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Newborn blood gas derangements of children born extremely preterm and neurocognitive dysfunctions at age 10 years

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Abstract

Among 740 children born extremely preterm, we evaluated the relationship between the highest and lowest quartiles of the distributions of PaO₂ and PaCO₂, as well as the lowest quartile of pH on one day, and separately on two days, and the risk of neurocognitive, language, and behavioral dysfunctions at age 10 years. Children who had hypoxemia, hyperoxemia, hypocapnia, hypercapnia, and acidemia, sometimes on only one day, and sometimes on two or more days, were more likely than others to have a high illness severity score (within the first 12 postnatal hours), and 10 years later to have multiple dysfunctions. The tendency of blood gas derangements to be associated with high illness severity scores and with multiple dysfunctions 10 years later is compatible with the possibility that blood gas derangements are indicators of physiologic instability/vulnerability/immaturity rather than contributors to brain damage.

Keywords

Infant; premature; infant; newborn; blood gas analysis; brain; development

1. Introduction

Several meta-analyses (Manja et al., 2015; Saugstad and Aune, 2014) and editorials (Doyle, 2015; Synnes and Miller, 2015) discussed studies that sought to find the optimum pulse oximeter oxygen saturation (SpO₂) target ranges for extremely preterm infants, including the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), (Vaucher et al., 2012), the Canadian Oxygen Trial (COT), (Schmidt et al., 2013) and the Benefits Of

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Oxygen Saturation Targeting (BOOST) II trials.(Darlow et al., 2014; Groups., 2016) The consensus is that compared to very preterm newborns targeted to be exposed to SpO₂ in the 90-95% range, those targeted to be exposed to SpO₂ in the 85-89% range were not at increased risk at 18-24 months of language or cognitive dysfunction or reduced head circumference. The SUPPORT study also found that elevated carbon dioxide concentrations (hypercapnia) were associated with increased risk of intraventricular hemorrhage and death, (Ambalavanan et al., 2015) but has not yet reported about dysfunctions in survivors.

Although some evidence suggests otherwise,(Breeman et al., 2015) function at age 2 years has limited prediction for later function.(Roberts et al., 2010) Consequently, we do not know how children exposed to lower amounts of oxygen in the intensive care nursery differ from their peers exposed to higher amounts of oxygen on assessments of function at older ages when the tasks are more complex than at age 2 years.

Although some observers want to emphasize hypoxia as a cause of brain injury in preterm newborns, (Salmaso et al., 2014; Volpe, 2009) other blood gas derangements, including hyperoxemia,(Gerstner et al., 2008; Leviton et al., 2010; Vottier et al., 2011) hypocapnia (hypocarbia),(Dammann et al., 2001; Fritz and Delivoria-Papadopoulos, 2006; Leviton et al., 2010) hypercapnia,(Fritz and Delivoria-Papadopoulos, 2006; Hagen et al., 2008; Leviton et al., 2010) and acidemia (acidosis)(Lavrijsen et al., 2005; Leviton et al., 2010) either are capable of contributing to brain damage in the immature brain, or are closely linked with related phenomena. We know of no study of the relationship between indicators of oxygenation or of carbon dioxide exchange shortly after birth among extremely preterm newborns and neurocognitive functions 10 years later.

The ELGAN Study of infants born before the 28th week of gestation, however, recorded blood gases measured during the first 72 hours after birth,(Hauspurg et al., 2010; Leviton et al., 2011a; Leviton et al., 2010) and assessed intelligence, indicators of executive function, social capabilities, and language, as well as academic achievement at age 10 years.(Joseph et al., 2016) In this report, we compare the frequency of undesirable scores on these 10-year assessments among children whose blood gases were in the top or bottom quartile of the distribution in this sample to the frequency among their peers.

2. Methods

2.1 Participants

The ELGAN study is a multi-center prospective, observational study of the risk of structural and functional neurologic disorders in children born before the 28th week of gestation. (O'Shea et al., 2009) Of the 889 children re-enrolled for assessments of neurocognitive function at age 10 years, 740 had blood gas assessments on at least one of the first three postnatal days. They constitute the population for the assessment of one-day measurements. The smaller number of children who had blood gas measurements of samples collected on multiple days (N = 156 - 171) constitute the population for the assessments of derangements on multiple days.

Enrollment and consent procedures for this follow up study were approved by the institutional review boards of all participating institutions.

2.2 Newborn variables

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), LMP without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

The birth weight Z-score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in referent samples not delivered for preeclampsia or fetal indications.(Leviton et al., 1999; Yudkin et al., 1987)

We collected all the physiology, laboratory and therapy data for the first 12 hours needed to calculate an illness severity score (Score for Neonatal Acute Physiology) (SNAP-II™). (Richardson et al., 2001) 28% of our sample had a SNAP-II value of >30. Mean blood pressure (MAP) was measured either directly from an intra-arterial catheter or from an automated blood pressure cuff. For this report, we include 2 measures of difficulty maintaining blood pressure during the first 24 postnatal hours, MAP in the lowest quartile for gestational age, and blood pressure lability, defined as the upper quartile of the difference between the lowest and highest MAP among gestational age categories (23-24, 25-26, and 27 weeks).(Logan et al., 2011a; Logan et al., 2011b)

Blood gases were measured when clinically indicated or when a physician requested them. The median number of blood gases obtained on each day declined rapidly from 8 on day 1 to 4 on day 3. Only arterial blood was used for oxygen measurements (indicated by the “a” in P_aO₂). Measurements of PCO₂, and pH were arterial except for 7 ELGANs on day 1, 15 on day 2 and 60 infants on day 3, all of whom had these measurements made on venous blood. The 14 intensive care nurseries differed considerably in their respiratory care and ventilator adjustment practices.

Children who did not have a blood gas on postnatal day 3 were more likely to be physiologically stable than children who had a set of blood gas measurements that day, and were also much less likely than others to have postnatal day 2 measurements that were in any extreme quartile. Assigning these non-extreme measurements to postnatal day 3 allowed us to include these children in this sample and avoid inflating odds ratios inappropriately. Imputations were classified as arterial or venous based on the most recent measurement.

Although dichotomization results in a significant loss of power,(Altman, 1994) epidemiologists prefer to study categorical entities rather than continua. This is exemplified by cut-offs for continuous measures of function/dysfunction (*e.g.*, hypertension, diabetes mellitus, glaucoma).(Lovasi et al., 2012; Ragland, 1992) However, we do not know where the along the continuum of blood gas measurements the risk of indicators of brain damage begins to increase sharply.

Some find fault with choosing an arbitrary cut-point for categorizing a continuous variable, (Rothman, 2014) but In the absence of data to help decide, however, we have no choice but to explore options and weigh costs of heterogeneity, bias, and loss of power. After having done so, we decided on extreme quartiles.

We classified ELGANs by their extreme blood gas measurements on postnatal days 1, 2, and 3. For each of these days we recorded the lowest and highest P_aO_2 , PCO_2 , and pH. In our sample, the blood gas measurement that defined the extreme quartile varied by gestational age and by postnatal day, and minimally by whether the specimen was arterial or venous. Consequently, we classified infants by whether or not their extreme value each day was in the extreme quartile for their gestational age (23-24, 25-26, and 27 weeks) and whether the specimen was arterial or venous. Because an extreme measure on one day could reflect a fleeting event, we evaluated that separately from an extreme quartile on at least two of the three days. The values that define the lowest and highest quartiles of each blood gas on each day in each gestational age group are presented in Table 1.

2.3 Procedures for the assessments at age 10 years

All families who participated in the previous follow up were contacted by mail and then by phone to invite them to participate in the 10-year follow up. Lost to follow-up families were searched for on state vaccination registries, and other openly-available websites. Facebook was also used where approved by the local institution's IRB.

Families willing to participate were scheduled for one visit during which all of the measures reported here were administered in 3 to 4 hours, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in one testing session. While the child was tested, the parent or caregiver completed questionnaires, including one about school placement and services.

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales.(Elliott, 2007) Expressive and receptive language skills were evaluated with the Oral and Written Language Scales (OWLS), which assess semantic, morphological, syntactic, and pragmatic production and comprehension of elaborated sentences.(Carrow-Woolfolk, 1996)

Attention and executive function were assessed with both the DAS-II(Elliott, 2007) and the NEPSY-II (A Developmental NEuroPSYchological Assessment-II).(Korkman et al., 1998) The DAS Recall of Digits Backward and Recall of Sequential Order measured verbal working memory, while the NEPSY-II Auditory Attention and Response Set measured auditory attention, set switching and inhibition, the NEPSY-II Inhibition Inhibition and Inhibition Switching measured simple inhibition and inhibition in the context of set shifting, respectively, and the NEPSY-II Animal Sorting measured visual concept formation and set shifting.

Speed of processing was assessed with NEPSY-II Inhibition Naming, which provides a baseline measure of processing speed and has no inhibitory component. Visual perception was assessed with NEPSY-II Arrows and Geometric Puzzles, while visual motor function

was measured with NEPSY-II Visuomotor Precision and Fingertip Tapping. The Wechsler Individual Achievement Test-III (WIAT-III [C]) provided standard scores in word recognition and decoding, spelling, and numeric operations.(Wechsler, 2009)

2.4 Data Analyses

We evaluated the generalized form of two null hypotheses. The first postulates that children who had a blood gas extreme (“abnormality” defined as in the top or bottom quartile) on one of the first three postnatal days are no more likely than their peers to have a neurocognitive, behavioral, language, academic achievement, or related dysfunction at age 10 years. The second postulates the same, except that it requires the blood gas extreme to be documented on two separate days.

We began by assessing correlates of extreme blood gas measurements during the first three days, including maternal demographic and newborn characteristics (Tables S-1 and S-7. Tables in the supplement are identified with an S). To allow for the differences in age at the time of the assessment, and to facilitate a comparison of our findings to those reported for children presumably born very near term, we used Z-scores based on distributions of values reported for the normative samples that are described by the authors of the assessments we used.

We created logistic regression models of the risk of a score more than one standard deviation below the normative mean of each assessment (*i.e.*, Z-score <-1), or below or above a cut-off suggested by the authors of the assessment. These models, which included potential confounders (including gestational age category (*i.e.*, 23-24, 25-26, and 27 weeks), sex, birth weight Z-score <-2, mother's eligibility for government-provided, medical-care insurance, and receipt of any antenatal glucocorticoid), allowed us to calculate odds ratios (and 95% confidence intervals) that each blood gas abnormality is associated with each outcome.

In this sample, high PCO₂ and low pH occurred in the same children more frequently than would be expected if their occurrences were independent. In order to estimate the effect of each in light of the other gases (lowest quartile of P_aO₂, highest quartile of P_aO₂ and lowest quartile of PCO₂), we fit them in two separate conditional logistic multivariable models, one that includes low pH but not high PCO₂ (model 1) and one that includes high PCO₂ but not low pH (model 2). Both models included terms for the other blood gases and potential confounders, as well as a hospital cluster term (to account for the tendency for infants born and cared for at a particular hospital to be more like each other than like infants born and cared for at other hospitals) (Begg and Parides, 2003).

3. Results

Approximately half of the 740 children in this cohort had at least one blood gas measure that was in the highest or lowest quartile for oxygen or carbon dioxide concentration for at least one day, while approximately 20-23% had a blood gas measure that was in the highest or lowest quartile for oxygen or carbon dioxide concentration on at least two days.

3.1 Search for possible confounders of derangements on one day (Supplement Table S-1)

Socioeconomic indicators (racial and Hispanic identity, years of formal education, marital status, and eligibility for government-provided insurance) were not associated uniformly with blood gas derangements on one day, while a birthweight Z-score < -1 was prominently associated with increased occurrence of hyperoxemia, hypocarbia, and acidemia, SNAP > 30 was prominently associated with elevated occurrence of all blood gas derangements except for hyperoxemia, which was prominently associated with low and labile MAP during the first 24 hours.

3.2 Search for possible confounders of derangements on 2 days (Supplement Table S-2)

The lowest birthweight Z-score was less associated with blood gas derangements on two or more days than was seen in for single-day derangements. On the other hand, high SNAPs continued to be associated with derangements (especially hypercarbia and acidemia), while low MAP was associated with hyperoxemia, hypercarbia, and acidemia.

3.3 Dysfunctions associated with single-day and multiple-day derangements (Supplement Tables S-3 through S-7)

Odds ratios of low scores on assessments of IQ, language, and academic achievement are presented in Supplement Table 3 for single-day derangements and in Supplement Table 4 for derangements on two or more days, while low scores on assessments of working memory and other components of executive dysfunction (as well as other dysfunctions identified with the NEPSY-II) are presented in Supplement Table 5 for single-day derangements and in Supplement Table 6 for derangements on two or more days. Odds ratios of parent-reported indicators of dysfunction in school are presented in Supplement Table 7a for single-day derangements and Supplement Table 7b for derangements on two or more days. Rather than describe the contents of each table separately, we offer an over-view with a description of the contents of Table 2 in the following paragraphs of the Results section.

3.4 Dysfunctions associated with single-day and multiple-day derangements (Supplement Tables S-3 through S-7)

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3.5 Summary of Supplement Tables S-3 through S-7 (Table 2)

No blood gas derangement, on either one day or on two or more days, is associated with increased risk of low verbal or non-verbal IQ, low scores on either component of the OWLS, and placement in a remedial class.

The following dysfunctions were associated with only one blood gas derangement: working memory (hyperoxemia on 2 days), WIAT-II Word Read (hypocarbica on 1 day), WIAT-II Numeric Operations, NEPSY-II auditory attention (hypercarbica on 2 days), NEPSY-II auditory response (acidemia on one day), NEPSY-II inhibition naming (hypercarbica on 1 day), and NEPSY-II Arrows (hypoxemia on 2 days).

Low scores on the WIAT-II I Pseudoword Decode assessment and repetition of a grade are the only indicators of dysfunction associated with two blood gas derangements (Pseudoword Decode with both hypocarbica and hypercarbica on one day, grade repetition with both hypercarbica and acidemia on one day).

Increased risks of four dysfunctions were associated with multiple blood gas derangements. Increased risks of low scores on the WIAT-III Spelling assessment were associated with hypoxemia and acidemia on 2 days, and hypercarbica on one day, while increased risks of low scores on the NEPSY-II geometric puzzles component were associated with hypercarbica and acidemia on 2 days, as well as hypoxemia and hypocarbica on only one day. Increased risks of both low scores on the NEPSY-II inhibition switching component and having an individual education plan had the same blood gas derangement profile, consisting of hyperoxemia, hypercarbica, and acidemia on 2 days, as well as hypercarbica and acidemia on only one day.

4. Discussion

Our main findings are that all five blood gas derangements are associated with increased risk of low scores on some assessments or dysfunctions on others, and that some of these derangements can be present on only one day, while other associations were found only if the derangement was identified on two days.

Each of the blood gas derangements we evaluated has been associated in this cohort with one form of brain damage or another before or at age 2 years (ultrasound-documented ventriculomegaly and hypoechoic lesions in the white matter, low score on a Bayley Scale, microcephaly, and cerebral palsy). (Gerstner et al., 2008; Leviton et al., 2010; Vottier et al., 2011) Although the dysfunctions at age 10 years differ from those assessed at age 2 years, we continue to see the diversity and lack of cohesiveness of associated dysfunctions.

4.1 Chronic, recurrent, intermittent derangements and not single severe acute episodes

Our goal was not so much to find evidence that a very extreme blood gas derangement can contribute to brain damage in the most vulnerable newborn, or even accompany whatever process is contributing to the brain damage. Rather, we wanted to find support for or against the hypothesis that repeated or perhaps even persistent low grade blood gas derangements contribute to brain damage. That is why we emphasize derangements on two separate days.

Because blood gas derangements are often the consequences of stimuli leading to physiologic instability, it is difficult to separate the direct effects of the stimulus from the effects of the indirect effects (which are also consequences of the stimulus). Consequently attributing brain damage to blood gas derangements identified in observational studies is difficult and fraught with error. But what if exposure to hypoxia was part of a clinical trial?

The recognition that even mild hyperoxia appears to increase the risk of retinopathy of prematurity has prompted controlled clinical trials to see how best to reduce the frequency of retinopathy of prematurity while avoiding levels of hypoxia that might damage the brain. These clinical trials compared “restricted” oxygen exposure (usually defined as an oxygen saturation (SpO₂) in the 85%–89% range) to liberal exposure (SpO₂, 91%–95%) among extremely preterm infants (<28 weeks' gestation at birth). (Darlow et al., 2014; Groups., 2016; Schmidt et al., 2013; Vaucher et al., 2012)

The endpoint for all the major clinical trials was the composite of death or disability. Although neither of the two trials that evaluated death alone found that children with restricted oxygen exposure were at increased risk of early death, combining data from these two trials allowed the increased risk of death before discharge associated with restricted oxygen exposure to achieve statistical significance. (Saugstad and Aune, 2014)

The risk of disability among survivors (defined as unable to walk and climb stairs without using hands for support) was not significantly elevated in any of the clinical trials. The authors of the meta-analysis of these clinical trials concluded, “Using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria, we found that the quality of evidence for these outcomes (including neurodevelopmental outcomes) was moderate to low.” (Manja et al., 2015) With this caveat, and the limited evidence available, we infer that hypoxia at levels clinicians can tolerate, does not appear to increase the risk of motor limitation at 18–24 months among children born extremely preterm, even though it might increase the risk of death.

4.2 In the causal chain?

If the blood gas derangements are in the causal chain, why are our findings so diverse? Here we discuss explanations that assume the derangements contribute to brain damage/dysfunction. Examples are based on the balance between injury and benefits that are the result of blood gas derangements. (Almendros et al., 2014) Yes, benefits.

“Preconditioning occurs when a sub-injurious exposure renders the brain less vulnerable to a subsequent damaging exposure.” (Hagberg et al., 2004) Hypoxic preconditioning has been demonstrated in the brains of newborn rodents. (Chen et al., 2015; Sheldon et al., 2014; Suryana and Jones, 2014) In a mouse model of apnea of prematurity, (that might or might not be equivalent to preconditioning) moderate intermittent hypoxia during the early postnatal period increased neurogenesis in the hippocampus, counteracted the adverse effects of brain lesions on memory, and was able to reduce lesion size following an excitotoxic insult. (Bousslama et al., 2015)

Apparent preconditioning can also be produced with hyperoxia,(Bigdeli et al., 2012) and hypercarbia/acidosis.(Ladilov, 2012; Tregub et al., 2016) These observations suggest that the blood gas derangements we anticipated might be associated with dysfunctions years later, can also provide neuroprotective benefits, and it is the balance between injury and these benefits that determines what we see.

Support for possible neuroprotective effects of intermittent hypoxia continues to grow, (Bousslama et al., 2015; Mateika et al., 2015; Navarrete-Opazo and Mitchell, 2014; Pourie et al., 2006; Ramanantsoa et al., 2013; Zhang et al., 2005) although the mechanisms remain unknown.

4.3 Not in the causal chain

It is possible that the lack of cohesiveness of our findings has another explanation. Here we discuss the possibility that the blood gas derangements we assessed are epiphenomena and do not contribute to brain damage.

Because we defined blood gas abnormalities within narrowly defined gestational age categories (and postnatal day), our associations between blood gas abnormalities and later dysfunctions are highly unlikely to reflect gestational age. Nevertheless, they have the potential to provide supplemental information about correlates of low gestational age including, physiologic instability, immaturity, and vulnerability.

The illness severity score we used is called the Score for Neonatal Acute Physiology (SNAP).(Richardson et al., 1993) This score is based on 6 indicators of disturbed physiology, including lowest mean arterial pressure (MAP), worst ratio of partial pressure of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂), lowest temperature, lowest serum pH, occurrence of multiple seizures, and low urine output (<1mL/kg/hr). The creators of SNAP and their advisors considered acidemia an indicator of physiologic instability. We argue that each blood gas derangement we evaluated is likely to be a reflection of physiologic instability. Others, too, consider SNAP an indicator of physiologic instability.(Dorling et al., 2005 ; Mattia and deRegnier, 1998)

Although gestational age might be our best indicator of immaturity/vulnerability,(Leviton et al., 2005) such information can be supplemented with illness severity scores,(Dammann et al., 2009) hypotension,(Logan et al., 2011a) which is a component of some illness severity scores, blood protein concentrations,(Leviton et al., 2011b; Matoba et al., 2009), metabolic profiles,(Jelliffe-Pawlowski et al., 2015) and rapid variations in blood gas concentrations. (Altaany et al., 2015) In this report, we document that several of the blood gas derangements were associated with high illness severity scores. We see this as support for the hypothesis that blood gas derangements convey some of the same risk information conveyed by high illness severity scores; specifically, information about the physiologic instability associated with immaturity/vulnerability.

An extension of this thinking is that moderate derangements of blood gases do not contribute to brain damage. Instead, these blood gas abnormalities are indicators of immaturity/vulnerability. Immaturity can be the equivalent of vulnerability when an early developmental

process is particularly prone to perturbation, and when growth promoters and potential protectors provided by the mother or placenta are not yet available.(Penn et al., 2015)

4.4 Quartiles are not very extreme

Table 1 documents that the criteria for lowest and highest blood gas quartiles are not extreme. For example, the day-1 criterion for a PO_2 in the lowest quartile among newborns delivered before the 25th week of gestation is 39 mm Hg, while the day-1 criterion for a PCO_2 in the highest quartile is 65 mm Hg. Consequently, many of the children in these “extreme” quartiles are really not exposed to blood gases many might consider unsafe. From an epidemiologic perspective, these children are being misclassified as exposed when they are not exposed to a potentially-damaging blood gas. On the other hand, our finding that each of the blood gas derangements is associated with multiple dysfunctions at school age raises the possibility that low level exposures might have adverse effects.

4.5 Severity of derangement not adequate in intensity or duration

Although we calculated extreme quartiles in the total sample, the number of children exposed was much higher than when we classified exposure as one or more days than exposure was classified as two or more days. This is documented in the bottom row of Supplement Tables S-1 and S-1. For example 49% (364/740) were classified as hypoxemic on one or more days (Table S-1), while only 21% (156/740) were classified as hypoxemic on two or more days (Table S-2).

In the absence of information about the magnitude of a derangement needed to contribute to dysfunctions (brain damage?), we might have failed to require a sufficiently disordered blood gas. For example, in re-analyses of the COT data, the highest decile of the number of hypoxemic episodes was needed to discriminate between those who died or had disability and those who did not.(Poets et al., 2015) In analyses of blood gas derangements and earlier assessments than reported here, extreme quintiles sometimes identified associations not seen with extreme quartiles.(Leviton et al., 2010) The consequence of classifying as exposed someone who should more appropriately be classified as non-exposed has the potential to lead to bias.(Hofler, 2005)

4.6 Implications for clinical care

Ours is not a randomized clinical trial. Rather, it is an observational study with all the limitations that follow from this.(Boyko, 2013) These include confounding by indication, where the apparent need for increased oxygen might reveal as much about the indication for the increased oxygen, or the physician's tolerance of blood gas variations, as about the effect of the increased oxygen. Unfortunately, such confounding probably can never be completely eliminated.(Bosco et al., 2010) Thus, we encourage consideration of what we found, but make no suggestion about the clinical implications.

4.7 Limitations and strengths

Among our weaknesses are the inability to eliminate confounding by indication, and the inability to calculate base excess (because we do not know if hypercarbia and acidemia were from the same specimen). One of the strengths of our study is the availability of multiple

early blood concentration measurements of oxygen, carbon dioxide, and pH. Among our study's other strengths are the large number of subjects we enrolled and were able to assess 10 years later, selection of infants based on gestational age and not birth weight, and prospective collection of data we consider to be of high quality.

4.8 Conclusion

In very preterm newborns exposed to ventilation variations within the bounds considered good clinical care, relatively low-grade hypoxemia, hyperoxemia, hypocapnia, hypercapnia, and acidemia were each associated with multiple neurocognitive dysfunctions and/or school-related dysfunctions 10 years later. Each of these blood gas derangements might contribute to brain damage or be an indicator of other processes capable of damaging or protecting the immature brain. On the other hand, the multiplicity and diversity of relationships between dysfunctions and blood gas derangements, the tendency of these derangements to be associated with high illness severity scores, and the likelihood that high illness severity scores convey information about immaturity/vulnerability, we raise the possibility that blood gas derangements do not contribute to brain damage. Consequently, blood gas derangements in the extremely preterm newborn might be indicators of vulnerability/immaturity that supplement information about immaturity/vulnerability conveyed by gestational age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Neonatologists are concerned that their efforts to minimize the risk of retinopathy of prematurity might increase the risk of school-related dysfunctions 10 years later.
- Extremely preterm newborns who had hypoxemia, hyperoxemia, hypocapnia, hypercapnia, or acidemia, on only one day, and on two or more days, were not more likely than others to have low IQ scores. They were at increased risk of some dysfunctions, but not in a cohesive pattern.
- The blood gas goals of clinicians 15 years ago do not seem to have placed extremely preterm newborns at increased risk of neurocognitive dysfunction and academic delay at age 10.

The values that define the lowest and highest quartiles of each blood gas on each day in each gestational age group.

Table 1

Blood gas quartile →	Lowest PO ₂ (mm Hg)			Highest PO ₂ (mm Hg)		
Postnatal day →	1	2	3	1	2	3
Gestational age (wks) ↓						
23-24	39	43	44	152	98	104
25-26	42	45	45	145	100	95
27	40	44	46	142	92	96
Blood gas quartile →	Lowest PCO ₂ (mm Hg)			Highest PCO ₂ (mm Hg)		
Postnatal day →	1	2	3	1	2	3
Gestational age (wks) ↓						
23-24	27	33	34	65	68	63
25-26	29	36	35	60	64	60
27	29	35	36	58	57	56
Blood gas quartile →	Lowest pH					
Postnatal day →	1	2	3			
Gestational age (wks) ↓						
23-24	7.15	7.14	7.16			
25-26	7.20	7.17	7.19			
27	7.22	7.22	7.22			

Table 2

Summary of the contents of all the odds-ratio tables in the supplement. The number in the cells is the number of days a blood gas derangement needed to be present to be associated with increased risk of the dysfunction or low score on the assessment listed on the left. ONE defines a blood gas extreme quartile on at least one of the first 3 days, while TWO defines a blood gas extreme quartile on at least 2 of the first 3 days.

	Blood gas extreme quartile during the first 3 postnatal days					
	Low PO ₂	High PO ₂	Low PCO ₂	High PCO ₂	Low pH	
Differential Abilities Scales-Second Edition (DAS-II)						
Verbal IQ						
Non-verbal IQ						
Working memory		TWO				
Oral and Written Language Scales-Second Edition (OWLS)						
Listening comp						
Oral express'n						
Wechsler Individual Achievement Test-Third Edition (WIAT-III)						
Word Read			ONE			
Pseudoword Decode			ONE	ONE		
Spelling	TWO			ONE	TWO	
Numeric Operations				ONE		
A Developmental Neuropsychological Assessment (NEPSY-II)						
Auditory attention				TWO		
Auditory response					ONE	
Inhibition switching		TWO		ONE, TWO	ONE, TWO	
Inhibition Naming				ONE		
Arrows	TWO					
Geometric puzzles	ONE		ONE	TWO	TWO	
Parent report						
Individual Ed Plan		TWO		ONE, TWO	ONE, TWO	
Repeated a grade				ONE	ONE	
Special remed class						

§ All models are adjusted for gestational age (23-24, 25-26, 27 weeks), sex, birth weight Z-score < -2, and receipt of any antenatal glucocorticoid. These models also include a birth hospital group/cluster term to account for the possibility that infants born at a particular hospital are more like each other than infants born at other hospitals.

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