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# Incidence of Hypocapnia, Hypercapnia, and Acidosis and the Associated Risk of Adverse Events in Preterm Neonates

Melissa K Brown RRT RRT-NPS, Deborah M Poeltler PhD, Kasim O Hassen RRT RRT-NPS, Danielle V Lazarus RRT, Vanessa K Brown, Jeremiah J Stout, Wade D Rich RRT RRT-NPS, and Anup C Katheria MD

**BACKGROUND: Permissive hypercapnia is a lung-protection strategy. We sought to review our current clinical practice for the range of permissive hypercapnia and identify the relationship between $P_{aCO_2}$ and pH and adverse outcomes. METHODS: A secondary analysis of a delayed cord-clamping clinical trial was performed on all arterial blood gas tests in the first 72 h in infants < 32 weeks gestational age. All arterial blood gas values were categorized into a clinical range to determine the percent likelihood of occurring in the total sample. The univariate and multivariate relationships of severe adverse events and the time-weighted $P_{aCO_2}$, fluctuation of $P_{aCO_2}$, maximal and minimal $P_{aCO_2}$, base excess, and pH were assessed. RESULTS: 147 infants with birthweight of 1,206 ± 395 g and gestational age of 28 ± 2 weeks were included. Of the 1,316 total samples, < 2% had hypocapnia ($P_{aCO_2}$ <30 mm Hg), 47% were normocapnic ($P_{aCO_2}$ 35–45 mm Hg), 26.5% had mild hypercapnia ($P_{aCO_2}$ 45–55 mm Hg), 13% had moderate hypercapnia ($P_{aCO_2}$ 55–65 mm Hg), and 6.5% had severe hypercapnia ($P_{aCO_2}$ ≥ 65 mm Hg). There were no adverse events associated with hypocapnia. Subjects with death/severe intraventricular hemorrhage had a higher mean $P_{aCO_2}$ of 52.3 versus 44.7 (odds ratio [OR] 1.16, 95% CI 1.04–1.29, $P = .006$), higher variability of $P_{aCO_2}$ with a standard deviation of 12.6 versus 7.8 (OR 1.15, 95% CI 1.03–1.27, $P = .01$), and a lower minimum pH of 7.03 versus 7.23 (OR 0, 95% CI 0–0.06, $P = .003$). There was no significant difference in any variables in subjects who developed other adverse events. CONCLUSION: The routine targeting of higher than normal $P_{aCO_2}$ goals may lead to a low incidence of hypocapnia and associated adverse events. Hypercapnia is common, and moderate hypercapnia may increase the risk of neurologic injury and provide little pulmonary benefit.** *Key words: hypercapnia; hypocapnia; ventilator-induced lung injury; bronchopulmonary dysplasia; carbon dioxide; very low birthweight infant; intraventricular hemorrhage; premature; mortality; blood gas analysis.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

## Introduction

Permissive hypercapnia, or allowing the $P_{aCO_2}$ levels to rise above normal, is a commonly utilized lung-protection strategy in the management of premature neonates.[1] However, the range of $P_{aCO_2}$ that provides benefit with the least risk is not yet known.[1,2] Permissive hypercapnia may allow the maintenance of an adequate minute ventilation with lower tidal volumes ($V_T$), and it may help avoid the lung injury that can occur from volutrauma and barotrauma.[3] The resultant reductions of mean airway pressure may also prevent lung injury as well as improve the car-

All authors are affiliated with the Neonatal Research Institute at Sharp Mary Birch Hospital for Women and Newborns, San Diego, California.

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Correspondence: Melissa K Brown RRT RRT-NPS, Neonatal Research Institute at Sharp Mary Birch Hospital for Women and Newborns, 3003 Health Center Drive, San Diego, CA 92123. E-mail: melissa.brown@sharp.com.

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diac output, which is frequently compromised in the critically ill premature neonate.[4] Enhanced delivery of oxygen to the brain and other vital tissues can also be facilitated by shifting the oxyhemoglobin dissociation curve to the right, with respiratory acidosis and increases in $P_{aCO_2}$ levels. Previous randomized, controlled trials have demonstrated a reduction in median ventilator days (2.5 vs 9.5) and the need for ventilator assistance at 36 week corrected gestational age (16% vs 1%)[5] with a strategy of mild hypercapnia ($P_{aCO_2}$ 45–55 mm Hg)[4] when compared to a normocapnic group ($P_{aCO_2}$ 35–45 mm Hg) in extremely low birthweight infants, without an increase in neurodevelopmental adverse effects. However, bronchopulmonary dysplasia (BPD) rates have not been significantly reduced by a strategy of permissive hypercapnia.[4-7]

Hypercapnia can increase cerebral vasodilation and cerebral blood flow; conversely, hypocapnia can lead to vasoconstriction and significantly decreased cerebral blood flow.[8-10] Progressive increases in the $P_{aCO_2}$ level can also impair the autoregulation of cerebral blood flow and may lead to ischemic damage of the neonatal brain.[2,8,9] Hypercapnia, hypocapnia, fluctuations in $P_{aCO_2}$, and acidosis have all been positively associated with intraventricular hemorrhage (IVH), periventricular leukomalacia, and poor neurodevelopmental outcomes in preterm neonates.[10-13]

Previous studies have questioned the safe ranges of permissive hypercapnia and the role that pH plays in the relationship. The acceptable limits for acidosis are poorly defined and difficult to isolate from the effects of hypercapnia. Moderate hypercapnia ($P_{aCO_2} > 55$ mm Hg) has not yet been demonstrated to be either beneficial or safe, although it has been reported to be a common clinical practice. Randomized controlled trials investigating the safety and effectiveness of moderate hypercapnia have been difficult to complete due to infant subjects' ability to regulate their own ventilation and override the study $P_{aCO_2}$ targets. Two randomized clinical trials attempted to determine whether targeting moderate levels of hypercapnia is safe or beneficial. Both had negative results, and the authors did not recommend that they be attempted again in the future.[7,14]

Although most of the early positive trial results that lead to the adoption of permissive hypercapnia of neonates compared mild levels of hypercapnia to normal values, Thome at al randomized mechanical ventilated infants < 28 weeks within 6 h of birth to a higher $P_{aCO_2}$ target of 55–65 mm Hg or 35–45 mm Hg for the first 7 postnatal days.[14] The primary outcome measure was BPD or death and neurodevelopmental outcome at 18–22 months corrected age. The trial was stopped early after enrolling 31% of the projected sample size. A $P_{aCO_2}$ target of 55–65 mm Hg was associated with trends toward higher mortality and higher incidence of neurodevelopmental impairment, and a significant increase in the combined outcome of mental impairment or death ($P < .05$). Higher ventilator rates to achieve gas exchange with low $V_T$ may have diminished the advantage of minimal ventilation. $V_T$ was kept similar in both groups (high-rate strategy pH > 7.25 with sodium bicarbonate administration). A strategy of reducing $V_T$ by increasing the $P_{aCO_2}$ target was not in effect in this cohort (as utilized in ARDSnet[15]), possibly negating any pulmonary impact between groups. The trial had difficulty achieving the high $P_{aCO_2}$ target in non-paralyzed infants, and although the $P_{aCO_2}$ difference was statistically significant (6 mm Hg, $P < .001$), it did not meet the study goal of 55–65 mm Hg.

The Permissive Hypercapnia in Extremely Low Birthweight Infants (PHELBI) trial enrolled 362 infants at 16 centers in Germany before being stopped early after an interim analysis.[7] The authors hypothesized that a higher target $P_{aCO_2}$ 55–65 mm Hg (day 1–3) as compared to 40–50 mm Hg and then escalating gradually over 14 d would reduce the rate of BPD or death. The trial was terminated when no benefit in the treatment group and a trend toward benefit in the control group was found. The high-target group had a significantly higher rate of necrotizing enterocolitis and did not have a shorter duration of ventilation. Although the high-target group did have lower ventilator pressures, it did not translate into better outcomes. The infants with severe disease in the high target group ($P_{aCO_2}$ 55–65 mm Hg) had a higher incidence of BPD, necrotizing enterocolitis, and death. The PHELBI investigators were unable to reach the desired targets with the high $P_{aCO_2}$ group. The mean $P_{aCO_2}$ difference was only 6.2 mm Hg between days 2 and 11. The authors suggest that the high targets may be impossible to achieve in a

**QUICK LOOK**

**Current knowledge**

A strategy of mild hypercapnia ($P_{aCO_2}$ = 45-55 mm Hg) can lead to a reduction in ventilator days and the need for ventilator assistance at 36 week corrected gestational age when compared to a normocapnic group (35-45 mm Hg) in extremely low birthweight infants, without an increase in neurodevelopmental adverse effects. Bronchopulmonary dysplasia rates have not been significantly reduced by a strategy of permissive hypercapnia.

**What this paper contributes to our knowledge**

Moderate to high levels of permissive hypercapnia (> 55 mm Hg) in the first 72 h of life has found its way into neonatal clinical practice, which may increase neurologic risk and provide little pulmonary benefit. Targeting higher than normal $P_{aCO_2}$ levels may help avoid the adverse events associated with hypocapnia.

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randomized, controlled trial and probably should not be attempted either clinically or in future studies.[7]

Our goal was to review our current clinical practice for the range of permissive hypercapnia in premature neonates < 32 weeks gestational age, and to identify a relationship between $P_{aCO_2}$ and pH during the first 72 h and adverse neonatal outcomes. This information may then allow us to identify $P_{aCO_2}$ and pH values that are associated with adverse events, which may advise good clinical practice.

## Methods

This is a secondary analysis of infants < 32 weeks gestational age previously enrolled in a prospective, randomized, controlled trial of delayed cord clamping ($n = 150$ subjects).[16] Subjects were enrolled in the primary trial between August 2014 and October 2015 at Sharp Mary Birch Hospital for Women and Newborns, and written informed consent was obtained from the parents or guardians of each participant. Infants with severe placenta abruption or congenital anomalies were excluded from the original trial, as were cases in which the attending physician believed care was futile. The Sharp Institutional Review Board approved the secondary analysis. Subjects with arterial blood gas (ABG) tests were included in the secondary study ($N = 147$). All ABG values from the first 72 h after birth along with the associated mode of ventilation were included in the analysis. An experienced research team, as part of the original clinical trial, prospectively collected all subject demographic and outcome data (Table 1). ABGs and the corresponding mode of ventilation were collected retrospectively from the electronic medical record. Study data were collected and managed using REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee). The trial data were exported from RedCap into SPSS version 23 for Windows (IBM, Armonk, New York) for the purpose of further analysis.

All $P_{aCO_2}$ and pH values were initially categorized into a clinical range to determine the percent likelihood of the value range occurring in the total sample (Table 2). The value ranges and associated mode of ventilation were described for the whole sample and a subset of the sample that was < 28 weeks gestational age. Value ranges were set to reflect areas of clinical interest: Moderate to severe hypocapnia ($P_{aCO_2}$ < 30 mm Hg), mild hypocapnia ($P_{aCO_2}$ 30–34 mm Hg), normal values ($P_{aCO_2}$ 35–44 mm Hg), mild hypercapnia ($P_{aCO_2}$ 45–54 mm Hg), moderate hypercapnia ($P_{aCO_2}$ 55–64 mm Hg), and severe hypercapnia ($P_{aCO_2}$ 65 mm Hg or higher), as well as the percentage of ABG tests with a pH < 7.20. The mean $P_{aCO_2}$ and pH values were stratified by < 28 weeks gestational age and ≥ 28 weeks gestational age, and each group was analyzed with a Student $t$ test with significance set at $P < .05$. The highest and the lowest $P_{aCO_2}$ values per subject over the first 72 h of life were identified and labeled $P_{aCO_2}$ maximum and $P_{aCO_2}$ minimum. Mean time-weighted $P_{aCO_2}$ was calculated as previously described by Fabres et al.[17] The sum of all $P_{aCO_2}$ values were multiplied by the time interval from the previous blood gas divided by the overall time period. This method takes into consideration the time exposure for each $P_{aCO_2}$ value. We capped the time weighting to no more than 12 h per blood gas to reduce the possibility of any one ABG having an outsized effect. $P_{aCO_2}$ fluctuation was identified in 2 ways: by the standard deviation of the time weighted $P_{aCO_2}$ per subject, and by the difference between $P_{aCO_2}$ maximum and $P_{aCO_2}$ minimum ($\Delta P_{aCO_2}$).

Table 1. Demographics and Neonatal Outcome Data

| Characteristics | All Subjects | Subjects < 28 Weeks Gestational Age |
|---|---|---|
| Gestational age (wk), mean ± SD | 28.4 ± 2.3 | 25.4 ± 1.3 |
| Birth weight (g), mean ± SD | 1,206 ± 395 | 840 ± 203 |
| 1 min Apgar (IQR) | 7 (5, 7) | 4.5 (2, 7) |
| 5 min Apgar (IQR) | 8 (7, 8) | 7 (6, 8) |
| Male, *n* (%) | 75 (51) | 28 (58) |
| Cesarean section, *n* (%) | 121 (82.3) | 39 (81.3) |
| Premature rupture of membranes, *n* (%) | 25 (17) | 10 (20.8) |
| Antenatal steroids, *n* (%) | 143 (97.2) | 47 (98) |
| Magnesium sulfate, *n* (%) | 133 (90.5) | 47 (98) |
| Chorioamnionitis, *n* (%) | 43 (29.3) | 23 (48) |
| Pregnancy-induced hypertension/pre-eclampsia, *n* (%) | 35 (23.8) | 9 (18.8) |
| Maternal diabetes, *n* (%) | 22 (15) | 6 (12.5) |
| Death/severe IVH, *n* (%) | 10 (6.8) | 9 (18.8) |
| Severe IVH, *n* (%) | 5 (3.4) | 5 (10.4) |
| Any IVH, *n* (%) | 19 (12.9) | 12 (25) |
| Necrotizing entercolitis, *n* (%) | 4 (2.7) | 4 (8.3) |
| Bronchopulmonary dysplasia, *n* (%) | 20 (13.6) | 18 (37.5) |
| Pneumothorax, *n* (%) | 9 (6.1) | 7 (14.5) |
| Retinopathy of prematurity, *n* (%) | 6 (4.0) | 6 (12.5) |

$N = 147$ for all subjects; $n = 48$ for subjects < 28 weeks gestational age.
IVH = intraventricular hemorrhage

$P_{aCO_2}$ and other variables were compared for infants with and without each of 7 outcomes: any IVH, severe IVH (grade 3–4), BPD (defined as oxygen or mechanical ventilation at 36 weeks postmenstrual age), necrotizing enterocolitis, retinopathy of prematurity (ROP), pneumothorax, and the combined outcome of death and/or severe IVH. IVH was categorized according to Papile's grading system, and necrotizing enterocolitis was defined as modified Bells Stage IIa or greater. Severe ROP was defined as stage 3 or greater with "plus" disease. All of the ABG variables and the prenatal and postnatal variables collected as part of the original trial (Table 1) were analyzed with a Student $t$ test and with univariate logistic regression. Those variables with $P < .10$ in the univariate analysis were

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Table 2. Arterial Blood Gas Analysis of All Subjects vs Subjects < 28 Weeks Gestational Age

| Mode of Respiratory Support | Samples, *n* | $P_{aCO_2}$, mm Hg | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Mean ± SD | < 30 | 30–34 | 35–44 | 45–54 | 55–64 | ≥ 65 |
| All Subjects, % | 1,316 | 46.7 ± 11.9 | 1.7 | 5.3 | 47.0 | 26.5 | 13.0 | 6.5 |
| High-frequency ventilation | 116 | 58.4 ± 14.4* | 0.9 | 0.8 | 7.8 | 35.3 | 37.1 | 18.1 |
| Continuous mandatory ventilation | 458 | 48.0 ± 13.5 | 2.0 | 7.0 | 39.7 | 27.5 | 15.7 | 8.1 |
| Noninvasive | 12 | 48.9 ± 15.3 | 0.0 | 8.3 | 50.0 | 16.7 | 8.3 | 16.7 |
| CPAP | 690 | 44.0 ± 8.8 | 1.9 | 7.3 | 55.2 | 24.3 | 7.8 | 3.5 |
| HFNC | 37 | 40.5 ± 4.9 | 0.0 | 13.5 | 70.3 | 16.2 | 0.0 | 0.0 |
| Room air | 3 | 38.5 ± 4.7 | 0.0 | 33.3 | 66.7 | 0.0 | 0.0 | 0.0 |
| Gestational age < 28 weeks, % | 584 | 48.7 ± 11.9 | 0.9 | 5.3 | 41.6 | 25.5 | 18.5 | 8.2 |
| High-frequency ventilation | 87 | 57.7 ± 12.6* | 1.0 | 0.1 | 7.0 | 40.2 | 36.8 | 14.9 |
| Continuous mandatory ventilation | 311 | 49.9 ± 14.4 | 0.9 | 6.0 | 36.3 | 26.1 | 20.3 | 10.3 |
| Noninvasive | 2 | 42.5 ± 7.13 | 0.0 | 0.0 | 50.0 | 50.0 | 0.0 | 0.0 |
| CPAP | 182 | 44 ± 8.8 | 0.0 | 7.1 | 66.5 | 17.6 | 7.1 | 1.7 |
| HFNC | 2 | 41.7 ± <1 | 0.0 | 0.0 | 100 | 0.0 | 0.0 | 0.0 |
| Room air | 0 | 0 ± 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

*Significant at $P < .01$.
HFNC = high-flow nasal cannula

retained to be examined in the stepwise logistic regression modeling.

## Results

The 147 subjects included in the secondary analysis had a mean ± SD gestational age of 28 ± 2 weeks and a mean ± SD birthweight of 1,206 ± 394 g (Table 1). A total of 1,316 ABG samples (9.3 ± 4.9 samples per subject) were evaluated. Antenatal steroids, magnesium sulfate, chorioamnionitis, pregnancy-induced hypertension, maternal diabetes, premature rupture of the membranes, cesarean section, gender, and Apgar scores at 1 min were not significantly different between any of the outcome groups.

Of the total ABG samples, 10% had a pH < 7.20. The mean pH for the 48 subjects < 28 weeks gestational age was 7.26 ± .08 as compared to 7.27 ± .07 for the 99 subjects ≥ 28 weeks ($P = .72$). Infants with an outcome of death/severe IVH, severe IVH, and with any grade IVH had significantly lower values for minimum pH than those without the adverse outcomes (Table 3). There was a significant association between the minimum pH in subjects with the outcome of death/severe IVH that remained after adjusting for other variables ($P = .003$) (Table 3). There was no significant difference in the minimum pH in subjects who developed necrotizing enterocolitis, BPD, ROP, or pneumothorax.

Less than 2% of all the $P_{aCO_2}$ values were < 30 mm Hg. Minimum $P_{aCO_2}$ was not significantly different for any of the outcomes, and none of the subjects included in this study were diagnosed with periventricular leukomalacia. Moderate hypercapnia of 55–64 mm Hg occurred in 13% of all samples, but in 18.5% of the samples of subjects < 28 weeks gestational age. $P_{aCO_2} \geq 65$ mm Hg occurred in 6.5% of all samples and in 8.2% of those < 28 weeks gestational age. Moderate levels of hypercapnia or higher were present in approximately 20–25% of the total samples and > 50% of those drawn during high-frequency ventilation (Table 2). $P_{aCO_2}$ values obtained without assisted respiratory support (nasal cannula ≤ 2 L/min or room air) were primarily in the normal range (35–45 mm Hg). Overall mean $P_{aCO_2}$ values obtained while on CPAP were lower and exhibited less fluctuation (smaller SD) than continuous mandatory ventilation and high-frequency ventilation. Table 2 provides the $P_{aCO_2}$ (mean ± SD) and the $P_{aCO_2}$ range by percent of the values for each category. The mean $P_{aCO_2}$ for subjects < 28 weeks gestational age was not significantly greater than subjects ≥ 28 weeks gestational age ($P = .09$). The mean $P_{aCO_2}$ on high-frequency ventilation was significantly greater than that on continuous mandatory ventilation ($P < .001$).

The multivariable models to predict the outcomes of interest included all parameters with $P \leq .10$ in the univariate analysis (gestational age, birthweight, and 5-min Apgar score < 7) and confirmed the independent association of only gestational age.

Subjects with the outcome of death/severe IVH had a mean ± SD $P_{aCO_2}$ of 52.3 ± 11 as compared to a $P_{aCO_2}$ of 44.7 ± 5.8 (adjusted OR 1.16, 95% CI 1.04–1.29, $P = .006$) and a higher variability of $P_{aCO_2}$ as measured by the SD 12.6 ± 8.7 as opposed to 7.8 ± 4.5 (adjusted OR 1.15, 95% CI 1.03–1.27, $P = .01$) for those without the negative outcome (Table 3). Maximum $P_{aCO_2}$ for subjects with death/severe IVH and any IVH as well as

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Table 3. Univariate and Multivariate Logistic Regression Analysis of Arterial Blood Gas Variables to Predict Adverse Outcome

| Outcome | Predictor Variable | Outcome, mean ± SD | | Univariate Odds Ratio (95% CI) | *P* | Gestational Age-Adjusted Odds Ratio (95% CI) | *P* |
|---|---|---|---|---|---|---|---|
| | | Yes | No | | | | |
| Death/severe IVH grade 3–4, *n* = 10 (6.8%) | Maximum $P_{aCO_2}$ | 75.0 ± 24.9 | 58.6 ± 15.7 | 1.04 (1.00–1.07) | .009 | 1.03 (1.00–1.06) | .09 |
| | Minimum $P_{aCO_2}$ | 38.4 ± 3.4 | 35.6 ± 5.0 | 1.14 (.98–1.32) | .09 | | |
| | Time-weighted mean $P_{aCO_2}$ | 52.3 ± 11 | 44.7 ± 5.8 | 1.152 (1.05–1.26) | .002 | 1.16 (1.04–1.29) | .006 |
| | SD $P_{aCO_2}$ | 12.6 ± 8.7 | 7.8 ± 4.5 | 1.127 (1.03–1.24) | .01 | 1.15 (1.03–1.27) | .01 |
| | $\Delta P_{aCO_2}$ | 37.1 ± 23.9 | 22.9 ± 15.3 | 1.04 (1.01–1.06) | .02 | | |
| | Minimum pH | 7.03 ± 0.25 | 7.23 ± 0.9 | 0–.00 | < .001 | 0–.06 | .003 |
| Severe IVH grade 3–4, *n* = 5 (3.4%) | Maximum $P_{aCO_2}$ | 69.7 ± 11.9 | 59.8 ± 17.7 | 1.02 (.99–1.06) | .23 | | |
| | Minimum $P_{aCO_2}$ | 38.7 ± 3.1 | 35.7 ± 5.0 | 1.15 (.93–1.43) | .19 | | |
| | Time-weighted mean $P_{aCO_2}$ | 50 ± 5.7 | 45 ± 6.5 | 1.09 (.98–1.22) | .11 | | |
| | SD $P_{aCO_2}$ | 11.0 ± 4.2 | 8.0 ± 5.0 | 1.81 (.96–1.22) | .21 | | |
| | $\Delta P_{aCO_2}$ | 31.0 ± 11.9 | 24.1 ± 17.2 | 1.02 (.98–1.06) | .38 | | |
| | Minimum pH | 7.05 ± 0.21 | 7.21 ± 0.11 | .00 (.00–.25) | .01 | .03 (.00–6.91) | .20 |
| Any grade IVH, *n* = 19 (12.9%) | Maximum $P_{aCO_2}$ | 69.2 ± 16 | 58.8 ± 17.4 | 1.03 (1.00–1.05) | .025 | 1.01 (.98–1.04) | .50 |
| | Minimum $P_{aCO_2}$ | 36.7 ± 5.2 | 35.7 ± 4.9 | 1.05 (.95–1.16) | .38 | | |
| | Time-weighted mean $P_{aCO_2}$ | 48.7 ± 6.5 | 44.7 ± 6.3 | 1.09 (1.02–1.17) | .02 | 1.05 (.97–1.13) | .23 |
| | SD $P_{aCO_2}$ | 10.3 ± 3.4 | 7.8 ± 5.1 | 1.08 (1.00–1.17) | .059 | | |
| | $\Delta P_{aCO_2}$ | 32.4 ± 15.9 | 23.1 ± 16.9 | 1.03 (1.00–1.05) | .035 | | |
| | Minimum pH | 7.13 ± 0.8 | 7.22 ± 0.15 | .01 (.00–.63) | .032 | .14 (.00–7.11) | .33 |

IVH = intraventricular hemorrhage
$\Delta P_{aCO_2}$ = the difference between $P_{aCO_2}$ maximum and $P_{aCO_2}$ minimum

time-weighted and $P_{aCO_2}$ fluctuations for subjects with any IVH were all significant with univariate analysis (Table 3) but were not significantly associated with those outcomes, after adjusting for the other variables in the model. There was no significant difference in any of the variables for those subjects who developed necrotizing enterocolitis, BPD, ROP, or pneumothorax in our cohort after adjusting for the other variables in the model.

## Discussion

Permissive hypercapnia is a ventilation strategy widely used to minimize the iatrogenic lung injury that can occur with mechanical ventilation. It is theorized that the main benefits come from the avoidance of volutrauma with the lower $V_T$ values that can be utilized to maintain lower minute ventilation and a higher $P_{aCO_2}$.[1] One of the possible advantages of a permissive hypercapnia strategy is the reduced incidence of hypocarbia and the avoidance of known hazards. Our study had a very low incidence of hypocarbia in our cohort (< 2% of all ABG samples had $P_{aCO_2}$ < 30 mm Hg), no cases of periventricular leukomalacia, and no adverse events associated with hypocarbia. In the past, many clinicians have attempted to keep $P_{aCO_2}$ < 40 mm Hg in ventilated neonates; this is, however, associated with an increased risk of developing BPD.[17,18] An analysis of preterm infants < 29 weeks gestational age comparing $P_{aCO_2}$ levels during the first 96 h with the incidence of severe IVH, periventricular leukomalacia, and BPD demonstrated that infants whose $P_{aCO_2}$ fell below 30 mm Hg at any stage in the first 48 h of life had an increased risk of severe IVH or periventricular leukomalacia (OR 2.38, 95% CI 1.27–4.49, *P* = .007). Infants with at least 3 $P_{aCO_2}$ values < 30 mm Hg in the first 24 h of life had an increased risk of BPD (OR 2.21, 95% CI 1.05–4.57, *P* = .036).[13] Our cohort's low incidence of hypocapnia and the absence of periventricular leukomalacia or other associated adverse events may be a direct result of routine targeting of higher than normal $P_{aCO_2}$ goals.[19-21]

Early randomized, controlled trials testing mild permissive hypercapnia in neonates found reduced ventilator days or ventilator dependence at 36 week corrected gestational age, although these differences did not reach statistical significance. There was also not a significant reduction in BPD rates with a mild hypercapnia strategy, but neither was there an increase in adverse neurologic events. The study by Mariani et al[4] had $P_{aCO_2}$ goals of 45–55 mm Hg, but actual $P_{aCO_2}$ values in the permissive hypercapnia group were primarily 45–50 mm Hg. Carlo et al[5] had $P_{aCO_2}$ goals of > 52 mm Hg, but actual $P_{aCO_2}$ values in the permissive hypercapnia group were primarily 45–50 mm Hg for the first 7 postnatal days. These 2 studies may be a reflection of possible neurologic safety of permissive hypercapnia of 45–50 mm Hg but not 50–55 mm Hg. In our cohort,

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26.5% of all $P_{aCO_2}$ values fell in the mild hypercapnia range of 45–55 mm Hg. There was no statistical difference in any of the $P_{aCO_2}$ parameters between our subjects with BPD or pneumothorax and those without the adverse event after adjustment for gestational age. In a meta-analysis, permissive hypercapnia did not reduce the rate of BPD or air leaks in ventilated, extremely low birthweight infants.[14]

Vannucci et al[22] postulated a neuroprotective effect of $CO_2$ in preterm rats and that $P_{aCO_2}$ of 45–55 mm Hg offered significant neuroprotection. Possible explanations include a shift of the oxygen–hemoglobin dissociation curve to the right, resulting in increased delivery of $O_2$ and increased cerebral blood flow preventing cerebral ischemia.[13] Hypercapnic cerebral vasodilation can also cause an increase in cerebral blood flow that may contribute to the development of IVH.[8] The most potent acute regulator of cerebral blood flow is $P_{aCO_2}$, and it can have more impact than increases in mean blood pressure.[10,23] Cerebral autoregulation must be intact to maintain steady blood flow to the brain despite disturbances to cerebral perfusion pressure that can occur with critically ill neonates.[8,23] Kaiser et al.[8] investigated the effects that $P_{aCO_2}$ levels of 30–60 mm Hg and mean blood pressure have on cerebral autoregulation. Cerebral blood flow was not influenced by mean blood pressure when cerebral autoregulation was intact, but a progressive loss of autoregulation was found with increasing $P_{aCO_2}$, starting with $P_{aCO_2} \geq 45$. The autoregulatory slope increased with increasing $P_{aCO_2}$, which raises concerns about the use of permissive hypercapnia.[8] Noori et al[24] examined the effect of $CO_2$ on cerebral blood flow in the first 3 postnatal days for neonates ≤ 30 weeks gestational age. They found the relationship was absent on day one, but a threshold existed on day 2 (52.7 mm Hg) and day 3 (51.0 mm Hg), at which point cerebral blood flow became reactive to $P_{aCO_2}$. The authors theorized that the enhanced cerebral blood flow response to $P_{aCO_2}$ contributes to the reperfusion injury and partly explains the association between hypercapnia and periventricular or intraventricular hemorrhage.[24] We found a mean $P_{aCO_2}$ of 52.3 ± 11 mm Hg to be associated with the outcome of death/severe IVH (OR 1.16, 95% CI 1.04–1.29, $P = .006$). Severe hypercapnia (defined by Kaiser et al[25] as a percentage of $P_{aCO_2}$ values ≥ 60 mm Hg, $P = .009$) has been associated with an increased risk of IVH, and most infants experience the IVH in the first week of life when $P_{aCO_2}$ levels may have been a factor. A causal relationship cannot be confirmed, however, because it is unclear whether hypercapnia precedes IVH or is a result of IVH.[25]

In neonates without intact cerebral autoregulation, the variability of $P_{aCO_2}$ may also be an important contributor to neurologic adverse events.[8,17,23] In our cohort, subjects who exhibited fluctuations of the $P_{aCO_2}$ as represented by the SD were more likely to experience the adverse event of death/severe IVH (OR 1.15, 95% CI 1.03–1.27, $P = .01$). Infants evaluated as a secondary analysis of the SUPPORT trial also demonstrated that greater fluctuation in $P_{aCO_2}$ was significantly associated with IVH and neurodevelopmental impairment at 18–22 months corrected age and an independent predictor of worse outcomes for extremely low birthweight infants.[26]

Almost 20% of our total ABG samples had $P_{aCO_2}$ values 55 mm Hg. Because our study is a retrospective cohort, subjects had similar ABG management, and we were thus unable to identify a possible positive association between higher $P_{aCO_2}$ and pulmonary adverse outcomes and necrotizing enterocolitis in our cohort. For subjects receiving high-frequency ventilation, 90% of the samples could be categorized as permissive hypercapnia > 45 mm Hg, and > 50% were in the moderate to severe range of > 55 mm Hg. It is possible that there is little pulmonary benefit to a permissive hypercapnia strategy in this mode of ventilation, because they are already receiving a low $V_T$ strategy and there may be in fact a neurologic risk at this level of $P_{aCO_2}$. Because high-frequency ventilation is often used as a rescue therapy or for active air leak, it is difficult to identify whether extremes of $P_{aCO_2}$ were due to extensive lung disease or to physician choice to allow permissive hypercapnia.

Acidosis may be an independent predictor of poor outcome or merely a reflection of the corresponding levels of $CO_2$.[6] Because the conditions are intertwined, it is difficult to separate their effects. The mean pH was more acidotic in samples taken during high-frequency ventilation as compared to conventional ventilation ($P < .001$), although the high-frequency ventilation samples also had higher levels of permissive hypercapnia. There was a significant association with minimum pH in the adjusted odds ratio for the outcome death/severe IVH (OR 0, 95% CI 0–.06, $P = .003$). There was no significant difference in the minimum pH in subjects that developed necrotizing enterocolitis, BPD, ROP, or pneumothorax.

Our study cohort is a sample from a single institution and may not be generalizable to other populations. Higher $P_{aCO_2}$ levels may be correlated with a greater magnitude of lung disease or physician intent to allow permissive hypercapnia. Only 5 subjects in our cohort had severe IVH, and they were all < 28 weeks gestational age. A larger sample size with more immature infants may have yielded different results. The ventilation strategies and clinical course after the first 72 h are also likely to have a considerable effect on the risk of morbidities.

## Conclusion

Moderate to high levels of hypercapnia were commonplace in our cohort. The low incidence of hypocapnia and the absence of periventricular leukomalacia or other associated adverse events may be a direct result of routine tar-

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geting of higher than normal $P_{aCO_2}$ goals. There was no significant difference in any of the pH or $P_{aCO_2}$ variables for those subjects who developed necrotizing enterocolitis, BPD, ROP, or pneumothorax. There was a significant association between the minimum pH, time-weighted mean $P_{aCO_2}$, and the fluctuations of $P_{aCO_2}$ in subjects with death/severe IVH. Although mild hypercapnia appears safe, moderate hypercapnia may increase neurologic risk and provide little pulmonary benefit.

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## REFERENCES

1. Woodgate PG, Davies MW. Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants. Cochrane Database Syst Rev 2001;(2):CD002061.
2. Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. J Pediatr 2014; 164(2):264-270.e261-e263.
3. Mariani G, Miller JD, Carlo WA. Permissive hypercapnia in neonates: specific experience and limitations. In: Rimensberger PC, ed. *Pediatric and Neonatal Mechanical Ventilation*. Berlin, Germany: Springer-Verlag; 2015.
4. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics 1999;104(5 Pt 1):1082-1088.
5. Carlo WA, Stark AR, Wright LL, Tyson JE, Papile LA, Shankaran S, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr 2002;141(3):370-374.
6. Thome UH, Carlo WA, Pohlandt F. Ventilation strategies and outcome in randomised trials of high frequency ventilation. Arch Dis Child Fetal Neonatal Ed 2005;90(6):F466-F473.
7. Thome UH, Genzel-Boroviczeny O, Bohnhorst B, Schmid M, Fuchs H, Rohde O, et al. Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomised controlled multicentre trial. Lancet Respir Med 2015;3(7):534-543.
8. Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. Pediatr Res 2005;58(5):931-935.
9. Kaiser JR, Gauss CH, Williams DK. Tracheal suctioning is associated with prolonged disturbances of cerebral hemodynamics in very low birth weight infants. J Perinatol 2008;28(1):34-41.
10. Murase M, Ishida A. Early hypocarbia of preterm infants: its relationship to periventricular leukomalacia and cerebral palsy, and its perinatal risk factors. Acta Paediatr 2005;94(1):85-91.
11. Ikonen RS, Janas MO, Koivikko MJ, Laippala P, Kuusinen EJ. Hyperbilirubinemia, hypocarbia and periventricular leukomalacia in preterm infants: relationship to cerebral palsy. Acta Paediatr 1992; 81(10):802-807.
12. Goldstein RF, Thompson RJ, Jr., Oehler JM, Brazy JE. Influence of acidosis, hypoxemia, and hypotension on neurodevelopmental outcome in very low birth weight infants. Pediatrics 1995;95(2):238-243.
13. Erickson SJ, Grauaug A, Gurrin L, Swaminathan M. Hypocarbia in the ventilated preterm infant and its effect on intraventricular haemorrhage and bronchopulmonary dysplasia. J Paediatr Child Health 2002;38(6):560-562.
14. Thome UH, Carroll W, Wu TJ, Johnson RB, Roane C, Young D, et al. Outcome of extremely preterm infants randomized at birth to different PaCO2 targets during the first seven days of life. Biology Neonate 2006;90(4):218-225.
15. ARDSNet. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301-1308.
16. Katheria A, Poeltler D, Durham J, Steen J, Rich W, Arnell K, et al. Neonatal resuscitation with an intact cord: a randomized clinical trial. J Pediatr 2016;178:75-80.
17. Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N. 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. Pediatrics 2007;119(2):299-305.
18. Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr 1989;115(1):115-120.
19. Garland JS, Buck RK, Allred EN, Leviton A. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. Arch Pediatr Adolesc Med 1995;149(6):617-622.
20. Laffey JG, Kavanagh BP. Hypocapnia. N Engl J Med 2002;347(1): 43-53.
21. Thome UH, Carlo WA. Permissive hypercapnia. Semin Neonatol 2002;7(5):409-419.
22. Vannucci RC, Towfighi J, Heitjan DF, Brucklacher RM. Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat. Pediatrics 1995;95(6): 868-674.
23. Noori S, Seri I. Hemodynamic antecedents of peri/intraventricular hemorrhage in very preterm neonates. Semin Fetal Neonatal Med 2015;20(4):232-237.
24. Noori S, Anderson M, Soleymani S, Seri I. Effect of carbon dioxide on cerebral blood flow velocity in preterm infants during postnatal transition. Acta Paediatr 2014;103(8):e334-e339.
25. Kaiser JR, Gauss CH, Pont MM, Williams DK. Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol 2006;26(5): 279-285.
26. Ambalavanan N, Carlo WA, Wrage LA, Das A, Laughon M, Cotten CM, et al. PaCO2 in surfactant, positive pressure, and oxygenation randomised trial (SUPPORT). Arch Dis Child Fetal Neonatal 2015; 100(2):F145-F149.