Published in final edited form as:
Arch Dis Child Fetal Neonatal Ed. 2015 March ; 100(2): F145–F149. doi:10.1136/archdischild-2014-306802.

$PaCO_2$ in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Namasivayam Ambalavanan, MD[1], **Waldemar A. Carlo, MD**[1], **Lisa A. Wrage, MPH**[2], **Abhik Das, PhD**[3], **Matthew Laughon, MD MPH**[4], **C. Michael Cotten, MD MHS**[5], **Kathleen A. Kennedy, MD MPH**[6], **Abbot R. Laptook, MD**[7], **Seetha Shankaran, MD**[8], **Michele C. Walsh, MD MS**[9], **Rosemary D. Higgins, MD**[10], and **For the SUPPORT Study Group of the NICHD Neonatal Research Network**

[1]Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

[2]Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

[3]Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD

[4]Department of Pediatrics, University of North Carolina, Chapel Hill, NC

[5]Department of Pediatrics, Duke University, Durham, NC

[6]Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX

[7]Department of Pediatrics, Women and Infants Hospital, Providence, RI

[8]Department of Pediatrics, Wayne State University, Detroit, MI

Corresponding author/Reprint requests: Namasivayam Ambalavanan, MD, 176F Suite 9380, Women and Infants Center, 619 South 20th St., University of Alabama at Birmingham, Birmingham, AL 35249, Tel (205) 934-4680 Fax (205) 934-3100 ambal@uab.edu.

Conflicts of interest: The authors have no conflicts of interest relevant to this article to disclose.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Contributor's Statement:
Namasivayam Ambalavanan: conceptualized and designed the study, drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.
Lisa A. Wrage and Abhik Das: assisted with the study design, acquisition of data, performed statistical analysis of the data, revised the manuscript, and approved the final manuscript as submitted.
Waldemar A. Carlo, Matthew Laughon, C. Michael Cotton, Kathleen A. Kennedy, Abbot R. Laptook, Seetha Shankaran, Michele C. Walsh, Rosemary D. Higgins: assisted with the study design, critically reviewed the manuscript, and approved the final manuscript as submitted.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:
Specific contributions of authors:
Namasivayam Ambalavanan, MD: Conception, design, data analysis & interpretation, drafting and revision of manuscript
Waldemar A. Carlo, MD: Conception, design, drafting and revision of manuscript
Michele C. Walsh, MD MS: Conception, design, drafting and revision of manuscript
Lisa Wrage MPH: Design, data analysis & interpretation
Abhik Das, PhD: Design, data analysis & interpretation,
Matthew Laughon MD MPH: Drafting and revision of manuscript
C. Michael Cotten MD: Drafting and revision of manuscript
Kathleen Kennedy MD: Drafting and revision of manuscript
Abbot Laptook MD: Drafting and revision of manuscript
Seetha Shankaran, MD: Drafting and revision of manuscript
Rosemary D. Higgins, MD: Conception, design, drafting and revision of manuscript

[9]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

[10]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Abstract

Objective—To determine the association of $PaCO_2$ 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 (SpO_2 target 85–89% vs 91–95%) and ventilation strategies.

Main Outcome Measures—Blood gases from postnatal days 0–14 were analyzed. Five $PaCO_2$ variables were defined: minimum [Min], maximum [Max], standard deviation, average (time-weighted), and a 4 level categorical variable (hypercapnic [highest quartile of Max $PaCO_2$], hypocapnic [lowest quartile of Min $PaCO_2$], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min $PaCO_2$]). $PaCO_2$ 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 $PaCO_2$ 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 $PaCO_2$ category and SpO_2 treatment group for sIVH/death, NDI/death, or death. Max $PaCO_2$ was positively correlated with maximum FiO_2 (r_s0.55, p<0.0001) & ventilator days (r_s0.61, p<0.0001).

Conclusions—Higher $PaCO_2$ was an independent predictor of sIVH/death, BPD/death, and NDI/death. Further trials are needed to evaluate optimal $PaCO_2$ 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 ($PaCO_2$) 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 $PaCO_2$ and wide fluctuations in $PaCO_2$ 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[9] 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 SpO_2 targets of either 85–89% or 91–95%, while also randomly allocated to either early CPAP and a limited ventilation strategy ($PaCO_2$>65 mm Hg permitted intubation, while $PaCO_2$<65 mm Hg with pH>7.20 was an extubation criterion) or intubation and surfactant ($PaCO_2$<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 SpO_2 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 SpO_2 target groups might be different when the combination of $PaCO_2$ and SpO_2 (actual or target group) is analyzed. We hypothesized that both extremes of $PaCO_2$ would be associated with sIVH, and that effect modification by SpO_2 would be observed, with hypercapnia associated with sIVH in the low but not high SpO_2 group (due to greater cerebral blood flow at lower SpO_2). We also hypothesized that BPD would be lower in infants with hypercapnia in the low SpO_2 group (due to less mechanical ventilation), and that higher $PaCO_2$ 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 population[13] (mean birth weight approximately 830 g, gestational age 26 weeks, 54% male) and the follow-up cohort[15] (93.6% evaluated at 18–22 months corrected age, 20.1% death, 28.8% with NDI/death) have been previously reported.

$PaCO_2$ variables

Five $PaCO_2$ variables were defined, using routine blood gas (arterial or capillary) measurements not governed by protocol. $PaCO_2$ closest to 8 am, 4 pm, and midnight was recorded for postnatal days 1–14. From these data, the minimum, maximum (Max $PaCO_2$), standard deviation, and average (time-weighted) $PaCO_2$ were derived. Average (time-weighted) $PaCO_2$ was calculated as defined previously[1]: the sum of all $PaCO_2$ 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 FiO_2 was the maximum FiO_2 at 24 hours and on days 3, 7, and 14. Severe illness was defined *a priori* as FiO_2 >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 $PaCO_2$, 4 level $PaCO_2$ variable, as well as average $PaCO_2$ 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 FiO_2, 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 $PaCO_2$ and the 4 level $PaCO_2$ variable. Interactions of $PaCO_2$ and treatment group variables assessed if effect of $PaCO_2$ varied by SUPPORT treatment group. Evaluation of interaction of actual median SpO_2 in the first 14 days and average $PaCO_2$ determined if the effect of

average $PaCO_2$ varied by level of actual SpO_2. Results are expressed as adjusted odds ratios and 95% confidence intervals.

As higher maximum $PaCO_2$ 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 FiO_2, days of mechanical ventilation, and severe illness), correlations of maximum $PaCO_2$ with maximum FiO_2 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 $PaCO_2$ 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 $PaCO_2$ category (Hypocapnic, Hypercapnic, etc) and treatment group (Higher or Lower SpO_2). Average $PaCO_2$ 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 $PaCO_2$ were associated with BPD/death. Interaction (p=0.026) was noted between the $PaCO_2$ category ‘fluctuators’ and treatment group (Higher or Lower SpO_2), hence results for $PaCO_2$ category are presented separately. For fluctuators in the higher SpO_2 group, the OR was 3.3 vs. 0.62 for fluctuators in the lower SpO_2 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 $PaCO_2$ was associated with NDI/death. No interactions were noted between $PaCO_2$ category and SpO_2 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 $PaCO_2$ was associated with death before discharge. No interactions were noted between $PaCO_2$ category and SpO_2 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 (~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.[15] An additional strength is that we evaluated both interaction with actual saturation and treatment group (higher or lower SpO_2 target), to distinguish illness severity and effects of treatment group allocation (e.g. higher average $PaCO_2$ was associated with sIVH/death only if actual SpO_2 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 $PaCO_2$ 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 $PaCO_2$ (even after statistical adjustment for maximum FiO_2, 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 CO_2 elimination for a given minute ventilation, due to a higher alveolar CO_2. Also, hypercapnia stimulates respiratory drive, assisting in ventilator weaning. An interesting unexplained finding was that greater fluctuation in $PaCO_2$ was associated with BPD/death only in the higher SpO_2 but not in the low SpO_2 group. It is speculated that greater oxygen exposure in the higher SpO_2 group may interact with volutrauma/atelectrauma associated with fluctuating $PaCO_2$ 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 sIVH[1] 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 $PaCO_2$ are independent predictors of worse outcome in ELBW infants. Higher $PaCO_2$ levels are also correlated with a greater magnitude of lung disease. Therefore, similar to oxygenation index, maximum $PaCO_2$ or magnitude of fluctuation of $PaCO_2$ 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 $PaCO_2$ soon after birth in ELBW infants, until optimal targets of $PaCO_2$ range are established in randomized clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial. The study sponsors were not involved in: (1) study design; (2) the

collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Lisa Wrage (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003–2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006–2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Betty R. Vohr, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksninis, PNP; Susan G. Barnett, RRT-NPS BSRC; William J. Cashore, MD; Melinda Caskey, MD; Regina A. Gargus, MD FAAP; Daniel J. Gingras, RRT; Katharine Johnson, MD; Shabnam Lainwala, MD; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Sarah Lillie, BS RRT; James R. Moore, MD; Lucy Noel; Rachel V. Walden; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Deanne E. Wilson-Costello, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN; Arlene Zadell RN BSN; Juliann Di Fiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Kurt Schibler, MD; Edward F. Donovan, MD; Kimberly Yolton, PhD; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Patricia L. Ashley, MD PhD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon Fridovich Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children’s Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, UL1 TR454, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Sheena L. Carter, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; Anna M. Dusick, MD FAAP; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute –Carol J. Blaisdell, MD.

RTI International (U10 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie G. Gantz, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O’Donnell Auman, BS; Carolyn Petrie Huitema, MS CCRP; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN CCRP.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 TR93, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; Susan R. Hintz, MD MS Epi; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Elisabeth C. McGowan, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Myriam Peralta-Carcelen, MD MPH; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodrigues, PhD; Amanda D. Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree Chapman York, PT DPT PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Yvonne E. Vaucher, MD MPH; Wade Rich, RRT; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Paul Zlotnik.

University of Iowa Children's Hospital (U10 HD53109, UL1 TR442, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Michael J. Acarregui, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MS; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Fajardo-Hiriart, MD; Elaine E. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Janell Fuller, MD; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) –Dale L. Phelps, MD; Gary J. Myers, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Julie Babish Johnson, MSW; Erica Burnell, RN; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Roy J. Heyne, MD; Luc P. Brion, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN BSN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, MS MA PA-C PsyD; Melissa H. Leps, RN; Linda A. Madden, RN CPNP; Melissa Swensen Martin, RN BSN RNC-NIC; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, BS RRT RCP; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia W. Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Roger G. Faix, MD; Bradley A. Yoder, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Michael Steffen, MS CPM; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Laura A. Goldston, MA; Mary E. Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 TR142, M01 RR125) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

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

REFERENCES

1. Fabres J, Carlo WA, Phillips V, et al. 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. [PubMed: 17272619]
2. Fujimoto S, Togari H, Yamaguchi N, et al. Hypocarbia and cystic periventricular leukomalacia in premature infants. Archives of disease in childhood. 1994; 71(2):F107–F110. [PubMed: 7979462]
3. Dammann O, Allred EN, Kuban KC, et al. Hypocarbia during the first 24 postnatal hours and white matter echolucencies in newborns < or = 28 weeks gestation. Pediatr Res. 2001; 49(3):388–393. [PubMed: 11228265]
4. Carlo WA, Stark AR, Wright LL, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr. 2002; 141(3):370–374. [PubMed: 12219057]
5. McKee LA, Fabres J, Howard G, et al. PaCO2 and neurodevelopment in extremely low birth weight infants. J Pediatr. 2009; 155(2):217–221 e1. [PubMed: 19447409]
6. Shankaran S, Langer JC, Kazzi SN, et al. Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. Pediatrics. 2006; 118(4):1654–1659. [PubMed: 17015558]
7. 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. [PubMed: 16257928]
8. Pryds O, Andersen GE, Friis-Hansen B. Cerebral blood flow reactivity in spontaneously breathing, preterm infants shortly after birth. Acta paediatrica Scandinavica. 1990; 79(4):391–396. [PubMed: 2112295]
9. Menke J, Michel E, Rabe H, et al. Simultaneous influence of blood pressure, PCO2, and PO2 on cerebral blood flow velocity in preterm infants of less than 33 weeks' gestation. Pediatr Res. 1993; 34(2):173–177. [PubMed: 8233721]
10. Victor S, Appleton RE, Beirne M, et al. Effect of carbon dioxide on background cerebral electrical activity and fractional oxygen extraction in very low birth weight infants just after birth. Pediatr Res. 2005; 58(3):579–585. [PubMed: 16148077]
11. Thome UH, Ambalavanan N. Permissive hypercapnia to decrease lung injury in ventilated preterm neonates. Semin Fetal Neonatal Med. 2009; 14(1):21–27. [PubMed: 18974027]
12. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics. 1999; 104(5 Pt 1):1082–1088. [PubMed: 10545551]
13. Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362(21):1959–1969. [PubMed: 20472937]
14. Finer NN, Carlo WA, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010; 362(21):1970–1979. [PubMed: 20472939]

15. Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. N Engl J Med. 2012; 367(26):2495–2504. [PubMed: 23268664]
16. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978; 92(4):529–534. [PubMed: 305471]
17. Walsh MC, Wilson-Costello D, Zadell A, et al. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol. 2003; 23(6):451–456. [PubMed: 13679930]
18. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004; 114(5):1305–1311. [PubMed: 15520112]
19. Reiss I, Landmann E, Heckmann M, et al. Increased risk of bronchopulmonary dysplasia and increased mortality in very preterm infants being small for gestational age. Archives of gynecology and obstetrics. 2003; 269(1):40–44. [PubMed: 12682849]

What's known on this topic

- Variations in arterial partial pressure of carbon dioxide ($PaCO_2$) are associated with adverse outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

What this study adds

- Higher $PaCO_2$ was associated with death or severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment.
- Maximum $PaCO_2$ is a marker of respiratory illness severity in extremely premature infants.

Table 1

Adjusted results for $PaCO_2$ variables in relation to outcome of sIVH /death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	***p*-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

Table 2

Adjusted results for $PaCO_2$ variables in relation to outcome of BPD/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	***p*-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 × treatment group (Higher or Lower SpO_2) was significant for Fluctuators

Table 3

Adjusted results for $PaCO_2$ variables in relation to outcome of NDI/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	***p*-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

Table 4

Adjusted results for $PaCO_2$ variables in relation to outcome of death before discharge

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	***p*-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