Published in final edited form as:
Pediatrics. 2008 September ; 122(3): e583–e589. doi:10.1542/peds.2008-1016.

Permissive hypercapnia and risk for brain injury and developmental impairment

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Abstract

Objective—Permissive hypercapnia is a respiratory care strategy used to reduce the risk of lung injury. The goal of this study was to evaluate whether permissive hypercapnia is associated with higher risk for intraventricular hemorrhage (IVH) and early childhood behavioral and functional problems than normocapnia among very low birthweight (VLBW) infants.

Patients and Methods—VLBW infants from a statewide cohort were eligible for this study if they were born <32 weeks gestational age and survived at least 24 hours. Infants were classified as receiving a permissive hypercapnia (N=122), normocapnia (N=235), or unclassifiable (N=791) respiratory strategy during the first 24 hours after birth according to an algorithm based on PCO_2 values and respiratory treatment decisions abstracted from medical records. IVH diagnosis was also abstracted from the medical record. Behavioral and functional outcomes were assessed by parent interview at 2-3 years. Logistic regression was used to evaluate the relationship between IVH and respiratory strategy; ordinary linear regression was used to evaluate differences in behavior and function scores between children by respiratory strategy.

Results—Infants who received a permissive hypercapnia strategy were not more likely to have IVH than those with normocapnia (odds ratio=1.0, 95% confidence interval: 0.59, 1.8). There were no differences in any of the behavioral or functional scores between children by respiratory strategy. There was a significant interaction between care strategy and one-minute Apgar score, indicating that infants with lower Apgar scores may be at higher risk for IVH with permissive hypercapnia.

Conclusion—This study suggests permissive hypercapnia does not increase risk for brain injury and impairment among VLBW children. The interaction between respiratory strategy and Apgar score is a potential worrisome exception to this conclusion. Future research should further evaluate the effect of elevated PCO_2 levels among those sickest at birth.

Keywords

Permissive hypercapnia; developmental follow-up; intraventricular hemorrhage; VLBW-very low birthweight

Very low birthweight (VLBW, <1500g) infants are often premature with incompletely developed respiratory systems, and most require respiratory assistance for survival.[1] However, mechanical ventilation and other respiratory care can injure fragile, immature lungs and

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increase risk for bronchopulmonary dysplasia (BPD), a chronic form of lung disease.[2] Permissive hypercapnia is a respiratory treatment strategy that accepts levels of partial pressure of carbon dioxide ($PaCO_2$) above normal, thus allowing less aggressive respiratory care and, as a result, less trauma to the lung.[3,4]

Despite the suggested benefit of permissive hypercapnia for decreasing risk of BPD, it is not well understood whether it is associated with risk of brain injury, such as intraventricular hemorrhage (IVH), and subsequent developmental impairment. IVH was evaluated as a secondary outcome in two clinical trials of permissive hypercapnia.[5,6] Neither trial found any relationship between permissive hypercapnia and risk of IVH, but the first[5] had a small sample size (n=49) and the second[6] was terminated early with a smaller than planned sample (n=220). A trial that targeted even higher $PaCO_2$ levels found that, at 18-22 months, children in this minimal ventilation group had worse scores on the Bayley mental developmental index than children randomized to standard ventilation.[7] Prior observational studies have found an association between high $PaCO_2$ levels and IVH,[8-12] and IVH is associated with increased risk for developmental impairments.[13-24] Hence, it is not clear whether permissive hypercapnia is safe for immature brains.

Clinical trials are both difficult and expensive. It can be challenging to enroll sufficient numbers of subjects, and trials can be terminated early. Additionally, trials tend to be conducted under circumstances different from those under which the general population receives care. Our detailed observational data on blood gases and ventilatory support in a large population of infants allows us to infer ventilation care strategy and address the impact of permissive hypercapnia. The objectives of this study were to evaluate (1) whether a permissive hypercapnia treatment strategy early in life is associated with higher risk for IVH than a normocapnia treatment strategy, and (2) whether permissive hypercapnia is associated with more behavioral and functional problems during early childhood.

Methods

Study sample and data collection

The Newborn Lung Project Statewide Cohort is a prospective study of all VLBW infants admitted to the 16 level III neonatal intensive care units (NICU) in Wisconsin 1/1/2003 - 12/31/2004, and Wisconsin residents admitted to a level III NICU in Duluth, Minnesota. Anonymous data on blood gases, ventilatory treatments, baseline characteristics, and neonatal diagnoses were collected from the medical records of all admitted VLBW infants. Designated NICU nurses approached parents for consent to collect identifiable data from the medical record and to obtain contact information for follow-up. Trained interviewers collected data on behavior, function, and socioeconomic status through parent telephone interviews when children were two to three years old (mean (standard deviation, SD) 32.2 (3.5) months corrected age; range 25.0-46.3 months).

Analyses were restricted to 24-hour survivors with gestational age <32 weeks, as classification of respiratory treatment strategy was based on the first 24 hours after birth and BPD is rare among infants ≥32 weeks gestation. Hence infants <32 weeks gestational age are the target population for BPD prevention and a permissive hypercapnia strategy of care.

Description of algorithm to classify infants according to permissive hypercapnia or normocapnia treatment strategy

An algorithm was devised to identify infants who could have been treated with either a normocapnia or a permissive hypercapnia strategy. The two-part algorithm was applied to blood gas measurements, and respiratory treatment decisions made during the following hour,

between NICU admission (median 16 minutes after birth, interquartile range 11-24 minutes) and 24 hours after birth.

First, each blood gas measurement was classified as indicative of permissive hypercapnia, normocapnia, or unclassifiable based on the PCO_2 value and the respiratory care actions within one hour of the blood draw. The vast majority of blood gas values were from arterial samples (91% for infants in the normocapnia group, 82% for infants in the permissive hypercapnia group). Capillary PCO_2 values were considered similar to those based on arterial samples. Venous values were interpreted as five mmHg higher than those from arterial samples and transformed accordingly. PCO_2 values and subsequent treatment decisions targeted at keeping PCO_2 values greater than 45 and less than or equal to 55 mmHg were taken as indicators of a permissive hypercapnia strategy, and PCO_2 values and treatment decisions targeted at keeping PCO_2 values greater than 35 and less than or equal to 45 mmHg were considered indicators of a normocapnia strategy. The following treatment decisions were considered less aggressive, allowing PCO_2 values to rise or stay the same: decreasing positive inspiratory pressure (PIP) settings, decreasing ventilator rate settings, switching from mechanical ventilation to either continuous positive airway pressure (CPAP) or oxygen only, or switching from CPAP to oxygen. Increasing PIP, increasing ventilator rate settings, and switching from CPAP to mechanical ventilation were considered more aggressive, with the potential to lower PCO_2 values.

Blood gas measurements were considered unclassifiable if the infant was not receiving CPAP or mechanical ventilation at the time of the blood draw or if there was an indication that the infant was too ill to be considered for a choice between permissive hypercapnia or normocapnia. Blood gas measurements with PCO_2 <35 or >55 mmHg were unclassifiable, as these values are likely indicative of illness severity that precludes the choice of a permissive hypercapnia treatment strategy.

The second step was to determine the percentage of blood gas measurements that met the criteria for permissive hypercapnia or normocapnia for each infant. If >50% of the blood gas measurements led to actions meeting the permissive hypercapnia or normocapnia criteria, the infant was classified as receiving that treatment strategy. If exactly 50% of the blood gas measurements fell into each of the permissive and normocapnia criteria, the infant was classified as receiving a permissive hypercapnia strategy (this was the case for 10 infants).

The algorithm classifications were validated against clinical judgments of three neonatologists. The charts of 30 infants were reviewed by two neonatologists each. The algorithm had good agreement with the neonatologists' judgment of whether an infant was treated with a strategy of permissive hypercapnia (kappa 0.63-0.89) (Table 1).

Outcome measures

Designated NICU nurses recorded the presence and grade of IVH, and death before discharge onto standard forms. IVH was graded on a scale of I to IV according Papile et al.[25] Severe IVH refers to grades III-IV. Neontatal outcomes included any grade IVH, severe IVH, and severe IVH or death.

Parents were interviewed by one of three interviewers when children were age 2 to 3 years. We evaluated total behavior problems, internalizing behavior, and externalizing behavior from the Achenbach Child Behavior Checklist,[26] and social function, self-care, and mobility from the Pediatric Evaluation of Disabilities Inventory.[27] The mean (SD) for each of these scales is 50 (10).

Statistical analysis

We used logistic regression to estimate odds ratios for IVH comparing children with permissive hypercapnia and normocapnia. We used linear regression to estimate differences in behavior and function scores between the two groups. All models were adjusted for indicators of baseline illness severity: gestational age, sex, one-minute Apgar score, outborn status (born at another hospital and transferred to one with a level III NICU), receipt of antenatal steroids, and the Score for Neonatal Acute Physiology, Version II (SNAP-II). SNAP-II is an index of newborn illness severity based on physiological measurements from the first 12 hours after birth, including the lowest recorded pH value.[28] As pH is associated with $PaCO_2$, a modified SNAP-II score was calculated excluding the pH scale. Birthweight and gestational age were collinear and gestational age was a stronger predictor of IVH, so birthweight was not included.

Models for behavioral and functional outcomes were also adjusted for interviewer and indicators of socioeconomic status: maternal education, household income, race, and single-parent household.

Interactions between respiratory strategy and each of the baseline severity variables were investigated for all outcomes.

Because a relatively large percentage of infants were not classified by respiratory strategy, a sensitivity analysis was conducted to explore whether unclassifiable infants affected the results. Models were weighted by the inverse of a propensity score computed by logistic regression as the probability of being classified by the algorithm.

Each of the early childhood behavioral and functional outcomes models was re-weighted by the inverse probability of follow-up to determine whether participation bias may have affected the results.

Results

Study population

There were 1479 VLBW infants admitted to the study NICUs during the recruitment period, of whom 1241 were 24-hour survivors <32 weeks gestational age. Of these, 1162 had blood gas data available (94%). Of the infants with blood gas data, 371 (32%) were classified as having a permissive hypercapnia (n=129) or normocapnia (n=242) strategy of respiratory care. Of those classified, 256 survived to age two with consent for follow-up, and data were obtained from 184 (72%). The mean (SD) number of blood gas values over the first 24 hours after birth was 5.6 (2.2), 6.5 (1.7), and 6.3 (2.9) for infants who received permissive hypercapnia, normocapnia, or were unclassifiable, respectively.

Infants classified as receiving a permissive hypercapnia strategy were similar to those with a normocapnia strategy with respect to birthweight and gestational age, but infants receiving permissive hypercapnia had better one-minute Apgar and SNAP-II scores. Infants not classified by respiratory strategy had lower mean birthweight, and worse Apgar and SNAP-II scores. The permissive hypercapnia group had higher mean PCO_2 values and lower mean PIP and ventilator setting rates than the normocapnia group (Table 2). The permissive hypercapnia group tended to have better respiratory outcomes, but only the difference in ventilation at 36 weeks PMA reached statistical significance.

Respiratory care strategy and IVH

Infants classified as receiving a permissive hypercapnia treatment strategy were not more likely to develop IVH than those with a normocapnia strategy. While the crude incidence rate of IVH

was slightly lower among infants with permissive hypercapnia than among those with normocapnia (24% and 27%, respectively), adjusted analyses indicated no difference in risk of IVH by care strategy (adjusted OR= 1.0, 95% CI: 0.59, 1.8). Additionally, severe IVH was not significantly more likely among infants with permissive hypercapnia, and the combined outcome of severe IVH or death indicated no higher risk associated with permissive hypercapnia (Table 3).

There was a significant interaction between respiratory care strategy and one-minute Apgar score for any grade IVH. The interaction was not significant for severe IVH or the combined outcome of severe IVH or death. The interaction indicated that for infants Apgar scores ≤4, a permissive hypercapnia strategy is associated with higher risk for IVH, while for Apgar scores ≥5, a permissive hypercapnia strategy is protective (Table 4).

Weighting models by the inverse of the propensity scores, based on the probability of being classified by respiratory care strategy, did not substantially change results.

Respiratory care strategy and early childhood behavior and function

There were no significant differences in behavior or function scores between children who received a permissive hypercapnia treatment strategy and those with a normocapnia strategy (Table 5). There were no significant interactions between respiratory care strategy and any of the baseline severity variables. Weighting models by the inverse of the probability of early childhood follow-up did not affect the conclusions for any of the behavioral or functional outcomes.

Discussion

Infants whose respiratory treatment pattern indicated a permissive hypercapnia strategy were not at higher risk for IVH than those whose respiratory treatment indicated a normocapnia strategy. There were no early childhood behavioral or functional differences by respiratory strategy. Permissive hypercapnia, a strategy of care in current use among neonatologists to reduce risk for lung injury, seems to be safe for immature brains.

An exception to this conclusion may be for infants with low Apgar scores. A significant interaction was found between respiratory care strategy and one-minute Apgar score for any grade IVH, indicating that for infants with lower Apgar scores, permissive hypercapnia is associated with higher risk for IVH, while for infants with higher Apgar scores, permissive hypercapnia is associated with lower risk. It is possible that infants who are very vulnerable at birth just cannot handle a less aggressive treatment strategy. However, due to the many interactions investigated this significant result could have occurred by chance. The reason for higher risk of any grade IVH associated with permissive hypercapnia among infants with low Apgar scores remains unclear.

To our knowledge, no other observational study has evaluated outcomes associated with patterns of respiratory care indicative of a permissive hypercapnia or normocapnia treatment strategy. Two clinical trials have evaluated the association between permissive hypercapnia and IVH among VLBW infants.[5,6] The first trial[5] randomized 49 infants to minimal ($PaCO_2$ target 45-55 mmHg) or standard ventilation ($PaCO_2$ target 35-45 mmHg). The result showed no relationship between permissive hypercapnia and any grade IVH (relative risk, RR=0.82, 95% CI: 0.43, 1.52) or severe IVH (RR=1.46, 95% CI: 0.47-4.82). The second trial[6] randomized 220 infants to $PaCO_2$ targets >52 mmHg or <48 mmHg. They found no association between permissive hypercapnia and severe IVH (RR=0.78, 95% CI: 0.48, 1.27). Another trial randomized 54 infants to either $PaCO_2$ levels targeted above the permissive hypercapnia range (55-65 mmHg) or within the normal range (35-45 mmHg).[7] These

researchers also found no association between respiratory strategy and severe IVH (OR=0.82, p=0.78). The difference in the mean $PaCO_2$ level between infants in the permissive hypercapnia and normocapnia groups in both our study and in the trial that targeted higher PaCO2 levels was relatively small (6 mmHg in each study). Our conclusion that there is no association between a permissive hypercapnia treatment strategy and risk for IVH is consistent with the results of these trials.

The trial of higher $PaCO_2$ levels investigated neurological and developmental impairments at 18-22 months corrected age.[7] There was no association between respiratory strategy and either cerebral palsy, hearing impairment, vision impairment, or low scores on the Bayley psychomotor developmental index, but infants in the minimal ventilation group had worse scores on the Bayley mental developmental index (mean (SD) for minimal ventilation group, 70 (21); mean (SD) for standard ventilation group, 88 (26), p=0.054). However, these results were based on 12 children from the minimal ventilation group (36% of original group) and 17 children from the standard ventilation group (56% of original group).

Our behavioral and functional follow-up also suggests that infants treated with permissive hypercapnia are not at a disadvantage during early childhood. The age at follow-up was older in our study than in the clinical trial. Perhaps any slight disadvantage on the mental developmental index at an earlier age has diminished by age 2.5-3.5 years. However, further follow-up is warranted to confirm that this suggested lack of disadvantage continues into later childhood and beyond.

Our study has important strengths. The rich observational data set allowed us to investigate the risk of IVH associated with actions by neonatologists indicative of less aggressive versus more standard respiratory care, comparing infants who could have been eligible for either strategy. Our study adds to the existing literature by evaluating the effect of the kind of care delivered to infants across an entire state across a variety of NICUs.

Due to the extensive amount of data collected on each infant during the NICU stay, analyses could be adjusted to take the illness severity of the infants into account. This adjustment is important to reduce the influence of confounding variables on the association between elevated $PaCO_2$ levels and IVH. Several indicators of illness severity are associated with higher risk for IVH (e.g., gestational age, SNAP-II score), as well as with high $PaCO_2$ levels.

The early childhood follow-up in this study provides important information about the ramifications of respiratory care during the NICU stay. While the immediate goal of neonatal intensive care is morbidity-free survival to discharge, the long-term goal should be to help infants grow into children as free from impairment as possible. Monitoring the long-term effects of neonatal treatments is important to understanding how these decisions affect the developmental course.

This study did have some limitations. We did not have a way to determine the neonatologists' target $PaCO_2$ levels. However, while we cannot be certain of the physicians' intentions, we were able to identify and compare groups of infants by de facto pattern of care. We used medical chart review to ascertain IVH diagnosis, which may miss IVH among some infants. However, it is unlikely that the clinical signs of severe IVH would go undetected, unless the infant died before diagnosis. As the associations with permissive hypercapnia are consistent across the outcomes any grade IVH, severe IVH, and severe IVH or death, it is unlikely that missed IVH diagnoses have affected our conclusions.

Our early childhood outcomes are based on parent report. While parents are likely the best reporters of how young children are doing in their everyday lives, the well-being of the interviewee (in almost all cases, the mother) can affect the way she answers questions about

her child. Stress and depression have been associated with worse reports of children's well-being.[29,30] While mothers of VLBW children are at higher risk for stress and depression throughout the first years of their child's life,[31] all mothers in this study had VLBW children. As neonatal morbidity was similar among infants in the permissive and normocapnia groups, stress due to child illness among mothers in each of the groups should be comparable.

Conclusion

The results of this study suggest that permissive hypercapnia does not increase risk for IVH and subsequent developmental impairment among VLBW children. These findings are consistent with the findings of clinical trials that randomized infants to a permissive hypercapnia or normocapnia respiratory treatment strategy. Together, these studies suggest that permissive hypercapnia is a treatment strategy that is safe for infant brains. However, the significant interaction between permissive hypercapnia and Apgar score for any grade IVH provides a potential worrisome exception to this conclusion. Further investigation should be undertaken to understand the effect of elevated $PaCO_2$ levels on the brains of the sickest infants.

Acknowledgements

The Newborn Lung Project involved the following investigators and project and center coordinators:

Coordinating Center, University of Wisconsin, Madison, Wisconsin: Dr. Mari Palta, Principal Investigator, Dr. Mona Sadek-Badawi, Project Director, Aggie Albanese, Kathleen Madden, Lisa Loder, and Tanya Watson;

Dr. Christopher Green, University of Wisconsin, Madison, Wisconsin;

Dr. David Carlton and Karin Smylie (University of Wisconsin, Madison, Meriter Hospital, Madison, Wisconsin);

Dr. Jeffrey Garland, Roberta Einsiedel, Kathy Weaver and Jackie Sevallius (St Joseph's Regional Medical Center, Milwaukee, Wisconsin);

Dr. Chandra Shivpuri, Susan Plachinski, and Karen Dorfler (Sinai Samaritan Medical Center, Milwaukee, Wisconsin);

Dr. James Opitz, Sandy Freeman, MaryAnne Lach, and Angie Linneman (St. Joseph's Hospital, Marshfield, Wisconsin);

Dr. Marie Weinstein and Laura Ziebarth (St. Mary's Hospital, Madison,Wisconsin);

Dr. Paul Meyers, Denise Turnmeyer, and Pamela Verhagen (Children's Hospital of Fox Valley, Neenah, Wisconsin);

Dr. Joseph Brand and Lana Reinke (St. Vincent Hospital, Green Bay, Wisconsin);

Dr. John Wolf, Jane Friday and Joan Hintz (Columbia - St Mary's Hospital, Milwaukee, Wisconsin);

Dr. Nancy Herrell and Sharon Nelson (Waukesha Memorial Hospital, Waukesha, Wisconsin);

Dr P Sasidharan (Childrens Hospital of Wisconsin, Milwaukee, Wisconsin);

Dr Gregory Milleville, Melissa Grooms and Carolyn Kraly (Aurora Women's Pavilion, West Allis, Wisconsin);

Dr. David.Sheftel, Michelle Stampa, Monica DaPra, Sandy Anderson and Diane Fiebig (St Luke's Hospital, Racine, Wisconsin);

Dr. Jeffrey Thompson, Shawn Dunlap (Gunderson Lutheran Hospital - La Crosse, La Crosse, Wisconsin);

Dr. Dennis Costakos, Karen Smith and Lynn Dahlen (Franciscan Skemp Hospital, La Crosse, Wisconsin);

Dr. Howard Kidd, Nicole Stephani and Tracy Heiman (St Elizabeth Hospital, Appleton, Wisconsin);

Dr. Frank Mattia and Patti Davis (Aurora BayCare, Green Bay, Wisconsin);

Dr. Lee A. Muscovitz and Deborah Peters (St Mary's Hospital, Duluth, Minnesota)

Source of funding: 5 RO1 HL38149-17 "Risk Factors in Bronchopulmonary Dysplasia"

List of abbreviations

BPD, bronchopulmonary dysplasia
CPAP, continuous positive airway pressure
IVH, intraventricular hemorrhage
mmHg, millimeters of mercury
NICU, neonatal intensive care unit
NLP, Newborn Lung Project
OR, odds ratio
$PaCO_2$, partial pressure of carbon dioxide
PIP, positive inspiratory pressure
RR, relative risk
SD, standard deviation
SNAP-II, Score for Neonatal Acute Physiology, II
VLBW, very low birthweight

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TABLE 1

Agreement between algorithm and three neonatologists on whether infant received a permissive hypercapnia strategy of care

Combination	% agreement	Kappa (95% confidence limit)
Algorithm - Dr A	85	0.63 (0.35, 0.90)
Algorithm - Dr B	85	0.64 (0.40, 0.90)
Algorithm - Dr C	95	0.89 (0.75, 1.0)
Dr A - Dr B	74	0.42 (-0.01, 0.84)
Dr B - Dr C	86	0.68 (0.35, 1.0)
Dr A - Dr C	90	0.78 (0.50, 1.0)

TABLE 2

Infant characteristics and incidence of intraventricular hemorrhage and death by normocapnia, permissive hypercapnia or unclassifiable strategy of care

	Strategy of respiratory care		
	Permissive hypercapnia	**Normocapnia**	**Unclassifiable**
N	129	242	791
Baseline characteristics			
Birthweight, grams	1007 ± 264	1007 ± 269	997 ± 289
Gestational age, weeks	27.3 ± 2.3	27.3 ± 2.1	27.5 ± 2.4
One-minute Apgar, median (IQR†)	5.5 (4-7)*	5.0 (3-6)	5.0 (3-7)
SNAP-II‡	16.8 ± 11.9	18.3 ± 12.1	19.5 ± 15.7
Male	60 (47)	134 (56)	391 (49)
Outborn	10 (8)	21 (9)	102 (13)
Received antenatal steroids	100 (80)	173 (74)	562 (72)
Ventilation characteristics			
Mean PIP#	13.1 ± 6.8*	17.0 ± 3.4	15.8 ± 5.9
Mean ventilator rate	29.3 ± 18.1*	37.8 ± 12.1	36.4 ± 16.6
Mean PCO_2	46.0 ± 3.8*	39.9 ± 4.3	40.1 ± 7.9
Mean PO_2	67.0 ± 15.5	69.1 ± 15.8	73.3 ± 23.9
Respiratory outcomes			
Day of final extubation	18.0 ± 21.8	21.3 ± 28.9	22.5 ± 31.3
Number of days on oxygen	27.0 ± 21.9	29.6 ± 22.1	25.4 ± 22.7
Ventilated at 36 weeks PMA§	4 (3)*	26 (11)	68 (9)
Oxygen at 36 weeks PMA§	36 (28)	74 (31)	224 (28)
Incidence of IVH and death			
Any grade IVH**	31 (24)	65 (27)	224 (28)
Severe IVH** (grades III-IV)	11 (9)	26 (11)	79 (10)
Died before NICU discharge	14 (11)	23 (10)	93 (12)
Severe IVH** or death before discharge	19 (15)	39 (16)	141 (18)

Numbers are mean ± standard deviation or frequency (percent) unless otherwise noted

* $p < 0.05$ for difference between permissive hypercapnia and normocapnia strategy

† interquartile range

‡ Score for Neonatal Acute Physiology - II

positive inspiratory pressure

§ post-menstrual age

** intraventricular hemorrhage

TABLE 3

Odds ratios (OR) and 95% confidence intervals (CI) for intraventricular hemorrhage comparing infants with permissive hypercapnia and normocapnia treatment strategies

Outcome	Unadjusted		Adjusted*	
	OR	95% CI	OR	95% CI
Any IVH	0.87	0.53, 1.4	1.0	0.59, 1.8
Severe IVH	0.77	0.37, 1.6	1.2	0.52, 2.8
Severe IVH or death	0.90	0.50, 1.6	1.1	0.53, 2.4

*Adjusted for gestational age, 1-minute Apgar score, sex, outborn status, receipt of antenatal steroids, and revised SNAP-II, $p > 0.28$ for all models based on Hosmer-Lemeshow goodness of fit test

†intraventricular hemorrhage

TABLE 4

Odds ratios (OR) and 95% confidence interval (CI) for intraventricular hemorrhage comparing infants with a permissive hypercapnia and normocapnia strategy of care, by one-minute Apgar score

Apgar score	N[†]	OR[*]	95% CI
1	32	3.6	1.1, 11.2
2	32	2.5	1.0, 6.3
3	31	1.8	0.88, 3.7
4	35	1.3	0.71, 2.3
5	71	0.91	0.51, 1.6
6	69	0.65	0.32, 1.3
7	51	0.46	0.19, 1.1
8	38	0.33	0.11, 0.99
9	7	0.23	0.06, 0.90

[*] adjusted for gestational age, sex, outborn status, antenatal steroids, and revised SNAP-II

[†] Apgar score was missing for 5 infants

TABLE 5

Mean scores and crude and adjusted differences in mean scores for early childhood behavior and function scores for children with a permissive hypercapnia and a normocapnia strategy of care

	Treatment strategy			
	Permissive hypercapnia N=61	**Normocapnia N=123**	**difference (p)**	**Adjusted difference (p)***
Behavioral outcomes†				
Total behavior	50.0 (10.0)	49.3 (9.9)	0.67 (0.7)	-0.20 (0.9)
Internalizing behavior	48.6 (10.4)	48.9 (9.6)	-0.30 (0.8)	-0.98 (0.5)
Externalizing behavior	50.9 (10.5)	48.9 (10.4)	2.0 (0.2)	1.0 (0.5)
Functional outcomes‡				
Social function	47.6 (11.9)	43.8 (13.2)	3.8 (0.07)	2.7 (0.2)
Self care	46.2 (9.9)	42.8 (11.9)	3.4 (0.06)	3.5 (0.09)
Mobility	45.2 (12.4)	42.0 (13.8)	3.2 (0.1)	3.6 (0.2)

*adjusted for gestational age, one-minute Apgar score, sex, outborn status, receipt of antenatal steroids, revised SNAP-II, maternal education, race, household income, single-parent household, and interviewer

†higher scores indicate more problems

‡higher scores indicate better function