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# Both Extremes of Arterial Carbon Dioxide Pressure and the Magnitude of Fluctuations in Arterial Carbon Dioxide Pressure Are Associated With Severe Intraventricular Hemorrhage in Preterm Infants

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## ABSTRACT

**OBJECTIVE.** The goal was to test the hypothesis that extremes of  $\text{Paco}_2$  during the first 4 days after birth are associated with severe intraventricular hemorrhage (grades 3 and 4).

**METHODS.** A single-center retrospective review of clinical and blood gas data in the first 4 postnatal days for 849 infants with birth weights of 401 to 1250 g was performed. The univariate and multivariate relationships of severe intraventricular hemorrhage with maximal and minimal  $\text{Paco}_2$ ,  $\text{Paco}_2$  averaged over time (time-weighted  $\text{Paco}_2$ ), and measures of  $\text{Paco}_2$  fluctuation (SD of  $\text{Paco}_2$  and difference in  $\text{Paco}_2$  [maximum minus minimum]) were assessed.

**RESULTS.** Birth weight (mean  $\pm$  SD) was  $848 \pm 212$  g, and the median gestational age was 26 weeks. Infants with severe intraventricular hemorrhage had higher maximal  $\text{Paco}_2$  (median: 72 vs 59 mm Hg) and time-weighted  $\text{Paco}_2$  (mean: 49 vs 47 mm Hg) values but lower minimal  $\text{Paco}_2$  values (32 vs 37 mm Hg). High  $\text{Paco}_2$ , low  $\text{Paco}_2$ , SD of  $\text{Paco}_2$ , and difference in  $\text{Paco}_2$  predicted severe intraventricular hemorrhage, but time-weighted average  $\text{Paco}_2$  was not as predictive.

**CONCLUSIONS.** Both extremes and fluctuations of  $\text{Paco}_2$  are associated with severe intraventricular hemorrhage. It may be prudent to avoid extreme hypocapnia and hypercapnia during the period of risk for intraventricular hemorrhage.

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### Key Words

infant, premature, hypercapnia, hypocapnia, intracranial hemorrhage

### Abbreviations

AUC—area under the curve  
BPD—bronchopulmonary dysplasia  
CBF—cerebral blood flow  
CPAP—continuous positive airway pressure  
IVH—intraventricular hemorrhage  
PVL—periventricular leukomalacia  
ROC—receiver operating characteristic  
VLBW—very low birth weight  
IMV—intermittent mechanical ventilation

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**I**NTRAVENTRICULAR HEMORRHAGE (IVH) is a major risk factor for poor neurodevelopmental outcomes for extremely premature infants.<sup>1,2</sup> Abnormal cerebral blood flow (CBF) regulation is considered to predispose patients to IVH.<sup>3-6</sup> Many animal and human studies have established  $Paco_2$  as one of the main regulators of CBF,<sup>7-12</sup> and several investigators have shown that extremely low or high levels of  $Paco_2$  may be associated with increases in neurologic morbidity rates.<sup>13-18</sup> Higher levels of  $Paco_2$  may be associated with an increased risk of IVH in very low birth weight (VLBW) infants, possibly because of an increase in CBF secondary to hypercapnia.<sup>19</sup> Low levels of  $Paco_2$  are associated with the development of periventricular leukomalacia (PVL) in ventilated premature infants, perhaps because of a decrease in CBF and subsequent ischemia.<sup>12,16</sup> Therefore, the safe upper and lower limits of  $Paco_2$  for VLBW infants need to be determined, because  $Paco_2$  targets for mechanical ventilation strategies are needed.

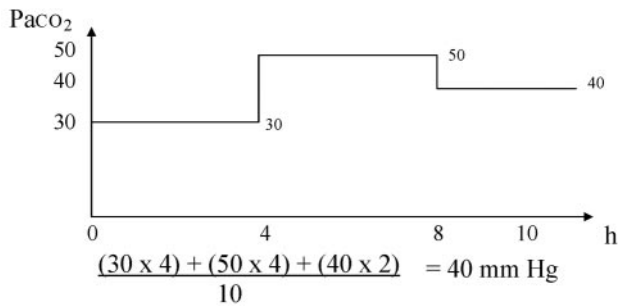
Permissive hypercapnia or "minimal ventilation," in which higher levels of  $Paco_2$  are tolerated, is often used in the ventilatory management of extremely premature infants, in an attempt to reduce ventilator-induced lung injury and thereby diminish bronchopulmonary dysplasia (BPD). BPD affects 25% of infants with birth weights of 501 to 1249 g, as defined with the new physiologic definition developed by the National Institute of Child Health and Human Development Neonatal Research Network.<sup>20</sup> The new physiologic definition, which uses a timed, room-air challenge for selected infants, has standardized the definition of BPD and reduced the variation among centers, but significant variation in BPD among centers persists.<sup>20</sup> Clinical trials of permissive hypercapnia in adults have shown reductions in mortality rates and the number of days of ventilation.<sup>21</sup> Three randomized, controlled trials of a permissive hypercapnia strategy for VLBW infants have been performed.<sup>22-24</sup> One of those studies reported reductions in rates of chronic lung disease and death in the subgroup of 501-g to 750-g infants.<sup>23</sup> However, a meta-analysis combining 2 of the trials failed to show any significant overall benefit of a permissive hypercapnia/minimal ventilation strategy targeting hypercapnia, compared with a routine ventilation strategy aiming for normocapnia, but also showed no adverse effects of a minimal ventilation strategy.<sup>25</sup> However, with the small sample sizes and the avoidance of a high or low target  $Paco_2$  in those trials, it is not clear whether the meta-analysis provided an adequately powered assessment of whether extremes of  $Paco_2$  might lead to a higher incidence of IVH in extremely premature infants. We performed this retrospective study to test the hypothesis that high and low levels of  $Paco_2$ ,  $Paco_2$  averaged over time (time-weighted  $Paco_2$ ), and measures of  $Paco_2$  fluctuation (SD of  $Paco_2$  and difference in  $Paco_2$ , ie, maximum minus minimum) in the first 4 days

after birth are associated with increased risk of severe IVH.

## METHODS

We studied all infants with birth weights between 401 and 1250 g who were admitted to the level III NICU at the University of Alabama at Birmingham between January 1, 2000, and December 31, 2003. The protocol was approved by the institutional review board for human use. Infants were included if they survived until  $\geq 96$  hours of life and underwent  $\geq 1$  head ultrasound examination during the hospital stay after 96 hours. The initial ultrasound examination was usually performed between postnatal day 5 and day 7; any examinations performed before 96 hours were not included for analysis. The ultrasound studies were performed by a certified radiology technician, and multiple images in angled coronal, sagittal, and parasagittal planes were obtained. The images were interpreted subsequently by a pediatric radiologist, who could access essential clinical data (birth weight, gestational age, postnatal age, and major clinical problems such as respiratory distress syndrome). Review of the ultrasound images was not performed for this study.

Data were obtained from an electronic hospital archive of laboratory data and a NICU database. All data in the NICU database were collected by a trained database specialist, immediately after discharge of the infant, with standard definitions. Data analyzed included main prenatal and neonatal variables that were shown previously to be associated with severe IVH,<sup>1,2</sup> including birth weight, gestational age, pregnancy-induced hypertension, premature prolonged rupture of membranes, any prenatal steroid use, 5-minute Apgar score, any use of nasal continuous positive airway pressure (CPAP), and use of intermittent mechanical ventilation (IMV). In addition, data were collected on severe IVH (grades 3 and 4 in the classification described by Papile et al<sup>26</sup>), cystic PVL, and blood gas results from the first 4 days after birth. The highest and lowest  $Paco_2$  values were identified from the blood gas results obtained during the first 96 hours of life. Measures of  $Paco_2$  dispersion for each patient, including the SD of  $Paco_2$  and the maximum to minimum range (difference in  $Paco_2$ ), were calculated. A time-weighted  $Paco_2$  was also calculated (Fig 1). As can be noted from Fig 1, the time period between 2 blood gas assessments is represented by the  $Paco_2$  of the second blood gas analysis, rather than by the average of the  $Paco_2$  results from the 2 blood gas analyses, because blood gas samples are usually obtained at intervals of a few hours and ventilator settings are changed soon after a blood gas sample is obtained. Therefore, because the  $Paco_2$  usually changes rapidly, most of the time period between blood gas analyses usually reflects the  $Paco_2$  associated with the subsequent



**FIGURE 1**  
Time-weighted  $\text{Paco}_2$  calculation. In this example, the infant has 3  $\text{Paco}_2$  values for a period of 10 hours. The equation shows how the time-weighted  $\text{Paco}_2$  value would be calculated.

blood gas assessment, rather than a mathematical average of the 2  $\text{Paco}_2$  values.

The relationships between the median highest, lowest, time-weighted average, SD, and difference in  $\text{Paco}_2$  and severe IVH were analyzed by using the Mann-Whitney rank sum test and by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. ROC curves plot sensitivity versus  $1 - \text{specificity}$ ; the more the AUC approaches 1, the higher the predictive value. Dot plots were also used to show the distribution and overlap of  $\text{Paco}_2$  values for infants with and without severe IVH, for each of the  $\text{Paco}_2$  variables. Similar analyses were performed for the subset of infants who received IMV/CPAP (because  $\text{Paco}_2$  could not be controlled for infants not on respiratory support). The relationships between median highest, lowest, and time-weighted average  $\text{Paco}_2$  and mild IVH (grades 1 and 2) were also evaluated, to determine whether there was dose dependence in the relationship between  $\text{Paco}_2$  and grade of IVH. A multivariate logistic regression analysis with severe IVH as the dependent variable was performed with independent variables including the main prenatal and postnatal variables and the highest, lowest, and time-weighted average  $\text{Paco}_2$ . All statistical analyses were performed with SigmaStat 2.03 for Windows (Jandel Scientific, San Rafael, CA) and MedCalc 7.6 (MedCalc, Mariakerke, Belgium).

## RESULTS

The 849 infants included in the study had a birth weight (mean  $\pm$  SD) of  $848 \pm 212$  g and a gestational age of  $26 \pm 2$  weeks (Table 1); 21% were diagnosed as having severe IVH and 5% as having PVL. A total of 71% required IMV, and 79% received either CPAP and/or IMV. Infants who did not require CPAP or IMV had a lower incidence of severe IVH, compared with those who received CPAP/IMV (6.3% vs 24.9%;  $P < .01$ ).

Infants with severe IVH had significantly higher maximal  $\text{Paco}_2$  and time-weighted average  $\text{Paco}_2$  values, whereas the minimal  $\text{Paco}_2$  was significantly lower (Table 2). Analysis of the AUC of the ROC curves indicated

**TABLE 1 Patient Demographic Features**

Birth weight, mean $\pm$ SD, g	848 $\pm$ 212
Gestational age, mean $\pm$ SD, wk	26 $\pm$ 2
Prenatal steroid use, %	73
IMV, %	71
IMV or CPAP, %	79
IVH (any degree), %	36
Severe IVH (grade 3 or 4), %	21
PVL, %	5

**TABLE 2 Univariate Analyses of Maximal  $\text{Paco}_2$ , Minimal  $\text{Paco}_2$ , Time-Weighted  $\text{Paco}_2$ , Difference in  $\text{Paco}_2$ , and SD of  $\text{Paco}_2$  in Relation to Severe IVH (Papile Grade 3 or 4)**

	Severe IVH (n = 179)	No Severe IVH (n = 670)	P
Maximal $\text{Paco}_2$ , median (25th to 75th percentile range), mm Hg	72 (61–89)	59 (50–70)	<.001
Minimal $\text{Paco}_2$ , median (25th to 75th percentile range), mm Hg	32 (27–37)	37 (31–42)	<.001
Time-weighted $\text{Paco}_2$ , median (25th to 75th percentile range), mm Hg	49 (44–54)	47 (41–52)	<.01
Difference in $\text{Paco}_2$ , median (25th to 75th percentile range), mm Hg	39 (26–55)	21 (11–35)	<.001
SD of $\text{Paco}_2$ , median (25th to 75th percentile range), mm Hg	11 (8–15)	7 (4–11)	<.001

that both extremes of  $\text{Paco}_2$  were good predictors of severe IVH (Table 3). AUC values of the ROC curves for SD of  $\text{Paco}_2$  and difference in  $\text{Paco}_2$  were similar, indicating that the magnitude of  $\text{Paco}_2$  fluctuation was also a good predictor of severe IVH. Statistically significant, time-weighted  $\text{Paco}_2$  did not predict severe IVH as well as other  $\text{Paco}_2$  variables. Maximal  $\text{Paco}_2$  and difference in  $\text{Paco}_2$  were associated significantly with severe IVH even for infants who did not receive either IMV or CPAP, although the sample size of infants without IMV/CPAP was limited and their incidence of severe IVH was lower ( $n = 174$ ; 11 with severe IVH) (Table 3). Infants receiving respiratory support (IMV or CPAP) had wider variations in their  $\text{Paco}_2$  values, compared with those not receiving support (maximal  $\text{Paco}_2$ : IMV/CPAP: median: 65 mm Hg; range: 54–77 mm Hg; no IMV/CPAP: median: 50 mm Hg; range: 45–57 mm Hg; minimal  $\text{Paco}_2$ : IMV/CPAP: median: 34 mm Hg; range: 29–40 mm Hg; no IMV/CPAP: median: 41 mm Hg; range: 35–45 mm Hg; time-weighted average  $\text{Paco}_2$ : IMV/CPAP: median: 48 mm Hg; range: 40–49 mm Hg; no IMV/CPAP: median: 45 mm Hg; range: 43–53 mm Hg; difference in  $\text{Paco}_2$ : IMV/CPAP: median: 30 mm Hg; range: 18–44 mm Hg; no IMV/CPAP: median: 8 mm Hg; range: 0–17 mm Hg; SD of  $\text{Paco}_2$ : IMV/CPAP: median: 9 mm Hg; range: 6–12 mm Hg; no IMV/CPAP: median: 4 mm Hg; range: 0–6 mm Hg; all  $P < .001$ ).

**TABLE 3** AUC of the ROC Curve for Paco<sub>2</sub> Variables in Relation to Severe IVH for All Infants and for the Subsets of Infants Who Received CPAP/IMV (*n* = 675) or Did Not Receive Such Respiratory Support (*n* = 174)

	AUC	95% Confidence Interval	<i>P</i>
Maximal Paco <sub>2</sub>			
All infants	0.70	0.67–0.73	<.0001
No CPAP/IMV	0.74	0.67–0.80	<.01
CPAP/IMV	0.66	0.65–0.70	<.0001
Minimal Paco <sub>2</sub>			
All infants	0.66	0.62–0.69	<.0001
No CPAP/IMV	0.57	0.50–0.65	.40
CPAP/IMV	0.63	0.60–0.67	<.0001
Time-weighted Paco <sub>2</sub>			
All infants	0.58	0.54–0.61	<.005
No CPAP/IMV	0.61	0.54–0.69	.20
CPAP/IMV	0.55	0.51–0.59	<.05
Difference in Paco <sub>2</sub>			
All infants	0.74	0.71–0.77	<.0001
No CPAP/IMV	0.73	0.66–0.79	<.01
CPAP/IMV	0.70	0.66–0.73	<.0001
SD of Paco <sub>2</sub>			
All infants	0.71	0.68–0.74	<.0001
No CPAP/IMV	0.68	0.60–0.74	.06
CPAP/IMV	0.68	0.64–0.71	<.0001

The AUC of the time-weighted Paco<sub>2</sub> was significantly lower than the AUCs of maximal Paco<sub>2</sub>, minimal Paco<sub>2</sub>, difference in Paco<sub>2</sub>, and SD of Paco<sub>2</sub> for all infants (*P* < .05).

With the ROC curve and a dot plot (Fig 2) for each of maximal Paco<sub>2</sub>, minimal Paco<sub>2</sub>, time-weighted Paco<sub>2</sub>, difference in Paco<sub>2</sub>, and SD of Paco<sub>2</sub>, an optimal threshold was identified at which the highest sensitivity was obtained with minimal loss of specificity (with increasing sensitivity, specificity is lower). This optimal threshold was determined automatically by the MedCalc software and was confirmed through manual adjustment of the threshold upward or downward and evaluation of the sensitivity and specificity after these adjustments. Maximal Paco<sub>2</sub> of >60 mm Hg had 76% sensitivity and 54% specificity, and minimal Paco<sub>2</sub> of <39 mm Hg had 81% sensitivity and 42% specificity for severe IVH. Time-weighted average Paco<sub>2</sub> of >52 mm Hg had 41% sensitivity and 72% specificity (Fig 2). Infants with maximal Paco<sub>2</sub> values of >60 mm Hg (*n* = 442; 52%) had a 31% incidence of severe IVH, whereas infants with minimal Paco<sub>2</sub> values of <39 mm Hg (*n* = 532; 63%) had a 27% incidence. Infants with both maximal Paco<sub>2</sub> values of >60 mm Hg and minimal Paco<sub>2</sub> values of <39 mm Hg (*n* = 282; 33%) had a 38% incidence, whereas those within the “optimal” range of Paco<sub>2</sub> values of 39 to 60 mm Hg (*n* = 156; 18%) had only a 3% incidence of severe IVH.

In the multivariate logistic regression analysis, maximal Paco<sub>2</sub>, minimal Paco<sub>2</sub>, and time-weighted average Paco<sub>2</sub> (either as continuous variables or as dichotomous variables, with the thresholds noted above) were all associated independently with severe IVH, in addition to

the clinical variables of lower gestational age, absence of pregnancy-induced hypertension, absence of premature rupture of membranes, lack of prenatal steroid exposure, lower 5-minute Apgar score, and need for IMV (Table 4). Additional multivariate logistic regression analyses with SD of Paco<sub>2</sub> and difference in Paco<sub>2</sub> as independent variables were performed, but the overall model fit was similar and, because the predictive ability was being parceled out among more variables, SD of Paco<sub>2</sub> and difference in Paco<sub>2</sub> reduced the statistical significance of the highest, lowest, and time-weighted average Paco<sub>2</sub> values (data not shown).

Any-grade IVH (grade 1, 2, 3, or 4) was also analyzed in relation to Paco<sub>2</sub> variables. In comparison with infants without IVH, infants with any-grade IVH had significantly higher maximal Paco<sub>2</sub> (any-grade IVH: 66 mm Hg; no IVH: 58 mm Hg; *P* < .001) and time-weighted average Paco<sub>2</sub> (any-grade IVH: 48 mm Hg; no IVH: 47 mm Hg; *P* < .05) values, whereas the minimal Paco<sub>2</sub> was significantly lower (any-grade IVH: 34 mm Hg; no IVH: 37 mm Hg; *P* < .001). However, these differences were mainly attributable to severe IVH, because no significant differences in Paco<sub>2</sub> were noted in infants with mild (grade 1 or 2) IVH, compared with infants without IVH (maximal Paco<sub>2</sub>: mild IVH: 59 mm Hg; no IVH: 58 mm Hg; *P* = .16; AUC: 0.54; 95% CI: 0.50–0.58; minimal Paco<sub>2</sub>: mild IVH: 36 mm Hg; no IVH: 37 mm Hg; *P* = .08; AUC: 0.55; 95% CI: 0.51–0.59; time-weighted average Paco<sub>2</sub>: mild IVH: 47 mm Hg; no IVH: 47 mm Hg; *P* = .71; AUC: 0.50; 95% CI: 0.46–0.54). Infants with PVL had significantly lower minimal Paco<sub>2</sub> values (33 vs 36 mm Hg; *P* < .05), but maximal and time-weighted average Paco<sub>2</sub> values were not different (66 vs 61 mm Hg and 48 vs 48 mm Hg, respectively).

## DISCUSSION

Our study indicates that extreme levels of Paco<sub>2</sub>, whether high or low, and wider variation in Paco<sub>2</sub> values for an individual neonate, as indicated by a larger SD or difference in Paco<sub>2</sub>, are associated with severe IVH in VLBW infants and this association persists even after adjustment for major perinatal variables. Although causality should not be inferred, it may be prudent to avoid extremes of Paco<sub>2</sub> during the period of risk for IVH.

There are limitations to this retrospective study, because of biases resulting from confounding by factors associated with the availability of data and imprecision of estimates resulting from lack of a standard clinical protocol and data collection procedures. Infants who are sicker may have more blood gas evaluations, with extremes in blood gas values being more likely to be detected. Paco<sub>2</sub> levels could not be controlled by clinicians for the 21% of the infants who did not receive IMV or CPAP. However, maximal Paco<sub>2</sub> and SD of Paco<sub>2</sub> were associated with severe IVH even in infants who did not receive IMV/CPAP, although the incidence of severe IVH

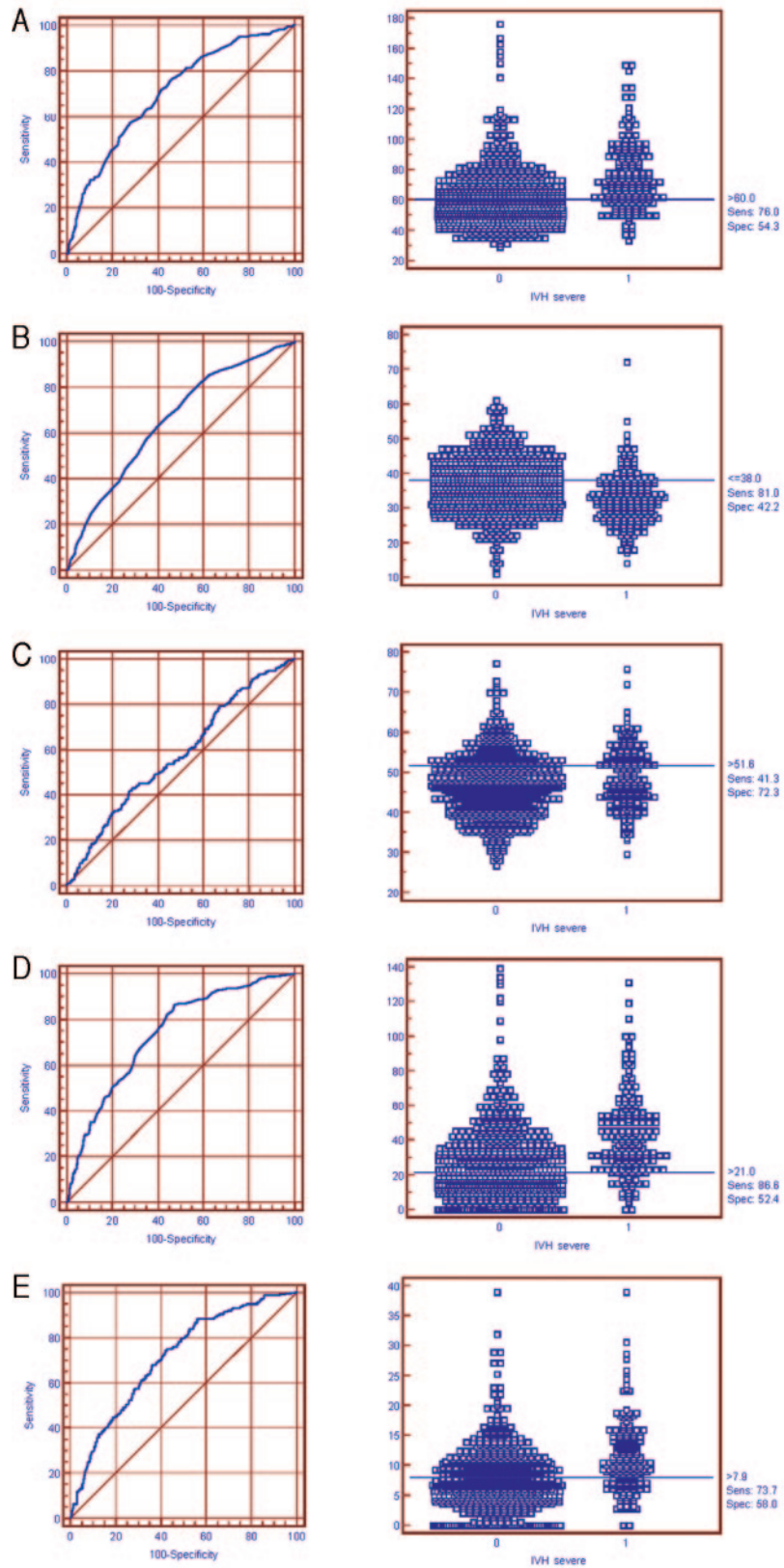


FIGURE 2

ROC curves (left) and dot plots (right) of maximal Paco<sub>2</sub> (A), minimal Paco<sub>2</sub> (B), time-weighted Paco<sub>2</sub> (C), Paco<sub>2</sub> maximum to minimum range (D), and SD of Paco<sub>2</sub> (E) in relation to the outcome of severe IVH (Papile grades 3 or 4). The optimal threshold and the sensitivity (Sens) and specificity (Spec) for severe IVH are included for each dot plot.

**TABLE 4 Identification of Variables Associated With Severe IVH in Multivariate Logistic Regression Analysis**

	Odds Ratio	95% Confidence Interval	P
Gestational age (per 1 wk)	0.82	0.74–0.91	<.001
Pregnancy-induced hypertension	0.51	0.31–0.83	<.01
Premature rupture of membranes	0.60	0.36–1.00	<.05
Prenatal steroid use (any)	0.51	0.34–0.76	<.01
Apgar score at 5 min (per 1 unit)	0.87	0.78–0.96	<.01
Mechanical ventilation	2.04	1.07–3.89	<.05
Maximal Paco <sub>2</sub> of >60 mm Hg	1.97	1.23–3.15	<.01
Minimal Paco <sub>2</sub> of <39 mm Hg	2.51	1.53–4.12	<.001
Time-weighted Paco <sub>2</sub> of >52 mm Hg	1.92	1.19–3.10	<.01

was lower in that population. Arterial blood gas samples were drawn usually from indwelling arterial catheters, but a few infants, especially those not requiring IMV, did not have arterial access or the arterial catheters were removed within 1 or 2 days after birth. Therefore, some blood gas samples were arterialized capillary blood gas samples or blood gas samples obtained through direct arterial puncture. The 21% incidence of severe IVH in this study is possibly higher than expected, because of the center practice of aggressive resuscitation and very low rates of early death (2% of all live-born extremely low birth weight infants died within the first 24 hours after birth), which led to an increase in early survival rates and perhaps also an increase in the number of infants at risk for IVH.

Our study has many strengths. The sample size for this study and the number of blood gas samples analyzed are larger than those of many similar studies. In addition, data from all blood gas samples from the first 4 days were included, without limiting the analyses to selected time points. Our study did not rely solely on measurements of maximal Paco<sub>2</sub> but also included estimations of both low Paco<sub>2</sub> and time-weighted Paco<sub>2</sub> and identified optimal thresholds of both high and low Paco<sub>2</sub>.

Time-weighted Paco<sub>2</sub> did not predict severe IVH as well as either extreme level of Paco<sub>2</sub>. Time-weighted Paco<sub>2</sub> would not change much if the same infant has alternating periods (fluctuations) of high and low Paco<sub>2</sub>. The association of a larger SD or difference in Paco<sub>2</sub> with severe IVH suggests that this may indeed be the case. Because the average Paco<sub>2</sub> was not much increased, it is likely that infants with IVH were not harder to ventilate and therefore did not have much sicker lungs (suggesting a greater degree of immaturity), compared with those without IVH. Extremes and fluctuations of Paco<sub>2</sub> were associated with severe IVH (grades 3 and 4) but not with milder grades of IVH (grades 1 and 2). Therefore, it is possible that abnormal levels of Paco<sub>2</sub> are more likely involved in extension of preexisting hemorrhage, rather than initiation or development of IVH. It is also possible that severe IVH may lead to fluctuations in spontaneous respiratory effort, resulting in fluctuations and more ex-

tremes in Paco<sub>2</sub>. Unlike IVH, PVL was associated only with a lower minimal Paco<sub>2</sub> and not with high, time-weighted average, or fluctuating Paco<sub>2</sub>, which confirms previous observations.<sup>12,13,16,17</sup> This difference may be attributable to differences in the pathophysiologic features of IVH and PVL.

Our study suggests that careful and frequent or continuous monitoring of Paco<sub>2</sub> may be important and that extreme or widely fluctuating Paco<sub>2</sub> levels should be avoided for VLBW infants. In the routine NICU setting, oxygenation is monitored easily with pulse oximetry but Paco<sub>2</sub> is monitored only infrequently with blood gas analyses. Alternative methods to indicate trends in Paco<sub>2</sub> values, such as transcutaneous or end-tidal carbon dioxide measurements, are not used commonly. Although moderate hypercapnia seems to be safe,<sup>22–25</sup> more extreme levels of hypercapnia during the period of risk for IVH have not been proved to be safe.

The main finding from this study is that both extremes of Paco<sub>2</sub> are associated with increased risk of severe IVH in VLBW infants. The sensitivities and specificities of the extremes of Paco<sub>2</sub> for severe IVH are not high enough for use in clinical settings, but these thresholds may prove useful in characterization of the pathogenesis of severe IVH. Additional studies are necessary to determine the mechanisms through which low and fluctuating Paco<sub>2</sub> levels can lead to severe IVH. Possible mechanisms may include ischemia during the period of hypocapnia, followed by hemorrhage or extension of existing hemorrhage during the period of reperfusion. It is also necessary to confirm that marked fluctuations in Paco<sub>2</sub> and secondarily in CBF are associated with severe IVH. Clinical trials will be required to demonstrate that avoidance of hypocapnia and extreme fluctuations of arterial Paco<sub>2</sub> leads to reductions in severe IVH.

## REFERENCES

1. Ambalavanan N, Nelson KG, Alexander G, Johnson SE, Biasini F, Carlo WA. Prediction of neurologic morbidity in extremely low birth weight infants. *J Perinatol*. 2000;20:496–503
2. Sherlock RL, Anderson PJ, Doyle LW. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. *Early Hum Dev*. 2005;81:909–916
3. Calvert SA, Ohlsson A, Hosking MC, Erskine L, Fong K, Shennan AT. Serial measurements of cerebral blood flow velocity in preterm infants during the first 72 hours of life. *Acta Paediatr Scand*. 1988;77:625–631
4. Perlman JM, Volpe JJ. Fluctuating blood pressure and intraventricular hemorrhage. *Pediatrics*. 1990;85:620–622
5. Bada HS, Korones SB, Perry EH, et al. Mean arterial blood pressure changes in premature infants and those at risk for intraventricular hemorrhage. *J Pediatr*. 1990;117:607–614
6. Kissack CM, Garr R, Wardle SP, Weindling AM. Postnatal changes in cerebral oxygen extraction in the preterm infant are associated with intraventricular hemorrhage and hemorrhagic

- parenchymal infarction but not periventricular leukomalacia. *Pediatr Res*. 2004;56:111–116
7. Leahy FA, Cates D, MacCallum M, Rigatto H. Effect of CO<sub>2</sub> and 100% O<sub>2</sub> on cerebral blood flow in preterm infants. *J Appl Physiol*. 1980;48:468–472
  8. Pryds O, Greisen G. Effect of Paco<sub>2</sub> and haemoglobin concentration on day to day variation of CBF in preterm neonates. *Acta Paediatr Scand*. 1989;360:33–36
  9. Hansen NB, Brubakk A, Bratlid D, Oh W, Stonestreet BS. The effects of variations in Paco<sub>2</sub> on brain blood flow and cardiac output in the newborn piglet. *Pediatr Res*. 1984;18:1132–1136
  10. Wilson DF, Pastuszko A, DiGiacomo JE, Pawlowski M, Schneiderman R, Delivoria-Papadopoulos M. Effect of hyperventilation on oxygenation of the brain cortex of newborn piglets. *J Appl Physiol*. 1991;70:2691–2696
  11. Wyatt JS, Edwards AD, Cope M, et al. Response of cerebral blood volume to changes in arterial carbon dioxide tension in preterm and term infants. *Pediatr Res*. 1991;29:553–557
  12. Ambalavanan N, Carlo WA. Hypocapnia and hypercapnia in respiratory management of newborn infants. *Clin Perinatol*. 2001;28:517–531
  13. Wiswell TE, Graziani LJ, Kornhauser MS, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics*. 1996;98:918–924
  14. Gannon CM, Wiswell TE, Spitzer AR. Volutrauma, Paco<sub>2</sub> levels, and neurodevelopmental sequelae following assisted ventilation. *Clin Perinatol*. 1998;25:159–175
  15. Graziani LJ, Spitzer AR, Mitchell DG, et al. Mechanical ventilation in preterm infants: neurosonographic and developmental studies. *Pediatrics*. 1992;90:515–522
  16. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res*. 2001;50:712–719
  17. Dammann O, Allred EN, Kuban KCK, et al. Hypocarbia during the first 24 postnatal hours and white matter echolucencies in newborns ≤28 weeks gestation. *Pediatr Res*. 2001;49:388–393
  18. Bifano EM, Pfannenstiel A. Duration of hyperventilation and outcome in infants with persistent pulmonary hypertension. *Pediatrics*. 1988;81:657–661
  19. Wallin LA, Rosenfeld CR, Laptook AR, et al. Neonatal intracranial hemorrhage, part II: risk factors in an inborn population. *Early Hum Dev*. 1990;23:129–137
  20. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics*. 2004;114:1305–1311
  21. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–1308
  22. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics*. 1999;104:1082–1088
  23. Carlo WA, Stark AR, Wright LL, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. *J Pediatr*. 2002;141:370–374
  24. Thome UH, Carroll W, Wu TJ, et al. Outcome of extremely preterm infants randomized at birth to different Paco<sub>2</sub> targets during the first seven days of life. *Biol Neonate*. 2006;90:218–225
  25. Woodgate PG, Davies MW. Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants [Cochrane review]. In: *The Cochrane Library*. Issue 1. Chichester, United Kingdom: John Wiley & Sons; 2004
  26. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;92:529–534

**Both Extremes of Arterial Carbon Dioxide Pressure and the Magnitude of Fluctuations in Arterial Carbon Dioxide Pressure Are Associated With Severe Intraventricular Hemorrhage in Preterm Infants**

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