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Blood protein concentrations in the first two postnatal weeks associated with early postnatal blood gas derangements among infants born before the 28th week of gestation. The ELGAN Study

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Author contributions

Alan Leviton played a role in every aspect of the ELGAN Study and played major roles in data analysis and manuscript preparation. Elizabeth Allred played a major role in designing the data collection forms and the database management system. She is also the person most responsible for maintaining data quality and for data analysis. In addition, she has read and edited multiple drafts of the manuscript and offered comments.

Karl C. K. Kuban participated in designing the data collection forms and implementing the procedures. He has participated in data analyses, and has read and edited multiple drafts of the manuscript and offered comments.

Olaf Dammann participated in designing the data collection forms and implementing the procedures. He has participated in data analyses, and has read and edited multiple drafts of the manuscript and offered comments.

Raina N Fichorova was most responsible for the high quality of the blood protein measurements. She participated in data analyses, and has read and edited multiple drafts of the manuscript and offered comments

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Conflict of interest statement

The authors do not see how they might benefit financially from publication of this manuscript, nor do they have any financial stake in any commercial organization that might benefit.

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Abstract

Aim—To explore the relationships between blood gas derangements and blood concentrations of inflammation-related proteins shortly after preterm birth.

Design—Observational cohort

Setting—14 neonatal intensive care units

Subjects—734 infants born before the 28th week of gestation who were classified by their blood gas derangements during the first three postnatal days and by the concentrations of 25 proteins in their blood on days 1, 7, and 14. We classified these newborns by whether or not they had a highest or lowest P_aO₂, PCO₂, and lowest pH in the most extreme quartile, and by whether or not they had a protein concentration in the highest quartile.

Results—Blood gas derangements on two days were much more likely to be accompanied or followed by sustained or recurrent systemic inflammation than a derangement on only one day. This was most evident for acidemia, and slightly less so for hypercapnia.

Conclusions—Our finding that protein concentration patterns indicative of systemic inflammation are associated with several blood gas derangements raises the possibility that organ damage attributed to these derangements might be accompanied by or involve an inflammatory response.

Keywords

preterm infant; blood; cytokine; inflammation; acidemia; hypercapnia

Introduction

Hypoxia-ischemia and inflammation have been implicated in the pathogenesis of encephalopathy of prematurity [1]. Does that mean either? Both together? In sequence?

Hypoxemia, however, is not the only blood gas derangement implicated in brain damage. Also implicated have been hyperoxemia (and oxidative stress) [2–4], hypocapnia [5, 6], hypercapnia [7, 8], and acidemia [9, 10]. Each of these blood gas derangements, hypoxemia: [11–13], hyperoxemia [14], hypocapnia [15, 16], hypercapnia [17], and acidemia [18, 19], also either contributes to, or can be a consequence of inflammation.

To explore the relationships between blood gas derangements and indicators of inflammation, we classified 734 infants born before the 28th week of gestation by their blood gas derangements during the first three postnatal days and by indicators (of the extent)

of (their) systemic inflammation during the first two postnatal weeks. In light of our findings that brain damage in this sample of preterm newborn is most strongly associated with inflammation evident on two or more occasions a week apart [20, 21], we were particularly interested in prolonged (or recurrent) inflammation that follows a blood gas derangement.

We recently found that children who had blood gas extremes were at increased risk of a number of indicators of early brain damage [22]. This prompted us to consider the hypothesis that blood gas abnormalities and elevated concentrations of inflammation-related proteins might be related.

Methods

The ELGAN Study

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs (the acronym for Extremely Low Gestational Age Newborns)[23]. During the years 2002–2004, women delivering before 28 weeks gestation at one of 14 participating institutions in 11 cities in 5 states were asked to enroll in the study. The enrollment and consent processes were approved by the individual institutional review boards.

Mothers were approached for consent either upon antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. 1249 mothers of 1506 infants consented. Approximately 260 women were either missed or did not consent to participate. Measurement of multiple proteins in blood was limited to the 939 infants who participated in developmental assessments at age 2-years. For this analysis, we included only the 734 infants who had blood gases values on at least two of the first three postnatal days and for whom we had protein measures from two of the three protocol days (Supplement Table 1).

A full description of the methods is provided elsewhere [23]. Here we focus on those most relevant to the topic at hand.

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%).

We relied on clinicians to select the times for blood gas measurements. The number of blood gases obtained on each day declined rapidly during the first post-natal week and varied among the participating institutions. We collected the minimum and maximum P_aO_2 , PCO_2 , and pH [22] on postnatal days 1, 2, and 3. Because we cannot tell if extreme pH and PCO_2 measurements are paired, we did not calculate base excess. In our sample, the blood gas measurement that defined the lowest or highest quartile varied by gestational age and by

postnatal day. Consequently, we classified infants as having hypoxemia, hyperoxemia, hypocapnia, hypercapnia, and academia based on whether or not their minimum or maximum value each day was in the lowest or highest quartile for their gestational age (23–24, 25–26, and 27 weeks) (Supplement Table 2).

When a day-1 measure was not available (10 children lacked a P_aO_2 , 1 lacked a PCO_2 , and 1 lacked a pH), we substituted the day 2 measure for the missing day-1 measure. When no day-2 measure was available (8 lacked a P_aO_2 , 5 lacked a PCO_2 , and 4 lacked a pH), the average of the day 1 and 3 measures was used. Finally, when a day-3 measure was missing (95 lacked a P_aO_2 , 42 lacked a PCO_2 , and 42 lacked a pH), we substituted the day-2 measure.

The upper bound of the lowest quartile of PO_2 among the least mature newborns (23–24 weeks gestation) varied between 39 mm Hg on day 1 and 44 on day 3, while the upper bound of the lowest quartile of PO_2 among the most mature (27 weeks gestation) varied between 40 mm Hg on day 1 and 46 on day 3. The lower bound of the top quartile of PO_2 was in the 142–152 range for all newborns on day 1, falling rapidly so that the range was 92–100 on day 2, and 95–104 on day 3.

The upper bound of the lowest quartile of PCO_2 varied between 27 mm Hg on day 1 for the least mature to 36 on day 3 among the most mature. The lower bound of the highest quartile of PCO_2 was highest in the least mature on the first day (65 mm Hg), rose on day 2 (68 mm Hg), and fell rapidly thereafter hovering about 63 mm Hg. In the most mature, the lower bound of the highest quartile of PCO_2 fell from 58 mm Hg on day 1 to 56 mm Hg on day 3. The upper bound of the lowest quartile of pH remained in the 7.14 to 7.16 range among the least mature, and did not vary at all among the most mature (7.22).

We collected the minimum and maximum blood gas values each day [22]. Because we cannot tell if extreme pH and PCO_2 measurements are paired, we did not calculate base excess.

Blood spot collection

The specimens for measurement of protein concentrations were drops of blood collected on (Schleicher & Schuell 903) filter paper on the first postnatal day (range: 1–3 days), the 7th postnatal day (range: 5–8 days), and the 14th postnatal day (range: 12–15 days). All blood was from the remainder after specimens were obtained for clinical indications. Dried blood spots were stored at $-70^{\circ}C$ in sealed bags with dessicant until processed.

Protein measurement

Details about elution of proteins from blood spots and measurement of the proteins with the Meso Scale Discovery (MSD) electrochemiluminescence system are provided elsewhere [24]. Validated by comparisons with traditional ELISA [25, 26], this system has inter-assay variations that are invariably less than 20%. Measurements of each protein were normalized to mg total protein.

The Laboratory of Genital Tract Biology of the Department of Obstetrics, Gynecology and Reproductive Biology at Brigham and Women's Hospital, Boston measured the following 25 proteins: IL-1beta (Interleukin-1beta), IL-6 (Interleukin-6), IL-6R (interleukin-6 receptor), TNF-alpha (tumor necrosis factor-alpha), TNF-R1 (tumor necrosis factor-alpha-receptor1), TNF-R2 (tumor necrosis factor-alpha-receptor2), IL-8 (CXCL8) (interleukin-8), MCP-1 (CCL2) (monocyte chemotactic protein-1), MCP-4 (CCL13) (monocyte chemoattractant protein-4) (CCL13), MIP-1B (CCL4) (Macrophage Inflammatory Protein-1 beta) (CCL4), RANTES (CCL5) (regulated upon activation, normal T-cell expressed, and [presumably] secreted), I-TAC (CXCL11) (Interferon-inducible T cell Alpha-Chemoattractant), ICAM-1 (CD54) (intercellular adhesion molecule-1), ICAM-3 (CD50) (intercellular adhesion molecule-3), VCAM-1 (CD106) (vascular cell adhesion molecule-1), E-SEL (CD62E) (E-selectin) (CD62E), MMP-1 (matrix metalloproteinase-1), MMP-9 (matrix metalloproteinase-9), CRP (C-Reactive Protein), SAA (serum amyloid A), MPO (myeloperoxidase), VEGF (vascular endothelial growth factor), VEGF-R1 (vascular endothelial growth factor-receptor1), VEGF-R2 (vascular endothelial growth factor-receptor2), and IGFBP-1 (Insulin Growth Factor Binding Protein-1).

Data analysis

We evaluated the hypothesis that a blood gas measurement in the lowest or highest quartile on two or three postnatal days is more likely than such a measurement on only one day or no days to be associated with a protein concentration in the highest quartile.

Using logistic regression models with adjustment for gestational age category, we calculated odds ratios and 99% confidence intervals of a protein concentration in the top quartile on two or more days or a single day with the referent group comprised of newborns who had no extreme measurement of that protein on any of the three days sampled. To balance the risks of type 1 and type 2 errors with our many evaluations (25 proteins measured at 3 times for each of five blood gas derangements), we selected the 99% confidence interval rather than the conventional 95% confidence interval.

Results

In this sample of 734 infants born before the 28th week of gestation, our antecedents were defined by the lowest or highest quartile of blood gas values and our outcomes were defined by the top quartile of blood protein concentration. Nevertheless, approximately half of all children had at least one blood gas derangement.

Hypoxemia (Table 1)

One or more days of hypoxemia was not accompanied or followed by a prominent systemic inflammation signal. MCP was the only protein whose concentration showed some tendency to be in the top quartile on two separate days if the newborn experienced any hypoxemia.

Hyperoxemia (Table 2)

Hyperoxemia was not associated with elevated concentrations of any of the proteins measured.

Hypocapnia (Table 3)

One day of hypocapnia was not accompanied by any systemic inflammation signal. Hypocapnia on two days, however, was associated with elevated concentrations of TNF-R1 and IL-8 on one day only, and TNF-R2 and ICAM-1 on two or more days.

Hypercapnia (Table 4)

Hypercapnia, whether on only one day or two or more days, was followed by an elevated concentration of IL-8 on two or more days a week apart. Hypercapnia on two or more days was associated with elevated concentrations of MCP-1 and with elevated concentrations of TNF-R1 and VEGF-R1 on two or three days. The probability of an elevated concentration of RANTES on two or more days was significantly *reduced* among children who had hypercapnia on two or more days.

Acidemia (Table 5)

Although one day of acidemia was associated with increased concentrations of IL-8 and MCP-1, the most prominent findings are associated with two or more days of acidemia. Infants who experienced acidemia on multiple days were much more likely than others to have elevated concentrations of IL-1beta, IL-6, TNF-alpha, TNF-R1, TNF-R2, IL-8, MCP-1, ICAM-1, and E-selectin on two days a week apart.

Discussion

We explored the relationships in ELGANs between blood gas derangements evident during the first postnatal days and indicators of systemic inflammation during the first two postnatal weeks. We did this as part of our evaluation of the antecedents of organ damage in these fragile newborns.

We are not sure if day-1 protein elevations preceded or accompanied the some of the blood gas derangements. On the other hand, we are sure that all the blood gas derangements during the first three postnatal days preceded the day-7 and day-14 protein measurements. Thus, we cautiously use the word stimulus in describing the relationship between early blood gas extremes and subsequent protein elevations. We acknowledge that the blood gas derangements might not have been the stimuli, but merely epiphenomena.

1. Some blood gas derangements on two or more days appear to provide a stronger inflammatory stimulus than the same blood gas derangement on only one day

The decision to draw blood for “gases” was left to each neonatologist. Consequently, we expected some of the blood gas values to be severely abnormal, and to be faced with the possibility of selection bias.

We reasoned that a blood gas derangement on one day only represented a significant, but transient physiologic disturbance, whereas a blood gas abnormality evident on two separate days represented a disturbance not readily responsive to efforts to restore homeostasis. Because some of the inability to restore homeostasis probably reflected immaturity, we classified blood gas abnormalities within gestational age categories. Nevertheless, we

acknowledge that such efforts might not eliminate residual confounding, likely related to immaturity.

As expected, a blood gas derangement on two or more days was considerably more likely to be accompanied or followed by elevated concentrations of inflammation-related proteins than a blood gas derangement on one day only. The most likely explanation is that the more severe (persistent/recurrent) the blood gas abnormality, the greater the likelihood of an inflammatory response. This is especially important because in this sample, the risks of two indicators of structural brain damage are much more strongly associated with elevated concentrations of inflammation-related proteins on two or more occasions a week apart than an elevated concentrations on only one day [20, 21].

2. Hypoxemia and hyperoxemia are not followed by an inflammatory response

Except for elevated concentrations of MCP-1, early hypoxemia was not followed by any inflammatory response. This is surprising given reports that reperfusion following ischemia/hypoxia “induces an important inflammatory response, characterized by a massive production of free radicals and by the activation of the complement and leucocyte neutrophils” [11] Indeed, the inflammation induced in the brain by hypoxemia in rats can persist for weeks [27]

Hyperoxemia can be expected to promote the creation of reactive oxygen species, which can influence NF- κ B signaling, a component of the inflammatory process [28]. Nevertheless, hyperoxemia was not accompanied by systemic inflammation.

Hyperoxemia appears to increase the risk of retinopathy of prematurity in these children [29]. Our findings reported here suggest that inflammation is unlikely to be involved in this process.

3. Hypocapnia is associated with early inflammation that was not sustained

Preterm newborns who experience hypocapnia are at increased risk of cerebral white matter damage [30–33]. We sought, but found only minimal evidence in support of the hypothesis that inflammation is an intermediary. We found that one day of hypocapnia was not accompanied by any systemic inflammation signal, whereas hypocapnia on two days was associated with elevated concentrations of TNF-R1 and IL-8 on one day only, and TNF-R2 and ICAM-1 on two or more days. We view this as a weak inflammatory signal.

4. Hypercapnia was associated with a late inflammatory response

Hypercapnia was followed by elevated concentrations of IL-8, MCP-1, TNF-R1, and VEGF-R1. In addition, the probability of an elevated concentration of RANTES was reduced among children who experienced hypercapnia. In our sample, elevated concentrations of the chemokine RANTES are associated with reduced risk of bronchopulmonary dysplasia [34].

In light of these findings, our data can be viewed as support for the view that hypercapnia conveys some information about inflammation. On the other hand, we advise caution in doing so. “Permissive” hypercapnia, sometimes used to minimize the risk of

bronchopulmonary dysplasia [35], can sometimes result in more severe hypercapnia than desired, as well as acidemia [19]. Consequently, hypercapnia might be an indicator of the characteristics that place a newborn at increased risk of bronchopulmonary dysplasia, such as immaturity of the lung (and perhaps brain as well).

5. Acidemia was associated with an early and sustained inflammatory response

Acidemia on two separate days was most clearly associated with an inflammatory signal. Although acidemia tends to co-occur with hypercapnia, it is clear from our data that acidemia conveys a stronger inflammatory signal than seen with hypercapnia. Thus, we view acidemia as conveying information above and beyond the acidosis associated with hypercapnia alone.

Although early sepsis at term is associated with acidemia, fetal sepsis in preterm newborns does not appear to increase the risk of cord blood acidemia [36]. In light of this information, early acidemia is less likely to be a consequence of an early inflammation stimulus than a stimulus for subsequent inflammation.

6. “Causes” of blood gas derangements and elevated concentrations of proteins

We are not sure to what extent antenatal inflammation might have contributed to any of the blood gas derangements. In temporal analyses (data not shown), much of the inflammation was first identified in the day-7 blood spot, and clearly after the blood gas assessments. Thus, the blood gas derangements are unlikely to be consequences of ongoing inflammation.

One inference based on these observations is that the systemic inflammation develops after the blood gas derangements. Support for this comes from observations that concentrations of inflammation-related proteins can be increased in the blood following stroke and head trauma [37–40]. One interpretation of such findings is that this inflammation is a consequence and not a cause of tissue damage. It is feasible, however, that the inflammation prompted by early tissue injury, especially in lung [41] and brain [42], contributes to continued or added brain injury since anti-inflammatory therapies given after the first manifestations of the brain damage from trauma or infarct can reduce the final amount of brain damage^[43–45].

Another inference is that early blood gas derangements and later systemic inflammation share common antecedent risks. Phenomena subsumed under the rubric of immaturity are among the most likely antecedents [46].

Hypercapnia can suppress the expression of genes related to innate immunity [47] and can also suppress responses to inflammatory stimuli [48]. These findings add to the complexity of the potential influence of blood gas levels on the synthesis and release of inflammation-related proteins.

7. Individual proteins are probably not individually important

An inflammatory stimulus can increase or decrease the expression of thousands of genes [49]. This has led to the view that each protein elevation should be seen as an indicator of a broad inflammatory process. We offer our findings with this view in mind.

8. Blood gas derangements, elevated concentrations of proteins, and organ damage

Our documenting protein concentration patterns indicative of systemic inflammation associated with several blood gas derangements raises the possibility that organ damage associated with these derangements might involve an inflammatory response. Some of the lung [41] and brain [42] damage attributed to blood gas derangements just might be influenced by inflammation.

In this sample, newborns who had early hypercapnia and/or acidemia were at increased risk of ventriculomegaly on a late ultrasound scan when the infant was in the intensive care nursery, hemiparetic cerebral palsy, and a mental development index on the Bayley Scales of Infant Development less than 70 (*i.e.*, more than two standard deviations below the expected mean) [22]. Thus, the very blood gas derangements most clearly associated with a strong inflammation signal are the ones prominently associated with disordered brain structure and function.

9. Strengths and limitations

The strengths of this study include a large number of infants, selection of infants based on gestational age, not birth weight [50], analyses that consider the effects of gestational age [46], prospective collection of data, and a protein measurement system that appears to be valid [25, 26] [51]. The limitations include restricting the sample to children who survived to age 2 years, potential confounding by indication [52] reflecting treatment effects, and an inability to distinguish between causation and association as explanations for what we found.

10. Conclusion

Sustained systemic inflammation was most prominent following two or more days of acidemia, and less prominent following two days of hypercapnia. Two days of hypoxemia, hyperoxemia, or hypocapnia were not followed by appreciable systemic inflammation. These findings raise the possibility that organ damage attributed to blood gas derangements is a consequence of inflammation, even when the systemic inflammation is initiated by organ damage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Odds ratio (and 95% confidence interval) of a concentration in the top quartile (for gestational age and day specimen was obtained) of the proteins listed on the left on one day only or on at least two days among children who had a P_aO_2 in the lowest quartile on 1 day only, or on 2 or more days compared to that of children who did not have a P_aO_2 in the lowest quartile on any of the first three days. The sample for these analyses consists of children who had proteins measured in blood collected on two separate days. The models are adjusted for gestational age (23–24, 25–26, 27 weeks) and birth weight Z-score (< -1 , -1). Odds ratios significant at $p < .01$ are in bold

Proteins	P_aO_2 in the lowest quartile on 1 day		P_aO_2 in the lowest quartile on 2 days	
	high protn, 1 day	high protn, 2 days	high protn, 1 day	high protn, 2 days
CRP	1.0 (0.6, 1.7)	0.9 (0.5, 1.7)	1.3 (0.7, 2.3)	1.2 (0.6, 2.3)
SAA	0.9 (0.6, 1.5)	0.9 (0.5, 1.7)	0.9 (0.5, 1.7)	1.0 (0.5, 2.1)
MPO	0.8 (0.4, 1.4)	1.2 (0.7, 2.1)	1.3 (0.7, 2.3)	1.5 (0.8, 2.8)
IL-1 β	0.7 (0.4, 1.2)	1.0 (0.6, 1.7)	0.9 (0.5, 1.7)	0.9 (0.5, 1.7)
IL-6	1.1 (0.7, 1.8)	1.2 (0.6, 2.2)	0.9 (0.5, 1.7)	1.6 (0.8, 3.1)
IL-6R	1.1 (0.6, 1.8)	1.0 (0.6, 1.7)	1.3 (0.7, 2.3)	0.9 (0.5, 1.7)
TNF- α	0.9 (0.5, 1.4)	1.2 (0.7, 2.2)	0.7 (0.4, 1.2)	1.2 (0.8, 2.2)
TNF-R1	1.3 (0.8, 2.2)	1.2 (0.7, 2.2)	1.3 (0.7, 2.3)	1.4 (0.8, 2.8)
TNF-R2	1.2 (0.7, 2.0)	1.4 (0.8, 2.5)	1.5 (0.8, 2.6)	1.3 (0.7, 2.5)
IL-8	1.0 (0.6, 1.6)	1.2 (0.6, 2.2)	1.1 (0.6, 2.0)	1.9 (0.97, 3.7)
MCP-1	1.0 (0.6, 1.6)	1.9 (1.04, 3.4)	1.3 (0.8, 2.3)	2.0 (1.04, 4.0)
MCP-4	1.0 (0.6, 1.7)	1.4 (0.8, 2.4)	1.0 (0.5, 1.8)	1.5 (0.8, 2.8)
MIP-1 β	1.3 (0.8, 2.1)	0.8 (0.4, 1.4)	1.1 (0.6, 2.0)	1.0 (0.5, 2.0)
RANTES	1.0 (0.6, 1.6)	0.7 (0.4, 1.4)	0.8 (0.4, 1.4)	0.9 (0.4, 1.7)
I-TAC	0.9 (0.5, 1.4)	1.2 (0.6, 2.1)	0.9 (0.5, 1.7)	1.0 (1.00, 3.5)
ICAM-1	1.3 (0.8, 2.1)	1.0 (0.6, 1.8)	1.5 (0.8, 2.6)	1.6 (0.9, 3.0)
ICAM-3	0.8 (0.5, 1.3)	1.1 (0.6, 1.9)	1.2 (0.7, 2.1)	1.5 (0.8, 2.9)
VCAM-1	0.7 (0.4, 1.2)	1.2 (0.7, 2.1)	0.9 (0.5, 1.6)	1.4 (0.7, 2.5)
E-SEL	0.8 (0.5, 1.4)	1.0 (0.6, 1.7)	1.6 (0.9, 2.8)	1.1 (0.6, 2.1)
MMP-1	1.0 (0.5, 1.7)	1.1 (0.6, 1.8)	1.2 (0.6, 2.2)	1.1 (0.6, 2.0)
MMP-9	1.1 (0.7, 1.8)	1.2 (0.7, 2.2)	1.2 (0.7, 2.0)	0.8 (0.4, 1.7)
VEGF	0.9 (0.5, 1.5)	1.1 (0.7, 2.0)	1.4 (0.8, 2.5)	1.1 (0.6, 2.1)
VEGF-R1	1.4 (0.9, 2.4)	1.6 (0.9, 2.8)	1.0 (0.5, 1.8)	1.5 (0.8, 2.9)
VEGF-R2	1.1 (0.6, 1.8)	0.8 (0.5, 1.4)	1.2 (0.6, 2.1)	1.2 (0.7, 2.2)
IGFBP-1	0.9 (0.6, 1.5)	1.1 (0.6, 2.1)	0.8 (0.5, 1.4)	1.0 (0.5, 2.1)

Table 2

Odds ratio (and 95% confidence interval) of a concentration in the top quartile (for gestational age and day specimen was obtained) of the protein(s) listed on the left on one day only or on at least two days among children who had a P_aO_2 in the highest quartile on 1 day only or on 2 or more days compared to that of children who did not have a P_aO_2 in the highest quartile on any of the first three days. The sample for these analyses consists of children who had proteins measured in blood collected on two separate days. The models are adjusted for gestational age (23–24, 25–26, 27 weeks) and birth weight Z-score (< -1 , -1). Odds ratios significant at $p < .01$ are in bold

Proteins	P_aO_2 in the highest quartile on 1 day		P_aO_2 in the highest quartile on 2 days	
	high protn, 1 day	high protn, 2 days	high protn, 1 day	high protn, 2 days
CRP	0.9 (0.5, 1.4)	1.2 (0.7, 2.2)	1.3 (0.7, 2.3)	1.6 (0.8, 3.2)
SAA	0.9 (0.6, 1.5)	1.1 (0.6, 2.0)	1.1 (0.6, 1.9)	1.2 (0.6, 2.5)
MPO	0.8 (0.5, 1.4)	0.7 (0.4, 1.2)	1.0 (0.6, 1.8)	0.9 (0.5, 1.6)
IL-1 β	0.7 (0.4, 1.1)	0.9 (0.5, 1.6)	1.4 (0.8, 2.5)	1.5 (0.8, 2.8)
IL-6	1.0 (0.6, 1.7)	0.6 (0.3, 1.1)	1.4 (0.8, 2.5)	1.0 (0.5, 2.0)
IL-6R	0.9 (0.5, 1.5)	1.2 (0.7, 2.0)	1.1 (0.6, 2.0)	1.1 (0.6, 2.2)
TNF- α	1.2 (0.7, 2.0)	1.2 (0.7, 2.1)	1.7 (0.9, 3.0)	1.7 (0.9, 3.3)
TNF-R1	1.1 (0.7, 1.8)	0.7 (0.4, 1.2)	1.2 (0.7, 2.2)	1.0 (0.5, 1.9)
TNF-R2	1.1 (0.7, 1.8)	0.9 (0.5, 1.7)	1.1 (0.6, 2.0)	1.4 (0.7, 2.6)
IL-8	0.9 (0.5, 1.4)	0.8 (0.4, 1.6)	1.6 (0.9, 2.8)	1.6 (0.8, 3.2)
MCP-1	0.8 (0.5, 1.3)	0.7 (0.4, 1.2)	0.9 (0.5, 1.6)	1.0 (0.5, 1.9)
MCP-4	0.9 (0.5, 1.5)	0.6 (0.4, 1.1)	1.1 (0.6, 1.9)	0.8 (0.4, 1.5)
MIP-1 β	1.0 (0.6, 1.7)	1.0 (0.6, 1.8)	1.0 (0.6, 1.9)	1.1 (0.6, 2.1)
RANTES	0.9 (0.6, 1.6)	0.7 (0.4, 1.2)	1.2 (0.7, 2.1)	0.7 (0.3, 1.5)
I-TAC	1.4 (0.8, 2.3)	0.8 (0.4, 1.4)	1.7 (0.9, 3.1)	1.4 (0.7, 2.6)
ICAM-1	0.9 (0.5, 1.5)	1.1 (0.6, 1.9)	1.5 (0.8, 2.6)	1.9 (0.99, 3.5)
ICAM-3	0.8 (0.5, 1.4)	0.7 (0.4, 1.3)	1.2 (0.7, 2.1)	0.7 (0.4, 1.4)
VCAM-1	0.8 (0.5, 1.4)	0.6 (0.3, 1.02)	0.9 (0.5, 1.7)	0.8 (0.4, 1.5)
E-SEL	1.2 (0.7, 2.0)	0.7 (0.4, 1.2)	1.6 (0.9, 2.9)	1.4 (0.7, 2.6)
MMP-1	1.0 (0.6, 1.8)	0.8 (0.4, 1.3)	1.2 (0.6, 2.2)	0.9 (0.5, 1.7)
MMP-9	0.9 (0.6, 1.5)	1.1 (0.6, 2.0)	1.0 (0.6, 1.7)	1.1 (0.5, 2.2)
VEGF	1.1 (0.7, 1.9)	0.7 (0.4, 1.2)	1.2 (0.6, 2.1)	1.0 (0.5, 1.8)
VEGF-R1	0.8 (0.5, 1.3)	0.7 (0.4, 1.1)	0.7 (0.4, 1.3)	0.7 (0.4, 1.3)
VEGF-R2	1.2 (0.7, 2.0)	1.0 (0.6, 1.7)	1.5 (0.8, 2.8)	1.6 (0.9, 3.0)
IGFBP-1	0.9 (0.5, 1.4)	0.8 (0.4, 1.6)	1.2 (0.7, 2.0)	0.9 (0.4, 1.9)

Table 3

Odds ratio (and 95% confidence interval) of a concentration in the top quartile (for gestational age and day specimen was obtained) of the protein(s) listed on the left on one day only or on two or more days among children who had a PCO₂ in the lowest quartile on 1 day only or on 2 or more days compared to that of children who did not have a PCO₂ in the lowest quartile on any of the first three days. The sample for these analyses consists of children who had proteins measured in blood collected on two separate days. The models are adjusted for gestational age (23–24, 25–26, 27 weeks) and birth weight Z-score (< −1, −1). Odds ratios significant at $p < .01$ are in bold

Proteins	PCO ₂ in lowest quartile on 1 day		PCO ₂ in lowest quartile on 2 days	
	high protn, 1 day	high protn, 2 days	high protn, 1 day	high protn, 2 days
CRP	1.4 (0.8, 2.3)	0.9 (0.5, 1.6)	1.4 (0.8, 2.5)	1.8 (0.96, 3.4)
SAA	1.0 (0.6, 1.7)	1.0 (0.5, 1.8)	1.0 (0.6, 1.8)	1.2 (0.6, 2.4)
MPO	1.0 (0.6, 1.6)	0.9 (0.5, 1.6)	1.1 (0.6, 2.0)	0.9 (0.5, 1.7)
IL-1 β	1.0 (0.6, 1.6)	1.2 (0.7, 2.0)	1.4 (0.8, 2.5)	1.6 (0.9, 3.1)
IL-6	1.2 (0.7, 1.9)	1.6 (0.9, 2.9)	1.6 (0.9, 2.8)	2.0 (1.00, 3.9)
IL-6R	1.3 (0.8, 2.2)	0.9 (0.5, 1.6)	1.2 (0.7, 2.2)	0.8 (0.4, 1.5)
TNF- α	1.2 (0.7, 2.0)	1.3 (0.7, 2.2)	1.6 (0.9, 2.8)	1.8 (0.9, 3.3)
TNF-R1	1.4 (0.9, 2.4)	1.1 (0.6, 2.1)	2.0 (1.1, 3.6)	1.8 (0.9, 3.4)
TNF-R2	1.6 (0.99, 2.7)	1.4 (0.8, 2.5)	1.3 (0.7, 2.3)	2.0 (1.1, 3.7)
IL-8	1.0 (0.6, 1.6)	1.0 (0.5, 1.8)	1.8 (1.04, 3.2)	1.2 (0.6, 2.4)
MCP-1	1.1 (0.7, 1.8)	0.8 (0.4, 1.5)	1.2 (0.7, 2.2)	1.5 (0.8, 2.9)
MCP-4	1.0 (0.6, 1.6)	1.4 (0.8, 2.4)	0.7 (0.4, 1.2)	1.1 (0.6, 2.1)
MIP-1 β	1.6 (0.99, 2.7)	1.0 (0.6, 1.9)	1.4 (0.8, 2.5)	1.2 (0.7, 2.4)
RANTES	0.9 (0.5, 1.5)	1.0 (0.6, 1.9)	1.1 (0.6, 1.9)	1.1 (0.6, 2.3)
I-TAC	1.6 (0.9, 2.6)	1.6 (0.9, 2.8)	1.3 (0.7, 2.3)	1.4 (0.7, 2.6)
ICAM-1	1.5 (0.9, 2.5)	1.3 (0.7, 2.3)	1.4 (0.8, 2.5)	1.9 (1.03, 3.6)
ICAM-3	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)	1.3 (0.7, 2.3)	1.2 (0.6, 2.2)
VCAM-1	1.2 (0.7, 2.0)	1.0 (0.6, 1.8)	0.7 (0.4, 1.4)	1.1 (0.6, 2.0)
E-SEL	0.9 (0.6, 1.6)	0.9 (0.5, 1.6)	1.2 (0.7, 2.2)	1.6 (0.8, 2.9)
MMP-1	1.5 (0.9, 2.7)	1.0 (0.6, 1.8)	1.7 (0.9, 3.3)	1.1 (0.6, 2.1)
MMP-9	1.1 (0.7, 1.7)	1.2 (0.7, 2.3)	0.9 (0.5, 1.6)	1.5 (0.7, 2.9)
VEGF	0.9 (0.5, 1.5)	1.3 (0.8, 2.2)	1.0 (0.5, 1.7)	1.0 (0.5, 1.9)
VEGF-R1	1.1 (0.6, 1.7)	1.1 (0.6, 1.9)	0.8 (0.4, 1.4)	1.3 (0.7, 2.5)
VEGF-R2	0.9 (0.4, 1.2)	1.1 (0.6, 1.8)	1.1 (0.6, 2.0)	1.3 (0.7, 2.3)
IGFBP-1	1.1 (0.6, 1.7)	1.6 (0.9, 3.1)	1.2 (0.7, 2.1)	1.7 (0.8, 3.4)

Table 4

Odds ratio (and 95% confidence interval) of a concentration in the top quartile (for gestational age and day specimen was obtained) of the protein(s) listed on the left on one day only or on two or more days among children who had a PCO₂ in the highest quartile on 1 day only or on 2 or more days compared to that of children who did not have a PCO₂ in the lowest quartile on any of the first three days. The sample for these analyses consists of children who had proteins measured in blood collected on two separate days. The models are adjusted for gestational age (23–24, 25–26, 27 weeks) and birth weight Z-score (< −1, −1). Odds ratios significant at $p < .01$ are in bold

Proteins	PCO ₂ in highest quartile on 1 day		PCO ₂ in highest quartile on 2 days	
	high protn, 1 day	high protn, 2 days	high protn, 1 day	high protn, 2 days
CRP	1.3 (0.8, 2.3)	1.6 (0.9, 2.9)	1.4 (0.8, 2.4)	1.7 (0.9, 3.2)
SAA	1.2 (0.7, 1.9)	1.4 (0.7, 2.6)	1.0 (0.6, 1.7)	1.3 (0.7, 2.5)
MPO	1.3 (0.8, 2.2)	1.4 (0.8, 2.6)	1.1 (0.6, 1.9)	1.8 (0.99, 3.3)
IL-1 β	0.7 (0.4, 1.2)	1.0 (0.6, 1.8)	0.7 (0.4, 1.2)	1.5 (0.8, 2.7)
IL-6	1.2 (0.7, 2.0)	1.1 (0.6, 2.0)	1.4 (0.8, 2.4)	1.2 (0.6, 2.3)
IL-6R	0.8 (0.5, 1.4)	1.0 (0.6, 1.7)	1.0 (0.6, 1.8)	1.1 (0.6, 2.0)
TNF- α	0.7 (0.4, 1.1)	1.0 (0.5, 1.7)	1.0 (0.6, 1.8)	1.4 (0.8, 2.7)
TNF-R1	1.1 (0.7, 1.9)	1.4 (0.7, 2.5)	1.6 (0.9, 2.9)	2.5 (1.3, 4.7)
TNF-R2	1.3 (0.8, 2.2)	1.5 (0.8, 2.6)	1.4 (0.8, 2.4)	1.4 (0.8, 2.7)
IL-8	0.7 (0.4, 1.2)	1.9 (1.01, 3.6)	1.2 (0.7, 2.1)	2.6 (1.3, 5.0)
MCP-1	1.2 (0.7, 2.1)	1.6 (0.8, 2.9)	2.5 (1.4, 4.4)	3.3 (1.7, 6.5)
MCP-4	1.1 (0.6, 1.8)	0.9 (0.5, 1.7)	1.5 (0.9, 2.7)	1.7 (0.95, 3.2)
MIP-1 β	0.8 (0.5, 1.4)	0.9 (0.5, 1.6)	0.7 (0.4, 1.2)	0.8 (0.4, 1.5)
RANTES	0.8 (0.5, 1.3)	0.7 (0.4, 1.4)	0.8 (0.5, 1.4)	0.4 (0.2, 0.9)
I-TAC	1.0 (0.6, 1.7)	1.4 (0.8, 2.5)	0.8 (0.4, 1.4)	1.2 (0.7, 2.3)
ICAM-1	1.0 (0.6, 1.8)	1.4 (0.8, 2.5)	1.5 (0.8, 2.6)	1.8 (0.9, 3.3)
ICAM-3	1.1 (0.7, 2.0)	1.4 (0.8, 2.4)	1.3 (0.8, 2.4)	1.4 (0.8, 2.6)
VCAM-1	1.3 (0.7, 2.2)	1.1 (0.6, 2.0)	1.3 (0.7, 2.4)	1.4 (0.7, 2.5)
E-SEL	1.0 (0.6, 1.8)	1.4 (0.8, 2.4)	1.8 (1.00, 3.1)	1.7 (0.9, 3.1)
MMP-1	0.8 (0.5, 1.5)	1.1 (0.6, 2.0)	0.9 (0.5, 1.6)	0.6 (0.3, 1.2)
MMP-9	1.4 (0.9, 2.3)	1.0 (0.5, 1.9)	1.0 (0.6, 1.7)	1.3 (0.7, 2.4)
VEGF	0.8 (0.5, 1.4)	1.0 (0.6, 1.8)	1.1 (0.6, 1.9)	1.1 (0.6, 2.0)
VEGF-R1	1.1 (0.7, 1.9)	1.6 (0.9, 2.8)	1.5 (0.9, 2.8)	2.4 (1.3, 4.4)
VEGF-R2	1.1 (0.6, 1.9)	1.0 (0.6, 1.8)	1.2 (0.6, 2.1)	0.9 (0.5, 1.7)
IGFBP-1	0.7 (0.4, 1.2)	1.1 (0.6, 2.1)	1.1 (0.6, 1.8)	1.5 (0.8, 3.1)

Table 5

Odds ratio (and 95% confidence interval) of a concentration in the top quartile (for gestational age and day specimen was obtained) of the protein(s) listed on the left on one day only or on two or more days among children who had a pH in the lowest quartile on 1 day only or on 2 or more days compared to that of children who did not have a PCO₂ in the lowest quartile on any of the first three days. The sample for these analyses consists of children who had proteins measured in blood collected on two separate days. The models are adjusted for gestational age (23–24, 25–26, 27 weeks) and birth weight Z-score (< -1, -1). Odds ratios significant at $p < .01$ are in bold

Proteins	pH in lowest quartile on 1 day		pH in lowest quartile on 2 days	
	high protn, 1 day	high protn, 2 days	high protn, 1 day	high protn, 2 days
CRP	1.3 (0.8, 2.2)	1.1 (0.6, 2.0)	1.4 (0.8, 2.5)	1.9 (1.01, 3.5)
SAA	0.8 (0.5, 1.3)	0.9 (0.4, 1.5)	0.9 (0.5, 1.6)	1.6 (0.9, 3.1)
MPO	1.1 (0.6, 1.8)	1.2 (0.6, 2.1)	1.2 (0.7, 2.2)	2.0 (1.1, 3.7)
IL-1 β	1.0 (0.6, 1.6)	1.2 (0.7, 2.2)	1.0 (0.6, 1.9)	2.6 (1.4, 4.9)
IL-6	1.0 (0.6, 1.6)	0.8 (0.4, 1.6)	1.7 (0.9, 2.9)	2.1 (1.1, 3.9)
IL-6R	0.8 (0.4, 1.3)	1.0 (0.6, 1.7)	1.2 (0.7, 2.1)	1.1 (0.6, 2.1)
TNF- α	0.9 (0.6, 1.6)	1.2 (0.7, 2.2)	1.2 (0.7, 2.2)	2.8 (1.5, 5.2)
TNF-R1	1.3 (0.8, 2.2)	1.5 (0.8, 2.8)	2.1 (1.1, 3.8)	2.8 (1.4, 5.3)
TNF-R2	1.3 (0.8, 2.1)	1.1 (0.6, 2.1)	1.8 (0.99, 3.2)	2.5 (1.3, 4.6)
IL-8	1.0 (0.6, 1.7)	2.5 (1.3, 4.8)	1.7 (0.95, 3.0)	4.6 (2.3, 9.1)
MCP-1	1.7 (1.02, 2.8)	1.5 (0.8, 2.7)	1.9 (1.05, 3.4)	3.0 (1.6, 5.7)
MCP-4	1.1 (0.6, 1.8)	0.9 (0.5, 1.7)	1.3 (0.7, 2.3)	1.4 (0.8, 2.6)
MIP-1 β	1.0 (0.6, 1.6)	0.8 (0.4, 1.5)	1.1 (0.6, 1.9)	1.2 (0.6, 2.3)
RANTES	0.9 (0.6, 1.5)	0.7 (0.4, 1.3)	0.8 (0.5, 1.4)	0.6 (0.3, 1.2)
I-TAC	0.8 (0.5, 1.4)	1.0 (0.6, 1.9)	1.0 (0.5, 1.7)	1.3 (0.7, 2.4)
ICAM-1	1.3 (0.8, 2.1)	1.3 (0.7, 2.4)	1.6 (0.9, 2.9)	2.3 (1.2, 4.2)
ICAM-3	1.0 (0.6, 1.7)	1.2 (0.7, 2.1)	1.4 (0.8, 2.4)	1.7 (0.9, 3.2)
VCAM-1	1.1 (0.6, 1.8)	1.2 (0.7, 2.1)	1.1 (0.6, 1.9)	1.2 (0.6, 2.1)
E-SEL	1.4 (0.8, 2.3)	1.6 (0.9, 2.8)	1.9 (1.03, 3.3)	2.4 (1.3, 4.4)
MMP-1	0.9 (0.5, 1.5)	0.8 (0.5, 1.4)	0.7 (0.4, 1.4)	0.7 (0.4, 1.3)
MMP-9	1.1 (0.7, 1.9)	1.0 (0.5, 1.8)	0.9 (0.5, 1.6)	1.3 (0.6, 2.4)
VEGF	1.2 (0.7, 2.0)	1.2 (0.7, 2.0)	1.7 (0.96, 3.0)	1.3 (0.7, 2.4)
VEGF-R1	0.8 (0.5, 1.4)	1.4 (0.8, 2.4)	1.3 (0.7, 2.4)	1.8 (0.98, 3.5)
VEGF-R2	1.0 (0.6, 1.7)	0.9 (0.5, 1.6)	1.3 (0.7, 2.3)	1.2 (0.7, 2.2)
IGFBP-1	1.0 (0.6, 1.7)	1.1 (0.6, 2.2)	1.1 (0.6, 1.9)	1.5 (0.7, 3.0)