



Changes in Internal Cerebral Vein Pulsation and Intraventricular Hemorrhage in Extremely Preterm Infants

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Abstract

Objectives This study aimed to investigate the relationship between internal cerebral vein (ICV) pulsation and intraventricular hemorrhage (IVH) and to identify the cut-off values that predict IVH. We hypothesized that the severity of ICV flow pulsations was related to IVH severity.

Study Design In this prospective observational study, ICV flow was measured in 61 extremely preterm infants using ultrasonography at every 12 hours until 96 hours after birth and on days 7, 14, and 28. The ICV pulsation index (ICVPI = minimum/maximum ICV speed) was calculated and compared among the groups determined by Papile's IVH classification. The ICVPI cut-off values for IVH were determined by receiver operating characteristic curve analysis.

Results Compared with those in the no IVH (NIVH) group ($n = 51$), the ICVPI median values in the severe IVH (SIVH; grades 3 and 4) group ($n = 5$) were lower at 25 to 96 hours and on day 7, whereas those in the mild IVH (MIVH; grades 1 and 2) group ($n = 5$) were lower at 37 to 60 hours. All SIVH events were initially detected within 60 hours after birth. The ICVPI cut-off values for SIVH were 0.92 at 13 to 24 hours, 0.42 at 25 to 36 hours, 0.58 at 37 to 48 hours, and 0.55 at 49 to 60 hours. Infants whose ICVPI values were below the cut-off value ≥ 3 times between 13 and 60 hours had a significantly higher SIVH incidence than those whose ICVPI values were below the cut-off value ≤ 2 times (57.1 vs. 1.9%, $p < 0.001$).

Conclusion Our results indicate that SIVH had sustained pronounced internal cerebral vein pulsations and that the ICVPI values may help predict SIVH. Further research on strategies to decrease venous pressure for IVH prevention is needed.

Keywords

- ▶ intraventricular hemorrhage
- ▶ internal cerebral vein pulsation
- ▶ infants
- ▶ postnatal circulatory adaptation

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Key Points

- IVH preterm infants had sustained ICV pulsations.
- ICV flow in SIVH pulsated stronger.
- ICVPI fluctuation implies postnatal adaptation.
- We newly defined ICVPI to predict SIVH.

Intraventricular hemorrhage (IVH) is a severe complication in infants with very low birth weight (VLBW), although accurate IVH predictors have not been established. The germinal matrix, as a focus of IVH, is a region where abundantly vascularized glial and neuronal precursor cells accumulate in the developing brain.¹ The multifactorial pathogenesis of IVH is primarily attributed to the intrinsic vulnerability of the germinal matrix vasculature and fluctuations in the cerebral blood flow.^{1,2} Elevated cerebral venous pressure has been suggested as a contributing factor for IVH.² Recently, pulsations or partial interruptions in the internal cerebral vein (ICV) blood flow have been described as candidate risk factors for IVH in infants with extremely low birth weight.³ The ICV constitutes the cerebral deep venous system and drains most of the subependymal veins into the great vein of Galen. The major source of IVH in VLBW infants involves capillaries or small venules of the subependymal germinal matrix which are thin-walled and fragile vessels that can easily cause bleeding.^{2,4} The venous blood flow from the germinal matrix drains into the subependymal veins upstream of the ICV.⁵ The junction of the subependymal veins and ICV in the foramen of Monro forms a U-shaped venous angle where the blood flow sharply changes its direction.² This “U-turn” might increase the venous pressure in the germinal matrix, and the anatomical peculiarity and vulnerability of the vessels may easily cause intraventricular bleeding in VLBW infants.

In newborns, the ICV blood flow normally exhibits a steady flow pattern.⁶ Ikeda et al measured the ICV blood flow in infants with extremely low birth weight at every 3 hours until 144 hours after birth and classified four patterns as follows: grade 0, constant perfusion speed; grade 1, mild pulsatile flow (minimum speed/maximum speed \geq 0.5); grade 2, pronounced pulsatile flow (minimum speed/maximum speed $<$ 0.5); and grade 3, partially interrupted flow (minimum speed = 0 cm/s). The infants were categorized according to these grades during the measurement period. The incidence of IVH was significantly higher in the high-grade (grades 2 and 3) than in the low-grade (grades 0 and 1) groups.³ These pulsations and interruptions may be induced by elevated central venous pressure, and an increase in ICV pulsation or the interruption of the ICV flow may be caused by stronger atrial contraction waves which are derived from increased atrial pressure.⁷ However, the use of ICV pulsation to prevent IVH has not been established yet. If augmentation of ICV pulsation precedes IVH, ICV pulsation could potentially be a predictor of IVH. In this study, we hypothesized that the severity of ICV flow pulsations is related to IVH severity, because ICV flow pulsations may directly reflect central venous pressure. The objective of this study

was to assess the relationship between a newly defined ICV pulsation index (ICVPI) and IVH in premature infants. Additionally, we determined the ICVPI cut-off value to predict IVH.

Materials and Methods

In this prospective observational study, we enrolled VLBW infants ($<$ 1,500 g) with $<$ 28 weeks of gestational age. The infants were born in our hospital between April 2015 and March 2020. All examinations and procedures were approved by the Institutional Review Board of Kumamoto University (registration no. 2204), and written informed consent was obtained from the parents of the patients before the ultrasound examination.

All six physicians who participated in this study were specialists in neonatal echography. Ultrasound examinations of the ICV blood flow were conducted via the anterior fontanelle to visualize the ICV in the sagittal plane using the pulsed wave Doppler method and to assess the presence of IVH. The right or left ICV was examined depending on whichever vein's shape was clearer on an initial assessment. The first examination was performed within 12 hours after birth, and measurements were subsequently continued at every 12 hours until 96 hours after birth; follow-up examinations were performed on days 7, 14, and 28. Thus, 11 measurements were performed. All participants, including those in the severe IVH (SIVH) group, did not have any complications that would have prevented their discharge. Therefore, before discharge, brain magnetic resonance imaging (MRI) was performed, and the presence of IVH was checked. Infants were excluded if they met one of the following criteria: (1) they died within 96 hours after delivery; (2) their ICV blood flow was measured less than six times; (3) they had congenital heart disease, major malformations, or chromosomal abnormalities; (4) IVH was confirmed at birth; (5) they did not undergo an MRI examination; or (6) IVH was only confirmed by MRI and not by ultrasonography. The ultrasound devices used were a General Electronics VIVID S6 (GE Healthcare, Milwaukee, WI) with a 5.7- or 8.0-MHz transducer or a VIVID S70 (GE Healthcare, Milwaukee, WI) with a 6.2- or 7.0-MHz transducer. The 7.0- and 8.0-MHz transducers were used for two-dimensional examinations, whereas the 5.7- and 6.2-MHz transducers were used for color Doppler flow recordings. We used VIVID S6 from April 2015 to March 2017 and VIVID S70 from April 2017 to March 2020.

The minimum and maximum speed values of ICV blood flow were determined, and the ICVPI was calculated as the ratio of the ICV minimum speed/ICV maximum speed. Each

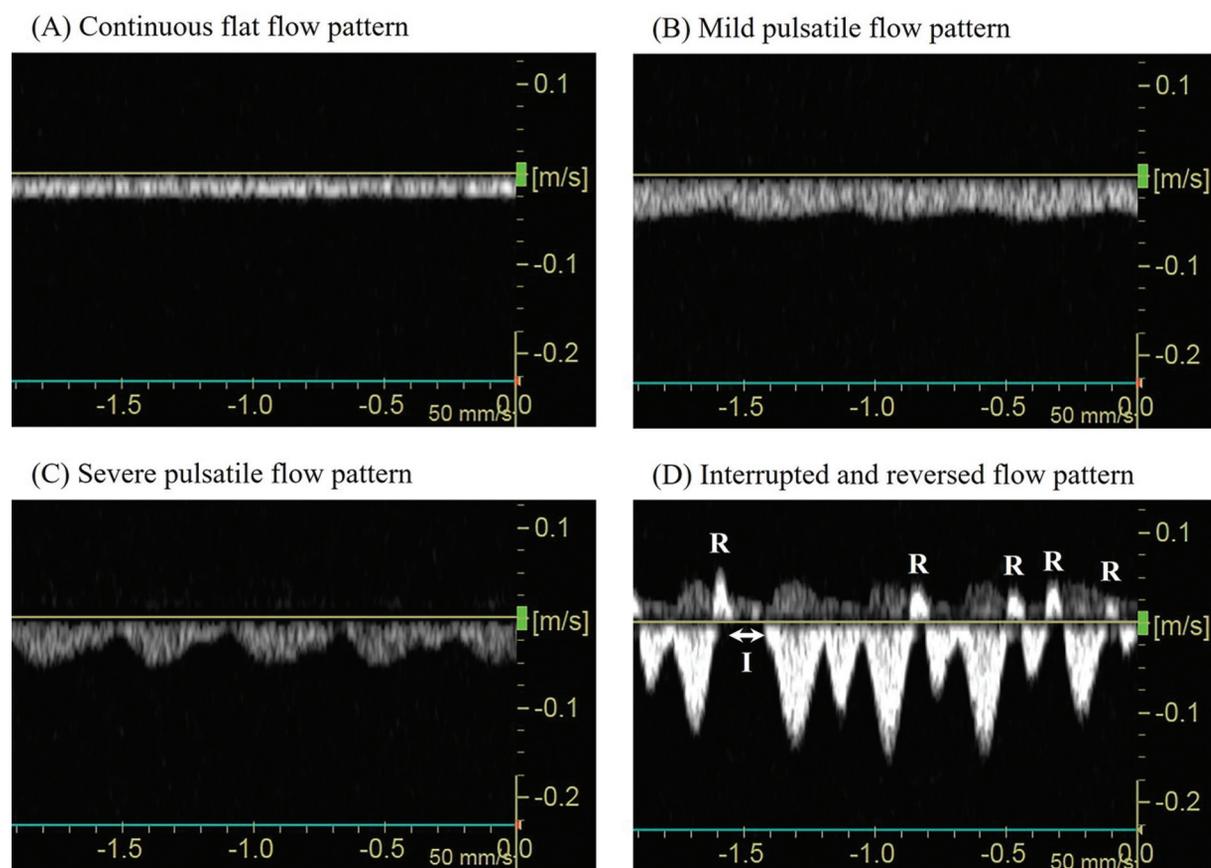


Fig. 1 Internal cerebral vein flow waveform and speed. (A) Continuous flat flow pattern. The ICVPI value is 1.00 (2.86 cm/s). (B) Mild pulsatile flow pattern. The ICVPI value is 0.77 (maximum speed, 5.13 cm/s; minimum speed, 3.96 cm/s). (C) Severe pulsatile flow pattern. The ICVPI value is 0.37. (maximum speed, 5.31 cm/s; minimum speed, 1.96 cm/s). (D) Interrupted (I) and reversed (R) flow pattern. The ICVPI value is 0.00. ICVPI, internal cerebral vein pulsation index.

ICVPI value was determined as the mean value of three to five measurements. The ICVPI is 1.00 if there is no fluctuation in ICV blood flow. If the ICV blood flow is interrupted (minimum speed = 0 cm/s) or partially reversed (minimum speed < 0 cm/s), the ICVPI is set as 0.00 (→ Fig. 1).

The patients were classified into three groups according to IVH severity.⁸ The IVH severity was determined by the highest Grade of IVH recorded during 28 days after birth. Those without IVH were categorized as having no IVH (NIVH), those with grade 1 or 2 IVH as having mild IVH (MIVH), and those with grade 3 or 4 IVH as having SIVH. We collected data regarding perinatal parameters, such as gestational age, birth weight, 1-minute Apgar's score, 5-minute Apgar's score, sex, mode of delivery, antenatal steroid use (if the mother received betamethasone 12-mg intramuscularly, repeated once in 24 hours for two doses, and delivered within 1 week after administration of a single course), histologically diagnosed chorioamnionitis, sepsis, hypotension (defined as a mean blood pressure [in mm Hg] less than the gestational age in weeks,⁹ treatment using volume load [bolus 10–15 mL/kg], and/or catecholamine administration during the first 3 days of life), and high-frequency oscillations.

JMP 14 (SAS Institute Inc., Cary, NC) was used for statistical analyses. The Mann–Whitney *U*-test was used to compare ICVPI values and other continuous variables among the three

groups, and Fisher's exact test was used to compare the incidence rates. The significance level was adjusted according to the Bonferroni correction in case of multiple testing. To determine the ICVPI cut-off value for predicting the IVH risk, we performed a receiver operating characteristic curve analysis. A *p*-value of < 0.05 was considered statistically significant.

Results

Of 91 VLBW infants with < 28 weeks' gestational age who were born in our institution, 61 were included in this study (→ Fig. 2). Ultrasound examinations were performed 601 of 671 times (89.6%; median value, 10 times [25th, 75th percentiles: 9, 11]). The reasons for not performing an examination were the critical conditions of patients (11 of 671 times), transferred to another hospital (twice), died after 96 hours of age (thrice), and if the examiner forgot to measure the ICV blood flow (54 times). The median (25th, 75th percentiles) values for gestational age and birth weight were 25 (24, 26) weeks and 712 (612, 863) g, respectively. The NIVH, MIVH, and SIVH groups comprised 51, 5, and 5 infants, respectively. In the MIVH and SIVH groups, two, three, four, and one infant(s) were diagnosed with IVH at 25 to 36, 37 to 48, 49 to 60, and 73 to 84 hours,

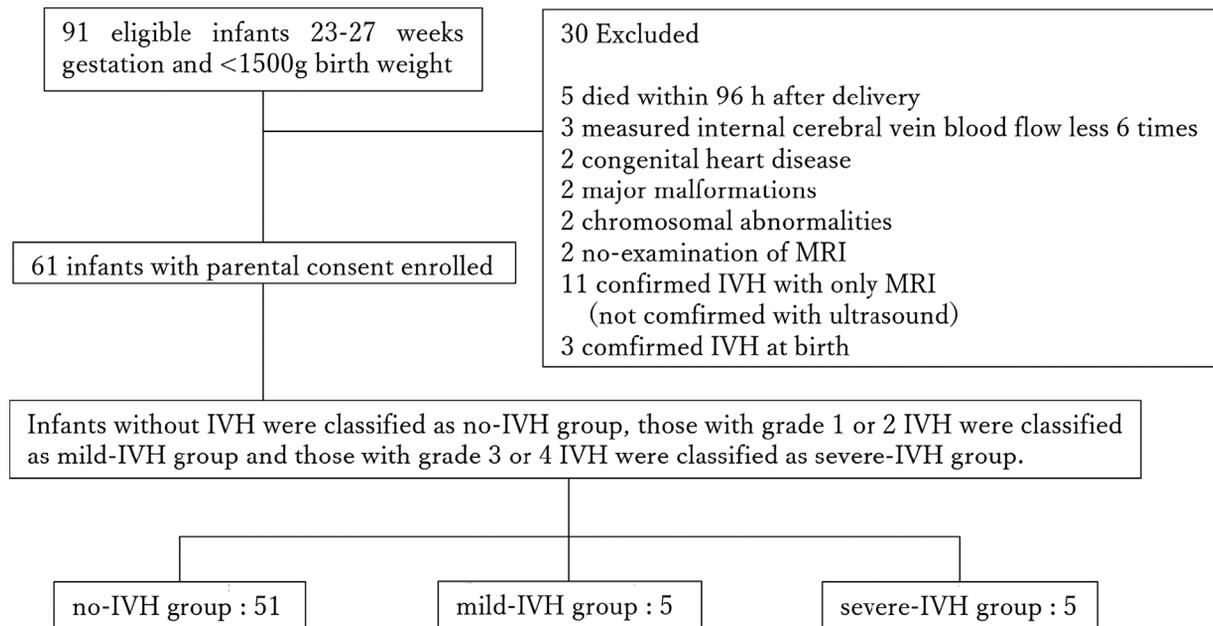


Fig. 2 Flowchart describing the enrollment of extremely preterm infants including their classification into the study groups. IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging.

respectively. **Table 1** shows the demographic and clinical characteristics of the study population; there were no significant differences among the three groups in this regard.

Fig. 3 and **Supplementary Table S1** (available in the online version) present the changes in ICVPI values in the three groups. The median ICVPI value of the NIVH group was 1.00 at 0 to 24 hours with a decrease in its minimum (0.73) at 37 to 48 hours, followed by an increase, returning to 1.00 on day 7 and sustained at this level afterward. In the MIVH group, the median ICVPI value was initially 1.00 at 0 to 24 hours, decreased to its minimum (0.48) at 37 to 48 hours,

and returned to 1.00 on day 14. The median ICVPI value of the SIVH group was 1.00 at 0 to 12 hours and decreased to the minimum of 0.00 at 37 to 72 hours which was followed by an increase to 1.00 on day 14 and sustained at this level afterward. The ICVPI values in the SIVH group were significantly lower than those in the NIVH group at 25 to 96 hours and on day 7, whereas those in the MIVH group were significantly lower than those in the NIVH group only at 37 to 60 hours. There was no significant difference in the ICVPI values between the SIVH and MIVH groups over the entire study period.

Table 1 Demographic and clinical characteristics of extremely preterm infants

	No IVH (n = 51) Medians (25th, 75th percentiles)/n (%)	Mild IVH (n = 5) Medians (25th, 75th percentiles)/n (%)	Severe IVH (n = 5) Medians (25th, 75th percentiles)/n (%)	p-Value (no vs. mild)	p-Value (no vs. severe)	p-Value (mild vs. severe)
Gestational age (wk)	26.0 (24.0, 26.0)	25.0 (24.0, 26.5)	24.0 (23.0, 26.5)	>0.99	>0.99	>0.99
Birth weight (g)	712 (608, 862)	702 (587, 852)	774 (626, 1,121)	>0.99	>0.99	>0.99
1-minute Apgar's score	3.0 (1.0, 4.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.5)	0.81	>0.99	>0.99
5-minute Apgar's score	6.0 (5.0, 6.0)	4.0 (2.5, 6.5)	5.0 (2.0, 5.5)	0.44	0.17	>0.99
Male sex	34 (67)	3 (60)	4 (80)	>0.99	>0.99	>0.99
Vaginal delivery	12 (24)	0 (0)	1 (20)	>0.99	>0.99	>0.99
Antenatal steroids	22 (43)	2 (40)	0 (0)	>0.99	0.43	>0.99
Chorioamnionitis	34 (67)	4 (80)	2 (40)	>0.99	>0.99	>0.99
Sepsis	4 (8)	1 (20)	1 (20)	>0.99	>0.99	>0.99
Hypotension	16 (31)	3 (60)	1 (20)	0.97	>0.99	>0.99
HFOV	9 (18)	0 (0)	3 (60)	>0.99	0.18	0.50

Abbreviations: HFOV, high frequency oscillatory ventilation; IVH, intraventricular hemorrhage.

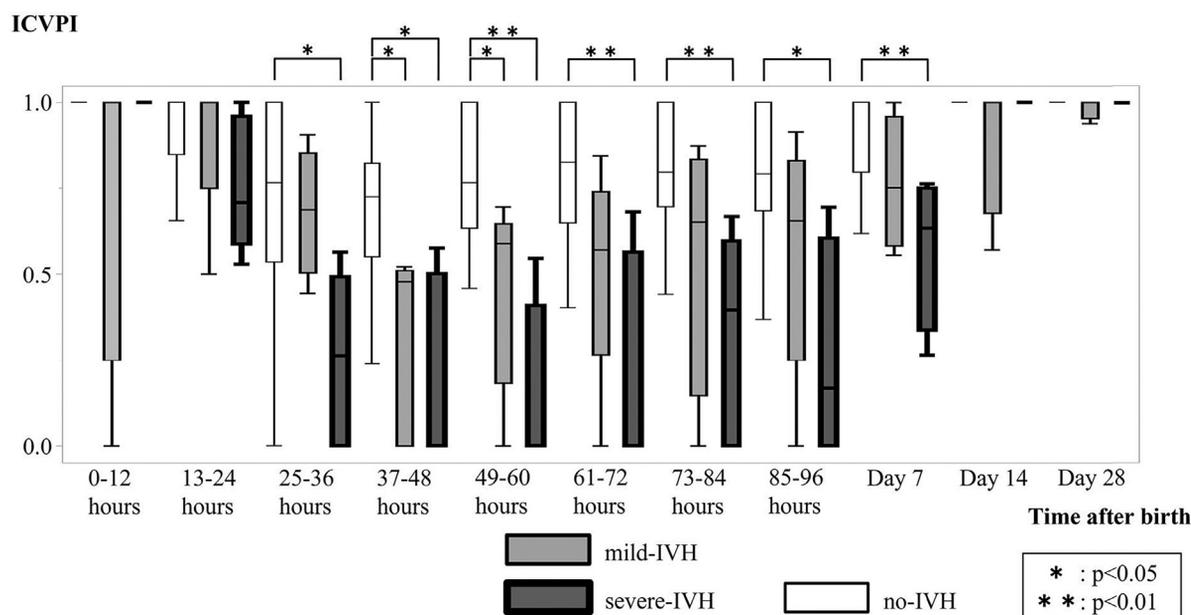


Fig. 3 Comparison of the internal cerebral vein pulsation index among the three study groups. ICVPI, internal cerebral vein pulsation index; IVH, intraventricular hemorrhage.

All cases of IVH in the SIVH group were first detected within 60 hours after birth (→Table 2). The ICVPI cut-off values for SIVH until 60 hours were 0.92 for 13 to 24 hours, 0.42 for 25 to 36 hours, 0.58 for 37 to 48 hours, and 0.55 for 49 to 60 hours (→Fig. 4). The cut-off value for 0 to 12 hours was unreliable due to the low area under the curve (AUC) value of 0.598.

→Table 2 shows the ICVPI transition in the SIVH group. The ICVPI values in the SIVH group were consistently lower than the cut-off values. Infants whose ICVPI values were below the cut-off value ≥ 3 times between 13 and 60 hours had a significantly higher SIVH incidence than those whose ICVPI values were below the cut-off value ≤ 2 times (57.1 vs. 1.9%, $p < 0.001$).

Discussion

The prediction of IVH in preterm infants has not been established yet. This study assessed the relationship between a newly defined ICVPI and IVH in premature infants and determined the ICVPI cut-off value to predict IVH. Our results indicated that the ICVPI value could be a useful predictor of SIVH because the ICVPI values were continuously lower for patients with SIVH than for those with NIVH.

Decreases in the ICVPI values indicate augmented ICV pulsations and might be caused by increases in the central venous pressure. Venous blood flow pulsatility, for instance, increases in fetuses that develop heart failure.¹⁰ The ICV pulsation waveform typically represents the venous triphasic waveform in echography.^{7,11} Decreases in venous flow are caused by the A- or V-wave generated by elevations in the right atrial pressure, leading to increased central venous pressure.^{7,12} Further deterioration causes an interrupted or reversed wave^{7,11,13,14} which corresponds to a 0 value in the ICVPI.

Ghazi-Birry et al reported that the hemorrhaging of IVH were venous sources,¹⁵ therefore IVH may be caused by an alternation in the cerebral venous system. In patients with IVH, the venous vessels within the germinal matrix are invariably distorted, probably reflecting an increase in the central venous pressure.⁴ IVH can develop as a complication of cerebral vein thrombosis, and the rupture of small blood vessels leading to IVH may be caused by increased venous pressure due to poor drainage of the vein of Galen or the straight sinus.¹⁶ Trevor Inglis et al reported that the mean central venous pressure was higher in a patient with parenchymal hemorrhage than in patients without parenchymal hemorrhage.¹⁷ As previously stated, an increase in venous pulsation indicates increased central venous pressure. Therefore, pronounced pulsations or an interrupted or reversed flow of the ICV (i.e., a low ICVPI score) may be a sign of IVH.⁷ In our population, the ICVPI values in the SIVH group were lower than those in the NIVH group between days 1 and 7, whereas the ICVPI values in the MIVH group were lower than those in the NIVH group for a shorter period (only at 37–60 hours). This finding suggested that patients with more severe IVH present a continuous pattern of low ICVPI values.

Immediately after birth, the median ICVPI value in each of the three study groups was 1.0. The ICVPI started to decrease from 13 to 24 hours in the SIVH group and from 25 to 36 hours in the MIVH and NIVH groups, reaching the minimum values of 0.0, 0.48, and 0.73 at 37 to 72 hours in the SIVH group, at 37 to 48 hours in the MIVH group, and at 37 to 48 hours in the NIVH group, respectively. Subsequently, the ICVPI increased in all groups and remained constant at a value of 1.0 from day 7 onward in the NIVH group and from day 14 onward in the MIVH and SIVH groups (→Fig. 3 and →Supplementary Table S1 [available in the online version]). Specifically, the median ICVPI values in the NIVH, MIVH, and

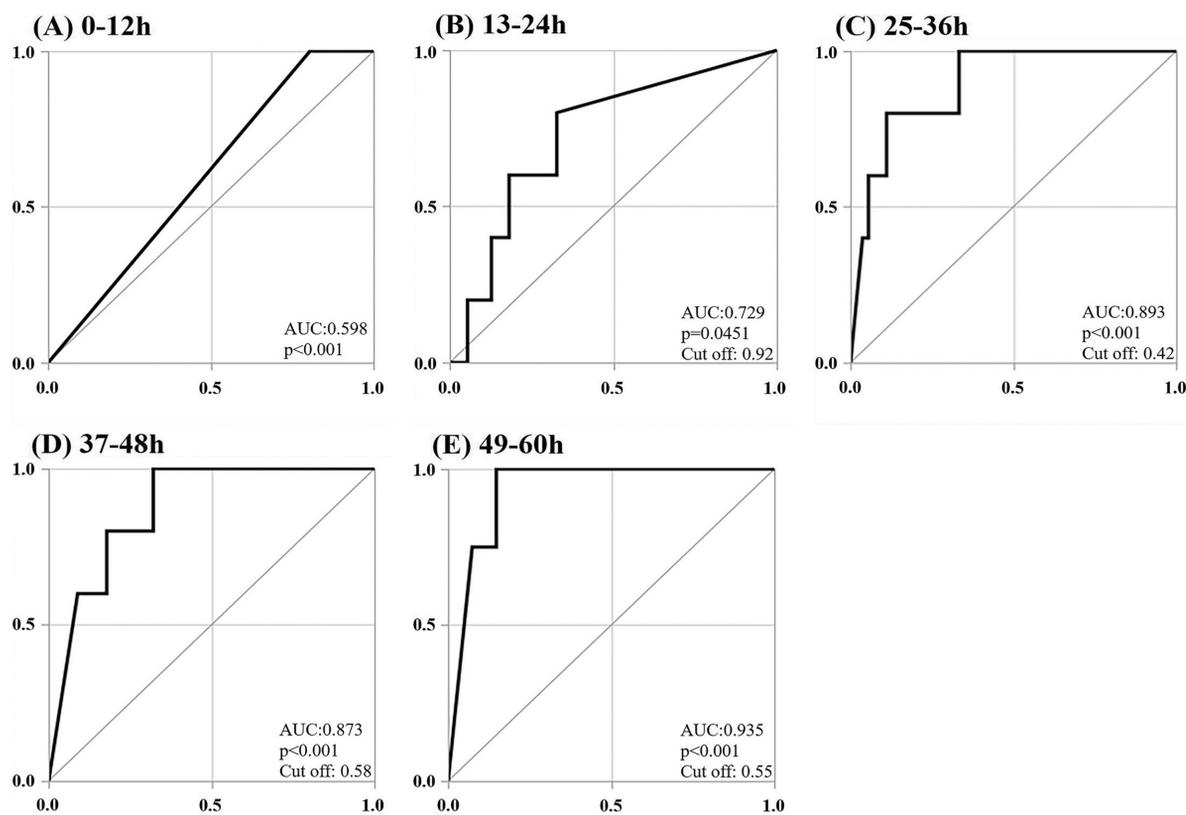


Fig. 4 Receiver operating characteristic curves of the internal cerebral vein pulsation index for the detection of severe intraventricular hemorrhage at (A) 0–12 hours, (B) 13–24 hours, (C) 25–36 hours, (D) 37–48 hours, and (E) 49–60 hours after birth. AUC, area under the curve.

SIVH groups declined from day 0 or 1 and increased after day 2. These ICVPI changes inversely reflect the fluctuations in the neonatal brain natriuretic peptide (BNP) levels which show a marked and rapid increase within the first days following delivery and a decline after the first 2 days of life.¹⁸ Therefore, the transient decrease in the ICVPI levels might represent the postnatal adaptation from fetal to neonatal circulation.

The ICVPI values decrease on days 0 and 1 might also indicate the increase in the right ventricular load. After birth, the right ventricular load increases over time. The right ventricular output and superior vena cava flow, a part of the venous return volume, increase progressively at least until 72 hours after birth.¹⁹ Additionally, the left ventricular load is also elevated. The left ventricle is exposed to increased preload because of a 5- to 10-fold higher pulmonary blood flow.^{20,21} Moreover, the perinatal loss of the low resistance placental circulation and a steady increase in blood pressure cause an increase in the afterload on the left ventricle.^{20,22} However, the left ventricle of a preterm infant has low distensibility, and preterm hearts might not be able to fully adapt to these load increases.²³ Consequently, the increase in the left ventricular load might increase the right ventricular load,^{21,24} causing an elevation in the central venous pressure and possibly a decrease in the ICVPI levels. Ikeda et al reported that elevated blood pressure values facilitated ICV pulsations.²⁵ This finding suggested that an increase in the left ventricle load caused a decrease in ICVPI.

ICVPI improvements after day 2 of life might reflect the postnatal circulatory adaptation. Plasma BNP levels decrease after day 2 of life.^{26,27} Ikemoto et al reported that these changes in BNP levels were paralleled by a decrease in pulmonary arterial pressure.²⁸ This indicated that a physiological decrease in pulmonary pressure after day 2 caused a decline in the right ventricular load, and this might have been one of the reasons for the observed ICVPI reevaluation.

In this study, all IVH events in the SIVH group were initially confirmed within 60 hours. Therefore, we assessed the ICVPI values at 0 to 60 hours as predictors of SIVH in extremely preterm infants using receiver operating characteristic curves. Our cut-off value was almost similar to that corresponding to grades 2 and 3 fluctuation of ICV flow identified by Ikeda et al ($0.0 \leq \text{ICVPI} < 0.5$) as a risk factor for IVH.³ However, the measured ICVPI values at 0 to 12 hours had insufficient accuracy for predicting SIVH because its AUC value of 0.598 was too low. The cut-off value at 13 to 24 hours (0.92) was higher than the values in all other periods (0.42–0.58) which corresponds to grade 2 based on Ikeda's classification. As aforementioned, the right ventricular load adjusts after birth, and this change may be responsible for the time-dependent variations in ICVPI cut-off values in our study. This also indicates that the ICVPI value, at which an intervention is needed, might change over time.

Regarding IVH prevention, a previous report evaluated pulsatile superior sagittal sinus flow in an infant affected by

large bilateral pleural effusion.²⁹ As experienced in our clinical setting, ICV pulsation tended to increase during crying or agitation, thus the elevation of intrathoracic pressure might cause the increase in ICV pulsation. In that work, following successful effusion treatment, the pulsation improved, thus suggesting that a reduction in intrathoracic pressure can relieve pulsations of the cerebral veins. Similarly, when low ICVPI values which may indicate an increase in central venous pressure, are recognized, load reduction therapy to decrease venous pressure might improve ICV pulsations and prevent IVH. In all SIVH cases except one, ICVPI values below the cut-off value were observed three or more times. Furthermore, in all SIVH cases, IVH was detected after at least one ICVPI value was below the cut-off. Therefore, to prevent SIVH, patients with continuously low ICVPI values may require load reduction therapy.

We analyzed this study according to Ikeda's grading system. The incident rate of grades 2 and 3 in the NIVH group was 41.2% (21/51), MIVH group was 60% (3/5), and SIVH group was 100% (5/5; [–Supplementary Table S2](#) [available in the online version]). We compared the incident rate of grades 0 and 1 with that of grades 2 and 3, among the three groups. The incident rate of grades 2 and 3 in the SIVH group was not significantly higher than the MIVH ($p = 1.000$) and NIVH ($p = 0.052$) groups and the incident rate of grades 2 and 3 in the MIVH group was not significantly higher than the NIVH group ($p = 1.000$), thus there was no significant difference among three IVH groups using Ikeda's grading system. However, due to the small number of cases for Ikeda's grading system, this study does not deny the usefulness of this system. Further investigation with a larger sample of infants is needed to estimate the Ikeda's grading system.

Limitations

This study had some limitations. First, cases in which IVH was only confirmed by MRI examination and not by ultrasound echography were excluded. Parodi et al reported that the sensitivity of cranial ultrasound examinations in detecting low-grade IVH is low (60%).³⁰ In these cases, the time of IVH onset was uncertain (i.e., the onset might have been in the antenatal period). Similarly, cases without brain MRI scans were also excluded from the study as IVH diagnosis was not confirmed. Second, cerebral venous flow is affected by many parameters, with intrathoracic pressure and cardiac function being the most important factors.^{7,29} In this study, respiratory and cardiac parameters were not sufficiently investigated; hence, further studies assessing these variables are needed. Third, we checked the right and left ICVs and measured whichever side showed a clearer form. However, the ICVs of both sides combine into the great vein of Galen and, thus, both sides may have almost the same pressure. Thus, the ICV flow pattern from one ICV may only be considered to be representative of both ICVs if no significant differences in vessel compliance or diameter are noted between the two sides.³¹ Further research is needed to investigate any difference in ICV pulsation between the left and right sides. Finally, this study included a limited number of patients with IVH; therefore, the

statistical analysis might have been inadequately powered to help identify a relationship between the low ICVPI levels and SIVH. Further investigation with more participants is needed to confirm our results.

Conclusion

The ICVPI values may be related to IVH, especially SIVH, in extremely preterm infants. A prolonged low ICVPI value might be a risk factor for SIVH, and the ICVPI value indicating the requirement of an intervention might change over time after birth. Further research on therapeutic strategies that decrease venous pressure to prevent IVH is needed.

Conflict of Interest

None declared.

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