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PaCO₂ in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

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Abstract

Objective—To determine the association of PaCO₂ with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18–22 months in premature infants.

Design—Secondary exploratory data analysis of SUPPORT.

Setting—Multiple referral NICUs.

Patients—1316 infants 24 0/7 to 27 6/7 weeks gestation randomized to different oxygenation (SpO₂ target 85–89% vs 91–95%) and ventilation strategies.

Main Outcome Measures—Blood gases from postnatal days 0–14 were analyzed. Five PaCO₂ variables were defined: minimum [Min], maximum [Max], standard deviation, average (timeweighted), and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO₂], hypocapnic [lowest quartile of Min PaCO₂], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO₂]). PaCO₂ variables were compared for infants with and without sIVH, BPD, and NDI (+/- death). Multivariable logistic regression models were developed for adjusted results.

Results—sIVH, BPD, and NDI (+/- death) were associated with hypercapnic infants and fluctuators. Association of Max PaCO₂ and outcomes persisted after adjustment (Per 10 mmHg increase: sIVH/death: OR 1.27 [1.13–1.41]; BPD/death: OR 1.27 [1.12–1.44]; NDI/death: OR 1.23 [1.10–1.38], Death: OR 1.27 [1.12–1.44], all p < 0.001). No interaction was found between PaCO₂ category and SpO₂ treatment group for sIVH/death, NDI/death, or death. Max PaCO₂ was positively correlated with maximum FiO₂ ($r_s0.55$, p < 0.0001) & ventilator days ($r_s0.61$, p < 0.0001).

Conclusions—Higher PaCO₂ was an independent predictor of sIVH/death, BPD/death, and NDI/death. Further trials are needed to evaluate optimal PaCO₂ targets for high risk infants.

Keywords

Infant; premature; Infant mortality; Infant; Premature; Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

INTRODUCTION

Variations in arterial partial pressure of carbon dioxide (PaCO₂) are associated with outcomes of prematurity such as intraventricular hemorrhage (IVH), ¹ periventricular leukomalacia (PVL), ², ³ bronchopulmonary dysplasia (BPD), ⁴ and neurodevelopmental impairment (NDI). ⁵ We have previously shown that both high and low PaCO₂ and wide fluctuations in PaCO₂ are associated with severe IVH (sIVH; IVH Grades III or IV). ¹ Periventricular leukomalacia (PVL) is associated with hypocapnia. ², ³, ⁶

Increased $PaCO_2$ increases cerebral blood flow, $^{7-9}$ while decreased $PaCO_2$ reduces cerebral blood flow. 10 Cerebral blood flow decreases with increased oxygenation but interactions between $PaCO_2$ and oxygenation have not been assessed in preterm infants. Lung injury may be reduced by tolerance of higher $PaCO_2^{4, 11, 12}$ as well as lower oxygen saturation (SpO_2) . 13 The combination of higher $PaCO_2$ (permissive hypercapnia) and lower SpO_2 might reduce BPD more than with either permissive hypercapnia or a lower SpO_2 target alone.

The NICHD Neonatal Research Network SUPPORT trial compared outcomes in infants randomly assigned to SpO₂ targets of either 85–89% or 91–95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (PaCO₂>65 mm Hg permitted intubation, while PaCO₂<65 mm Hg with pH>7.20 was an extubation criterion) or intubation and surfactant (PaCO₂<50 mm Hg with pH>7.30 was an extubation criterion). ^{13, 14} Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although CPAP group infants received fewer days of mechanical ventilation. ^{13, 14} In the lower SpO₂ target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes. ¹³ However, no significant differences in the composite outcome of death or NDI were noted among infants in any of the treatment groups. ¹⁵

Clinical outcomes not significantly different by SpO₂ target groups might be different when the combination of PaCO₂ and SpO₂ (actual or target group) is analyzed. We hypothesized that both extremes of PaCO₂ would be associated with sIVH, and that effect modification by SpO₂ would be observed, with hypercapnia associated with sIVH in the low but not high SpO₂ group (due to greater cerebral blood flow at lower SpO₂). We also hypothesized that BPD would be lower in infants with hypercapnia in the low SpO₂ group (due to less mechanical ventilation), and that higher PaCO₂ will be associated with a higher NDI (due to increased risk of sIVH).

PATIENTS AND METHODS

Patient characteristics

This was a secondary exploratory analysis of data from infants (n=1316) in the SUPPORT trial.^{13, 14} Characteristics of this population¹³ (mean birth weight approximately 830 g, gestational age 26 weeks, 54% male) and the follow-up cohort¹⁵ (93.6% evaluated at 18–22 months corrected age, 20.1% death, 28.8% with NDI/death) have been previously reported.

PaCO₂ variables

Five PaCO₂ variables were defined, using routine blood gas (arterial or capillary) measurements not governed by protocol. PaCO₂ closest to 8 am, 4 pm, and midnight was recorded for postnatal days 1–14. From these data, the minimum, maximum (Max PaCO₂), standard deviation, and average (time-weighted) PaCO₂ were derived. Average (time-weighted) PaCO₂ was calculated as defined previously¹: the sum of all PaCO₂ values multiplied by the time interval from previous blood gas was divided by the overall time

period. This measure enables an estimate of the magnitude of exposure to $PaCO_2$ by taking into account the duration of time for each $PaCO_2$ value. To avoid any one blood gas value from having an unduly large effect in this "time-weighting", we capped the maximum duration for any $PaCO_2$ at 24h. Infants were categorized into 4 groups (hypercapnic, hypocapnic, fluctuators, and normocapnic) by first separately ranking the maximum and minimum $PaCO_2$ over days 1-14 into quartiles. Infants with minimum $PaCO_2$ in lowest quartile and not in highest quartile of maximum $PaCO_2$ were categorized as 'hypocapnic'. Infants with maximum $PaCO_2$ in highest quartile and not in lowest quartile of minimum $PaCO_2$ were considered 'hypercapnic'. Infants in both lowest quartile of minimum $PaCO_2$ and highest quartile of maximum $PaCO_2$ were considered 'fluctuators'. Remaining infants with minimum $PaCO_2$ level in quartiles 2-4 and maximum $PaCO_2$ in quartiles 1-3 were categorized as 'normocapnic'.

Other variables

Maternal hypertension was defined as pregnancy-induced hypertension (PIH). Premature rupture of membranes (PROM) was rupture of membranes > 24 hours prior to birth. Prenatal steroids were any use of antenatal steroids. Maximum FiO₂ was the maximum FiO₂ at 24 hours and on days 3, 7, and 14. Severe illness was defined *a priori* as FiO₂ > 0.4 and mechanical ventilation for 8+ hours in the 1st 14 days. sIVH was IVH grade 3–4. ¹⁶ BPD was defined using the physiologic definition at 36w PMA. ^{17, 18} NDI was any of: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition < 70, a modified Gross Motor Function Classification System score 2, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment. ¹⁵ PVL was not evaluated as the incidence (4%) was too low for detailed analysis.

Statistical Analysis

 $PaCO_2$ and other variables for infants with outcome were compared to those without outcome for each of 7 outcomes: sIVH, sIVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. $PaCO_2$ variables were also compared by SpO_2 treatment groups. Statistical significance (p<0.05) for these unadjusted comparisons was assessed by Chi Square tests for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. In keeping with the exploratory goals of this study, no adjustments were made for multiple comparisons.

Adjusted results for maximum PaCO₂, 4 level PaCO₂ variable, as well as average PaCO₂ were obtained using generalized estimating equations, assuming an exchangeable correlation between infants within familial clusters (i.e. multiples). Other variables included were birth weight, GA group (24–25 vs. 26–27 weeks), gender, race, prenatal steroids, PIH, PROM, center, and three measures of illness severity: maximum FiO₂, severe illness, number of mechanical ventilation days in first 14 days. SUPPORT treatment group variables (High/Low SpO2; CPAP/ventilator) were included in models containing maximum PaCO₂ and the 4 level PaCO₂ variable. Interactions of PaCO₂ and treatment group variables assessed if effect of PaCO₂ varied by SUPPORT treatment group. Evaluation of interaction of actual median SpO₂ in the first 14 days and average PaCO₂ determined if the effect of

average PaCO₂ varied by level of actual SpO₂. Results are expressed as adjusted odds ratios and 95% confidence intervals.

As higher maximum PaCO₂ may be either deliberate (clinician intent for permissive hypercapnia, possibly accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (associated with higher maximum FiO₂, days of mechanical ventilation, and severe illness), correlations of maximum PaCO₂ with maximum FiO₂ and days of ventilation, and its relationship with severe illness (as previously defined) were calculated.

All analyses were done using SAS software v. 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Adjusted results for sIVH /Death (Table 1):

Higher maximum PaCO₂ was associated with increased odds of sIVH/death. Hypercapnic infants had higher odds of sIVH/death compared to normocapnic infants whereas hypocapnic and fluctuators did not differ significantly. No interaction was found between PaCO₂ category (Hypocapnic, Hypercapnic, etc) and treatment group (Higher or Lower SpO₂). Average PaCO₂ was not associated with the outcome. Other variables associated with sIVH/death included severe illness, lower birth weight and gestational age, male gender, no PIH, and center.

Adjusted results for BPD/Death (Table 2):

Higher maximum and average PaCO₂ were associated with BPD/death. Interaction (p=0.026) was noted between the PaCO₂ category 'fluctuators' and treatment group (Higher or Lower SpO₂), hence results for PaCO₂ category are presented separately. For fluctuators in the higher SpO₂ group, the OR was 3.3 vs. 0.62 for fluctuators in the lower SpO₂ group. Other variables associated with BPD/death were severe illness, lower birth weight, male gender, not being non-Hispanic white, and center. As growth restriction increases the risk of BPD/death, ¹⁹ birth weight z-score was initially included in the model, but did not change odds ratios, and was therefore excluded from the final model.

Adjusted results for NDI/Death (Table 3):

Higher maximum PaCO₂ was associated with NDI/death. No interactions were noted between PaCO₂ category and SpO₂ treatment group. Hypercapnic infants and fluctuators, but not hypocapnic infants, had increased odds of NDI/death. Other variables associated with NDI/death were severe illness, lower birth weight and gestational age, male gender, and no PIH.

Adjusted results for Death before discharge (Table 4):

Higher maximum PaCO₂ was associated with death before discharge. No interactions were noted between PaCO₂ category and SpO₂ treatment group. Hypercapnic infants, but not hypocapnic and fluctuators, had increased odds of death, versus normocapnic infants. Other

variables associated with death were severe illness, lower birth weight, male gender, and no PIH.

Maximum $PaCO_2$ was positively correlated with both maximum FiO_2 (Spearman correlation coefficient $[r_s] = 0.55$, p < 0.0001) and days of ventilation $(r_s = 0.61, p < 0.0001)$. $PaCO_2$ in infants having severe illness was higher than in infants without severe illness (median maximum $PaCO_2 = 78$ vs. 61, p < 0.0001).

Unadjusted Results (Supplemental Table):

Infants developing sIVH had a lower minimum, higher maximum and greater variation in $PaCO_2$ compared to those without sIVH. Maximum $PaCO_2$ demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum $PaCO_2$. Separation in minimum, standard deviation, and average $PaCO_2$ was statistically significant (p<0.01) but clinically small (\sim 2 mm Hg). Results for BPD, BPD or death, NDI, and NDI or death were similar to results for sIVH and sIVH or death. There were no significant differences in the $PaCO_2$ variables by SpO_2 treatment groups.

DISCUSSION

We found that a higher maximum $PaCO_2$ in the first two postnatal weeks was an independent predictor of worse outcome even after adjustment for available indicators of illness severity such as maximum FiO_2 , days of ventilation, and severe illness. However, it is not certain that high $PaCO_2$ is in the causal pathway of these outcomes. As statistical adjustment in the analysis can only adjust for known variables and not unknown or unmeasured variables (e.g. oxygenation index), and $PaCO_2$ was correlated with duration of ventilation and oxygen requirement, generally considered markers of illness severity, it is possible that high $PaCO_2$ is a surrogate marker for some of these unknown/unmeasured variables. Our results suggest that further trials are needed to evaluate optimal $PaCO_2$ targets in extremely premature infants.

A limitation is that data on ventilator settings and oxygenation index were not available to better estimate lung disease severity. However, this study has the strengths of prospective data collection by trained research coordinators and follow-up in almost 94% of infants by certified personnel in SUPPORT, a large recent multi-center trial. An additional strength is that we evaluated both interaction with actual saturation and treatment group (higher or lower SpO₂ target), to distinguish illness severity and effects of treatment group allocation (e.g. higher average PaCO₂ was associated with sIVH/death only if actual SpO₂ was lower, but without interaction with treatment group (see Table 1)).

In this cohort, the average $PaCO_2$ even in infants without sIVH was 48 mm Hg with a relatively narrow interquartile range (~10 mm Hg). Our data suggest clinical practices have evolved to maintain $PaCO_2$ in the "permissive hypercapnia" range (45–55 mm Hg).¹² However, tight control of $PaCO_2$ within this narrow range is difficult as the maximum $PaCO_2$ exceeded this range even in infants without sIVH.

Hypercapnic infants had higher odds of sIVH/death and death even after statistical adjustment for illness severity, indicating that higher maximum $PaCO_2$ is an independent risk factor for these adverse outcomes. Maximum $PaCO_2$ correlated with longer mechanical ventilation and higher oxygen supplementation, suggesting that infants with higher maximum $PaCO_2$ had more severe lung disease, rather than permissive hypercapnia and more aggressive weaning from mechanical ventilation. No interaction was observed between maximum $PaCO_2$ and SpO_2 groups for sIVH, probably because randomization in this trial likely led to a similar range of lung disease severity and resultant $PaCO_2$ in both SpO_2 groups.

A higher maximum, average, and greater fluctuation in PaCO₂ were associated with a greater risk of BPD and BPD/death (see Table 2). This may be due to more severe lung disease being associated with a higher PaCO₂ (even after statistical adjustment for maximum FiO₂, days of ventilation, and severe illness) rather than because of physician intent (similar to sIVH/death). Although hypercapnia was associated with increased illness severity and worse outcomes, hypercapnia within a limited range may be acceptable and beneficial. Hypercapnia increases CO₂ elimination for a given minute ventilation, due to a higher alveolar CO₂. Also, hypercapnia stimulates respiratory drive, assisting in ventilator weaning. An interesting unexplained finding was that greater fluctuation in PaCO₂ was associated with BPD/death only in the higher SpO₂ but not in the low SpO₂ group. It is speculated that greater oxygen exposure in the higher SpO₂ group may interact with volutrauma/atelectrauma associated with fluctuating PaCO₂ possibly increasing the risk for BPD/death.

Maximum $PaCO_2$ was associated with higher NDI/death (see Table 3). This association may be secondary to maximum $PaCO_2$ being an indicator of illness severity, but it is also known that alterations in $PaCO_2$ can directly mediate brain injury. Increased cerebral blood flow secondary to a spike in $PaCO_2^{7-9}$ may result in sIVH¹ while reduced flow due to decreased $PaCO_2^{10}$ may result in $PVL.^{2,3,6}$

In conclusion, our work demonstrates that higher and greater fluctuations of PaCO₂ are independent predictors of worse outcome in ELBW infants. Higher PaCO₂ levels are also correlated with a greater magnitude of lung disease. Therefore, similar to oxygenation index, maximum PaCO₂ or magnitude of fluctuation of PaCO₂ may be useful for risk-stratification in clinical trials or for prognosis. However, physician intent cannot be entirely ruled out, and caution may be needed about intentional use of high PaCO₂ soon after birth in ELBW infants, until optimal targets of PaCO₂ range are established in randomized clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BSID Bayley Scales of Infant Development

CP Cerebral palsy

IVH Intraventricular hemorrhage

sIVH severe intraventricular hemorrhage

NICU neonatal intensive care unit

NDI Neurodevelopmental impairment

PIH Pregnancy Induced Hypertension

PVL Periventricular leukomalacia

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What's known on this topic

 Variations in arterial partial pressure of carbon dioxide (PaCO₂) are associated with adverse outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

What this study adds

- Higher PaCO₂ was associated with death or severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment.
- Maximum PaCO₂ is a marker of respiratory illness severity in extremely premature infants.

 $\label{eq:Table 1} \textbf{Table 1}$ Adjusted results for PaCO $_2$ variables in relation to outcome of sIVH /death

PaCO ₂ Variable	Adjusted Odds Ratio (95% CI)	<i>p</i> -value
Max PaCO ₂ (per 10 mm Hg)	1.27 (1.13–1.41)	< 0.0001
PaCO ₂ Category:		-
Hypocapnic	1.16 (0.76–1.78)	0.50
Hypercapnic	1.62 (1.05–2.51)	0.029
Fluctuator	1.68 (0.95–2.97)	0.077
Normocapnic	REFERENCE	-
Average PaCO ₂ (per 10 mm Hg)	1.11 (0.80–1.55)	0.52

 $\label{eq:Table 2} \textbf{Adjusted results for PaCO}_2 \ variables \ in \ relation \ to \ outcome \ of \ BPD/death$

PaCO ₂ Variable	Adjusted Odds Ratio (95% CI)	<i>p</i> -value	
Max PaCO ₂ (per 10 mm Hg)	1.27 (1.12–1.44)	0.0002	
PaCO ₂ Category:	Higher SpO ₂ Target		
Hypocapnic	0.78 (0.48–1.3)	0.34	
Hypercapnic	1.24 (0.67–2.29)	0.49	
Fluctuator	3.28 (1.1–9.79)	0.03	
Normocapnic	REFERENCE	-	
Lower SpO ₂ Target			
Hypocapnic	1.07 (0.64–1.79)	0.79	
Hypercapnic	1.71 (0.95–3.07)	0.07	
Fluctuator	0.62 (0.23–1.69)	0.35	
Normocapnic	REFERENCE	-	
Average PaCO ₂ (per 10 mm Hg)	1.65(1.24–2.21)	0.0007	

 $^{^{**}} interaction \ term \ for \ PaCO_2 \ category \times treatment \ group \ (Higher \ or \ Lower \ SpO_2) \ was \ significant \ for \ Fluctuators$

 $\label{eq:Table 3} \mbox{Adjusted results for PaCO}_2 \mbox{ variables in relation to outcome of NDI/death}$

PaCO ₂ Variable	Adjusted Odds Ratio (95% CI)	<i>p</i> -value	
Max PaCO ₂ (per 10 mm Hg)	1.23 (1.10–1.38)	0.0003	
PaCO ₂ Category:			
Hypocapnic	1.11 (0.73–1.68)	0.63	
Hypercapnic	1.75 (1.15–2.65)	0.009	
Fluctuator	2.04 (1.16–3.6)	0.014	
Normocapnic	REFERENCE	-	
Average PaCO ₂ (per 10 mm Hg)	1.11 (0.79–1.56)	0.55	

 $\label{eq:Table 4} \textbf{Adjusted results for PaCO}_2 \ variables \ in \ relation \ to \ outcome \ of \ death \ before \ discharge$

PaCO ₂ Variable	Adjusted Odds Ratio (95% CI)	<i>p</i> -value	
Max PaCO ₂ (per 10 mm Hg)	1.27 (1.12–1.44)	0.0002	
PaCO ₂ Category:			
Hypocapnic	0.96 (0.56–1.63)	0. 86	
Hypercapnic	1.65 (1.02–2.66)	0.04	
Fluctuator	1.17 (0.60–2.31)	0.64	
Normocapnic	REFERENCE	-	
Average PaCO ₂ (per 10 mm Hg)	1.26 (0.88–1.82)	0.20	