ORIGINAL ARTICLE

Normative Values of Cerebral Blood Flow Velocities in Very Low Birth Weight Neonates During First 28 Days of Life

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Received: Feb 21, 2024; Initial review: Apr 20, 2024; Accepted: Jun 08, 2024

PII: S097475591600661

Note: This early-online version of the article is an unedited manuscript and under editorial revision. It has been posted to the website for making it available to readers, ahead of its publication in print. This version will undergo copy-editing, typesetting, and proofreading, before final publication; and the text may undergo minor changes in the final version.

ABSTRACT

Objective: To determine normative values of cerebral blood flow (CBF) velocities in very low birth weight (VLBW) neonates during first 28 days of life.

Methods: In this prospective observational study, doppler assessment of CBF velocities was performed from the anterior cerebral artery (ACA), middle cerebral artery (MCA) and basilar artery (BA) at 2-8 hours, 24 hours, day 3, 7, 14 and 28 of life. Neonates with gross congenital malformations, those requiring extensive resuscitation at birth, mechanical ventilation with mean airway pressure >12 mbar, requiring inotropes, or those who developed intraventricular hemorrhage (Grade II or more) were excluded.

Results: A total of 103 VLBW neonates were enrolled, in whom 1178 doppler measurements were recorded. The mean (SD) peak systolic velocity, end diastolic velocity and mean velocity (cm/s) in ACA increased from 26.53 (8.56) to 51.35 (9.36), 9.22 (2.91) to 13.9 (3.24) and 17.75 (3.97) to 25.84 (3.27) respectively from 2 to 8 hours to day 28 of life. In MCA and BA also, CBF velocities increased with post-natal age.

Conclusion: We report normative data of CBF velocities in VLBW neonates in first 28 days of life.

***Keywords*:** End Diastolic Velocity, Mean Velocity, Peak Systolic Velocity

Trial Registry: CTRI/2017/07/009104

INTRODUCTION

Doppler sonography is a non-invasive real-time method, which allows accurate and reliable hemodynamic assessment in neonates. Cerebral blood flow (CBF) velocities of major vessels in the brain can be assessed in neonates with good reproducibility by pulsed wave doppler technique [1]. Preterm very low birth weight (VLBW) neonates undergo considerable change in hemodynamics during transition in early neonatal period [2] and are susceptible to cerebral hemodynamic perturbations [3].

Alteration in cerebral blood velocities have been reported in neonatal diseases like intraventricular hemorrhage (IVH), periventricular leukomalacia, hemodynamically significant patent ductus arteriosus, hydrocephalus, sepsis, shock, hypoxic–ischemic encephalopathy, and vascular malformations [3-5]. Changes in CBF velocities can be detected before the onset of clinical decompensation of circulatory response. Therefore, knowledge of postnatal age-specific normative data on CBF during the first few weeks of life might be valuable to predict neonatal morbidities before they occur or manifest clinically. However, data regarding normative values of CBF velocities in VLBW neonates is limited [6,7]. We planned this study to determine normative values for blood flow velocities in anterior cerebral artery (ACA), middle cerebral artery (MCA) and basilar artery (BA) in hemodynamically stable VLBW neonates during the first 28 days of life.

METHODS

This prospective observational study was conducted at the neonatal intensive care unit (NICU) of a tertiary care centre in India from July 2017 to February 2022. All intramural VLBW neonates admitted to the NICU during the study period were screened for enrolment. Neonates with gross congenital malformations, those requiring extensive resuscitation at birth, mechanical ventilation with mean airway pressure >12 mbar, requiring inotropes, or those who developed IVH (Grade II or more) were excluded. A written informed consent was obtained from parents of eligible neonates. The study was approved by the institutional ethics committee.

Doppler assessment of CBF velocities was performed at 2-8 hours, 24 hours, day 3, 7, 14 and 28 of life, by using Sonosite M turbo machine (FUJIFILM Sonosite, Bothell, WA, USA) with 4-8 MHZ phase array probe. Pulse doppler flow velocity was recorded from the ACA, MCA, and BA. The ACA was sampled in sagittal plane through the anterior fontanel, with the infant lying in supine position, and the signals were recorded from the point midway between the inferior-most border of the corpus callosum and the vessel's origin from the circle of Willis. The BA was visualized in the sagittal plane just in front of the pons. The MCA was visualized through the temporal bone in the region above the zygomatic arc, in the fold of the temporal lobe from the straight mid-portion of the artery. Attempt was made to to accurately capture the blood flow velocities by having an angle of insonation as low as possible. If the angle of insonation was more than 15°, the measurement was not considered for analysis. Guided by the velocity signal displayed on an oscilloscope, the highest possible velocity was captured in the range-gated mode with sample volume of 1-2 mm. A trace with uniform doppler waveforms was recorded and an average of five waveforms was calculated for the following parameters: Peak Systolic Velocity (PSV), End-Diastolic Velocity (EDV), Mean Velocity (MV) and Resistive Index (RI) [defined as (PSV-EDV)/PSV].

Doppler assessments were performed by one of the two study investigators (AT, PJ), formally trained in performing cranial ultrasonography. To evaluate inter-rater reliability, doppler measurements of the ACA were performed in 10 neonates by the investigators, blinded to each other. The intraclass correlation coefficient (95% CI) for measurement of PSV, EDV and RI were 0.98 (0.93, 0.99), 0.96 (0.84, 0.99) and 0.95 (0.79, 0.98), respectively.

Statistical analysis: Statistical analysis was done by using IBM SPSS Statistics software version 19, for Windows (IBM Corp., Armonk, NY, USA). Mean and standard deviation (SD) was used to represent normally distributed data. Neonates were classified into three categories based on gestational age: 25^0 - 27^{+6}, 28^0 - 29^{+6} and ≥ 30 weeks.

RESULTS

Of a total of 521 VLBW neonates born during the study period, 329 were excluded due to various reasons; consent not available (*n* = 132), investigators not available (*n* = 165), congenital malformation (*n* = 7), extensive resuscitation at birth (*n* = 11) and mechanical ventilation with mean airway pressure >12 mbar (*n* = 14). Of the 192 neonates, who underwent initial enrolment, 89 neonates were excluded further; developed IVH grade 2 or more (*n* = 12) or needed inotropes (*n* = 77). 103 neonates (59 males) were finally enrolled in whom 1178 doppler measurements were recorded.

The mean (SD; range) birth weight and gestational age of study population was 1225 (31; 440 - 1495) g and 30.9 (2.6; 25.8 - 37.0) weeks, respectively. The doppler parameters in ACA, MCA and BA are provided in **Table I**. There was an increase in CBF velocities with advancing postnatal age. These findings were consistent in all the three arteries. The CBF velocities across various gestational age categories are given in **Table II**.

DISCUSSION

We evaluated normative data of CBF in ACA, MCA and BA in hemodynamically stable VLBW neonates at 2-8 hours, 24 hours, day 3, 7, 14 and 28 of life. We observed that there was an increase in CBF velocities parameters of PSV, EDV and MV with increasing postnatal age, the lowest values being at 2-8 hours of life and the highest velocities were recorded at 28 days of life. These findings were consistent in all the three arteries and across different gestational sub-groups of 25^0 - 27^{+6}, 28^0 - 29^{+6} and ≥ 30 weeks.

Similar observations were made by Evans et al on evaluation of doppler velocities of ACA and MCA in 27 VLBW neonates during the first 7 days of life [6]. They reported an increase in blood flow velocity in each of these vessels and a fall in RI. However, the time points were not well defined. Recordings were made daily, whenever feasible, for the first 7 days of life from two cerebral arteries-ACA and MCA. Further, they did not report any data on PSV and EDV. Other authors have also reported doppler flow velocities in cerebral vessels longitudinally, albeit in term neonates or in heterogenous newborn population. Bode and Wais reported flow velocities in the basal cerebral arteries on 25 relatively more mature neonates on day 1, 5, 10, 15 and 20, and found an increase in all flow velocities linearly in the first 20 days of life. The mean birth weight (SD) of study population was 2248 (776) g and gestation 35.6 (3.0) weeks. Their study had a relatively smaller sample size, included mostly larger babies and did not evaluate transitional changes in doppler flows in first 24 hours of life [8]. Ilves et al evaluated doppler velocities in healthy term neonates in cerebral, mesenteric and renal vessels wherein the blood flow velocity increased and the resistive index decreased in all arteries [9]. Two other studies [7,10] have also reported cerebral blood flow velocities in neonates, however both these studies being cross-sectional do not adequately indicate transitional or longitudinal changes in CBF velocities with increasing postnatal age. Pezzati et al reported normative values for ACA and MCA velocity, cerebral relative vascular resistance and RI in 120 healthy neonates during first 8 hours of life. The gestational age ranged from 24-41 weeks and birth weight ranged from 450g -3800g. The authors found that CBF velocities increased significantly with increasing gestational age and birth weight [10]. Orey et al reported cerebral blood velocities in 120 newborns during first 7 days of life. The authors observed a linear increase of all flow velocities with increasing gestational age and birth weight. Mean gestational age of the infants were 35.9 (3.7) weeks and 29 infants were VLBW [7].

To the best of our knowledge, this is the first study that has evaluated CBF in a relatively large sample of hemodynamically stable VLBW neonates who were followed up longitudinally till 28 days of life. All dopplers measurements were done by one of the two operators, who had excellent inter-rater reliability in measurements of ACA. However, inter-rater reliability could have been assessed in all three arteries. Additional limitations of our study were that the sample size in various gestational age categories was relatively small and we did not evaluate sequential changes in sicker babies. Of 12 VLBW neonates who developed severe IVH, there were a few doppler recordings and meaningful interpretation of the data was not possible. We did not account for some factors that can probably affect CBF such as hematocrit, routine blood gases, transient flares in periventricular region or other unknown physiological variables. In addition, we did not perform MRI Brain or followed up these infants for long term neurological outcomes.

To summarize, our study describes the normative values of cerebral doppler velocities in stable VLBW neonates during first 28 days of life. We found an increase in CBF velocities with increasing postnatal age. An important perspective to interrogate in future would be if deviation from these data is predictive of morbidities such as impending IVH, PVL, shock or poor long term neurological outcomes.

Ethics clearance: No. EC/07/17/1192) dated July 17, 2017.

Contributors: All authors contributed to the study conception and design. Protocol was prepared by NK, AT, MM and BK. Data was collected by AT and PJ. Material preparation and analysis was performed by AT and AS. The first draft of the manuscript was written by AT, MM and AS. All authors read and approved the final manuscript.

Funding: None. *Competing Interest:* None stated

WHAT THIS STUDY ADDS?

- This study reports normative values of cerebral doppler velocities in stable VLBW neonates during first 28 days of life.

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Table I Cerebral Blood Flow Velocities (Cm/S) and Resistive Index In VLBW Neonates During The First 28 Days of Life

	2-8 h (n = 50)	*24 h (n = 75)*	*Day 3 (n = 71)*	*Day 7 (n = 72)*	*Day 14 (n = 70)*	*Day 28 (n = 55)*
Anterior cerebral artery						
PSV	26.53(8.56)	29.96 (6.41)	31.80 (7.62)	36.29 (8.29)	41.69 (7.39)	51.35 (9.36)
EDV	9.22 (2.91)	10.88 (2.85)	10.87 (2.80)	11.51 (3.47)	11.98 (3.23)	13.90 (3.24)
MV	17.75 (3.97)	17.80 (3.92)	18.34 (3.48)	20.48 (5.30)	21.69 (3.82)	25.84 (3.27)
RI	0.64 (0.08)	0.64 (0.06)	0.65 (0.08)	0.68 (0.08)	0.71 (0.07)	0.72 (0.07)
Middle cerebral artery						
PSV	28.12 (8.89)	31.85 (8.24)	33.78 (8.20)	39.01 (8.98)	42.50 (9.19)	53.13 (15.40)
EDV	8.96 (2.99)	10.64 (3.40)	11.63 (3.62)	11.53 (3.23)	12.00 (3.15)	14.68 (4.48)
MV	17.33 (4.55)	19.11 (5.22)	20.26 (4.86)	20.50 (3.41)	20.83 (3.81)	25.40 (4.69)
RI	0.66 (0.10)	0.67 (0.07)	0.65 (0.08)	0.70 (0.08)	0.71 (0.08)	0.72 (0.08)
Basilar artery						
PSV	28.72(10.21)	29.21 (7.77)	32.37 (8.21)	35.09 (8.01)	41.59 (8.63)	49.91 (11.04)
EDV	9.45 (3.38)	10.94 (3.21)	11.51 (3.55)	11.08 (3.16)	11.64 (3.06)	13.59 (3.76)
MV	18.43 (5.06)	18.28 (4.91)	19.69 (5.18)	19.89 (3.78)	21.26 (3.92)	24.96 (3.76)
RI	0.65 (0.08)	0.62 (0.07)	0.64 (0.07)	0.68 (0.08)	0.71 (0.08)	0.72 (0.09)

Data are presented in Mean (SD)
EDV End-diastolic velocity, MV Mean velocity, PSV Peak systolic velocity, RI Resistive index

Table II Cerebral Blood Flow Velocities (cm/s) and Resistive Index in VLBW Neonates During First 28 Days of Life in Different Gestational Sub-Groups

	Gestation (wks)		
	25^0 - 27^{+6}	*28^0- 29^{+6}*	*≥ 30*
ACA PSV			
2-8 h	23.90 (8.91)	26.89 (9.46)	27.71 (8.19)
24 h	27.03(4.88)	28.59 (5.53)	30.98 (6.71)
Day 3	29.63 (8.17)	30.82 (7.02)	32.57 (7.68)
Day 7	30.67 (4.21)	32.67 (5.45)	38.03 (8.69)
Day 14	37.68 (6.48)	39.61 (4.87)	43.32 (7.82)
Day 28	45.81 (9.39)	50.55 (8.73)	53.26 (9.22)
ACA EDV			
2-8 h	7.55(2.38)	9.31 (2.61)	10.00(2.94)
24 h	9.28(2.37)	10.67 (3.1)	11.34(2.81)
Day 3	8.84(2.04)	12.09 (3.32)	11.01(2.6)
Day 7	9.66(3.54)	11.65 (3.48)	11.81(3.42)
Day 14	10.44(3.43)	11.44(2.98)	12.52(3.17)
Day 28	12.91(5.00)	14.32(3.19)	13.99(2.68)
ACA RI			
2-8 h	0.66 (0.08)	0.64 (0.07)	0.63 (0.09)
24 h	0.65 (0.07)	0.63 (0.06)	0.63 (0.06)
Day 3	0.69 (0.07)	0.60 (0.09)	0.65 (0.08)
Day 7	0.67 (0.11)	0.64 (0.09)	0.69 (0.07)
Day 14	0.72 (0.08)	0.71 (0.06)	0.70 (0.07)
Day 28	0.72(0.09)	0.71(0.08)	0.73(0.05)
MCA PSV			
2-8 h	24.00 (11.12)	28.71(8.44)	30.03 (7.25)
24 h	29.07(5.34)	30.21(5.77)	32.88(9.08)
Day 3	32.00(8.67)	32.64(7.81)	34.52(8.27)
Day 7	32.57(7.37)	34.95(6.55)	40.98(8.96)
Day 14	37.84(8.27)	41.65(7.03)	43.91(9.72)
Day 28	51.5(19.79)	50.64(9.60)	54.68(16.36)
MCA EDV			
2-8 h	7.06 (1.69)	9.22 (2.48)	9.84 (3.23)
24 h	8.66(2.11)	10.52 (3.20)	11.18 (3.55)
Day 3	9.91 (2.63)	12.16 (3.82)	11.89(3.71)
Day 7	9.30 (3.37)	11.83 (2.74)	11.86 (3.20)

Day 14	10.97 (3.48)	12.30(3.45)	12.16 (2.99)
Day 28	12.47 (4.78)	14.77 (4.46)	15.19 (4.39)
MCA RI			
2-8 h	0.67(0.12)	0.66(0.08)	0.66(0.09)
24 h	0.70(0.07)	0.65(0.07)	0.66(0.06)
Day 3	0.68(0.07)	0.62(0.08)	0.65(0.08)
Day 7	0.71(0.10)	0.65(0.10)	0.70(0.07)
Day 14	0.70(0.10)	0.70(0.09)	0.71(0.07)
Day 28	0.76(0.08)	0.70 (0.12)	0.72(0.05)
BA PSV			
2-8 h	23.11(8.05)	30.81(4.50)	30.92(11.24)
24 h	25.06(6.27)	29.87(5.66)	30.21(8.17)
Day 3	31.47(8.05)	31.62(6.76)	32.93(8.71)
Day 7	30.78(3.26)	32.13(5.75)	36.46(8.61)
Day 14	35.77(7.53)	38.63(5.07)	43.93(8.91)
Day 28	45.13(12.86)	48.39(11.17)	51.91(10.28)
BA EDV			
2-8 h	7.26 (1.97)	9.79 (1.93)	10.42 (3.75)
24 h	9.42 (3.14)	11.37(3.25)	11.28(3.16)
Day 3	9.74(2.74)	12.46(3.67)	11.66(3.6)
Day 7	9.93(2.42)	10.78(3.47)	11.34(3.21)
Day 14	9.58(3.16)	12.03(2.62)	12.02(3.02)
Day 28	11.99(3.81)	13.95(3.70)	13.88(3.77)
BA RI			
2-8 h	0.67(0.08)	0.68(0.05)	0. 65(0.09)
24 h	0.63(0.08)	0.62(0.06)	0.62(0.07)
Day 3	0.69(0.06)	0.67(0.06)	0.64(0.07)
Day 7	0.68(0.06)	0.66(0.1)	0.68(0.07)
Day 14	0.73(0.09)	0.69(0.08)	0.72(0.07)
Day 28	0.72(0.1)	0.69(0.11)	0.73(0.07)

Data are presented in Mean (SD)
ACA Anterior cerebral artery, BA Basilar artery, EDV End-diastolic velocity, MCA Middle cerebral artery, PSV Peak systolic velocity, RI Resistive index
Numbers (*n*)

1. 25^0 - 27^{+6} wks, *n* (2-8 hrs) = 14, *n* (24 hrs) = 14, *n* (day 3) = 11, *n* (day 7) = 9, *n* (day 14) = 11, *n* (day 28) = 9
2. 28^0 - 29^{+6} wks, *n* (2-8 hrs) = 7, *n* (24 hrs) = 9, *n* (day 3) = 13, *n* (day 7) = 11, *n* (day 14) = 14, *n* (day 28) = 14
3. ≥ 30 wks, *n* (2-8 hrs) = 29, *n* (24 hrs) =52, *n* (day 3) = 47, *n* (day 7) = 52, *n* (day 14) = 45, *n* (day 28) = 32