Acid-Base Parameters for Predicting Magnetic Resonance Imaging Measures of Neurologic Outcome after Perinatal Hypoxia-Ischemia: Is the Strong Ion Gap Superior to Base Excess and Lactate?

Christian Mann, M.D.[1] Beatrice Latal, M.D.[2] Beth Padden, M.D.[3] Ianina Scheer, M.D.[4] Georg Goebel, Ph.D.[5] Vera Bernet, M.D.[6]

[1] Neonatal and Pediatric Intensive Care Unit, Graubuenden Cantonal Hospital, Chur, and College for Intensive Care, Emergency and Anesthesia Nursing, University Children's Hospital Zurich, Zurich, Switzerland
[2] Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland
[3] Rehabilitation Center, University Children's Hospital Zurich, Zurich, Switzerland
[4] Department of Pediatric Radiology, University Children's Hospital Zurich, Zurich, Switzerland
[5] Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria
[6] Department of Neonatology, University Children's Hospital Zurich, Zurich, Switzerland

Address for correspondence and reprint requests Christian Mann, M.D., Neonatal and Pediatric Intensive Care Unit, Graubuenden Cantonal Hospital, Chur, CH-7000 Switzerland (e-mail: christian.mann@ksgr.ch).

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Abstract

We conducted this study to compare the strong ion gap (SIG) with base excess (BE) and lactate for predicting neurologic outcome measured by magnetic resonance imaging (MRI) in newborns with hypoxic-ischemic encephalopathy (HIE). In a retrospective cohort of 39 newborns with HIE treated with whole-body surface cooling ($n = 17$) and no cooling ($n = 22$), we measured blood SIG, BE, and lactate at 4, 24, and 48 hours after birth, and determined cerebral injury severity by T1-, T2-, and diffusion-weighted MRI scores at age 5 days. Lower SIG levels correlated with better neurologic outcome. The highest correlation coefficient (0.63) was in the "no cooling" subcohort between diffusion-weighted scores and SIG levels at 24 hours; the latter also had the highest area under the receiver operating characteristic curve (AUC), 0.90, with positive and negative predictive values of 84 and 90%. SIG outperformed lactate in the "no cooling" subcohort, and vice-versa in the "cooling" subcohort. All BE AUCs were <0.6. Overall, the SIG is similar to lactate as a prognostic parameter. BE levels at 4, 24, and 48 hours after birth do not predict neurologic outcome. While not displacing lactate the SIG is an additional prognostic parameter for newborns in the first 2 days after hypoxia-ischemia.

Keywords
- acidosis
- asphyxia neonatorum
- cerebral palsy
- hypoxia-ischemia
- magnetic resonance imaging
- strong ion gap

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Perinatal hypoxia-ischemia can be associated with major adverse outcome. Despite the increasing use of neuroimaging for predicting outcome,[1–3] guidelines continue to recommend base excess (BE) and pH as the primary risk indicators for sequelae following a hypoxic-ischemic event.[4–8] The main drawback of BE is that it represents a composite parameter of all metabolic components affecting acid-base balance.[9,10] In contrast, the strong ion gap (SIG), as proposed by Kellum et al,[11] specifically assesses unmeasured ions. It comprises all the anions of organic acids, strong or weak, not measured by standard methods,[12] and can thus be used to calculate the unmeasured fraction of acids produced by compromised tissue.[12–14] It has been linked to amino acids and organic acids, Krebs cycle intermediates, citrate and isocitrate, acetate, alfa-ketoglutarate, malate, fumarate, succinate, and sulfates.[9,14–17] Lactate has ceased being regarded as an unmeasured ion as it is readily measured in most intensive care units (ICUs).

The SIG has become an important mortality predictor in the critically ill.[18–21] In pediatric ICUs it predicts mortality better than BE, the anion gap, and/or lactate.[12,22,23] But we know little about its ability to predict neurologic morbidity. In particular, there have been no studies on the relationship between the SIG and neurologic outcome in neonates with perinatal hypoxia-ischemia.[21]

Importantly, it has been pointed out that the type of acidosis correlates strongly with mortality in ICU patients.[24] For example, adults in metabolic acidosis with increased SIG levels have a poorer prognosis than those in acidosis due to hyperchloremia, in which pH and BE are decreased but the SIG remains unchanged.[11,17,25] This study was therefore designed to determine the reliability of SIG compared with BE or lactate in predicting cerebral magnetic resonance imaging (MRI) measures of outcome in the specific setting of newborns after hypoxia-ischemia.

Methods

We conducted a retrospective cohort study of 39 consecutive newborns after 36 weeks' gestation diagnosed with moderate or severe hypoxic-ischemic encephalopathy (HIE) (Sarnat stages II or III[26]) hospitalized at our institution between June 2006 and January 2009. Birth had been complicated by maternal trauma or cardiac arrest, uterine rupture, placental abruption, umbilical cord prolapse, and/or variable or late decelerations. We excluded patients with an additional diagnosis of sepsis. Patient characteristics are presented in ►**Table 1**.

Therapeutic hypothermia was expected to significantly impact acid-base balance. The cohort was therefore split into two subcohorts, one with whole-body surface cooling ("cooling") (17/39) and the other without cooling ("no cooling") (22/39).

Whole-body cooling was administered according to Swiss hypothermia guidelines, adapted from Shankaran.[27] To qualify for cooling, three treatment criteria had to be met: Umbilical cord pH or first pH in any blood sample within 60 minutes of birth had to be $\leq$7.0 or BE ≥ -12 mmol/L. Second, there must have been evidence of a perinatal sentinel event together with 5 and 10 minute Apgar scores $\leq$6 or a

Table 1 Patient Characteristics

	N	Total	No Cooling	Cooling	*P*
		n = 39	*n* = 22	*n* = 17	
Male (*n* [%])	39	21 (54)	15 (75)	6 (35)	0.06
GA, median (wk [range])	39	39.9 (36.6–42.0)	39.8 (37.7–41.6)	40.1 (36.6–42.0)	0.75
Birth weight, median (g [range])	39	3470 (2170–5000)	3480 (2210–5000)	3400 (2170–4500)	0.77
Head circumference, median (cm [range])	37	35.0 (32.0–39.0)	35.0 (32.0–39.0)	34.6 (32.5–38.0)	0.44
Deaths (*n* [%])	39	8 (21)	2 (9)	6 (35)	0.06
Age at imaging, median (d [range])	39	5 (2–11)	5 (2–11)	5 (2–11)	0.92
Length of hospital stay, median (d [range])	39	17.0 (2–60)	17.5 (5–60)	16.0 (2–27)	0.12
Mechanical ventilation or resuscitation at 10 minute (yes [%])		24 (62)	9 (41)	15 (88)	0.003
10 minute Apgar, median (range)	36	6 (1–6)	5 (1–10)	4 (1–10)	0.01
10 minute Apgar $<$6 (*n* [%])	36	15 (38)	6 (27)	9 (53)	0.18
Umbilical cord pH, median (range)	33	6.90 (6.64–7.32)	7.14 (6.72–7.32)	6.80 (6.64–7.32)	$<$0.001
HIE, Sarnat Stage (*n* [%])					
II	39	32 (82)	20 (91)	12 (71)	
III		7 (18)	2 (9)	5 (29)	

cm, centimeter; d, day; g, gram; GA, gestational age; HIE, hypoxic-ischemic encephalopathy; wk, week.

perinatal sentinel event together with continued need for bag and mask ventilation at 10 minutes after birth. Third, moderate to severe HIE had to be present. Passive cooling was used to a target rectal temperature of 33.0 ± 0.5°C. If this temperature range was not achieved within 1 to 2 hours, cooling packs (surgical gloves filled with ice-cold water) were applied. Cooled neonates were sedated with morphine 10 to 20 µg/kg/h, with additional sedation as appropriate for mechanical ventilation or seizure treatment.

Blood gases, sodium, potassium, ionized calcium, chloride, and lactate were analyzed as per clinical routine at three time points (TP) during the 2-day monitoring period: 3.5 ± 1.4 hours, 24 hours, and 48 hours after hypoxia-ischemia. These TP are rounded to 4, 24, and 48 hours (TP4, TP24, and TP48) in the following text and tables. Our ICU had received 28/39 patients by TP4 and 39/39 by TP24 from the delivery rooms of our university clinic or from transferring hospitals. Blood samples were drawn from arterial lines or obtained by heel prick. Data were retrieved from patient charts, including referral letters and diagnostic reports.

Age-appropriate normal values were used for albumin (3.4 g/dL), magnesium (0.95 mmol/L), and phosphate (7.1 mg/dL [2.9 mmol/L]).

We used an ABL 735 blood gas analyzer (Radiometer, Copenhagen, Denmark) to measure blood pH, PaO_2, and $PaCO_2$ (standard electrodes), and sodium, potassium, ionized calcium, and chloride (ion-sensitive electrodes).

The SIG was calculated using the SIG calculator developed by Kellum et al,[11,28,29] as follows:

$$\begin{aligned}\mathrm{SIG} = {} & \{[\mathrm{Na^+}] + [\mathrm{K^+}] + [\mathrm{Mg^{2+}}] + [\mathrm{Ca^{2+}}] - [\mathrm{Cl^-}] - [\mathrm{lactate^-}]\} \\ & - \{(1000 \times 2.46 \times 10^{-11} \times (\mathrm{pCO_2}/10^{-\mathrm{pH}}) + [\mathrm{albumin^-}](\mathrm{g/dL}) \\ & \times (0.123 \times \mathrm{pH} - 0.631) + [\mathrm{phosphate^-}](\mathrm{mg/dL}) \times (0.309 \times \mathrm{pH} - 0.469)\}\end{aligned}$$

Early postnatal brain MRI was used as the reference investigation for neurologic prognosis. It was performed in all 39 patients using a 1.5 and 3T scanner (GE Healthcare, Milwaukee, Wisconsin). Conventional noncontrast sequences were obtained with T1-weighted (repetition time/echo time/excitations 700/21/1) and fast T2-weighted (5100/100/2) spin echo sequences. Slice thickness was 3 mm with a 0.3-mm gap. Additional T2-weighted coronal and sagittal plane imaging was done (2.5/0.2 mm). A single-shot echo-planar diffusion-weighted imaging (DWI) sequence was acquired in the axial plane with 3 mm slice thickness, no gap (repetition time 10,000 ms, echo time 98 ms, b values of 0 and 1000 seconds/mm^2 in 6 or 21 directions).

In keeping with Zurich University Hospital guidelines, MRI was performed between days 2 and 5 of life where possible.[1] However, transport to the radiology department had to be postponed in some medically unstable patients. Overall, imaging was performed at a median age of 5 days (range, 2 to 11 days). During imaging, patients were sedated with chloral hydrate (50 mg/kg, repeated if required) or with morphine in case of mechanical ventilation.

MR images were scored by a pediatric neuroradiologist (I. S.) blinded to the patient data and to the clinical course during the patients' hospitalization. Scans were scored for injury pattern and severity according to Barkovich et al.[2] We used T1-, T2-, and DWI to calculate basal ganglia, watershed, overall, and summary scores. Neurologic imaging outcome was defined as poor when the injury severity score was in the upper quartile of scores determined from T1-, T2-, or diffusion-weighted images and as good when the injury severity score was in the lower three quartiles.

Statistics

Groups were compared using the Mann-Whitney U-test for continuous variables and the chi-squared or Fisher's exact test for categorical variables. Correlations between biochemical parameters (SIG, BE, lactate) and outcome (MRI summary scores and mortality) were described using Spearman's rank correlation coefficient. Power in discriminating between poor and good MRI outcome was analyzed using receiver operating characteristic (ROC) curves and area under the curve (AUC) statistics (C-statistics) with 95% confidence limits. Thresholds for determining sensitivity and specificity were derived from the ROC results to find the best possible values by balancing sensitivity and specificity against each other and to avoid values below 50%. The statistical analysis was performed blind to patients' clinical course. SPSS 18.0 (IBM SPSS 18, IBM Corporation, Armonk, NY) and a significance level of $p<0.05$ were used for all analyses.

Results

Acid-base parameters at TP4, TP24, and TP48 hours after hypoxia-ischemia are presented in ►**Table 2**.

Calculation of Spearman's rank correlation coefficients revealed correlations with MRI abnormalities in the "no cooling" subcohort for SIG and BE at TP4 and for SIG, BE, and lactate at TP24. In the "cooling subcohort," correlations with MRI abnormalities were found at TP48 for SIG and BE. No correlation was found between SIG and mortality (►**Table 3**).

Areas under the ROC curves were as follows: In the "no cooling" subcohort, SIG at TP24 had the largest AUC, followed by SIG at TP4, lactate at TP24, and lactate at TP48. In the "cooling" subcohort, lactate AUCs at TP4 and TP48 were greater than the SIG AUC at TP48 (►**Table 4**). ►**Table 4** omits parameters with an AUC <0.6 as this was considered the threshold for practical clinical relevance. BE AUCs at all TPs were <0.60 in both subcohorts.

The highest positive predictive value in the "no cooling" subcohort was for SIG at TP24 (84%), followed by SIG at TP4, lactate at TP48, and lactate at TP24. The highest positive predictive value in the "cooling" subcohort was for lactate at TP4 (84%), followed by lactate at TP48, and SIG at TP48 (►**Table 4**). ►**Table 4** also presents data for sensitivity, specificity, and positive and negative predictive values.

Discussion

This study assessed the potential of the SIG to predict neurologic outcome in newborns after perinatal hypoxia-ischemia in comparison to conventional acid-base parameters. SIG and lactate were similar in prognostic potential,

Table 2 Acid-Base Parameters at TP4, TP24, and TP48 Hours after Hypoxia-Ischemia in the "No Cooling" and "Cooling" Subcohorts

	N	No Cooling		*P*	Cooling		*P*
		MRI Good	MRI Poor		MRI Good	MRI Poor	
BE TP4	28	−11.2 (−20.2–−3.2)	−9.9 (−14.3–−7.1)	0.93	−12.1 (−18.3–−2.4)	−14.5 (−22.4–−8.5)	0.79
BE TP24	33	−4.4 (−6.8–2.8)	−8.4 (−12.4–−4.1)	0.04	−7.7 (−15.1–−2.2)	−8.2 (−12.5–−5.0)	0.96
BE TP48	38	−2.5 (−6.3–0.1)	−5.9 (−11.1–0.2)	0.03	−7.0 (−11.1–−0.8)	−9.2 (−17.3–−7.5)	0.31
Lactate TP4	28	9.5 (2.0–14.2)	7.4 (4.2–12.8)	0.81	8.9 (1.7–12.2)	16.5 (6.2–18.0)	0.56
Lactate TP24	33	2.5 (1.6–6.9)	4.8 (2.7–7.4)	0.04	4.0 (1.2–7.2)	3.6 (2.3–9.1)	0.89
Lactate TP48	38	1.2 (1.0–3.7)	2.9 (1.2–4.6)	0.04	2.2 (0.7–6.6)	3.4 (1.4–5.7)	0.74
SIG TP4	28	−2.2 (−4.1–7.2)	5.3 (1.4–8.7)	0.05	0.9 (−4.5–13.0)	1.05 (−2.5–5.6)	0.87
SIG TP24	33	−1.5 (−13.6–2.0)	2.2 (−1.3–6.6)	0.01	−2.6 (−7.0–2.1)	−1.4 (−5.8–1.1)	0.42
SIG TP48	38	−1.1 (−9.7–5.6)	0.6 (−5.7–5.3)	0.60	−2.9 (−6.7–2.8)	−1.6 (−4.1–18.3)	0.27

Note: MRI good, injury severity score in three lower quartiles; MRI poor, injury severity score in upper quartile of T1-, T2-, or diffusion-weighted imaging scores.
BE, base excess; MRI, magnetic resonance imaging; SIG, strong ion gap; TP, time points.

assessed by AUCs and positive and negative predictive values. The two parameters differed only slightly insofar as SIG was better in the "no cooling" subcohort while lactate had a higher prognostic potential in the "cooling" subcohort. SIG and lactate were both superior to BE in predicting neurologic outcome. BE failed to achieve an AUC above the clinically relevant level (0.6) and thus had no prognostic potential for neurologic outcome. This does not contradict former studies where BE had prognostic impact when assessed in umbilical cord blood or in blood drawn in the delivery room.

Normal SIG values are population-specific: In healthy adults the normal value was 1.2 mmol/L, as against 5 mmol/L in adult ICU patients.[16,30,31] Normal levels have not yet been established in neonates. In our study, median SIGs of patients with a good prognosis were all below normal for a healthy adult population 4 hours after hypoxia-ischemia. During the observation period there was a downward trend in median SIG levels in all patient groups. These data might point to a counter-regulatory process started rapidly after the hypoxic event to achieve successful recovery.[32]

Correlation between the severity of acidosis detected after complicated delivery and short- and long-term outcome is well documented.[4,5,7,8,33–38] In a study of 297 term newborns an arterial BE of −14.0 mmol/L taken at between 30 and 45 minutes of life predicted moderate or severe encephalopathy with a sensitivity of 81% and specificity of 76%.[39] In a later study cord blood pH in 512 acidotic neonates correlated better with clinical asphyxia scores than cord blood BE.[40]

Table 3 Spearman's Correlation Coefficients for Correlation between Acid-Base Parameters at TP4, TP24, and TP48 Hours after Hypoxia-Ischemia and Summary T1-, T2-, and DWI Injury Scores in the "No Cooling" and "Cooling" Subcohorts

	"No Cooling" MRI Score				"Cooling" MRI Score		
	T1	T2	DWI		T1	T2	DWI
BE TP4 ($n = 12$)	−0.18	−0.08	−0.55[a]	BE TP4 ($n = 16$)	0.39	0.03	−0.26
BE TP24 ($n = 16$)	−0.52[a]	−0.47	−0.63[b]	BE TP24 ($n = 17$)	−0.17	−0.18	−0.36
BE TP48 ($n = 21$)	−0.35	−0.06	−0.24	BE TP48 ($n = 17$)	−0.13	−0.41	−0.54[a]
Lactate TP4 ($n = 12$)	0.29	0.09	0.04	Lactate TP4 ($n = 16$)	−0.48	−0.06	0.06
Lactate TP24 ($n = 16$)	0.63[b]	0.48	0.64[b]	Lactate TP24 ($n = 17$)	−0.16	0.33	0.11
Lactate TP48 ($n = 21$)	0.37	0.38	0.40	Lactate TP48 ($n = 17$)	−0.23	0.20	0.17
SIG TP4 ($n = 12$)	0.27	0.51[a]	0.50[a]	SIG TP4 ($n = 16$)	−0.34	0.18	0.20
SIG TP24 ($n = 16$)	0.49	0.58[a]	0.63[b]	SIG TP24 ($n = 17$)	−0.24	−0.25	−0.02
SIG TP48 ($n = 21$)	−0.21	0.10	−0.03	SIG TP48 ($n = 17$)	−0.09	0.16	0.50[a]

[a] $p < 0.05$.
[b] $p < 0.01$.
BE, base excess; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; SIG, strong ion gap; TP, time point.

Table 4 Acid-Base Parameters with AUCs >0.6 Evidencing Prognostic Power in Predicting Cerebral Injury as Measured with MRI after Hypoxia-Ischemia

No Cooling	*N*	AUC (CI−/CI+)	*P*	SE/SP (%)	PPV/NPV (%)	Threshold
SIG TP24	16	0.90 (0.7–1.0)	<0.01	83/90	84/90	0.9
SIG TP4	12	0.88 (0.7–1.0)	0.042	100/75	71/100	−0.3
Lactate TP24	16	0.81 (0.6–1.0)	0.043	100/50	55/100	2.5
Lactate TP48	21	0.77 (0.6–1.0)	0.045	75/85	75/85	2.5
Cooling						
Lactate TP4	16	0.78 (0.5–1.0)	0.10	100/88	84/100	2.6
Lactate TP48	17	0.74 (0.5–1.0)	0.13	80/58	54/83	2.6
SIG TP48	17	0.68 (0.4–1.0)	0.27	100/33	48/100	−4.2

Note: Parameters with AUC <0.6 not listed.
AUC, area under curve; CI, confidence interval; MRI, magnetic resonance imaging; PPV/NPV, positive predictive value/negative predictive value; SE/SP, sensitivity/specificity; SIG, strong ion gap; TP4, TP24, TP48, time points 4, 24, and 48 hours after hypoxia-ischemia.

Additionally, in 85 infants treated with cooling for HIE, Apgar scores proved a better predictor of mortality than either pH or BE from the first blood gas analysis after birth.[41] Another candidate parameter, lactate was found to be more sensitive and a better predictor of HIE than either pH or BE in a study of 61 neonates after intrapartum asphyxia,[42] despite earlier conflicting results on lactate as a prognostic parameter.[37,43] More recently, a study in 50 neonates found no correlation between lactate levels in the first 30 minutes of life and the degree of HIE, but instead a correlation between time to normalization of lactate levels and grade of EEG abnormalities was detected.[44] The results of our study add to these data by demonstrating that the level of tissue acidosis as assessed by lactate and the SIG on day 1 and 2 correlates with brain injury severity on day 5.

It has been reported that 5 to 20% of neonates develop encephalopathy after moderate to severe intrapartum hypoxia-ischemia but only about 1% proceeds to cerebral palsy. This highlights the need for reliable outcome predictors.[7,36,45–47] As single parameters correlate poorly with outcome a combination of cardiotocography, Apgar scores, acid-base variables, neurologic examination, and ambulatory electroencephalography has been proposed for improving prognostication in the first few days after hypoxia-ischemia.[48] In this respect, our study describes a new acid-base variable which could serve as an additional prognostic parameter.

We used the severity of cerebral injury on MRI as the reference indicator of neurologic outcome. The degree of cerebral injury and in particular the structure involved (basal ganglia vs. white matter) strongly predict early infancy and preschool neurodevelopmental outcome in infants with hypoxia-ischemia.[2,3,49] For example, neonatal watershed brain injury on MRI correlates with verbal intelligence quotient at 4 years.[50]

Limitations

The use of MRI for case definition of hypoxic-ischemic injury on day 5 might be limited due to nonvisualization of hypoxic-ischemic injury with conventional T1- and T2-weighted sequences during the first few days after the event and, on the other hand, due to early pseudonormalization in DWI.

In this study we investigated the correlation between whole-body acid-base status and the degree of brain injury. The SIG is not representative of brain tissue metabolism only; it is the sum of unmeasured ions from all metabolically active cells in the entire body. Brain tissue in the newborn represents 10% of total body weight and under physiologic conditions 10% of cardiac output is directed to the brain. The brain accounts for 20% of whole-body O_2 consumption. It seems justified to assume that the proportional influence of brain tissue on plasma acid-base parameters corresponds to these percentages. Hence in assessing the ability of the SIG to predict neurologic outcome we must allow for the fact that only a fraction of the tissue acids reflected in the SIG originates in the brain.

The SIG has been criticized as being too complicated to assess in the clinical setting. However, rapid calculators have been published.[29,51–53] The SIG might perform better if not only sodium, potassium, ionized calcium, and lactate but also albumin, magnesium, and phosphorus were available for its calculation. We do not think this would make a major difference. First, we excluded patients with albumin-reducing conditions (e.g., sepsis, inborn errors of metabolism), and study patients received only a limited volume of albumin-diluting infusions during the observation period. Ionized magnesium concentrations are of minor influence on acid-base status and are often omitted in calculations.[54] Second, we wanted to perform the study under routine ICU conditions where serial albumin, magnesium, and phosphorus determination is not immediately available.

Conclusion

The SIG and lactate are similar in prognostic potential for predicting neurologic outcome assessed by MRI after birth complicated by hypoxia-ischemia. Our study confirmed the role of lactate as a prognostic parameter and presents the SIG

as a potentially useful additional acid-base parameter for predicting outcome in newborns after hypoxia-ischemia.

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