Elevated diastolic closing margin is associated with intraventricular hemorrhage in premature infants

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Abbreviations:

ABP – arterial blood pressure

CBF – cerebral blood flow

CBFV – cerebral blood flow velocity

$PaCO_2$ – arterial carbon dioxide tension

CrCP – critical closing pressure

DCM – diastolic closing margin

EGA – estimated gestational age

IVH – intraventricular hemorrhage

NICU – neonatal intensive care unit

Abstract

Objective

To determine if the diastolic closing margin (DCM), defined as diastolic blood pressure minus critical closing pressure, is associated with the development of early severe intraventricular hemorrhage (IVH).

Study Design

A reanalysis of prospectively collected data from infants born from July 2002 to April 2008 was conducted. Mechanically ventilated premature infants (n = 185) with gestational age 23–31 weeks had ~1 hour continuous recordings of umbilical arterial blood pressure, middle cerebral artery cerebral blood flow velocity, and arterial carbon dioxide tension during the first week of life. Models using multivariate generalized linear regression and purposeful selection were used to determine associations with severe IVH.

Results

Severe IVH (grades 3–4) was observed in 14.6% of infants. Apgar score at 5-minutes and DCM were significantly associated with severe IVH, irrespective of the model. A clinically relevant 5-

mm Hg increase in DCM was associated with a 1.83–1.89 increased odds of developing severe

IVH.

Conclusion

Elevated DCM was associated with severe IVH, consistent with previous animal data showing

IVH is associated with hyperperfusion. Measurement of DCM may be more useful than blood

pressure in defining cerebral perfusion in premature infants.

Introduction

Instability of systemic and cerebral hemodynamics during transition and the early neonatal period in premature infants is thought to be associated with developing intraventricular hemorrhage (IVH). The most immature infants have the highest incidence of IVH, and subsequently have worse developmental delay, poorer cognition, and more cerebral palsy, seizure disorders, and visual impairment.[1]

A delicate balance is required to maintain adequate cerebral perfusion while avoiding too much (hyperperfusion) or too little (ischemia) cerebral blood flow (CBF), both of which may result in injury to the brain. IVH in premature infants originates from thin-walled, poorly supported, immature vessels of the germinal matrix.[2,3] Hypotension and low-flow states, as well as reperfusion hyperemia after ischemia have both been implicated in the pathogenesis of IVH in both human premature infants[4-6] and in experimental animal models.[7,8]

Blood flow to the brain of mammals is largely determined by cerebral perfusion pressure, which has been classically defined as arterial blood pressure (ABP) minus intracranial pressure.[9] A reasonable goal of hemodynamic management in the neonatal intensive care unit (NICU) is to target a cerebral perfusion pressure that prevents both ischemic and hyperemic states. However,

multiple efforts have failed to determine threshold values of mean ABP in premature infants to define either hypotension or hypertension.[10,11] Despite the theoretical benefits of maintaining mean ABP in an "optimal range" to maintain intact cerebral autoregulation, there is no evidence that outcomes have been improved by such efforts.[12,13] Treatment of hypotension may be deleterious and has been associated with developing IVH.[14] We have shown that hypotensive and normotensive premature infants have similar baseline CBF velocity (CBFV) prior to the treatment of hypotension, and that treatment of hypotension with dopamine was associated with CBFV that exceeded the typical values seen in normotensive premature infants.[15,16]

In this study, we propose an explanation for the lack of clear relationship between ABP, CBF, and IVH in premature infants. We suggest that, in premature infants, ABP is a poor surrogate for cerebral perfusion pressure. The reason for this assertion is that the critical closing pressure (CrCP) of the cerebral vasculature of premature infants is at or near resting mean ABP.[17]

CrCP is the ABP at which blood flow to the brain ceases due to vascular collapse. CrCP is posited to be the sum of vascular wall tension and intracranial pressure.[18] Thus, CrCP can be conceptualized as a point of zero reference for converting ABP to an "effective cerebral perfusion pressure" or "closing margin."[19,20] When diastolic ABP is equal to CrCP, CBF occurs

only during systole (Figure 1). The difference between diastolic ABP and CrCP is the diastolic

closing margin (DCM).[21] The DCM may be a better measure than mean ABP for defining

adequacy of brain perfusion pressure in premature infants, as it accounts for intracranial pressure

and developmental changes in vascular wall tension.

Our objective was to measure CrCP and calculate DCM in a cohort of premature infants during

the first week of life and evaluate the association of DCM and severe IVH. We hypothesized that

higher effective cerebral perfusion pressure (i.e., higher DCM) is associated with IVH in

premature infants. CrCP can be calculated from the interaction between CBFV measured with

transcranial Doppler and ABP at the frequency of the cardiac cycle. To test the hypothesis that

DCM is associated with severe IVH, we reanalyzed a historical data set containing high-

resolution recordings of both CBFV and umbilical artery ABP tracings, combined with the short-

term outcome of abnormal cranial ultrasound findings during the first week of life.

Methods

The present study is a reanalysis of previously published data prospectively collected from

infants born from July 2002 to April 2008.[15,22-25] Approval was obtained by the University of

Arkansas for Medical Sciences IRB, and informed parental consent was obtained before enrollment. Very low birth weight (<1500 grams) infants who were mechanically ventilated and had an umbilical artery catheter in place were potential subjects. Those with major congenital anomalies and chromosomal abnormalities, and those in extremis were excluded. Cranial ultrasounds were performed as close to birth as possible (usually within 1–2 hours) to assess for early and preexisting brain injury, between days of life 2–4, and finally at day of life 7.

Monitoring equipment, data acquisition and data handling

All infants had ABP measurement with an umbilical artery catheter placed for clinical monitoring. Middle cerebral artery CBFV was recorded with transcranial Doppler (Nicolet Vascular/Natus Medical Incorporated, San Carlos, CA). Arterial carbon dioxide tension ($PaCO_2$) was continuously recorded with a Neotrend-L fiber-optic sensor (Diametrics Medical Ltd, St. Paul, MN). Analog data were collected simultaneously using a PowerLab 8 Channel data acquisition system (AD Instruments, Mountain View, CA).

Physiologic data processing

Digitized files were analyzed using ICM+ software (ICM+, Cambridge Enterprise, UK). Artifact was removed using valid values range filters and by visual inspection of each individual recording. For all subjects, there were two 1-hour recording sessions on days of life 1 to 3 and

then a daily 1-hour session on days 4 to 7. Of 1,042 subject sessions, 688 subject sessions from

185 subjects had sufficient data to render a CrCP (median 4 recording sessions per subject). A

single mean CrCP was reported for each infant averaged across all subject sessions. We chose to

collapse the data to one-averaged session per subject as we felt that the multiple subject sessions

would create confusion because the number of sessions was inconsistent from subject to subject,

and there was only a small degree of variability between individual subject sessions. Trends of

systolic and diastolic CBFV and ABP were made by sequential analysis of transformed 10-

second segments. The algorithm implemented in ICM+ detects systolic peaks and diastolic

valleys using a modified Pan-Tompkins method, rendering a single vector for systole and

diastole covering the specified (10-second) buffer. Trends of mean CBFV and ABP were made

from consecutive 10-second averages of the 200 Hz primary signals.

Calculating critical closing pressure and diastolic closing margin

CrCP was calculated from ABP and CBFV tracings using equations derived from a model of the

cerebral vasculature with resistance and compliance in a parallel circuit. In this model, CBFV is

described by an alternating flow velocity at the frequency of the cardiac cycle, and CrCP is

derived from an equation of impedance to flow velocity. The full derivation of this method has

been previously described in detail and validated.[17,21] In brief, CrCP is first estimated from the

model by the equation:

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$$CrCP = ABP - \frac{ABP}{\sqrt{(CVR \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}}$$

where CVR is cerebral vascular resistance and Ca is cerebral arterial compliance, which are not directly measureable, but can be calculated using CBFV and ABP waveforms. The product of resistance and compliance is termed the time constant τ.[26] For each subject-session, DCM was calculated as diastolic ABP minus CrCP.

Statistics

A multivariate logistic model was built including univariate covariates with a threshold of p<0.1. A purposeful selection modeling approach guided the building of an additional multivariate logistic regression model to determine associations of covariates with severe IVH (grades 3–4).[27] Variables and characteristics potentially related to severe IVH (vs 0–2) were tested in univariate analyses (t-test, Wilcoxon rank-sum test, or chi-square test, as appropriate) and included: estimated gestation age (EGA), gender, mode of delivery, multiple gestation, 5-minute Apgar score, use of vasopressors, mean ABP, mean CBFV, mean DCM, and mean $PaCO_2$. Multicollinearity between mean ABP, mean CBFV, and mean DCM was ruled out using the REG procedure.[28]

Results

Infant characteristics

The EGA of the cohort was 26.3 ± 2 weeks (mean ± SD, range 23–31 weeks) and birth weight

was 822 ± 236 g. In this cohort, 96 (52%) were female, 129 (70%) were born by Cesarean

section, 163 (88%) were exposed to antenatal steroids, 47 (25%) were from multiple gestation

pregnancies, 62 (34%) received vasopressor support, and all were mechanically ventilated during

the monitoring sessions. The Apgar scores at 1 and 5 minutes were 4 (2–6) and 6 (5–7),

respectively. A total of 172 (93%) infants survived to hospital discharge, with 3 deaths occurring

outside of the first week of life. For the severe IVH group, the median (IQR) number of

recording sessions was 4 (2–6) compared to the non-severe IVH/no IVH group where the median

number of recording sessions was 4 (2.8–6). The median (IQR) DCM was 5.6 mm Hg (4.2–6.9).

DCM decreased with GA from 6.0 mm Hg (4.3–7.2) at 23 wk to 2.9 mm Hg (2.6–4.5) at 31

weeks' gestation. The full spectrum of DCM is summarized across GA in Table 1.

Univariate analysis

The results of univariate analysis of factors related to severe IVH are shown in Table 2. EGA

(p=0.011), 5-minute Apgar score (p=0.0038), use of vasopressors (p=0.081), mean ABP

(p=0.089), and mean DCM (p=0.0063) were associated with severe IVH.

Multivariate analyses

A multivariate model that included univariate analysis covariates with p-values <0.1 is shown in

Table 3. After controlling for covariates, lower 5-minute Apgar score (p=0.02) and increased

mean DCM (p=0.02) were significantly associated with severe IVH. A 5-mm Hg increase in

mean DCM was associated with 1.89-increased odds of developing severe IVH.

The final multivariate model was judged to be the best balance of significance and variable

inclusion by the purposeful selection procedure. After controlling for one another, lower 5-

minute Apgar score by 1 score unit (odds ratio (OR) 0.72 [0.58 – 0.90]; p=0.003) and increased

mean DCM by 1 mm Hg (OR 1.13 [1.02 – 1.25]; p=0.02) and by 5 mm Hg (OR 1.83 [1.11 –

3.01]) were significantly associated with severe IVH. The odds ratio of Apgar score at 5-minutes

and mean DCM were remarkably similar between the regression models.

Discussion

The main finding of this study is that elevated DCM during the first week of life is associated

with severe IVH in premature infants. When mean ABP alone is used as a proxy for cerebral

perfusion pressure, it is unclear if elevated or low perfusion pressure plays a role in the

development of IVH. Therefore, mean ABP may not be the best indicator of cerebral perfusion

pressure. When CrCP is used as a zero point reference to convert diastolic ABP to an effective

cerebral perfusion pressure as was done in this study, the association between elevated perfusion

pressure and severe IVH became evident.

CrCP is the sum of vascular wall tension and intracranial pressure.[29] Intracranial pressure alone

is a more familiar zero point reference for calculating cerebral perfusion pressure.[30] This is valid

when small differences in vascular wall tension are not significant relative to ABP. During

transition and the early newborn period, ABP in premature infants is low enough that small

variances of either vascular wall tension or intracranial pressure can substantively impact the

effective cerebral perfusion pressure. In theory then, by adjusting for changes in both vascular

wall tension and intracranial pressure, CrCP is a more reliable zero point reference for

calculating perfusion pressure than intracranial pressure alone in premature infants.

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Beginning at 23–24 weeks' gestation, as ABP is increasing, CrCP is also increasing at a rate of 1.4 mm Hg per week, maintaining a low DCM.[17] At term gestation and into adulthood, ABP continues to increase but CrCP plateaus at ~30 mmHg, rendering a progressive increase in the DCM. The wide DCM in term infants and adult patients minimizes the effect of relatively small vascular wall tension and intracranial pressure changes on cerebral perfusion pressure.

Our observation that DCM is associated with severe IVH when mean ABP is not supports our assertion that mean ABP alone is not informative of cerebral perfusion pressure in premature infants. This association between high DCM and severe IVH does not necessarily indicate causation. The mechanistic link between the two may be explained as a reduction in CrCP due to IVH, or an unmeasured phenomenon such as post-ischemic hyperemia leading to both high DCM and IVH. While the results of this study cannot inform hemodynamic management of premature infants, it does however suggest that DCM may be more informative than standard ABP as a proxy of cerebral perfusion pressure. To test this hypothesis more widely would require routine bedside transcranial Doppler monitoring for calculating the DCM. Continuous transcranial Doppler ultrasound, however, is a research technique that is not routinely clinically used in the NICU. Further, there are limitations to its use as it is technically difficult to apply and maintain accurate CBFV recordings (i.e., there is a long learning curve), and it can potentially

heat the fragile skin and underlying tissues of premature infants if left in place for a long duration. Due to its limitations, intermittent rather than continuous DCM determination could eventually be used at the bedside to guide hemodynamic management of premature infants.

During the early postnatal period, premature infants are exposed to a variety of hemodynamic stressors and are at risk for both high- and low-perfusion injuries. In particular, premature infants are at risk of myocardial stun during the first 48 hours of life and low flow states that may play a role in brain injury.[31,32] Although we found an association between elevated cerebral perfusion pressure and severe IVH, we did not evaluate low perfusion pressure as a risk factor for ischemic injury, such as periventricular white matter injury. This is because our study used cranial ultrasound instead of MRI, which is insensitive for diagnosing ischemic white matter damage. Until such data are available from our ongoing studies using MRI, we would discourage any suggestion that lower perfusion pressures render overall more favorable outcomes. This study is the first examination of the relation between effective perfusion pressure and severe IVH in premature infants, and is best suited as preliminary data for further investigation.

One limitation of the study is that previously published data were reanalyzed for the new variables of CrCP and DCM. The need for high-quality resolution of systolic and diastolic ABP

and CBFV resulted in some data dropout, which could have introduced unexpected bias. Despite the limitations of this pilot study, its results provide new perspective on unique aspects of premature cerebrovascular physiology that will be informative for subsequent studies examining the complex relationship between ABP, CrCP, autoregulation, and acute brain injury of infants born at the limits of viability. In addition, due to the observational nature of this study, we were unable to determine the exact timing of the IVH, so we used all sessions in the analysis irrespective of if they occurred before or after the IVH. Another limitation was an inability to determine the impact of antenatal steroids on the development of IVH as both the severe IVH and non-severe/no IVH groups had nearly 90% exposure to antenatal steroids.

Finally, uncertainty remains with respect to which area of the premature brain is most important for long-term neurodevelopment. The cerebral cortex, a vital organ later in life, is the area of the brain most readily and easily monitored in premature infants. However, it is possible that the cerebral cortex is actually not vital during the early newborn period in premature infants and may only require CBF during a portion of the cardiac cycle (i.e., systole).[33] Thus, the treatment of hypotension and its impact on the DCM and risk for brain injury warrants further investigation in future clinical trials.

Conclusion

Elevated effective perfusion pressure estimated by the DCM was associated with severe IVH in

this cohort of premature infants. DCM, a Doppler-ultrasound based assessment of cerebral

perfusion, may be more useful than mean ABP in guiding individualized hemodynamic

management and mitigate the risk for severe IVH in this vulnerable population.

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Figure Legends

Figure 1. Critical closing pressure (CrCP) is a point of zero reference for determining effective

cerebral perfusion pressure from arterial blood pressure (ABP).

A) ABP is shown in the top panel with systolic values (purple) and diastolic values (blue). The

panel displays a single patient recording over a one-hour session. Cerebral blood flow velocity

(CBFV) is shown in the bottom panel. During increases of systolic ABP from the baseline of 40 -

45 mm Hg the systolic CBFV is constrained, demonstrating pressure autoregulation. By contrast,

diastolic CBFV is zero (blood flow limited to systolic events) until diastolic ABP is increased

above a threshold of 32 mm Hg. B) CBFV is plotted as a function of ABP for systole (purple)

and diastole (blue). The lack of correlation between systolic CBFV and ABP again demonstrates

pressure autoregulation of systolic CBF. The diastolic data demonstrates the CrCP at 32 mm Hg,

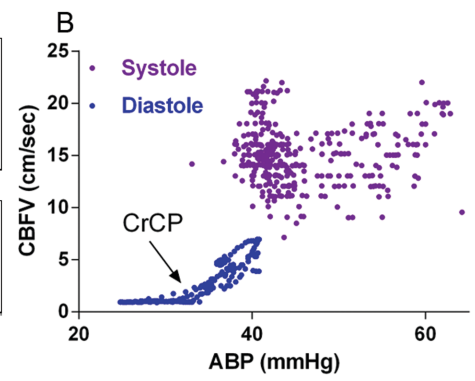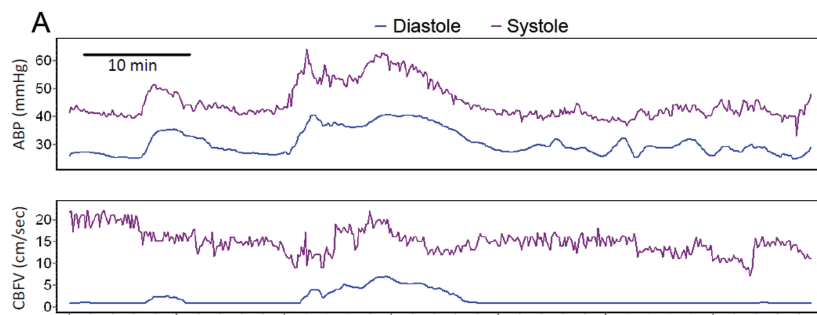the minimum vascular pressure required to sustain CBF.

Table 1: Diastolic closing margin (DCM) in premature newborns 23 weeks–31 weeks.

GA (weeks)	n	Mean	Median	IQR
23	12	5.9	6.0	4.3 – 7.2
24	34	6.1	6.1	4.7 – 7.1
25	22	6.7	6.4	4.6 – 8.3
26	29	5.6	5.6	4.6 – 6.9
27	29	5.4	4.6	3.9 – 6.3
28	29	5.2	4.8	3.7 – 6.6
29	18	6.0	5.6	4.5 – 6.7
30	4	3.3	3.3	2.7 – 3.8
31	2	3.8	2.9	2.6 – 4.5

IQR – interquartile range.

Tables
Table 2. Univariate analysis of variables related to severe IVH

Characteristics	Non-severe IVH (0, 1, 2) (N=158)	Severe IVH (3, 4) (N=27)	p–value
EGA	26.3 (1.99)	25.3 (1.58)	0.011
Female gender	52.9%	44.4%	0.40
Vaginal delivery	30.6%	29.6%	0.94
Multiple gestation	23.4%	37.0%	0.13
Apgar 5 min	6 (5 – 7)	5 (3 – 6)	0.0038
Vasopressor use	31.0%	48.1%	0.081
Mean ABP	37.0 (5.07)	35.3 (4.29)	0.089
Mean CBFV	16.6 (3.51)	17.4 (3.76)	0.29
Mean DCM	8.5 (3.77)	10.7 (4.26)	0.0063
$PaCO_2$	47.5 (4.61)	48.8 (5.34)	0.22

EGA – mean estimated gestational age; Apgar 5 min – median 5-minute Apgar score

(IQR); ABP – arterial blood pressure; CBFV – middle cerebral blood flow velocity;

DCM – diastolic closing margin; $PaCO_2$ – arterial carbon dioxide tension.

Table 3. Multiple logistic regression model (using covariates with univariate p-values <0.1) for factors significantly associated with severe IVH

Metric	Effect Size	Odds Ratio	95% CI	p-value
Apgar 5 min	1 score unit	0.76	0.60 – 0.96	0.02
Mean ABP	1 mmHg	0.96	0.86 – 1.07	0.44
EGA	1 day	0.95	0.70 – 1.29	0.76
Mean DCM	1 mmHg	1.14	1.02 – 1.26	0.02
	5 mmHg	1.89	1.11 – 3.23	
Vasopressor use		1.62	0.65 – 4.06	0.30

Apgar 5 min – 5-minute Apgar score; ABP – arterial blood pressure; EGA – estimated

gestational age; DCM – diastolic closing margin, shown for 1-mmHg unit effect size and

a more clinically relevant effect size of 5-mmHg.