First, Do No Harm. Consequences of Permissive Hypercapnia in the Neonate

In this issue of RESPIRATORY CARE, Brown et al[1] report their findings of a secondary analysis of arterial blood gases obtained from a cohort of 147 infants born < 32 wk gestational age. The aim of the study was to review historical blood gas data, obtained within the first 72 h after birth, to inform future clinical practice regarding the safety and efficacy of a rather commonly used lung-protective strategy, permissive hypercapnia. The authors sought to explore the relationship between P_{aCO_2} and adverse respiratory and brain-related outcomes.

The authors provide a succinct summary of the relevant literature regarding the outcomes of infants in clinical and observational studies undergoing permissive hypercapnia as a strategy for decreasing the rate of bronchopulmonary dysplasia (BPD). The theoretical benefits of this strategy derive from minimizing ventilator-induced lung injury. These benefits, however, have been questioned in recent years, with an accumulating body of evidence that BPD rates are not significantly decreased among infants undergoing permissive hypercapnia.[2,3] The potential benefits of exposing infants to hypercapnia do not appear to improve pulmonary outcomes, and in some studies improvements in respiratory outcomes are accompanied by unintended neurologic consequences.

The authors provide a summary of physiologic mechanisms relevant to the discussion. Permissive hypercapnia, the authors offer, is attained by minimizing tidal ventilation, and this by providing just enough ventilatory support to achieve minute-ventilation sufficient for a $P_{aCO_2} > 45$ mm Hg.[4] The pathophysiology of adverse brain-related outcomes is also discussed. Hypercapnia, for example, increases cerebral vasodilation, thus increasing cerebral blood flow (CBF), and results in a progressive loss of cerebral autoregulation, which in prior studies has been associated with brain injury.[5] By contrast, hypocapnia decreases CBF, which in prior studies has correlated linearly with ischemic white matter injury. Progressive decreases in CBF lead to impaired cerebral autoregulation and, by extension, to ischemic brain injury in animal models.[6,7]

SEE THE ORIGINAL STUDY ON PAGE 943

While the literature is somewhat conflicting, there still remains some evidence that permissive hypercapnia could decrease the risk of BPD.[8-11] However, the theoretical benefits of this strategy have not been appreciated in well-designed randomized clinical trials[2] Importantly, the authors correctly state that the range of P_{aCO_2} that provides benefit (without increasing the risk of adverse neurologic consequences) has not yet been proven. Moreover, alterations in P_{aCO_2} and pH are sometimes accompanied by an increase in the risk of important brain-related adversities.[12] Both extremes of P_{aCO_2}, it seems, as well as the magnitude of fluctuations in P_{aCO_2}, are associated with severe intraventricular hemorrhage (IVH) in preterm infants.[13]

Both the study design and methods were appropriate for the current analysis. Abnormalities of pH and P_{aCO_2} (independent variables) were analyzed with respect to 7 dependent outcomes variables: any IVH, severe IVH, BPD, necrotizing enterocolitis, retinopathy of prematurity, pneumothorax, and the combined outcome death/severe IVH. All available blood gas data from the first 72 h after birth were collected and correlated with clinical and demographic data obtained prospectively from a previous clinical trial. Collection of early postnatal blood gas data increases the likelihood of detecting a correlation between P_{aCO_2} and adverse brain-related outcomes because the early postnatal period is a period of great risk for neurologic adversity in preterm infants.[14] P_{aCO_2} data were categorized into ranges that accompany the generally accepted P_{aCO_2} categories of hypocapnia, normocapnia, mild hypercapnia, moderate hypercapnia, and severe hypercapnia. Mean P_{aCO_2} was stratified by gestational age, that is < 28 wk and ≥ 28 wk for each of the ranges of P_{aCO_2}. Finally, highest and lowest P_{aCO_2}, the mean time-weighted P_{aCO_2}, fluctuations in P_{aCO_2} (by 2 definitions), and minimum pH were analyzed with respect to outcome variables.

The author has disclosed no conflicts of interest.

Correspondence: J Wells Logan MD, Comprehensive Center for Bronchopulmonary Dysplasia Nationwide Children's Hospital, The Ohio State University, Columbus, OH 43205. E-mail: jwells.logan@nationwidechildrens.org.

DOI: 10.4187/respcare.06381

The authors found that the routine targeting of higher than normal P_{aCO_2} goals led to a low incidence (2%) of hypocapnia in their sample, but without a significant improvement in the respiratory outcomes, BPD, or pneumothorax. Twenty-six percent of the sample were mildly hypercapnic, 13% were moderately hypercapnic, and 6.5% were severely hypercapnic. When combined, roughly half of the infants in the sample were exposed to some degree of hypercapnia. After adjusting for potentially important confounding variables, the composite outcome death or severe IVH was associated with higher fluctuations in the arterial P_{aCO_2} and the lowest arterial pH. The individual outcomes severe IVH and any IVH were not associated with either fluctuations in P_{aCO_2} or lowest pH after adjusting for confounders. There were no differences in BPD, necrotizing enterocolitis, retinopathy of prematurity, or pneumothorax. The authors' findings provide additional support for researchers concerned about the negative consequences of permissive hypercapnia, which, while intended to improve care and outcomes, may actually increase the risk of morbidity for an already at-risk population.[2,3]

The sample size was adequate, including 147 subjects and $>$ 1,300 arterial blood gas samples, 584 of which were from infants $<$ 28 wk gestational age. Statistical methods were appropriate, and both univariate and multivariate analyses were presented. Taken together, efforts to address potential confounders were appropriate. Confidence intervals were fairly narrow, suggesting that the study findings are fairly reliable. Trends toward an association with the individual outcomes severe IVH and any IVH were noted on univariate analysis, suggesting the possibility that, in a larger sample, associations with these outcomes might also have been significant. The authors report that there was no relationship between pH or P_{aCO_2} and the respiratory outcomes of BPD and pneumothorax, nor was there an association with necrotizing enterocolitis and retinopathy of prematurity.

The authors' findings are both interesting and important, and support the prevailing consensus among neonatal researchers that the benefits of permissive hypercapnia do not appear to outweigh the potential risks of the exposure. Moreover, the pathophysiology of BPD is so complex and is mediated by so many exposures (eg, prenatal, perinatal, and postnatal) that efforts to affect only a single exposure (ie, ventilator-induced lung injury) is not likely to affect BPD rates in a broad population of very preterm infants. While decreasing the risk of ventilator-induced lung injury has plausible therapeutic benefits, it targets only one of many mechanisms known to contribute to the complex pathophysiology of BPD.[15] Failure to treat threatened preterm labor with antenatal steroids, for example, likely increases the risk of BPD among infants in a broad population of preterm infants. So, too, does exposure to oligohydramnios/anhydramnios, maternal chorioamnionitis, early-onset postnatal sepsis, necrotizing enterocolitis, and other biological/oxidative stressors beyond the scope of this discussion.

In conclusion, the authors' study, like others published in recent years, disproves the notion that permissive hypercapnia is a safe and effective means of minimizing the risk of BPD. Despite the paucity of evidence that this strategy prevents BPD, it continues to be used with some frequency, and often during a period of great risk for this fragile population. The authors are to be commended for this honest report, which likely reflects a common practice in many neonatal ICUs worldwide. This is a valuable contribution to the ever-growing list of studies demonstrating that efforts to achieve a normal physiologic state remain an essential aspect of care for preterm newborns, especially in the first few days after birth.[16]

J Wells Logan MD
Comprehensive Center for Bronchopulmonary Dysplasia
Nationwide Children's Hospital
Columbus, Ohio

REFERENCES

1. Brown MK, Poeltler DM, Hassen KO, Lazarus DV, Brown VK, et al. Incidence of hypocapnia, hypercapnia, and acidosis and the associated risk of adverse events in preterm neonates. Respir Care 2018;8:943-949.
2. Thome UH, Genzel-Boroviczeny O, Bohnhorst B, Schmid M, Fuchs H, et al. Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomised controlled multicentre trial. Lancet Respir Med 2015;3(7):534-543.
3. 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.
4. Reiterer F, Schwaberger B, Freidl T, Schmölzer G, Pichler G, Urlesberger B. Lung-protective ventilatory strategies in intubated preterm neonates with RDS. Paediatr Respir Rev 2017;23(6):89-96.
5. 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.
6. Greisen G, Vannucci RC. Is periventricular leucomalacia a result of hypoxic-ischaemic injury? Hypocapnia and the preterm brain. Biol Neonate 2001;79(3-4):194-200.
7. Liao SL, Lai SH, Chou YH, Kuo CY. Effect of hypocapnia in the first three days of life on the subsequent development of periventricular leukomalacia in premature infants. Acta Paediatr Taiwan 2001;42(2):90-93.
8. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics 1999;104(5 Pt 1):1082-1088.
9. Carlo WA, Stark AR, Wright LL, Tyson JE, Papile LA, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr 2002;141(3):370-374.
10. Thome UH, Carlo WA. Permissive hypercapnia. Semin Neonatol 2002;7(5):409-419.

11. 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.
12. Leviton A, Allred E, Kuban KC, Dammann O, O'Shea TM, Hirtz D, et al. Early blood gas abnormalities and the preterm brain. Am J Epidemiol 2010;172(8):907-916.
13. 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.
14. Dammann O, Naples M, Bednarek F, Shah B, Kuban KC, O'Shea TM, et al. SNAP-II and SNAPPE-II and the risk of structural and functional brain disorders in extremely low gestational age newborns: the ELGAN study. Neonatology 2010;97(2):71-82.
15. Day CL, Ryan RM. Bronchopulmonary dysplasia: new becomes old again! Pediatr Res 2017;81(1-2):210-213.
16. Logan JW, Dammann O, Allred EN, Dammann C, Beam K. Early postnatal illness severity scores predict neurodevelopmental impairments at 10 years of age in children born extremely preterm. J Perinatol 2017;37(5):606-614.