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ORIGINAL ARTICLE

Cranial Doppler resistance index measurement in preterm newborns with cerebral white matter lesion

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Abstract

Objective: To investigate whether the resistance index (RI) within the first 72 hours of life of newborn infants with cerebral white matter lesion (WML) is correlated with the adverse outcome of WML.

Methods: Retrospective study. Newborn infants with WML were identified based on cranial ultrasound results, and those with Doppler imaging and RI measurement were selected. The newborn infants were placed in three groups: low (< 0.61), normal (0.61-0.85) or high (> 0.85) RI. The sample was analyzed as a whole at first and then stratified according to birth weight.

Results: According to the RI, cerebral blood flow was abnormal in 46 (68.7%) patients, low in 42 (62.7%), and high in four (6%). Among those with a low RI, 15 (35.7%) had an adverse outcome, with ultrasonographic signs of cerebral atrophy in 10 (23.8%) and intraventricular hemorrhage in five (11.9%) patients. The four newborn infants with a high RI also had an adverse outcome, one (25%) with signs of cerebral atrophy and three (75%) with intraventricular hemorrhage. No statistically significant differences were observed between RI groups and the group with a fatal outcome.

Conclusion: The study showed that abnormal RI within the first 72 hours was associated with healing complications in newborn infants with cerebral WML. Abnormal RI results were not correlated with the fatal outcome. Therefore, RI is an important parameter that should be measured in newborn infants.

J Pediatr (Rio J). 2006;82(3):221-6: Newborn infants, brain white matter lesion, periventricular leukomalacia, periventricular white matter infarction, resistance index, Doppler ultrasound, birth weight.

Introduction

Cerebral blood flow (CBF) is autoregulated, being therefore uncorrelated to systemic arterial blood pressure. The brain in unhealthy preterm newborns does not autoregulate the CBF, and circulation then occurs through passive pressure. In this case, there is a direct linear relationship between CBF and mean arterial pressure.[1] The association between the absence of CBF autoregulation and systemic hypotension has been implicated in the pathogenesis of cerebral white matter lesions (WML) and intraventricular hemorrhage (IVH).[2-4]

WML is the most common brain injury among preterm newborns,[5] and may also be found in full-term newborns when the injury occurs *in utero*. In the latter situation, the injury can be detected by obstetric or neonatal ultrasound examination, by demonstration of cysts or ventriculomegaly.[6,7] The two major types of WML are periventricular leukomalacia (PVL) and periventricular hemorrhagic venous infarction (PHVI). PHVI is the most frequent unilateral hemorrhagic lesion found ipsilaterally to extensive intraventricular hemorrhage.[8] This association suggests that IVH causes compression of the veins that drain blood from the periventricular white matter, leading to venous infarction at the affected site. PVL is a bilateral nonhemorrhagic lesion, which may result in cyst formation,[8] whose pathogenesis has been ascribed to fetal hypoxia-ischemia or, more recently, to inflammatory fetal factors.[9,10] IVH is secondary to the rupture of immature vessels of the germinal matrix located in the lateral ventricles, and is frequent in preterm newborns, but not in full-term ones. This rupture occurs in blood reperfusion after an episode of cerebral hypotension.[4] This way, CBF

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measurement in preterm newborns provides useful information about cerebral perfusion and risks for intraventricular and germinal matrix hemorrhage and for WML.[11] Another cause of WML is chorioamnionitis, which can be diagnosed by placental examination.[9] Ascending infection compels the fetus to produce systemic cytokines that cross the blood-brain barrier and attack oligodendrocytes, which are responsible for producing myelin in the central nervous system.

The method of choice for measuring CBF in the neonatal period consists in determining CBF velocity in the anterior cerebral artery, recorded by transcranial Doppler ultrasound, using the anterior fontanelle as acoustic window. It is a sensitive, specific, bedside diagnostic tool that neither exposes newborn infants to ionizing radiation, nor requires their sedation.[12] The sound waves given off by the transducer are reflected and their frequency travels proportionally to the velocity of circulating red blood cells in the vessel.[13] Thus, the peak systolic and diastolic pressures are measured. In 1976, Pourcelot[14] introduced the concept of RI, which is calculated by the following formula: RI = (S - D)/S, where S and D stand for systolic and diastolic pressures, respectively. As its name itself suggests, RI measures vascular resistance. A high RI corresponds to vasoconstriction and low blood flow velocity, whereas a low RI is related to vasodilation and high blood flow velocity. In newborn infants with hypoxic ischemic injury, RI is low due to compensatory vasodilation after hypoxia-ischemia.[15] In preterm newborns who are to develop hemorrhage, studies show that there is a fluctuating pattern in CBF velocity. Initially, CBF diminishes, with a high RI and vasoconstriction and probable infarction of germinal matrix vessels, followed by a low RI and vasodilation with bleeding of germinal matrix vessels. This hypothesis was confirmed in an experiment conducted by Goddard-Finegold et al.[6]

The aim of this study was to investigate whether RI within the first 72 hours of life in preterm and full-term newborns with cerebral WML is correlated with an adverse outcome (cerebral atrophy, hemorrhagic infarction, intraventricular hemorrhage) and/or death.

Methods

This is a cross-sectional and retrospective study based on the results of cranial Doppler ultrasound examinations performed in preterm and full-term newborns with WML, between January 1994 and December 2001. The maternity ward where the study was carried out is a primary, secondary and tertiary care center, with a neonatal intensive care unit (NICU), also being a referral center for high-risk pregnancies. This hospital has a collaborative document system in healthcare that allows the undertaking of scientific studies. Cranial ultrasound is regularly performed in all NICU babies on the first three days of life and on the 7th, 14th and 21st days of life, or after any clinical intercurrent event. All cranial ultrasound examinations were conducted by an experienced neonatologist (S.R.) with great expertise in the management of newborns.

In order to assess RI within the first 72 hours of life and its correlation with an adverse outcome, newborns with WML were divided into three subgroups: 1. low RI (< 0.61), 2. normal RI (0.61-0.85) and 3. high RI (> 0.85), which were compared in terms of the outcome of the white matter lesion on ultrasound examination (adverse or not) and in terms of survival or not.

A color Doppler examination (Doppler velocimetry) was performed together with the first ultrasound examination, using the anterior fontanelle for the vascular analysis of anterior cerebral arteries in their distal segment, bilaterally, on the coronal and sagittal plane. All cranial ultrasound examinations were performed by one experienced neonatologist with great expertise in the management of newborns. All those preterm newborns with cerebral WML detected by ultrasound examination were included in the study, and full-term newborns or those newborns with malformation were excluded.

Outcome criteria: favorable outcome – resolution of increased periventricular echodensity (without ultrasonographic signs of brain parenchymal loss); adverse outcome – presence of echolucency and/or ventriculomegaly (signs of brain parenchymal loss), and/or intraventricular hemorrhage (compression of brain parenchyma).

The worst result of a series of ultrasound examinations was used for the classification of newborns into either of the two groups. The following data were collected from the newborns' medical records: demographic characteristics, prenatal, perinatal and postnatal problems and diagnoses, and fatal outcome. Newborns without RI measurements, those transferred from or to another maternity ward, those submitted to Doppler ultrasonography after 72 hours of life, and full-term newborns with WML outside the prenatal period were not included in the analysis.

WML was diagnosed in 93 cases. Of these, 67 (72.04%) were submitted to Doppler ultrasound examination with RI measurement within the first 72 hours of life, and 53 preterm newborns were selected to participate in the study. As birth weight is an important variable for determining the severity of WML,[4] the group was assessed as a whole and later stratified into two groups: birth weight less than 1,500 grams and birth weight greater than or equal to 1,500 grams.

The following nonparametric tests were carried out for the statistical analysis: chi-square test, Mann Whitney test, and Kruskal Wallis test. A $p < 0.05$ value (two-tailed)

was established as statistically significant. All variables with a p value < 0.05 were weighted by binary logistic regression for the determination of independent predictors. A p value ≤ 0.05 was regarded as statistically significant.

The study was approved by the Research Ethics Committee of Maternidade Climério de Oliveira, Graduate Program in Medicine and Health of Universidade Federal da Bahia (Protocol no. 27/2002).

Results

Of 53 analyzed patients, there was a female predominance in the group with normal RI (11 patients or 57.9%), but this difference was not statistically significant, and neither were the other analyzed variables (Table 1).

Among the 53 newborns submitted to Doppler ultrasound examination, RI was low in 31 (58.5%), normal in 19 (35.9%) and high in three (5.6%), and the outcome was favorable in 26 (49.1%) and adverse in 27 (50.9%). All newborns with a high RI had complications, compared to nine (17.0%) patients in the normal RI group and 15 (28.3%) in the low RI group. The difference between the three groups was statistically significant (Kruskal Wallis test: p = 0.025), due to the difference between the high RI group and the other two groups (Mann Whitney test: low x high: p = 0.011 and normal x high: p = 0.009) (Table 2). On the other hand, no differences were found between RI groups in terms of fatal outcome (Kruskal Wallis test: p = 0.471) (Table 3).

Birth weight was less than 1,500 grams in 35 (67.31%) newborns. No statistically significant difference was observed between RI groups in terms of birth weight (Kruskal Wallis test: p = 0.419), however, 20 newborns in the group with birth weight < 1,500 g had complications, compared to seven in the group with birth weight ≥ 1,500 g (Table 4). The outcome of hyperechogenicity was 37% better among the newborns with birth weight greater than 1,500 g, whereas WML had a 108% better outcome among those in the same weight category but with a normal RI.

Other 106 variables related to complications during the gestational period, labor and neonatal period were assessed as to their outcome, and six of them had a p value < 0.05 (hypernatremia, hypercalcemia, hypoalbuminemia, atelectasis, respiratory failure and presence of infection), however, none of them was statistically significant after binary logistic regression analysis (Table 5).

Table 1 - Clinical and demographic characteristics of the three resistance index groups

Characteristic	Resistance index			p *
	Low	Normal	High	
Maternal age (years),				
mean ± SD	26.91±6.01	28.14±7.11	22.50±3.54	0.386
Median (range)	28 (16-37)	28.50 (15-41)	22.50 (20-25)	
Gestational age (weeks),				
mean ± SD	30.48±3.09	30.29±3.15	31.33±2.31	0.832
Median (range)	30 (25-36.3)	31 (25-36)	30 (30-34)	
Male gender (%)	17 (54.8)	8 (42.1)	3 (100)	0.171
Birth weight (grams),				
mean ± SD	1,275.00±457.45	1,444.44±548.04	1,566.67±251.66	0.262
Median (range)	1,090.00 (630-2,765)	1,345.00 (750-2,860)	1,600.00 (1,300-1,800)	
Hospital stay (days),				
mean ± SD	49.81±30.45	39.05±29.30	65.33±21.83	0.118
Median (range)	47.00 (6-133)	32.00 (3-130)	61.00 (46-89)	
Apgar score,				
mean ± SD	7.8±1.38	7.94±1.35	7.50±2.12	
Median (range)	8.00 (4-10)	8.00 (4-10)	7.5 (6-9)	0.903
Resistance index,				
mean ± SD	0.54±0.051	0.67±0.05	0.96±0.08	
Median (range)	0.56 (0.38-0.60)	0.65 (0.61-0.76)	1.00 (0.87-1.00)	
Total (%)	31 (58.5)	19 (35.9)	3 (5.7)	

SD = standard deviation.
* Kruskal Wallis test.

Table 2 - Distribution of resistance indices according to the outcome of white matter lesion

Outcome of white matter lesion	Resistance index (%)			Total (%)
	Low	Normal	High	
Favorable				
Resolution of echodensity	16 (51.6)	10 (52.6)	0 (0.0)	26 (49.1)
Adverse	10 (32.3)	7 (36.8)	0 (0.0)	17 (33.0)
Echolucency and/or ventriculomegaly				
Hemorrhage	5 (16.1)	2 (10.5)	3 (100.0)	10 (18.9)

Kruskal Wallis test: p = 0.025; Mann Whitney test: low x normal, p = 0.816; low x high, p = 0.011; normal x high, p = 0.009.

The placenta was examined in only 26 (49.1%) cases, and of these, five (19.23%) revealed chorioamnionitis: three with a low RI and two with a normal RI; moreover, RI was low in two patients and normal in one who had an adverse outcome (Kruskal-Wallis test: p = 0.389).

Table 3 - Distribution of resistance indices according to the fatal outcome

Fatal outcome	Resistance index (%)		
	Low	Normal	High
Survival	29 (93.5)	16 (84.2)	3 (100.0)
Death	2 (6.5)	3 (15.8)	0 (0.0)
Total (%)	31 (100.0)	19 (100.0)	3 (100.0)

Kruskal Wallis test: p = 0.471.

Discussion

The pathogenesis of several neuropathological injuries in the neonatal period is related to CBF impairment, but most of the methods used to assess cerebral blood flow are technically complex, invasive, or costly. Doppler ultrasonography has been used in several studies to determine CBF velocity in intracranial cerebral arteries of asphyxiated newborns.[16-18] These studies have shown some correlation between velocity measurements and poor neurological outcome.[16-18]

In this study, CBF measured by RI was abnormal (predominantly low) in most newborn infants. The three newborns with a high RI had an adverse outcome, with intraventricular hemorrhage. Tsuji et al.[19] demonstrated that approximately half of those newborns with abnormal CBF will have WML or intraventricular hemorrhage, whereas among those with a normal CBF only 13% will develop

Table 4 - Distribution of resistance indices and outcome on ultrasound examination according to birth weight

Weight (grams)	Outcome on ultrasound	Resistance index (%)			Total (%)
		Low	Normal	High	
< 1,500	Resolution of echodensity	10 (47.6)	5 (38.5)	0 (0.0)	15 (42.9)
	echolucency + ventriculomegaly	8 (38.1)	6 (46.2)	0 (0.0)	14 (40.0)
	Intraventricular hemorrhage	3 (14.3)	2 (15.4)	1 (100.0)	6 (17.1)
Total (%)		21 (100.0)	13 (100.0)	1 (100.0)	35 (100.0)
≥ 1,500	Resolution of echodensity	6 (60.0)	4 (80.0)	0 (0.0)	10 (58.8)
	echolucency + ventriculomegaly	2 (20.0)	1 (20.0)	0 (0.0)	3 (17.7)
	Intraventricular hemorrhage	2 (20.0)	(0.0)	2 (100.0)	4 (23.5)
Total (%)		10 (100.0)	5 (100.0)	2 (100.0)	17 (100.0)

Kruskal Wallis test for resistance index groups: p = 0.419.
n = 52 (newborn not weighed).

Table 5 - Diseases associated with adverse outcome and/or death in white matter lesion

Diseases	Bivariate analysis p*	Binary logistic regression p
Hypernatremia	0.05	0.419
Hypercalcemia	0.006	0.873
Hypoalbuminemia	0.007	0.121
Atelectasis	0.041	0.060
Respiratory failure	0.007	0.864
Infection	0.010	0.074

* Chi-square test (Fisher's exact test, when indicated).

these complications. Similar results were obtained by other authors[20,21] and were experimentally confirmed in animals.[6] Although none of these authors assessed the outcome in newborns previously diagnosed with WML, as in the present study, the data obtained herein are comparable: among 27 newborns who had an adverse outcome, 18 (66.7%) showed abnormal RI in the first 72 hours of life, and among those who revealed absence of echodensity in the follow-up ultrasound examinations (26), only 10 (38.5%) had a normal RI. The worst outcome occurred among those with a high RI, since all patients had an adverse outcome on the ultrasound examination. The predominance of low RI (31 – 58.5%) was expected, as WML is a hypoxic-ischemic injury,[16] whereas a high RI was rare in this population (3-5.7%).

In 1979, Bada et al.[22] were the first to describe the association between the fluctuating pattern of CBF and the risk for intraventricular hemorrhage, later confirmed by other authors in animal[6] and observational experimental studies with newborns.[19,23,24] In this study, only one RI measurement was assessed and the high RI probably reflected the fluctuation of this index. As the study included newborns with hypoxic-ischemic cerebral injury, the CBF must have been initially low, with a high RI on Doppler ultrasound. This assumption is also valid for the presence of hemorrhage among five (16.1%) newborns with a low RI and two (10.5%) with normal RI. This finding indicates the necessity of serial RI measurements for the diagnosis of CBF fluctuations, as only one abnormal RI result is not a sign of intraventricular hemorrhage; however, the occurrence of at least one high RI result within the first 72 hours of life indicates a higher probability for this complication. Nevertheless, since cranial ultrasound has low sensitivity for the diagnosis of mild cerebral hemorrhage and WML (50% and 58%, respectively),[25] the ultrasound examination may not have identified injury among the 16 newborns with a low RI and 10 with normal RI, all of them with a favorable outcome. Among those with normal RI, 10 (52.6%) showed an adverse outcome on ultrasound.

With regard to the fatal outcome, Baenziger et al.[26] assessed 71 newborns using xenon-133 and found a higher baseline CBF among survivors than among those who did not survive. In this study, no statistically significant differences were observed as to the fatal outcome in the three RI groups, but the number of deaths was small (seven cases). Since the study conducted by Baenziger et al. and the present study used different methods and samples, a comparison cannot be made. The authors did not find other studies that related RI to a fatal outcome.

The literature data are controversial regarding the influence of birth weight on RI parameters. Muniz et al.[27] found a reduction in CBF (increase in RI), whereas Scherjon et al.[28] and Madazili et al.[29] detected an increase in CBF levels (decrease in RI), or no correlation in the study by Martinussen et al.[30] in small-for-gestational-age newborns. In the present study, no difference was noted as to the outcome in the three RI groups when stratified by birth weight < and $\geq$ 1,500 grams. Several factors have been described to influence CBF and RI, including patent ductus arteriosus, pneumothorax, hyperviscosity, respiratory distress syndrome, birth weight, postnatal age and gestational age among the most important ones.[13,20,23,27] On the other hand, birth weight is influenced by different factors, such as previous maternal and gestational diseases, use of drugs during pregnancy, and gestational age. The combination of these different factors acting on RI and on birth weight may be responsible for the differences observed between the studies. In this study, the outcome of WML in newborns with birth weight greater than 1,500 g was 37% better, whereas among those in the same weight category but with normal RI, the outcome was 108% better. Although there was no statistical significance, these values are clinically significant.

Chorioamnionitis, an important etiopathogenic factor of WML,[9] is diagnosed by placental examination, but this examination was performed in less than 50% of this patient population, since health plans do not cover its cost; thus, it was not possible to compare it with RI and outcome. Other variables were not associated with an adverse outcome and/or death.

In the present study, RI was associated with greater severity of WML, but not with death and, among newborns with cerebral WML, an abnormal RI result within the first 72 hours of life was associated with 64.2% of complications related to the outcome. However, abnormal RI was not associated with the fatal outcome. In newborns with birth weight greater than 1,500 g, the outcome of WML was more adverse in 37%, and in those with normal RI it was 108% more adverse. This difference is clinically important, even without showing any statistical significance. Therefore, RI is an important parameter that should be assessed in newborns. It is an important

and easily obtained measurement that requires diagnostic validation through a gold standard exam for these two complications (cranial magnetic resonance).

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