ORIGINAL ARTICLE

Cerebral Blood Flow Velocities and Cerebrovascular Resistance in Normal Term Neonates in the first 72 hours

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Cerebral Blood Flow Velocities and Cerebrovascular Resistance in Normal Term Neonates in the first 72 hours

Keywords: *Infant, newborn; Cerebral Arteries; Ultrasonography, Doppler, Transcranial; Vascular Resistance; Cerebrovascular circulation*

What is already known on this topic:

- The Resistive Index (RI) is an accepted indicator of cerebrovascular resistance.
- In previous studies the normal RI in term neonates has been established as greater than 0.55.
- An RI lower than 0.55 may be observed after periods of hypoxia.

What this paper adds:

- It is preferable to measure cerebral blood flows in the Anterior Cerebral Artery (ACA) as they exhibit less variance and are therefore more reproducible than Middle Cerebral Artery (MCA) measurements.
- Low RI's which may be considered clinically significant ($RI < 0.55$) were observed in 2 normal infants without a known pathological cause.
- The RI and PI can remain unchanged if component velocities decrease or increase together.

Abstract

Aim

The objective was to determine the range of cerebral blood flow velocities and Doppler indices of cerebrovascular resistance in normal term neonates as a baseline for a study of Hypoxic-Ischemic Encephalopathy.

Methods

The Cerebral Blood Flow Velocities (CBFV's), Resistive Index (RI) and Pulsatility Index (PI) were measured in the Anterior and Middle Cerebral Arteries (ACA and MCA) of 38 normal neonates.

Results

The mean Peak Systolic, End Diastolic and Time-Averaged Velocities (PSV, EDV and TAV) were 36.3 ± 6.6 , 12.4 ± 3.9 and 22.0 ± 4.0 cm/s (ACA) and 41.4 ± 13.2 , 13.0 ± 5.5 and 25.8 ± 7.9 cm/s (MCA). All CBFV's in the ACA correlated with gestation; only EDV was correlated to post-natal age.

The RI in the ACA (0.67 ± 0.06) and MCA (0.68 ± 0.07) were correlated ($r=0.72$, $p<0.001$); RI correlated to post-natal age. Two infants with $RI < 0.55$ were fed within 25 minutes of the study; a correlation was detected with post-prandial time as a dichotomous variable (pivot 25 mins).

The mean PI was 1.11 ± 0.18 (ACA) and 1.17 ± 0.23 (MCA). Correlations were with post-natal age and post-prandial time (dichotomous).

The average angle of insonation was greater in the ACA than in the MCA (5° vs 18°).

Conclusions

Results corresponded with previous published studies. Although CBFV's increase with advancing gestation, component velocities all increase so there is no correlation between Doppler indices and gestation. The smaller angle of insonation in the ACA led to less variation and smaller standard deviation in CBFV's and better reliability. Low RI's (<0.55) were measured in 2 neonates without a pathological cause warranting further study.

Introduction

The Doppler indices, the Resistive Index (RI) and the Pulsatility Index (PI), are considered a measure of downstream Cerebrovascular Resistance (CVR) and provide a non-invasive means of investigating the neonatal circulation¹. These indices are calculated from the cerebral arterial velocities measured using Doppler in the neonate through the “acoustic windows”, the fontanelles and sutures of the skull². Doppler Sonography exploits the Doppler Effect in order to measure the velocity of the red blood cells and estimate the blood flow velocity in a blood vessel³. As Doppler indices are ratios they reduce the error of the velocity measurement associated with the angle of insonation⁴.

Pourcelot's Resistive (Resistance) index (RI) is the ratio of the difference in pulsatile flow velocities, Peak Systolic Velocity (PSV) – End Diastolic Velocity (EDV), divided by the Peak Systolic Velocity (PSV)^{5,6}:

$$(i) \text{ Resistance Index (RI)} = \frac{PSV - EDV}{PSV}$$

The Pulsatility Index of Gosling (PI) is a ratio of the difference in pulsatile flow velocities divided by Time-Averaged Mean (TAV)⁷:

$$(ii) \text{ Pulsatility Index (PI)} = \frac{PSV - EDV}{TAV}$$

The RI is more often referred to when studying the CVR of the neonate, whereas the PI is more commonly determined for the evaluation of CVR of the foetus in utero. Bada et al suggested that the PI provided a greater “data spread” and for this reason should be preferred to the RI for neonates⁶. Alternatively, Couture et al recommend cerebral blood flow velocities in preference to the RI, as the RI alone is of poor prognostic value and may be the source of severe errors⁸.

A normal RI is greater than 0.55 and is often lower than this in infants who have suffered a hypoxic-ischemic event⁴. Initially due to the “brain-sparing” effect^{6,9,10}, a compensatory reduction of CVR in order to maintain or restore O₂ delivery to the brain⁸, and may persist when there is an impairment to autoregulation resulting in vasoparalysis¹⁰.

Aim

To establish a baseline of cerebral blood flow velocities, Resistive and Pulsatility indices (RI & PI) in normal neonates for comparison against infants with hypoxic-ischemic encephalopathy (HIE) in future studies.

Patients and Methods

Neonates experiencing normal births with Apgar scores of >7 at 5 mins and >36 weeks gestation and <72 hours postnatal age were recruited from the maternity ward of the Mercy Hospital for Women in Heidelberg (Victoria, Australia). Patient records including details of antenatal care, the birth and subsequent feeding regime were available to the study.

Cranial Ultrasounds were performed on each neonate with a Philips HD11 XE Ultrasound System with a C8-5; 5-8 MHz Curved Array Transducer probe suitable for neonatal cephalic use. A complete diagnostic cranial ultrasound was conducted and all subjects presented with normal cranial anatomy.

Three Doppler traces of 3 cardiac cycles were obtained in the Anterior Cerebral Artery (ACA) and the Middle Cerebral Artery (MCA) by methods previously described^{1,11-14}. Angle correct was used. Figure 1 demonstrates the views used to visualise and interrogate the ACA and the MCA respectively. The recorded parameters were the Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV), and Time-Averaged Velocity (TAV) from which the Resistive Index (RI) and Pulsatility Index (PI) were derived. Three observations were obtained by two operators each during the same examination (the Principal researcher and Head Sonographer of the Medical Imaging Department at the Mercy Hospital for Women). The three most consistent observations for each participant are included in the results.

Figure (1a) and Figure (1b)

Data was analysed with Matlab 2015a (The MathWorks, Inc., Natick, Massachusetts, U.S.A). The Pearson's linear correlation coefficient and p-value is presented for comparison of continuous variables and the point biserial correlation coefficient for dichotomous variables. The similarity between paired sets of measurements was analysed using the paired sample t-test for means. The agreement between the ACA and MCA was analysed and presented by a Bland-Altman plot. Multivariate analysis was conducted using multivariate linear regression. A p-value of <0.05 was considered significant.

Ethics approval was obtained from the Mercy Health Human Ethics Committee prior to commencement and the study conforms to the provisions of the Declaration of Helsinki (as revised in Brazil 2013). Full informed, written consent was obtained from at least one parent before an infant was admitted into the study.

Results

38 singleton neonates were recruited with mean post-natal age of 33 hours (range 5-71), mean gestation of $39^{+1/7}$ weeks (range $36^{+4/7}$ - $41^{+6/7}$) comprising: $36^{+4/7}$ (n=1), Early Term ($37^{+0/7}$ - $38^{+6/7}$ wks, n=15), Full Term ($39^{+0/7}$ - $40^{+6/7}$ wks, n=19), Late Term (≥ 41 wks, n=3)¹⁵. Every participant in the study received standard antenatal surveillance as per hospital protocol, no antenatal corticosteroids were given and all were born in good condition (mean Apgar score at 5 mins of 9.42 (range 9-10)). 23 of 38 (61%) were female, 15 were male (39%). No correlations were detected with mode of delivery, Apgar scores. There was a mean post-prandial time of 101 min (15-300).

The birthweight range was 2420-4310g. All birthweights, bar one, were $\geq 10^{\text{th}}$ percentile according to the "Australian national birthweight percentiles by sex and gestational age, 1998-2007"¹⁶. The infant with the lowest birthweight (2420g) was a female of 38^{+0} wks gestation who was only 20g less than the 10^{th} percentile. The measured parameters for this infant were within the 95% confidence level of the group mean for all parameters and so included in the study. Birthweight correlated to gestation (0.57, $p<0.001$) and sex (-0.36, $p<0.05$).

Results are displayed in Table 1.

Cerebral Blood Flow Velocities (CBFV's)

The CBFV's were of approximate normal distribution as confirmed by Quantile-Quantile (Q-Q) normality tests. Between the ACA and MCA, the mean Peak Systolic Velocity (PSV) and Time-Averaged Velocity (TAV) were statistically different as determined by t-test ($t=2.03$, $p=0.015$ and $t=2.04$, $p=0.013$ respectively); the EDV was statistically similar ($t=2.03$, $p=0.48$). The boxplots of the CBFV's in the ACA and MCA are displayed in Figure 2.

Figure (2)

In the ACA, the average angle of insonation was 7° (range 0° - 20°) with a median of 5° ; the angle altered between measurements in only 6 cases (21%) and there was at least one measurement with an angle $> 10^{\circ}$ in only 10 cases (25%). In comparison, the average angle of insonation in the MCA was greater at 18° (range 0° - 42°) with median 17° ; the angle differed between measurements in 9 cases (23%) and was $> 10^{\circ}$ in 29 cases (74%). The CBFV's mostly increase with post-natal age (as shown in Table 2). A statistically significant correlation was only detected between the EDV and the post-natal age in the ACA ($r=0.42$, $p=0.009$). Correlations were observed between all CBFV's and

gestation in the ACA; consequently, birthweight was also correlated to the ACA CBFV's and to the PSV in the MCA. Sex was correlated to the ACA PSV only.

Multivariate linear regression for the CBFV's was undertaken to determine the relative influence of individual independent variables. Initially all recorded variables were considered for inclusion as predictors and analysis determined the most optimal model was a 3-dimensional model of the most significant predictors; post-natal age, the dichotomous post-prandial time and birthweight. Models fit best to the ACA measurements as R_Square values were higher. The ACA EDV was the CBFV best represented by a linear regression model; with coefficients of determination were $\beta=2.94$ ($p<0.001$) for post-natal age (Days), $\beta=7.71$ ($p<0.001$) for the dichotomous post-prandial time ($\beta=7.71$ $p<0.001$) and $\beta=4.05$ ($p<0.01$) for birthweight (kg) ($\beta=4.05$ $p<0.01$) and an overall model fit of R_Square=0.51.

Resistive Index (RI)

The overall mean RI ($\pm$ SD) in the ACA was 0.67 ± 0.06 and 0.68 ± 0.07 in the MCA. The ACA and MCA RI measurements were correlated ($r=0.72$, $p<0.001$); the Bland-Altman plot (Figure 3) demonstrates this agreement, albeit with a small positive bias (0.016) in the MCA measurements. This relationship was also confirmed with a paired sample t-test ($t=2.0$, $p=0.06$). The interobserver correlation was $r=0.69$ $p<0.0001$.

Figure (3)

A correlation between RI and post-natal age was observed (ACA $r=-0.33$ $p=0.045$, MCA $r=-0.39$, $p=0.016$), with the highest RI measurement observed in the youngest infant at a post-natal age of 5 hours, although only 2 infants less than 12 hours of age were included in the study. There was no correlation detected between the RI and the gestation.

The two lowest RI measurements (both 0.54 in the ACA) occurred in two infants most recently fed (15 and 23 min) with postnatal ages of 24 and 39 hours respectively. Therefore, although there was no correlation between RI and post-prandial time if taken as a continuous variable, if the post-prandial time was converted to a dichotomous variable with 25 minutes as the pivot there was a statistically significant correlation with the RI. This was the result of a decrease in the EDV not the PSV.

Multivariate linear regression for the RI determined that only the post-natal age (Days) ($\beta_{ACA}=-0.03$, $\beta_{MCA}=-0.05$, $p<0.01$) and dichotomous post-prandial time ($\beta_{ACA}=-0.15$, $\beta_{MCA}=-0.15$, $P<0.01$) were significant predictors of the RI in both the ACA and MCA. Although birthweight was a significant predictor for CBFV's, it was not a significant predictor for the RI in either the ACA or MCA.

Pulsatility Index (PI)

The mean PI $\pm$ SD was 1.11 ± 0.18 in the ACA and 1.17 ± 0.23 in the MCA and the measurements in the ACA and MCA were strongly correlated ($r=0.68$, $p<0.001$). There was a correlation between the PI in the ACA and the post-natal age ($r=-0.32$, $p=0.049$); this correlation in the MCA was not statistically significant. There was no statistically significant correlation between the PI and the gestational age (or birthweight). Like the RI, there was a correlation between the PI and the dichotomous post-prandial time (ACA $r=-0.46$, $p=0.005$; MCA $r=-0.36$, $p=0.038$).

Multivariate linear regression for the PI determined the post-natal age ($\beta_{ACA}=-0.09$ $p<0.05$) and dichotomous post-prandial time ($\beta=-0.37$, $p<0.01$) to be the most significant predictors of PI in the ACA ($R_Square=0.44$). Only the dichotomous post-prandial time was a significant predictor in the MCA ($\beta_{MCA}=-0.35$ $p<0.05$). Birthweight was not a significant predictor for the PI in either the ACA or MCA.

Discussion

All results were in agreement with previous published studies^{1,8,14,17-23}. The average RI as determined in this study corresponds to those studies with similar post-natal age and gestation (refer to *Appendix I* for an overview of relevant studies)^{1,8,14,17,19-21,23-25}. Studies with earlier post-natal ages reported higher RI's; RI's of greater than 0.74 were reported in the 10 hours after birth in the Ando et al, Wright et al, Connors et al and Pezzati et al studies^{1,17,19}. This study detected a weak inverse correlation between post-natal age and RI, and this may be due to the limited number of infants studied within the first 12 hours. One infant studied within the first 5 hours demonstrated the highest RI of 0.81 (ACA) and 0.84 (MCA). This may be a result of a reduced diastolic velocity due to the presence of ductal flow known as the "steal" phenomenon^{6,14,26} although studies by Connors et al¹ and Batton et al²⁷ suggest the higher RI associated with post-natal age due to cerebrovascular remodelling for improved impedance matching rather than ductal steal¹.

Several studies have suggested that the RI is inversely proportional to the gestational age^{18,20,23}, and so differences in gestational ages of the research population may account for further variations in reported RI. The mean RI in the Seibert et al study was 0.75 ± 0.1 with a mean gestational age of 34 weeks but this consisted of two groups of < 33 weeks and > 34 weeks that had RI's of 0.77 ± 0.09 and 0.71 ± 0.07 respectively, demonstrating that a higher RI is associated with lower gestation²⁰. No correlation was observed between RI and gestational age in this study, which may have been due to the narrow gestational age range ($36^{+4/7}$ - $41^{+6/7}$ weeks).

Couture et al suggests that cerebral blood flow velocities should be constantly preferred to the RI, as the RI alone is of poor prognostic value and may be the source of severe errors⁸. *Appendix II* provides an overview of the reported CBFV's for this and other studies^{8,14,17,18,24,25,28,29}. Higher Cerebral Blood Flow Velocities (CBFV's) in the MCA have been previously reported³⁰ and we found the PSV in the MCA to be statistically greater than in the ACA. Our results correlate well to the Aranha et al¹⁸ study where the gestational and post-natal ages are most similar.

Correlations were observed between all the cerebral blood flow velocities in the ACA and the gestation which suggests velocities increase with gestation. Birthweight, which correlated to gestation, was similarly correlated to ACA CBFV's. Correlations of the RI and PI with gestation and birthweight were not statistically significant, most likely because a matched increase in contributing velocities to a ratio may result in that ratio being less or un-affected. Thus, information gained with individual values may be hidden when those values are combined in a ratio. This supports the assertion by Couture et al that velocities should be preferred to the RI and suggests that changes to CBFV's may not always be transmitted to a calculated index. Although the RI's and CBFV's established in this study are slightly lower than reported by Couture et al⁸ and Deeg et al²⁵, this is thought to be a result of the study method. Both these studies use corrected gestation age rather than separately reporting the contribution of gestation and post-natal age. The time-course of the increase in RI and CBFV's may well be altered by the gestation at birth thereby obviating a direct comparison between studies with corrected gestation versus actual gestation with post-natal age included.

The correlations observed between the post-natal age and the post-prandial time with the RI in both the ACA and MCA can be largely explained by the variation in the EDV, as the EDV and RI are significantly and strongly inversely correlated (ACA $r=-0.67$, $p<0.001$; MCA $r=-0.54$, $p<0.001$). Similarly, Couture et al observed that in all 41 cases of Perinatal Asphyxia studied there was a decrease in the RI to below 0.55 as a direct result of an increase in the diastolic amplitude of the cerebral blood flow velocity⁴, although this is the only other known reference to this phenomenon.

The PI determined in this study correlates well with Aranha et al who reported normal PI's of 1.12 ± 0.21 in the ACA and $1.25-1.29 \pm 0.23-0.27$ in the MCA (L-R)¹⁸. The only other known study of the PI in neonates was that of Couture et al which reported a Pulsatility Index (PI) of 1.34^8 . The higher PI in the Couture et al study aligns with their higher RI and may again be explained by the differing contributions to the corrected gestational age. The same correlations observed with the post-natal age and post-prandial time and the RI in the ACA were also observed with the PI in the ACA. As the

Pulsatility Index (PI), used primarily in obstetrics, demonstrated the same correlations as the RI it could be considered as an alternative for neonates.

An interesting observation in this study was a lower than normal RI in 2 infants. These 2 infants had been the most recently fed of the cohort and thus if the post-prandial time was converted to a dichotomous variable with 25 minutes as the pivot there is a correlation with RI, and this corresponds to a concurrent increase in EDV. This observation is supported by the Monteiro et al study which reported a lower RI in feeding infants than those at rest before or after feeding²². As only 2 infants were measured soon after feeding in this study further investigation is required before any definitive conclusion may be drawn, but indicates that a lower than normal RI (<0.55) may be observed in normal neonates without any known pathological cause.

The angle of insonation was much lower in the ACA than in the MCA, and the angle differed in only 20% (ACA) and 23% (MCA) of cases suggestive that the angle is dependent on the anatomy. A smaller angle of insonation would be expected to result in less error in the velocity measurements³¹ and should translate to greater reliability and reproducibility. The boxplot (Fig 2) indicates that there was less variability in the CBFV measurements in the ACA versus the MCA. In addition, the Bland-Altman plot (Fig 3) of the RI measurements in the ACA versus the MCA indicated a bias in the MCA measurements and the p-value for the paired sample t-test was suggestive of an almost significant variance between ACA and MCA measurements. The bias and the variance in the ACA and MCA measurements may be attributed to the greater variance in the MCA.

The ACA is easier to interrogate given its proximity to the transducer in the anterior fontanelle and its trajectory towards the probe. The smaller temporal window used for interrogation of the MCA, and the increased angle onto the MCA from this direction is reflected in the greater variance in the MCA measurements in comparison to the ACA, and was especially prevalent in the PSV measurements. Correct measurement of the peak systolic velocity relies on an axisymmetric velocity profile with the interrogated sample volume consisting of the maximum velocity, otherwise the maximum velocity may be significantly underestimated³². The observation that a significant correlation observed between the CBFV's and gestation in the ACA was not detected with the MCA measurements supports the reduced reliability hypothesis. The ratio in the calculation of the RI cancels out this error, and was found to be significantly similar in both the ACA and MCA regardless of the angle of insonation and so confirms that there is value in using an index such as the RI especially where access to the interrogated vessel may be difficult.

Conclusion

The cerebral blood flow velocities and resistive indices determined in this study agree with previously published studies and provide a baseline against which comparisons may be made with other populations such as infants with HIE as was the objective. The smaller angle of insonation required for ACA measurements corresponded to greater reliability and reproducibility when compared to measurements in the MCA. Lower than normal RI's were observed in two normal neonates without any known pathological cause which suggests a degree of caution needs to be utilised when relying on a low RI to diagnose pathology. Further study of this phenomenon with serial measurements before, during and after feeding on the same infants may assist in answering this question.

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Table 1 - The Resistive Index (RI), Pulsatility Index (PI) and Cerebral Blood Flow Velocities (CBFV's) in the Anterior and Middle Cerebral Arteries (ACA and MCA respectively) as determined in this study and the corresponding significant correlations with Postnatal Age (PN), Postprandial Time (PP), Gestation (G) and Birthweight (B)². (Results shown as mean $\pm$ SD).

Index	ACA	Correlations				MCA	Correlations			
		PN	PP	G	B		PN	PP	G	B
Resistive Index (RI)	0.67 $\pm$ 0.06	-0.33*	-0.51***			0.68 $\pm$ 0.07	-0.39*	-0.41*		
Pulsatility Index (PI)	1.11 $\pm$ 0.18	-0.33*	-0.46**			1.17 $\pm$ 0.23		-0.36*		
Peak Systolic Velocity (PSV) ¹	36.3 $\pm$ 6.6			0.35*	0.41**	41.4 $\pm$ 13.2				-0.33*
End Diastolic Velocity (EDV)	12.4 $\pm$ 3.9	0.42*	0.38*	0.44**	0.35*	13.0 $\pm$ 5.5		0.44*		
Time-Averaged Velocity (TAV) ¹	22.0 $\pm$ 4.0			0.42*	0.48**	25.8 $\pm$ 7.9				

¹PSV and TAV differed significantly between the ACA and MCA

²Although all cross correlations were calculated, only the r-values for significant correlations are displayed.

* - indicates significant correlation with p-value <0.05

** - indicates significant correlation with p-value <0.01

*** - indicates significant correlation with p-value <0.001

Table 2: Cerebral Blood Flow Velocities (Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV) and Time-Averaged Velocity (TAV)), Resistive and Pulsatility Indices (RI and PI) in the Anterior and Middle Cerebral Arteries (ACA and MCA) grouped by post-natal age (PN).

PN	RI ACA	RI MCA	PI ACA	PI MCA	PSV ACA cm/s	PSV MCA cm/s	EDV ACA cm/s	EDV MCA cm/s	TAV ACA cm/s	TAV MCA cm/s
ALL (n=38)	0.7 ± 0.06	0.7 ± 0.07	1.1 ± 0.18	1.2 ± 0.23	36.3 ± 6.6	41.4 ± 13.2	12.4 ± 3.9	13 ± 5.5	22.0 ± 4.0	25.8 ± 7.9
0-12 HRS (n=2)	0.8 ± 0.06	0.8 ± 0.06	1.3 ± 0.44	1.7 ± 0.29	28.1 ± 6.6	40.3 ± 15.0	6.2 ± 0.1	7.7 ± 0.5	17.7 ± 0.8	18.6 ± 5.3
12-24 HRS (n=10)	0.7 ± 0.05	0.7 ± 0.05	1.2 ± 0.18	1.3 ± 0.18	35.8 ± 4.9	42.2 ± 10.0	10.2 ± 1.5	11.3 ± 2.6	20.9 ± 2.3	23.8 ± 5.7
24-48 HRS (n=20)	0.6 ± 0.04	0.7 ± 0.07	1.0 ± 0.12	1.1 ± 0.23	36.2 ± 6.7	39.4 ± 15.0	13.4 ± 3.1	13.6 ± 6.4	22.3 ± 4.1	26.2 ± 8.7
48-72 HRS (n=6)	0.7 ± 0.04	0.7 ± 0.06	1.1 ± 0.14	1.2 ± 0.27	40.3 ± 7.3	46.9 ± 12.7	14.7 ± 6.2	15.4 ± 5.0	24.5 ± 5.0	28.1 ± 9.0

Appendix I: Comparison of RI's from prominent studies. Gestation and Resistive Index (RI) quoted with one standard deviation (SD) where available.

Study	Cohort Size	Post-natal Age (Hrs [†])	Gestation (Weeks)	Artery	RI	Correlations
Ando et al, 1983 ¹⁹	43	< 6	Term	ACA	0.76 ± 0.05	<ul style="list-style-type: none"> • RI & EDV inversely correlated to post-natal age (ductal closure) • No correlation with delivery type
		> 6			0.68 ± 0.07	
		72			0.69 ± 0.04	
Wright et al, 1988 ¹⁴	10	< 8	39.6 ± 1.3	ACA	0.74 ± 0.08	<ul style="list-style-type: none"> • RI inversely correlated to EDV and post-natal age (ductal closure) • Systemic blood pressure influence on RI, not vice versa
				MCA	0.78 ± 0.07	
				ACA	0.65 ± 0.07	
				MCA	0.70 ± 0.07	
Bode et al, 1988 ²⁴	25	Day 1	Preterm & Term	MCA	0.69	<ul style="list-style-type: none"> • Positively correlated to postnatal age
		Day 20		MCA	0.72	
Deeg et al, 1989 ²⁵	121	Corrected gestational age – Post-natal age not known.	29-45 weeks	ACA	0.73±0.08	<ul style="list-style-type: none"> • Positively correlated to postnatal age
Seibert et al, 1989 ²⁰	57	< 7 days	< 33	ACA/MCA/ICA [‡]	0.77 ± 0.09	<ul style="list-style-type: none"> • RI inversely correlated to post-natal age. • RI inversely correlated to gestation
			> 34		0.71 ± 0.07	
			Pre-term & Term		0.75 ± 0.10	

Connors et al, 1992 ¹	16	4.6 ± 0.2	41.0 ± 0.1	ACA	0.75 ± 0.01	• RI correlated to post-natal age, due to vascular re-modelling for impedance matching rather than ductal shunting
		23.9 ± 0.3			0.66 ± 0.02	
		47.5 ± 0.3			0.65 ± 0.02	
Allison et al, 2000 ³³	40	< 24	38-42	ACA/MCA/ICA [‡]	0.73 ± 0.06	
Couture et al, 2001 ⁸	491	Not known	32-43	ACA	≈ 0.75-0.80 [§]	• CBFV correlated to gestation & post-natal age (progressive increase in CBFV from 32 weeks to 8 months)
Pezzati et al, 2002 ¹⁷	30	2-8	38-41	ACA	0.78 ± 0.07	• CBFV correlated to birth weight & post-natal age. • RI correlated with gestational age.
				MCA	0.81 ± 0.07	
Monteiro et al, 2012 ²²	256	10-48	Term - (Feeding)	ACA	0.67	• RI inversely correlated to breastfeeding, associated with increased CBFV
			Term - (Rest)	ACA	0.71	
Zamora et al, 2014 ²³	63	7.1 ± 13.6 days	> 37	ACA	0.66 ± 0.07	• RI inversely correlated to gestational age.
This Study	38	5-71	37.0-41.6 weeks	ACA	0.67 ± 0.06	• Inverse correlation to gestation & postnatal age. • Correlation with post-prandial time as binomial with pivot as 25 minutes
				MCA	0.68 ± 0.07	

† Hours unless otherwise specified

‡ Overall mean of all interrogated vessels, ICA=Internal Carotid Artery

§ Value approximated from graph – RI reported as unchanged from 32-40 weeks

Appendix II: Mean (SD) Cerebral Blood Flow Velocities in the ACA and MCA as reported in the following trials. (Gestation – mean $\pm$ SD)

Study	Cohort Size	Gestation (Weeks)	Post-natal Age (Hours) [†]	ACA (Mean - cm/s)			MCA (Mean - cm/s)		
				PSV	EDV	TAV	PSV	EDV	TAV
Wright et al, 1988 ¹⁴	10 (Longitudinal)	39.6 $\pm$ 1.3	< 8	24.9 $\pm$ 6.9	6.6 $\pm$ 2.9	-	39.9 $\pm$ 9.5	8.7 $\pm$ 2.7	-
			24-30	28.2 $\pm$ 5.4	9.3 $\pm$ 2.4	-	50.5 $\pm$ 5.0	15.3 $\pm$ 2.0	-
Bode, 1988 ²⁴	25 (Longitudinal)	Preterm & Term	Day 1	32 $\pm$ 7	11 $\pm$ 5	17 $\pm$ 5	42 $\pm$ 10	13 $\pm$ 4	22 $\pm$ 6
			Day 5	42 $\pm$ 7	13 $\pm$ 3	21 $\pm$ 6	54 $\pm$ 10	15 $\pm$ 4	26 $\pm$ 6
Deeg, 1989 ²⁵	121	29-45 weeks	Corrected gestational age – Post-natal age not known.	54	13	25	-	-	-
Low, 1993 ²⁸	95	Term	1	-	-	-	43.2	9.3	-
Maesel, 1994 ²⁹	18	38-41	Pre-cord cut	-	-	-	67.2 $\pm$ 13	26.3 $\pm$ 10	44 $\pm$ 10
			Post-cord cut				48.3 $\pm$ 10	14.6 $\pm$ 6	29.1 $\pm$ 8
			1				39.3 $\pm$ 4	7.9 $\pm$ 4	20.6 $\pm$ 4
			Day 1				44.2 $\pm$ 7	15.6 $\pm$ 5	26.7 $\pm$ 6
Couture et al, 2001 ⁸	491	32	Corrected gestational age – Post-natal age not known.	43.1	9.6	21.9	-	-	-
		40		52.9	13.2	28.7			
Pezzati et al, 2002 ¹⁷	120	38-41	< 8	24	4.7	12	31	5.7	16

Aranha et al, 2009¹⁸	50	37-41 (mean 38.94)	12-72	44.4	15.4	26.1	47.9	15.1	26.4
Current study conducted 2014	38	39.4±1.2	12-72	36.3 ± 6.6	12.4 ± 3.9	22.1 ± 4.0	41.5 ± 13.2	13.2 ± 5.5	26.7 ± 7.9

† Hours unless otherwise specified

Figure 2: Boxplots of Cerebral Blood Flow Velocities in the ACA and MCA

Figure 2.tif

Figure 3.tif

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FIGURE 1b.tif

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