Neuroendocrinology Letters Volume 46 No. 4 2025
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Association between middle cerebral artery doppler flow parameters and intraventricular hemorrhage in preterm infants

Selvi GÜLAŞI[1], Mustafa Kurthan MERT[1], Eren Kale ÇEKINMEZ[1], Murat BAŞARANOĞLU[1]

1 Health Sciences University, Adana City Training and Research Hospital, Adana, Turkey.

Correspondence to: Assistant Professor MD Selvi Gülaşı
Health Sciences University, Adana City Training and Research Hospital
Neonatology, Adana, Turkey.
TEL.: +90–322–4559000; FAX: +90–322-4559000; E-MAIL: selvigulasi@mynet.com

Submitted: 2025-04-27 *Accepted: 2025-10-25* *Published online: 2025-11-06*

Key words: **Intraventricular hemorrhage; middle cerebral artery; Doppler ultrasound; cerebral blood flow; preterm infants**

Neuroendocrinol Lett 2025; **46**(4):205–212 **PMID:** 41213141 NEL46042501 © 2025 Neuroendocrinology Letters • **www.nel.edu**

Abstract

PURPOSE: To evaluate whether middle cerebral artery (MCA) Doppler flow parameters measured in the first week of life are associated with intraventricular hemorrhage (IVH) in preterm infants.
METHODS: A prospective cohort study was conducted in a level 4A neonatal intensive care unit (NICU) at Adana City Training and Research Hospital between March 2022 and April 2023. Preterm infants born weighing ≤1250 g and ≥500 g were included. MCA flow parameters, including peak systolic velocity (PSV), peak diastolic velocity (PDV), pulsatility index (PI), resistivity index (RI) and time-averaged maximum velocity (TAMAX) were measured via transfontanel Doppler ultrasonography within the first five days of life every day. The association between MCA Doppler parameters and IVH development was analyzed.
RESULTS: Ninety-two preterm infants were included. IVH was detected in 34.7% (n = 32). Infants with IVH had lower gestational age and birth weight. Logistic regression revealed that lower birth weight, the presence of PDA, and early-onset sepsis increased IVH risk. Both increased and decreased MCA Doppler parameters (PSV, PDV, PI and TAMAX) preceded IVH.
CONCLUSION: MCA Doppler flow fluctuations were associated with IVH in preterm infants. These associations warrant further investigation to determine whether MCA Doppler measurements can prospectively identify infants at risk for IVH.
WHAT IS KNOWN: Cerebral autoregulation is a developmental process that can be disrupted in neonates with congenital heart disease, hypoxic-ischemic encephalopathy, and those born preterm.
WHAT IS NEW: Novel methods to assess cerebral autoregulation in these populations can be used to target patient-specific hemodynamic parameters.

ORIGINAL ARTICLE

Abbreviations:

ANS	- Antenatal corticosteroid,
BPV	- Blood pressure variability
CBF	- Cerebral blood flow
CRP	- C-reactive protein
Csat	- Cerebral oxygen saturation
EOS	- Early onset sepsis
FOE	- Fractional oxygen extraction
IVH	- Intraventricular hemorrhage
NIRS	- Near-infrared spectroscopy
PCT	- Procalcitonin
PDA	- Patent ductus arteriosus
PDV	- Peak diastolic velocity
PI	- Pulsatility index
PSV	- Peak systolic velocity
PPROM	- Preterm prolonged rupture of membranes
RI	- Resistivity index,
TAMAX	- Time average maximum velocity

INTRODUCTION

Intraventricular hemorrhage (IVH) is a common brain injury in premature infants and can lead to acute mortality and severe neurological sequelae (McCrea & Ment 2008; Perlman 2022; Cizmeci *et al.* 2020). Unfortunately, treatment options for severe hemorrhage remain limited. Although the survival rate of very low birth weight (VLBW) infants has improved, the incidence of IVH has not decreased (Hwang-Bo *et al.* 2022). Studies have reported that 20-25% of VLBW premature infants develop IVH, whereas the incidence is as high as 45% in extremely low birth weight (ELBW) infants (McCrea & Ment 2008).

Several interventions may reduce the likelihood of IVH development. These include monitoring and optimizing cerebral blood flow using near-infrared spectroscopy (NIRS), preventing glucose and sodium imbalances, avoiding off-label erythrocyte transfusions, correcting coagulation abnormalities, managing respiratory disorders, administering surfactant, preferring non-invasive respiratory support whenever possible in preterm infants, and maintaining a neutral head position (Vesoulis *et al.* 2020; Lightburn *et al.* 2013; Pellicer & del Carmen Bravo 2011).

Cerebral blood flow (CBF) autoregulation in preterm infants is immature; thus, changes in systemic perfusion are directly transmitted to brain tissue. This phenomenon, referred to as "pressure-passive" circulation, indicates that cerebral blood flow cannot be maintained during fluctuations in systemic blood pressure. Consequently, CBF fluctuations are among the most critical factors contributing to brain injury (Perlman 2022; Vesoulis *et al.* 2020; Lightburn *et al.* 2013). Moderately high CBF increases the risk of cerebral hemorrhage, whereas moderate hypoperfusion exposes the brain to ischemic injury (Pezzati *et al.* 2002).

There is a lack of robust evidence regarding the association between CBF parameters and IVH development. Investigating the predictive value of CBF alterations in the development of IVH is essential to determine their role in the early assessment and interpretation of hemodynamic changes (Pezzati *et al.* 2002). Changes in CBF parameters may also serve as predictive markers for morbidities such as IVH, sepsis, and patent ductus arteriosus (PDA).

Transcranial Doppler ultrasonography (US) is a noninvasive, radiation-free, safe, and bedside neuroimaging method for measuring blood flow in cerebral arteries (Taylor *et al.* 1990). In some neonatal intensive care units (NICUs), CBF measurement using Doppler US is frequently combined with cerebral oxygen saturation (Csat) evaluation via NIRS to assess cerebral perfusion and autoregulation. Measurements of the anterior cerebral artery (ACA) and middle cerebral artery (MCA) flow have become standard practice in NICUs.

This study aimed to evaluate whether MCA flow parameters measured during the first week of life are associated with intraventricular hemorrhage (IVH) in preterm infants.

MATERIALS AND METHODS

Study Design and Patient Population

This prospective cohort study was conducted in a level 4A Neonatal Intensive Care Unit (NICU) at Adana City Training and Research Hospital between March 2022 and April 2023. The study was approved by the local ethics committee, and written informed consent was obtained from the parents of each infant prior to enrollment.

Preterm infants with birth weights between ≤1250 grams and ≥500 grams were included in the study. Between 10:00-14:00 hours each day during the first five days of life, peak systolic velocity (PSV), peak diastolic velocity (PDV), pulsatility index (PI), and resistivity index (RI) were measured from the middle cerebral artery (MCA) using transfontanel ultrasonography (US) when infants were in a quiet, non-feeding state. The operator was not blinded to clinical status but was blinded to laboratory results and clinical management decisions at the time of measurement.

Severe intraventricular hemorrhage (IVH), classified as stages 3 and 4, was defined according to the criteria developed by Volpe (Volpe 2025). Demographic data, including gestational age (GA), birth weight (BW), gender, mode of delivery, Apgar scores, maternal antenatal steroid (ANS) administration, small for gestational age (SGA), preeclampsia, chorioamnionitis, and multiple pregnancies, were collected from medical records.

PDA was evaluated during the same daily echocardiographic sessions in which cerebral Doppler measurements were obtained (between 10:00 and 14:00 hours during the first five days of life). Patent ductus arteriosus (PDA) with a ductal diameter >1.5 mm and a left atrium-to-aortic root (LA:Ao) ratio >1.4 was considered hemodynamically significant (hsPDA). Hypotension was defined as systolic, diastolic, and mean blood pressure values below the 95% confidence

 ISSN 0172–780X • www.nel.edu

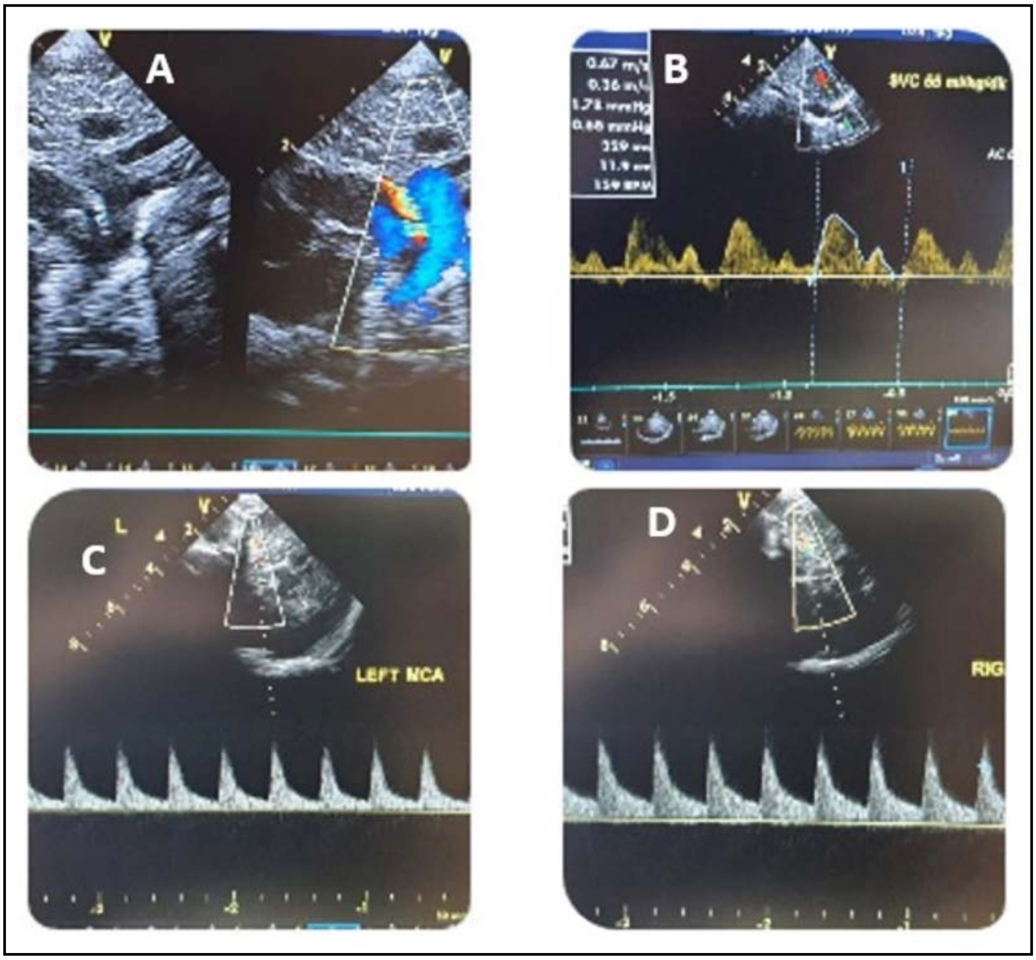

Fig. 1. A. Patent ductus arteriosus (PDA). B. Measurement of superior vena cava flow. C. Left middle cerebral artery Doppler imaging. D. Right middle cerebral artery Doppler imaging. Note the rapidly rising and pointed appearance of peak systolic velocity (PSV) in the presence of PDA.

interval for gestational age, with data obtained from patient records (Zubrow *et al.* 1995).

Early-onset sepsis (EOS) was defined as sepsis occurring within the first 72 hours of life, based on compatible clinical and laboratory findings. Clinical indicators included respiratory distress, temperature instability, lethargy, or poor perfusion, while laboratory criteria encompassed elevated C-reactive protein (CRP) and/or procalcitonin (PCT) levels and abnormal complete blood count findings. Perinatal asphyxia was defined as a pH <7.0, base excess (BE) < -12, lactate >5 mmol/L in cord blood or in a blood gas analysis obtained within the first 30 minutes after birth, and 5th-minute Apgar score <5.

Infants with major congenital anomalies, twin-to-twin transfusion syndrome, hydrops fetalis, congenital metabolic diseases, or missing data were excluded from the study.

Cranial Ultrasonography (cUS) and Doppler US, and NIRS Recording

Daily cranial ultrasonography (cUS) and Doppler measurements were performed by a neonatologist certified and experienced in neonatal neuroimaging. Measurements were taken using the ultrasonography feature integrated into the targeted neonatal echocardiography device (Vivid E series with applied cranial ultrasound, GE Healthcare Medical Systems, United Kingdom). The device was equipped with micro-convex (CV) array transducers operating at frequencies between 8 and 10 MHz.

Cranial ultrasonography was performed in the coronal and sagittal planes. In infants with severe bleeding, the presence of hemorrhage in the cerebellum was evaluated through the mastoid window. The middle cerebral artery (MCA) was accessed via trans-temporal windows. Peak systolic velocity (PSV) and peak diastolic velocity (PDV) were calculated from at least three consecutive cardiac cycles of optimal quality using the system's built-in calculation program. The resistivity index (RI) of the MCA was automatically calculated after recording both PSV and PDV, according to the Pourcelot index of resistance. The angle of insonation was adjusted, and flow measurements were obtained in pulse wave mode (Figure 1). Thus, brain anatomy and vascular structures, as well as PSV (cm/s), PDV (cm/s), PI, and RI analyses of the MCA, were performed.

The RI, also known as the Pourcelot index or resistance index, was defined by the equation:

$RI = (PSV – PDV) / PSV.$

RI values between 0.60 and 0.80 in the cerebral artery were considered normal (Camfferman *et al.* 2020; Arman *et al.* 2020; Vohr 2022).

Tab. 1. Prenatal and postnatal characteristics

Characteristics of infants	IVH (+) (n=32)	IVH (-) (n=60)	p
Gestational age, mean ± SD (med, IQR)	25.7±2.2 26 (24.8-27)	27.1±1.8 27.4 (26-28)	**0.002**
Birth weight, mean ± SD (med, IQR)	812.2±203.3 830 (620-972.5)	961.2±198.1 995 (840-1130)	**0.001**
Male, n (%)	21 (%66)	30 (%50)	0.151
Apgar 1. min, mean ± SD (med, IQR)	5.3±1.8 6 (4-7)	5.9±1.8 6 (6-7)	0.171
Apgar 5. min, mean ± SD (med, IQR)	7.3±1.5 8 (6.5-8)	7.9±1.2 8 (7.5-9)	0.081
Characteristics of mothers, n(%)			
ANS, n (%)	10 (31%)	25 (42%)	0.327
Chorioamnionitis	6 (19%)	4 (7%)	0.091
Preeclampsia	2 (6%)	7 (12%)	0.488
PPROM	8 (25%)	15 (25%)	0.999
Asphyxia	12 (38%)	13 (22%)	0.104
EOS	18 (56%)	18 (30%)	**0.014**
PDA	14 (44%)	12 (20%)	**0.016**
PDA and EOS	13 (41%)	6 (10%)	**0.001**
Death within first week	13 (41%)	4 (7%)	**<0.001**
First laboratory tests			
pH, mean ± SD	7.25±0.12	7.28±0.09	0.418
BE (med, IQR)	-4.7 (-6.15 - -1.95)	-2.3 (-5.15 - -0.6)	0.270
Lactat (med, IQR)	2.55 (1.55 – 3.5)	2.1 (1.4 – 4.45)	0.838
0-24 hour CRP (med, IQR)	2 (2 – 2.2)	2 (2 - 2)	0.445
0-24 hour PCT (med, IQR)	1.46 (0.72 – 8.72)	0.43 (0.33 – 0.94)	**0.021**

ANS: Antenatal corticosteroid, PPROM: Preterm prolonged rupture of membranes, EOS: Early onset sepsis, PDA: Patent ductus arteriosus.

The time-averaged maximum velocity (TAMAX) (cm/s), representing the average velocity, was calculated using the equation:

PI = (PSV – PDV) / TAMAX (Camfferman *et al.* 2020; Arman *et al.* 2020).

The primary outcome was to evaluate the association between MCA Doppler parameters measured in the first five days of life and subsequent development of IVH. Secondary outcomes were to determine which parameters and clinical characteristics were associated with MCA Doppler flow changes in infants with IVH.

Statistical Analysis

Categorical variables were summarized as numbers and percentages, while numerical variables were presented as mean and standard deviation or as median and interquartile range (IQR), where appropriate. Chi-square tests were used to compare categorical variables between groups. When the assumption of expected frequencies was met, the Pearson Chi-square test was applied; otherwise, the Fisher's Exact test was used.

The normality of numerical data distribution was assessed using the Shapiro-Wilk test. If the assumption of normality was satisfied, comparisons between groups were performed using the Independent Samples T-test. If normality assumptions were not met, the Mann-Whitney U test was applied.

Logistic regression analysis was conducted to determine the risk factors associated with the IVH outcome. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant for all tests. Given the multiple comparisons performed in Table 2 (over 60 tests), we applied the Benjamini-Hochberg correction to control the false discovery rate at 5%. Adjusted p-values are reported where applicable.

RESULTS

During the study period, 101 infants were born weighing between ≤1250 grams and ≥500 grams. Nine infants were excluded from the study: two due to twin-to-twin transfusion syndrome, one with congenital heart disease and limb anomalies, one with trisomy 18, one due to missing data, and four who died on the first day of life. The mean birth weight of the remaining 92 infants was 909.4 ± 211.2 grams, and their mean gestational age was 26.6 ± 2.1 weeks. A total of 60.8% (n = 56) of these infants weighed less than 1000 grams. IVH was detected in 32 of the 92 infants (34.7%). IVH severity distribution was as follows: Grade 1 (n = 6), Grade 2 (n = 10), Grade 3 (n = 6), and Grade 4 (n = 10). The timing of IVH detection relative to daily Doppler measurements was 2.75 ± 0.98 days (median [IQR]: 3 days).

In infants who developed IVH, gestational age and birth weight were lower. Additionally, the presence of early-onset sepsis (EOS), patent ductus arteriosus (PDA), both EOS and PDA together, and mortality rates were significantly higher ($p = 0.002$, $p = 0.001$, $p = 0.014$, $p = 0.016$, $p = 0.001$, and $p < 0.001$, respectively). Procalcitonin (PCT) values in the first 24 hours were also significantly higher in infants who developed IVH ($p = 0.021$). The characteristics of the groups are presented in Table 1.

Multivariable logistic regression analysis including birth weight, gestational age, EOS, PDA, and their interactions revealed that for every 100-gram decrease in birth weight, the risk of IVH increased by 1.41 times (95% CI: 1.11–1.79, $p = 0.005$). The presence of both sepsis and PDA increased the risk of IVH by 5.65 times (95% CI: 1.77–18.06, $p = 0.003$). [Model fit: Nagelkerke $R^2 = 0.269$; Hosmer-Lemeshow test $p = 0.237$. Variance inflation factors were <2.5 for all predictors, indicating no significant multicollinearity.]

When we examined whether there were any early warning differences in MCA Doppler measurements before IVH onset, it was determined that changes in MCA blood flow were bidirectional. In other words, some patients exhibited lower blood flow values, while others showed higher blood flow values compared to the day IVH was detected (Table 2). Due to the large number of statistical comparisons performed (>60 tests) without correction for multiple testing, many of these p-values should be interpreted with caution as they may represent false-positive findings. Additionally, comparisons involving very small subgroups (n = 2 for Day 5 IVH group) lack statistical validity and are presented for descriptive purposes only.

DISCUSSION

Cerebral blood flow (CBF) dysfunction, caused by immature or irregular cerebral vascular autoregulation, is an important factor in the pathogenesis of intraventricular hemorrhage (IVH) (Vohr 2022; Garvey *et al.* 2022). Premature neonates are exposed to various factors leading to hemodynamic instability, such as maternal chorioamnionitis, early neonatal sepsis, patent ductus arteriosus (PDA), and neonatal hypoxia, all of which can affect CBF perfusion both before and after birth. Both high and low perfusion can lead to fluctuating CBF, increasing the risk of brain injury (Soul *et al.* 2007).

Although premature infants may establish an autonomous regulatory mechanism for CBF, they are more susceptible to regulatory dysfunction caused by these external factors (Rhee *et al.* 2014). Therefore, using systemic blood pressure measurements alone to indirectly reflect abnormal CBF dynamics may not provide an accurate assessment (Rhee *et al.* 2016). In premature infants, changes in cerebrovascular hemodynamics and fluctuations in CBF velocity have been reported to increase the risk of IVH (Farag *et al.* 2022).

Some studies have used superior vena cava flow (SVCF) as an indirect reflection of CBF and concluded that fluctuations in SVCF are a critical risk factor for IVH, whereas SVCF stability may prevent IVH (Rhee *et al.* 2016). In a study by Kluckow *et al.* it was suggested that low SVCF may result from an immature myocardium struggling to adapt to increased extrauterine vascular resistance (Kluckow & Evans 2000). Critically low flow can occur when high mean airway pressure and large ductal shunts divert blood from the systemic circulation, and late-onset IVH development is strongly associated with these low-flow conditions. They proposed that IVH may develop as perfusion improves.

McNamara *et al.* suggested that SVCF is not a direct surrogate for total body blood flow. They argued that, since the brain is primarily perfused by preductal cardiac output, the expected increase in left ventricle output (LVO) in the presence of a left-to-right PDA shunt should lead to an increase in SVCF (Bischoff *et al.* 2021). However, they found that SVCF was preserved in patients with left-to-right shunts, independent of increased preductal cardiac output, suggesting that SVCF may not reliably predict cerebral perfusion autoregulation.

In a study investigating the relationship between abnormal blood pressure variability (BPV) and anterior cerebral artery resistive index (ACA-RI) in premature infants, systolic blood pressure (SBP) in infants with IVH showed a significant positive correlation with ACA-RI, while BPV indicators were not correlated with ACA-RI in the non-IVH group (Jiang *et al.* 2023).

Several studies have reported that cerebrovascular blood flow velocity and RI are important indicators of CBF in premature neonates (Altit *et al.* 2022; Pazandak *et al.* 2020). Schneditz *et al.* found that higher ACA-RI levels in premature infants were associated with cerebral ischemia and hypoxia (Baik-Schneditz *et al.* 2020).

In our clinic, infants weighing less than 1500 g are routinely evaluated with near-infrared spectroscopy (NIRS), cranial ultrasonography (cUS), and targeted echocardiography during the first three days of life, and their treatments are planned accordingly. When deviations are detected in MCA flow parameters compared

Tab. 2. Measurements before IVH development

Measures (cm/sn), mean ± SD	**IVH (+) (n=32)**	**IVH (-) (n=60)**	***p***
Comparison of those with IVH on day 2 with those without IVH (n=10)			
1st day measures			
PSV	29.2±9.1	26.7±8.0	0.379
PDV	4.83±3.12	5.08±2.92	0.808
PI	1.51±0.41	1.58±0.35	0.617
RI	0.79±0.11	0.80±0.09	0.826
TAMAX	15.8±5.4	14.0±4.3	0.243
Comparison of those with IVH on day 3 with those without IVH (n=12)			
1st day measures			
PSV	32.9±12.4	26.7±8.0	0.119
PDV	4.98±3.65	5.08±2.92	0.920
PI	1.84±0.41	1.58±0.35	**0.024**
RI	0.84±0.08	0.80±0.09	0.176
TAMAX	16.3±6.5	14.0±4.3	0.251
2nd day measures			
PSV	38.4±18.2	31.4±10.2	0.220
PDV	7.28±5.69	7.08±3.21	0.909
PI	1.61±0.41	1.51±0.4	0.439
RI	0.79±0.09	0.77±0.08	0.380
TAMAX	24.3±9.4	17±5.3	**0.022**
Comparison of those with IVH on day 4 with those without IVH (n=6)			
1st day measures			
PSV	30.2±10.6	26.7±8.0	
PDV	7.04±2.94	5.08±2.92	
PI	1.4±0.42	1.58±0.35	
RI	0.76±0.08	0.80±0.09	
TAMAX	18±8.5	14.0±4.3	
2nd day measures			
PSV	42.2±16	31.4±10.2	
PDV	9.64±10.39	7.08±3.21	Explarotary/ descriptive only - no statistical testing[§]
PI	1.71±0.68	1.51±0.4	
RI	0.78±0.13	0.77±0.08	
TAMAX	22±13.1	17±5.3	
3rd day measures			
PSV	34.3±13.9	36.5±11.0	
PDV	5.74±1.51	7.66±3.24	
PI	1.86±0.48	1.55±0.38	
RI	0.82±0.06	0.77±0.09	
TAMAX	15.1±3.9	19.2±5.7	

Measures (cm/sn), mean ± SD	IVH (+) (n=32)	IVH (-) (n=60)	*p*
***Comparison of those with IVH on day 5 with those without IVH (n=2)**			
1st day measures			
PSV	33.1±0.3	26.7±8.0	Explarotary/ descriptive only - no statistical testing§
PDV	2.61±1.49	5.08±2.92	
PI	2.36±0.23	1.58±0.35	
RI	0.88±0.0	0.80±0.09	
TAMAX	12.9±0.4	14.0±4.3	
2nd day measures			
PSV	38.2±5.2	31.4±10.2	
PDV	4.15±0.9	7.08±3.21	
PI	2.12±0.58	1.51±0.4	
RI	0.86±0.08	0.77±0.08	
TAMAX	16.3±1.6	17±5.3	
3rd day measures			
PSV	33.3±15.3	36.5±11.0	
PDV	2.77±1.56	7.66±3.24	
PI	1.98±0.47	1.55±0.38	
RI	0.88±0.08	0.77±0.09	
TAMAX	15.1±5.1	19.2±5.7	
4th day measures			
PSV	53.3±9.6	37.0±13.2	
PDV	5.09±5.72	8.38±3.71	
PI	2.24±0.81	1.53±0.40	
RI	0.9±0.14	0.76±0.12	
TAMAX	22±0.7	19.8±7.8	

PSV: Peak systolic velocity, PDV: Peak diastolic velocity, PI: Pulsatility index, RI: Resistivity index, TAMAX: Time average maximum velocity.
§: Small group analysis do not support clinical decision-making
*Sample size insufficient for valid statistical inference - presented for descriptive purposes only.
(Note: Comparisons with sample sizes n<5 are statistically underpowered and should not be used for clinical inference. P-values from multiple comparisons have not been adjusted and should be interpreted cautiously.)

to previously established reference values, treatment is selected based on the underlying cause of these deviations.

In this study, we observed that there were both increases and decreases in MCA flow parameters preceding IVH. Hemodynamic corrective measures applied to these patients (such as closure of hsPDA and prevention of blood pressure fluctuations) were successful. After treatment, MCA flow values normalized, and hemorrhages were limited to stage 1 or 2. However, this observational design limits our ability to determine whether the observed associations reflect causal relationships or whether interventions targeting these fluctuations can prevent IVH. Since the model explains <27% of IVH variance, indicating substantial unmeasured or residual confounding (e.g., cerebral metabolism, autoregulatory reserve, genetic susceptibility), MCA Doppler parameters should not be used in isolation for clinical decisions. This suggests multiple pathophysiologic pathways. MCA Doppler alone cannot predict hemorrhage directionality or severity; the underlying etiology (PDA, systemic hypotension, sepsis) requires targeted investigation. Prospective interventional trials are needed to establish causality.

This study has several important limitations. First, it was a single-center study with a relatively small sample size, which limits generalizability. Second, transcranial ultrasound and Doppler assessments were performed only once daily, providing point-in-time data rather than continuous monitoring and potentially missing transient hemodynamic fluctuations. Third, the lack of blinding in outcome assessment introduces potential bias. Fourth, multiple statistical comparisons (>60 tests) without correction increase the risk of false-positive findings. Fifth, subgroup analyses with very small sample sizes (n = 2-6) lack statistical power and validity. Sixth, the retrospective identification of associations does not demonstrate prospective predictive utility or establish causation. Seventh, inter-observer reliability was not assessed as measurements were performed by a single operator. As a result, the study could not capture the full extent of dynamic cerebral hemodynamic fluctuations that may precede intraventricular hemorrhage. Future multicenter studies with larger cohorts and continuous monitoring approaches are needed to confirm and expand upon our findings.

In conclusion, MCA Doppler flow fluctuations (bidirectional changes in PSV, PDV, PI and TAMAX) preceded IVH. However, the bidirectional nature of these changes, small sample size, and single-center design limit conclusions regarding predictive utility. This study cannot establish causality or predictive clinical utility. Prospective multicenter studies with blinded outcome assessment and continuous hemodynamic monitoring are required before MCA Doppler can be recommended for clinical implementation in IVH prevention strategies.

REFERENCES

1 Arman D, Sancak S, Gürsoy T, Topcuoğlu S, Karatekin G, Ovalı F (2020). The association between NIRS and Doppler ultrasonography in preterm infants with patent ductus arteriosus. J Matern Fetal Neonatal Med **33**: 1245–1252.

2 Baik-Schneditz N, Höller N, Urlesberger B, Schwaberger B, Schmölzer GM, Pichler G (2020). Cerebral Doppler resistance index (RI) is associated with regional cerebral oxygenation. Acta Paediatr **109**: 2299–2301.

3 Bischoff AR, Giesinger RE, Stanford AH, Ashwath R, McNamara PJ (2021). Assessment of superior vena cava flow and cardiac output in different patterns of patent ductus arteriosus shunt. Echocardiography **38**: 1524–1533.

4 Camfferman FA, De Goederen R, Govaert P, Dudink J, Van Bel F, Pellicer A, Cools F (2020). Diagnostic and predictive value of Doppler ultrasound for evaluation of the brain circulation in preterm infants: a systematic review. Pediatr Res **87**: 50–58.

5 Cizmeci MN, De Vries LS, Ly LG, Van Haastert IC, Groenendaal F, Kelly EN, Traubici J, Whyte HE, et al. (2020). Periventricular hemorrhagic infarction in very preterm infants: characteristic sonographic findings and association with neurodevelopmental outcome at age 2 years. J Pediatr **217**: 79–85.e71.

6 Farag MM, Gouda MH, Almohsen AMA, Khalifa MA (2022). Intraventricular hemorrhage prediction in premature neonates in the era of hemodynamics monitoring: a prospective cohort study. Eur J Pediatr **181**: 4067–4077.

7 Garvey AA, Walsh BH, Inder TE (2022). Pathogenesis and prevention of intraventricular hemorrhage. Semin Perinatol **46**: 151592.

8 Hwang-Bo S, Seo Y-M, Oh M-Y, Im S-A, Youn Y-A (2022). The prognosis of refractory hypotension and severe intraventricular hemorrhage in very low birth weight infants. Medicine (Baltimore) **101**:e29598.

9 Jiang L, Yu Q, Wang F, Wu M, Liu F, Fu M, Gao J, Feng X, et al. (2023). The role of blood pressure variability indicators combined with cerebral blood flow parameters in predicting intraventricular hemorrhage in very low birth weight preterm infants. Front Pediatr **11**: 1241809.

10 luckow M, Evans N (2000). Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Arch Dis Child Fetal Neonatal Ed **82**: F188–F194.

11 Lightburn MH, Gauss CH, Williams DK, Kaiser JR (2013). Observational study of cerebral hemodynamics during dopamine treatment in hypotensive ELBW infants on the first day of life. J Perinatol **33**: 698–702.

12 McCrea HJ, Ment LR (2008). The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol 3**5**: 777–792.

13 Pazandak C, Mir IN, Brown LS, Chalak LF (2020). Placental pathology, cerebral blood flow, and intraventricular hemorrhage in preterm infants: is there a link? Pediatr Neurol **108**: 65–69.

14 Pellicer A, Del Carmen Bravo M (2011). Near-infrared spectroscopy: a methodology-focused review. Semin Fetal Neonatal Med **16**: 42–49.

15 Perlman JM (2022). Periventricular-intraventricular hemorrhage in the premature infant: a historical perspective. Semin Perinatol **46**: 151591.

16 Pezzati M, Dani C, Biadaioli R, Filippi L, Biagiotti R, Giani T, Rubaltelli FF (2002). Early postnatal Doppler assessment of cerebral blood flow velocity in healthy preterm and term infants. Dev Med Child Neurol **44**: 745–752.

17 Rhee CJ, Fraser III CD, Kibler K, Easley RB, Andropoulos DB, Czosnyka M, Varsos GV, Smielewski P, et al. (2014). The ontogeny of cerebrovascular pressure autoregulation in premature infants. J Perinatol **34**: 926–931.

18 Rhee CJ, Kaiser JR, Rios DR, Kibler KK, Easley RB, Andropoulos DB, Czosnyka M, Smielewski P, et al. (2016). Elevated diastolic closing margin is associated with intraventricular hemorrhage in premature infants. J Pediatr **174** :52–56.

19 Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, Disalvo DN, Moore M, et al. (2007). Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. Pediatr Res **61**: 467–473.

20 Taylor GA, Short B, Walker L, Traystman R (1990). Intracranial blood flow: quantification with duplex Doppler and color Doppler flow US. Radiology **176**: 231–236.

21 Vesoulis ZA, Flower AA, Zanelli S, Rambhia A, Abubakar M, Whitehead HV, Fairchild KD, Mathur AM (2020). Blood pressure extremes and severe IVH in preterm infants. Pediatr Res **87**: 69–73.

22 Vohr BR (2022). Neurodevelopmental outcomes of premature infants with intraventricular hemorrhage across a lifespan. Semin Perinatol **46**: 151594.

23 Volpe JJ (2025). Neurology of the Newborn. 8th ed. Philadelphia, PA: Elsevier.

24 Zubrow AB, Hulman S, Kushner H, Falkner B (1995). Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. J Perinatol **15**: 470–479.

