonation window that allowed for technically adequate exam n=19
·Determined to have sickle cell disease n=3
·Determined to have significant neurologic deficits at baseline n=1
·Determined to have hypertension (mean arterial blood pressure >125% for age) n=1

Included in the study: n=710

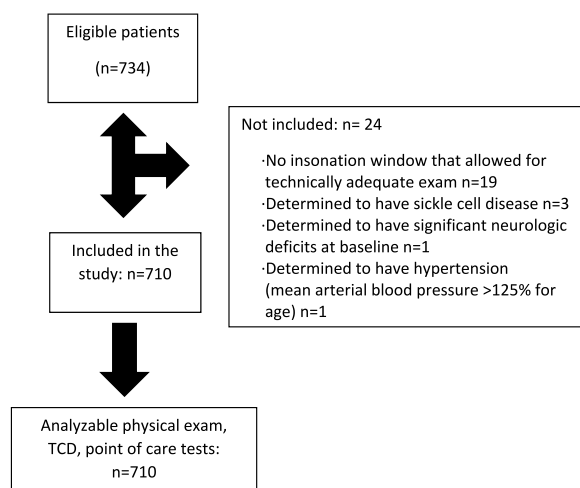Analyzable physical exam, TCD, point of care tests: n=710

Fig. 1. Flow diagram of patient screening and enrollment.

Table 1

Cerebral blood flow velocities (in cm/second) and pulsatility index in cerebral vessels in African children (n = 710).

| TCD Measurement by Age	~Number	Middle Cerebral Artery	Anterior Cerebral Artery	Posterior Cerebral Artery	Vertebral Artery	Basilar Artery	Ophthalmic Artery	Ex-Internal Carotid Artery[a]	Lindegaard Ratio[a]	Middle Cerebral Vein[a]	Jugular Vein[a]
Systolic flow velocity											
3–11.9 mo	48	102 (20)	71 (19)	57 (18)	66 (17)	72 (16)	21 (4)				
1–1.9 years	38	125 (26)	77 (19)	63 (21)	72 (17)	81 (17)	26 (5)				
2–2.9 years	57	124 (22)	79 (19)	64 (19)	76 (19)	87 (16)	33 (10)				
3–3.9 years	88	129 (22)	80 (18)	64 (19)	79 (18)	86 (17)	36 (10)				
4–4.9 years	65	131 (20)	82 (20)	66 (18)	79 (18)	87 (19)	40 (7)				
5–5.9 years	52	135 (22)	89 (23)	67 (20)	79 (16)	87 (15)	36 (10)				
6–6.9 years	64	125 (20)	70 (25)	64 (17)	75 (15)	82 (17)	31 (8)				
7–7.9 years	53	125 (21)	81 (18)	63 (15)	75 (16)	80 (17)	34 (9)				
8–8.9 years	33	126 (18)	79 (20)	64 (17)	72 (14)	80 (17)	37 (8)				
9–9.9 years	35	121 (14)	78 (19)	62 (15)	71 (14)	80 (14)	35 (11)				
10–10.9 years	47	115 (21)	77 (17)	64 (16)	66 (14)	74 (15)	36 (10)				
11–11.9 years	51	113 (23)	71 (16)	58 (12)	63 (14)	71 (17)	32 (9)				
12–12.9 years	22	114 (24)	71 (14)	58 (17)	60 (11)	67 (13)	34 (6)				
13–13.9 years	27	119 (18)	71 (15)	59 (15)	66 (14)	76 (14)	36 (5)				
>14 years	30	104 (19)	69 (20)	52 (15)	59 (10)	65 (14)	42 (3)				
Diastolic flow velocity											
3–11.9 mo	48	42 (11)	31 (9)	26 (10)	27 (8)	31 (8)	7 (3)				
1–1.9 years	38	54 (12)	36 (11)	30 (12)	33 (10)	36 (10)	8 (3)				
2–2.9 years	57	53 (11)	37 (9)	31 (10)	35 (9)	40 (9)	12 (4)				
3–3.9 years	88	56 (11)	37 (9)	31 (10)	37 (10)	40 (9)	13 (4)				
4–4.9 years	65	58 (12)	38 (10)	32 (11)	38 (10)	43 (11)	14 (4)				
5–5.9 years	52	60 (11)	41 (11)	32 (12)	38 (10)	41 (8)	12 (2)				
6–6.9 years	64	58 (11)	38 (10)	33 (10)	36 (8)	39 (10)	12 (4)				
7–7.9 years	53	58 (11)	39 (10)	31 (10)	36 (10)	39 (9)	13 (2)				
8–8.9 years	33	56 (13)	37 (11)	31 (12)	34 (7)	38 (9)	13 (4)				
9–9.9 years	35	53 (8)	37 (10)	30 (9)	34 (8)	37 (8)	12 (2)				
10–10.9 years	47	53 (10)	37 (10)	32 (9)	32 (7)	37 (8)	12 (3)				
11–11.9 years	51	52 (12)	34 (9)	29 (7)	31 (9)	34 (10)	13 (4)				
12–12.9 years	22	51 (14)	32 (8)	29 (11)	28 (7)	30 (6)	13 (2)				
13–13.9 years	27	54 (11)	35 (11)	29 (10)	32 (9)	35 (9)	10 (2)				
>14 years	30	45 (7)	32 (9)	26 (9)	26 (7)	29 (9)	11 (1)				
Mean flow velocity											
3–11.9 mo	48	66 (15)	47 (12)	38 (13)	43 (11)	47 (11)	13 (2)	51 (13)	1.3 (.4)	17 (9)	20 (11)
1–1.9 years	38	83 (19)	53 (14)	42 (16)	50 (12)	55 (12)	14 (1)	59 (12)	1.4 (.3)	19 (9)	23 (13)
2–2.9 years	57	81 (16)	54 (13)	43 (14)	53 (13)	59 (10)	19 (6)	59 (12)	1.4 (.2)	18 (10)	21 (14)
3–3.9 years	88	84 (16)	54 (12)	43 (13)	55 (13)	59 (11)	20 (5)	60 (12)	1.5 (.3)	22 (15)	18 (10)
4–4.9 years	65	85 (16)	55 (14)	45 (13)	55 (12)	61 (12)	22 (5)	57 (10)	1.5 (.4)	16 (9)	20 (16)
5–5.9 years	52	88 (16)	60 (15)	45 (15)	55 (12)	61 (11)	21 (6)	57 (10)	1.6 (.3)	19 (11)	25 (17)
6–6.9 years	64	84 (14)	54 (13)	44 (11)	52 (10)	56 (12)	18 (5)	53 (13)	1.6 (.4)	17 (9)	24 (17)
7–7.9 years	53	82 (14)	55 (12)	42 (12)	52 (12)	56 (11)	19 (4)	53 (10)	1.6 (.4)	16 (8)	22 (15)
8–8.9 years	33	80 (14)	53 (12)	43 (14)	49 (9)	54 (11)	20 (5)	53 (9)	1.6 (.4)	14 (7)	20 (14)
9–9.9 years	35	77 (9)	52 (13)	41 (11)	49 (10)	54 (9)	18 (5)	53 (13)	1.5 (.4)	13 (6)	18 (13)
10–10.9 years	47	74 (13)	52 (12)	43 (11)	45 (8)	51 (10)	19 (4)	49 (8)	1.6 (.4)	13 (6)	17 (7)
11–11.9 years	51	74 (15)	47 (11)	39 (9)	43 (11)	49 (13)	19 (5)	47 (9)	1.6 (.4)	13 (6)	18 (12)
12–12.9 years	22	74 (19)	48 (9)	38 (13)	41 (9)	44 (8)	20 (3)	45 (9)	1.6 (.4)	11 (8)	16 (7)

Table 1 (*continued*)

TCD Measurement by Age	~Number	Middle Cerebral Artery	Anterior Cerebral Artery	Posterior Cerebral Artery	Vertebral Artery	Basilar Artery	Ophthalmic Artery	Ex-Internal Carotid Artery[a]	Lindegaard Ratio[a]	Middle Cerebral Vein[a]	Jugular Vein[a]
13–13.9 years	27	76 (13)	49 (11)	39 (12)	45 (11)	51 (10)	17 (2)	44 (10)	1.8 (.5)	17 (11)	16 (7)
>14 years	30	64 (10)	44 (12)	34 (11)	37 (9)	41 (11)	20 (2)	43 (8)	1.6 (.3)	10 (3)	15 (6)
Pulsatility Index											
3–11.9 mo	48	0.93 (.19)	0.86 (.2)	0.87 (.2)	0.87 (.19)	0.86 (.19)	1.1 (.2)				
1–1.9 years	38	0.84 (.15)	0.78 (.13)	0.79 (.15)	0.78 (.15)	0.82 (.18)	0.98 (.3)				
2–2.9 years	57	0.89 (.15)	0.79 (.14)	0.77 (.13)	0.78 (.17)	0.79 (.18)	0.97 (.2)				
3–3.9 years	88	0.87 (.16)	0.80 (.16)	0.79 (.15)	0.80 (.19)	0.79 (.19)	1.0 (.3)				
4–4.9 years	65	0.84 (.14)	0.79 (.15)	0.78 (.18)	0.75 (.15)	0.73 (.15)	1.2 (.3)				
5–5.9 years	52	0.84 (.15)	0.80 (.14)	0.80 (.15)	0.75 (.16)	0.76 (.14)	1.1 (.3				
6–6.9 years	64	0.80 (.14)	0.76 (.16)	0.70 (.16)	0.74 (.14)	0.74 (.27)	1.1 (.3)				
7–7.9 years	53	0.81 (.18)	0.79 (.16)	0.78 (.15)	0.75 (.15)	0.71 (.13)	0.98 (.3)				
8–8.9 years	33	0.86 (.18)	0.79 (.17)	0.83 (.19)	0.77 (.19)	0.77 (.17)	1.2 (.2)				
9–9.9 years	35	0.88 (.15)	0.81 (.18)	0.81 (.16)	0.80 (.16)	0.81 (.12)	1.1 (.4)				
10–10.9 years	47	0.84 (.15)	0.75 (.14)	0.77 (.13)	0.76 (.15)	0.72 (.15)	1.2 (.3)				
11–11.9 years	51	0.85 (.17)	0.78 (.16)	0.76 (.16)	0.77 (.17)	0.78 (.18)	1.1 (.3)				
12–12.9 years	22	0.88 (.13)	0.83 (.19)	0.74 (.14)	0.81 (.15)	0.84 (.10)	0.92 (.3)				
13–13.9 years	27	0.84 (.13)	0.74 (.13)	0.83 (.22)	0.76 (.17)	0.83 (.24)	1.2 (.2)				
>14 years	30	0.91 (.14)	0.85 (.18)	0.82 (.15)	0.89 (.24)	0.91 (.24)	1.4 (.1)				

Mo = months; Ex-internal carotid artery = Extra-cranial internal carotid artery (Ex-ICA).

~ All vessels were not able to be insonated in every patient; numbers represent ±5 patients in each category.

[a] The mean flow of the Ex-ICA is used to calculate the LR and therefore only the mean values for the Ex-ICA are noted. Additionally, venous flow is non-pulsatile and is therefore also presented in the table as only "mean" flow.
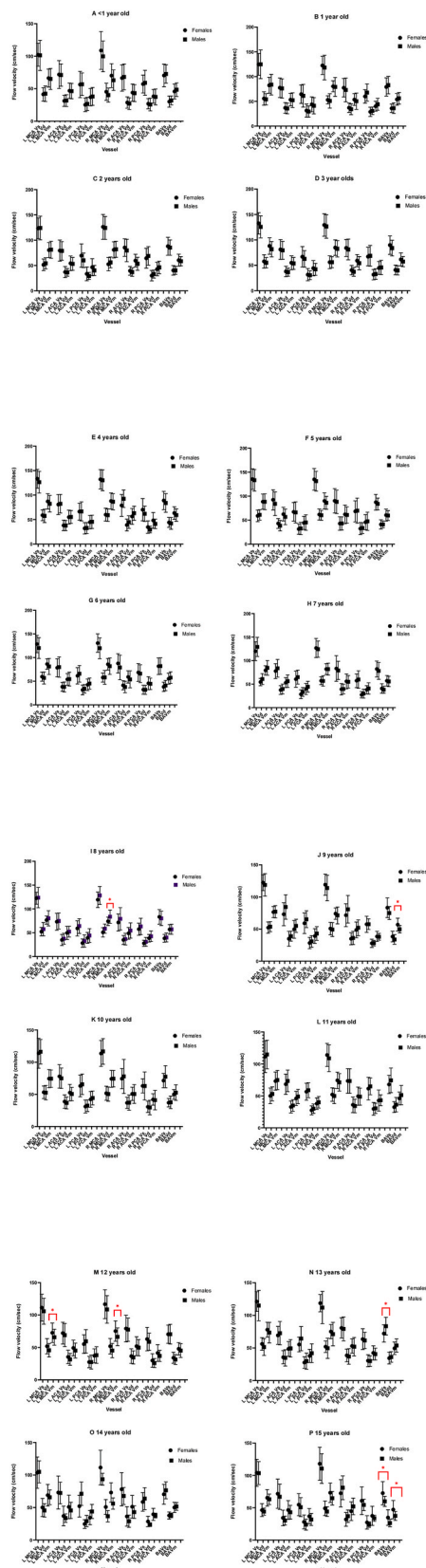
(caption on next page)

Fig. 2. Gender differences in flow velocities by vessel by age **A** <1-year old **B** 1 year old **C** 2 years old **D** 3 years old **E** 4 years old **F** 5 years old **G** 6 years old **H** 7 years old **I** 8 years old **J** 9 years old **K** 10 years old **L** 11 years old **M** 12 years old **N** 13 years old **O** 14 years old **P** 15 years old. Significant differences noted with bracket and asterisk where $p < 0.05$.

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4. Discussion

We report, for the first time, normative TCD values for all major intracranial vessels in a large cohort of healthy African children. To accommodate rapid brain growth and cerebral metabolic demand, cerebral blood flow increases from early through mid-childhood and then decreases through adolescence to adult levels. Accordingly, TCD measured CBFVs should also follow this age-related pattern, which was identified in our study with the highest average flow velocities in children 4–6 years of age.

Gender differences in TCD derived CBFVs have been reported in both adult and pediatric studies, with females typically having higher measured flows [11–14]. Tontisirin et al. evaluated 48 children (24 boys and 24 girls) between the ages of 4–8 years and reported girls had higher MCA CBFV (99 ± 11 vs 91 ± 13 cm/s) and BA CBFV (70 ± 10 vs 61 ± 9 cm/s) than boys [13]. Similar findings were reported by Vavilala et al. in a smaller cohort of adolescents (13 girls and 13 boys >10 years of age) [14]. The basis for these reported findings is not clear, but a number of factors have been proposed including: estrogen enhancing endothelial-derived nitric oxide and prostacyclin pathways with reductions in cerebral vascular tone; a baseline higher heart rate and cardiac index; and increased cerebral metabolic rate with increased flow to match metabolism. Other work in healthy adults has failed to identify gender differences in cerebral blood flow [15,16]. Our study also did not identify any clearly consistent differences in CBFVs between genders. We found no significant differences at all in any cerebral vessel for any age group <8 years, or in 10-, 11-, and 14-year-olds. Eight-year-old boys had higher right but not left MCA mean flows than girls, 9-year-old girls had higher BA mean flows than boys, 12-year-old females had bilateral mean MCA flows significantly higher than boys, 13-year-old males had higher systolic flow in the BA than females, and 15-year-old girls had higher systolic and mean flow in the BA than boys. While these differences were statistically determined, they do not likely represent clinically meaningful differences. Thus, it appears in African children, gender does not need to be considered when interpreting TCD examinations.

To accurately interpret TCD findings, pathologic states in the cerebrovasculature must be distinguished from changes to measured CBFVs that occur in a predictable way in response to physiologic changes. The major factors determining CBFVs include the pressure gradient along the vessel, blood viscosity, and the cross-sectional area of the vessel [17]. Therefore, we evaluated relationships between some of these components and CBFVs in this large cohort of children. Regarding the pressure gradient, healthy children should have similar downstream pressures (i.e., intracranial pressure and/or central venous pressure), thus the major driving force of cerebral blood flow is the mean arterial pressure (MAP). When evaluating by age groups, we found no significant correlations between MAP and measured CBFVs in any vessel. This finding is not particularly surprising given that autoregulation is a homeostatic process that works to maintain nearly constant cerebral blood flow over a range of MAPs, and that autoregulation should be intact in healthy children.

Hematocrit is the major determinant of blood viscosity, and cerebral blood flow has been shown to be inversely correlated with hematocrit level in adult patients [18]. A similar relationship has not been reliably seen in healthy children. In 64 children, knowledge of the hematocrit made no contribution to the prediction of TCD-derived CBFVs after age was considered [19]. In another report, Aliefendioglu et al. evaluated CBFVs in children with iron deficiency anemia [20]. In 36 children aged 6–36 months, those with more severe anemia (mean Hbg 8.1 ± 1.5 g/dL) did not have significantly increased systolic flow velocities compared to those with less severe anemia (mean Hbg 10.2 ± 3.8 g/dL). Our cohort involved a relatively high overall proportion of anemic patients (28% with a Hbg <10 g/dL). We found no significant correlation between hemoglobin value and measured CBFVs following correction for age. With these studies taken together, it appears that anemia is not a significant contributor to measured CBFVs in children. The reason for this is not clear, though other determinants of whole blood viscosity such as serum fibrinogen or other plasma proteins may be higher in children than adults and result in minimal changes to flow despite alterations to hematocrit.

One significant finding of our work was that we identified significantly lower CBFVs in nearly every cerebral vessel (with the exception of the BA) in all age groups ≥3 years when compared to Bode et al. [4] Undernutrition is prevalent in African children and contributes to negative effects on brain structure, neurometabolism, and cerebral function [21]. Roberts et al. evaluated 1059 African children aged 15 months to 7 years at risk of undernutrition in rural Guinea-Bissau [21]. Using near-infrared spectroscopy and diffuse correlation spectroscopy, they estimated cerebral blood flow and cerebral metabolic rate of oxygen consumption (CMRO2) at baseline and then following the introduction of targeted meal supplementation. Compared to control children who ate typical locally prepared food and were considered undernourished, those with improved nutrition had substantial increases in estimated cerebral blood flow and CMRO2. While a relatively small proportion of our overall cohort met absolute criteria for moderate to severe malnutrition, according to USAID, 42% of Congolese children, 35% of Zambian children, and 37% of Malawian children have evidence of undernutrition based on stunted growth. Thus, undernutrition may have contributed to our findings of lower CBFVs in most age groups compared to previously published normal values. In further support of this hypothesis, nutritional status in African children typically declines after approximately 2 years of age following weaning from breastfeeding due to food insecurity and limited complementary feeding. Measured flow velocities in our youngest cohorts of children (<2.9 years) were more similar to previously published normative values than were identified in older children.

Other possibilities may have also contributed to the observed difference in measured flow velocities. There are large anatomic variations in the Circle of Willis in human populations, including the caliber of intracranial arteries [22,23]. If the cross-sectional area of the cerebral vessels is higher in African children than in the children studied by Bode et al. measured flow velocities would be lower. However, given that the younger age groups had similar CBFV measurements as Bode et al. reported, this may be less likely.

Table 2

Cerebral blood flow velocities (in cm/second) in cerebral vessels in African children compared to previous published normative values.

TCD Measurement by Age	O'Brien n	Bode n	O'Brien Middle Cerebral Artery	Bode Middle Cerebral Artery	p value
Systolic flow velocity					
3–11.9 months	48	13	102 (20)	114 (20)	0.06
1–2.9 years	95	9	124 (23)	124 (10)	0.99
3–5.9 years	205	18	130 (23)	147 (17)	0.002
6–9.9 years	185	20	124 (19)	143 (13)	<0.001
>10 years	177	20	112 (21)	129 (17)	<0.001
Diastolic flow velocity					
3–11.9 months	48	13	42 (11)	46 (9)	0.22
1–2.9 years	95	9	54 (11)	65 (11)	0.01
3–5.9 years	205	18	57 (12)	65 (9)	0.01
6–9.9 years	185	20	57 (11)	72 (9)	<0.001
>10 years	177	20	51 (11)	60 (8)	<0.001
Mean flow velocity					
3–11.9 months	48	13	66 (15)	74 (14)	0.07
1–2.9 years	95	9	82 (17)	85 (10)	0.57
3–5.9 years	205	18	85 (17)	94 (10)	0.03
6–9.9 years	185	20	81 (13)	97 (9)	<0.001
>10 years	177	20	72 (14)	81 (11)	0.007
TCD Measurement by Age	**O'Brien n**	**Bode n**	**O'Brien Anterior Cerebral Artery**	**Bode Anterior Cerebral Artery**	**P value**
Systolic flow velocity					
3–11.9 months	48	13	71 (19)	77 (15)	0.34
1–2.9 years	95	9	78 (19)	81 (19)	0.67
3–5.9 years	205	18	82 (21)	104 (22)	<0.001
6–9.9 years	185	20	79 (19)	100 (20)	<0.001
>10 years	177	20	72 (17)	92 (19)	<0.001
Diastolic flow velocity					
3–11.9 months	48	13	31 (9)	50 (11)	0.57
1–2.9 years	95	9	37 (10)	55 (13)	0.31
3–5.9 years	205	18	38 (10)	71 (15)	<0.001
6–9.9 years	185	20	38 (10)	65 (13)	<0.001
>10 years	177	20	35 (10)	56 (14)	<0.001
Mean flow velocity					
3–11.9 months	48	13	47 (12)	50 (11)	0.35
1–2.9 years	95	9	53 (13)	55 (13)	0.72
3–5.9 years	205	18	56 (14)	71 (15)	<0.001
6–9.9 years	185	20	54 (13)	65 (13)	<0.001
>10 years	177	20	48 (12_	56 (14)	0.008
TCD Measurement by Age	**O'Brien n**	**Bode n**	**O'Brien Posterior Cerebral Artery**	**Bode Posterior Cerebral Artery**	**p value**
Systolic flow velocity					
3–11.9 months	48	13	57 (18)	–	–
1–2.9 years	95	9	64 (20)	69 (9)	0.43
3–5.9 years	205	18	65 (19)	81 (16)	<0.001
6–9.9 years	185	20	63 (16)	75 (10)	0.002
>10 years	177	20	59 (15)	66 (10)	0.05
Diastolic flow velocity					
3–11.9 months	48	13	26 (10)	–	–
1–2.9 years	95	9	31 (11)	36 (13)	0.27
3–5.9 years	205	18	31 (11)	40 (12)	0.19
6–9.9 years	185	20	31 (10)	42 (7)	0.004
>10 years	177	20	29 (9)	39 (8)	0.05
Mean flow velocity					
3–11.9 months	48	13	38 (13)	–	–
1–2.9 years	95	9	43 (14)	50 (17)	0.15
3–5.9 years	205	18	44 (14)	56 (13)	0.21
6–9.9 years	185	20	43 (12)	57 (9)	0.002
>10 years	177	20	39 (11)	50 (10)	0.03
TCD Measurement by Age	**O'Brien n**	**Bode n**	**O'Brien Basilar Artery**	**Bode Basilar Artery**	**P value**
Systolic flow velocity					
3–11.9 months	48	13	71 (16)	–	–
1–2.9 years	95	9	85 (17)	71 (6)	0.02
3–5.9 years	205	18	86 (18)	88 (9)	0.61
6–9.9 years	185	20	81 (17)	85 (17)	0.26
>10 years	177	20	72 (15)	68 (11)	0.29
Diastolic flow velocity					
3–11.9 months	48	13	31 (8)	–	–

Table 2 (*continued*)

TCD Measurement by Age	O'Brien n	Bode n	O'Brien Middle Cerebral Artery	Bode Middle Cerebral Artery	p value
1–2.9 years	95	9	39 (9)	35 (6)	0.24
3–5.9 years	205	18	41 (10)	41 (5)	0.96
6–9.9 years	185	20	36 (9)	44 (8)	0.01
>10 years	177	20	34 (9)	36 (7)	0.45
Mean flow velocity					
3–11.9 months	48	13	47 (11)	–	–
1–2.9 years	95	9	58 (11)	51 (6)	0.07
3–5.9 years	205	18	60 (12)	58 (6)	0.57
6–9.9 years	185	20	56 (11)	58 (9)	0.35
>10 years	177	20	48 (11)	46 (8)	0.34

Furthermore, while the genetic ancestry of Africans and African Americans is not identical, two studies in adult patients did not identify sweeping differences in measured TCD CBFVs between Caucasians and African Americans [11,24]. Tegeler et al. determined that the only intracranial arterial segment that showed interracial CBFV difference was the OA [11]. Thus, differences in anatomic variations of the main cerebral vessels due to race and ethnicity alone likely do not explain our findings.

Lastly, given our significantly larger sample size, it must be considered that our reported values more accurately represent normative CBFVs in children. Larger studies to determine appropriate reference values for CBFVs in non-African populations of children need to be undertaken.

A strength of our study is the rigorous TCD training protocol that was required of technicians prior to involvement. TCD is highly operator dependent, and thus ensuring a standardized training approach where a low coefficient of variance between a learner and an expert is achieved is necessary to decrease variability in the results of TCD examinations. One limitation of our study is that we screened participants for moderate to severe malnutrition based on the MUAC. However, while excellent at determining significant malnutrition, passing an anthropometric measure such as the MUAC does not ensure adequate dietary intake or good overall nutritional status [25]. Thus, we remain unclear if undernutrition contributed to our findings. Future work could focus on undernutrition as a contributor to altered CBFVs.

5. Conclusions

Transcranial doppler ultrasound is a portable noninvasive neurodiagnostic and neuromonitoring tool that has often been referred to as the stethoscope into the brain. Pediatric applications for TCD utilization are expanding globally, but proper interpretation of examinations is limited by a lack of normative values in large populations of healthy children. This work establishes TCD reference values for all major intracranial arteries in African children, which should improve the overall diagnostic utilization of the tool on the continent.

Author contribution statement

O'Brien: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Johnson: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Ambitapio, Ekandji, Mbaka, Babatila, Bayandoni, Giresse, Chilima, Mwanza, Lupumpaula, Nanyangwe, Kabemba, Nkole, Chunda-Liyoka, Phiri, June, Gushu,
Moons: Performed the experiments; Wrote the paper.
Tshimanga: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data will be made available on request.

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