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Mechanisms for Brain-Damaging Acute Birth Asphyxia Associated with Normal or Near-Normal Umbilical Acid-Base balance

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Abstract:

It is a common misconception to believe that brain-damaging birth asphyxia is consistently associated with an umbilical cord arterial pH of less than 7.00 at the time of birth. Approximately 40% of infants with brain damage attributable to birth asphyxia have an umbilical artery (UA) pH of 7.00 or greater. This paper describes the various explanations for observing brain-damaging acute birth asphyxia associated with normal or near-normal UA pH values.

What is known: Approximately 40% of infants with brain damage attributable to birth asphyxia have a UA pH of 7.00 or greater.

What this study adds: Various explanations are presented to explain the occurrence of brain-damaging asphyxia with normal or near-normal acid-base values. This phenomenon has not been previously described.

Key messages:

- Approximately 40% of infants with brain-damaging birth asphyxia have an umbilical artery cord pH of 7.00 or greater, with most having of these having a pH greater than 7.20.
- Technical explanations for this phenomenon include sampling only the umbilical vein and sampling blood with air bubbles.
- The two most common pathophysiologic mechanisms to explain the lack of acidemia are complete occlusion of the umbilical cord and circulatory collapse.
- Other brain-damaging processes without fetal acidemia include birth trauma, synergism, intra-uterine resuscitation, and post-asphyxial hypoxia.

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Introduction:

It is a common misconception to believe that brain-damaging birth asphyxia is consistently associated with an umbilical cord arterial (UA) pH of less than 7.00 at the time of birth. (1,2) In reality, many infants with brain damage attributable to birth asphyxia have a UA pH of 7.00 or more at birth. (3-7) Most infants have a *normal* UA pH of 7.20 or more. (6, 7) This paper describes the various explanations for observing brain-damaging acute birth asphyxia associated with normal or near-normal UA pH values.

Normal umbilical cord blood gas values are shown in Table 1 and derived from Yeomans and colleagues' data. (8, 9) All blood gases are be expressed as: pH / pCO_2 (mmHg) / pO_2 (mmHg) / base excess (mmol/L). This paper is not intended to serve as an instructional manual for umbilical cord gas interpretation. The reader is referred to the Pomerance's authoritative text *Interpreting Umbilical Cord Blood Gases*. (9)

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Technical considerations:

Occasionally umbilical cord blood gas analysis will not identify fetal acidemia for technical, not physiologic, reasons. The most common of these technical sources of errors are 1) failure to sample the umbilical artery and 2) air bubble(s) in the sample.

Failure to sample the umbilical artery:

The pH of the umbilical UV is always greater than that of the UA. Under normal circumstances, the 95th percentile range of difference between the UV and UA pH is between 0.04 and 0.10 pH units. (9) One might be tempted to analyze blood from the UV, then extrapolate those values to estimate the acid-base values in the UA. (10) However, sometimes, there may be a vast discrepancy between the pH of the UV and the UA, in which case such extrapolation would produce errant results.

The most common cause of a wide pH difference between the UV and UA is partial umbilical cord occlusion (11), where the thin-walled UV becomes occluded while the thick-walled UA remains patent and free-flowing. As the fetal tissues become progressively more acidotic, the UA pH falls. However, the blood flow in the UV had already ceased at the time of the occlusion, and the UV pH will not fall after that time of occlusion. The UV pH analysis is being performed on blood that entered the cord at the time of the occlusion when the fetus had not yet become acidemic and is not representative of fetal blood or tissues from the time of birth when the infant was severely acidemic. In these cases, it is not uncommon to observe a normal UV pH associated with a UA pH of less than 7.00. (9) If only the UV is sampled, one would not be aware of the severe fetal acidemia.

Theoretically, if only one sample is analyzed, the sample may be from either the UV or UA. However, because it is technically easier to obtain blood from the relatively large UV than from the smaller UA if only one sample is obtained, it is usually from the UV. (9,10) And because of the possibility of a wide disparity in pH values in partial umbilical cord occlusion, a UV blood gas cannot be used to extrapolate the blood gas values of the UA. Because of this, it has been recommended that both UV and UA blood samples be analyzed and compared. (12,13,14)

Even when two samples are analyzed, sometimes they are drawn from the same blood vessel. (10) When this happens, the samples are usually from the umbilical vein because of its ease of sampling. If the pH difference is less than 0.02 (10, 15) or 0.04 (9), the clinician should compare the other components of the blood gases. The samples are likely from the same vessel, most likely the umbilical vein, if they are very similar. If the UV is sampled twice, there is no reliable way to estimate the UA blood gas values. For example, if the UV showed 7.23/45/38/-12 and the UA was reported as 7.22/46/40/-12, then it is likely that both samples are from the same vessel because the pH difference is so small with the pCO_2, pO_2, and base excess values also being very similar. In this example, we can conclude that the UV pH was 7.22 or 7.23, and the UA values are unknown.

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Air Bubbles:

Air bubbles in the sample will alter the blood gas analysis results. An air bubble will cause an elevation of the pO_2, with a decrease in the pCO_2 and a corresponding rise in the pH. (9) If a baby's true UA pH is less than 7.00, an air bubble may demonstrate an elevated pO_2, a decrease in the pCO_2, and a normal or near-normal pH. Of note, an air bubble does not affect the determination of the base excess. (9) Thus, a UA blood gas showing 7.41/15/95/-16 is most consistent with an air bubble (high pH/low pCO_2/high pO_2) in the presence of a severe fetal metabolic acidemia (very negative base excess).

Pathophysiologic mechanisms:

Complete occlusion of umbilical cord blood flow

With complete umbilical cord occlusion, blood flow stops in both the UV and UA, and acid-base analysis will yield results representing the blood in the cord at the occlusion. Findings often do not represent the fetal acid-base status at birth. If the fetus has a normal acid-base status at an acute cessation of cord blood flow, the UV and UA blood gases will demonstrate normal values. But a simultaneous arterial blood gas analysis from the baby, not the umbilical cord, might demonstrate severe fetal acidemia at the time of birth. Common examples of this phenomenon include umbilical cord prolapse, shoulder dystocia, and breech delivery with an entrapped head. (16)

Circulatory collapse, impaired tissue perfusion, and the reperfusion acidemia

Anaerobic metabolism results in the production of lactic acid, primarily in the body's muscles. As blood perfuses the tissues, the lactic acid enters the bloodstream resulting in metabolic acidemia. However, if there is complete or near-complete circulatory collapse, from whatever cause, there will be inadequate perfusion of the muscles, and lactic acid may not enter the fetal circulation. Additionally, circulatory collapse results in a cessation of blood flowing from the fetus into the umbilical arteries, and whatever acid that may have entered the fetal bloodstream from the tissues are not pumped into the umbilical cord. After resuscitation, blood begins to reperfuse the tissues, lactic acid enters the circulation, and a corresponding fall in the blood pH is termed a "reperfusion acidemia." Typical cord gases might show UV 7.31/42/44/-5 and UA 7.26/45/22/-8, with an arterial blood gas at 30 minutes of age showing 6.99/52/75/-18. Common causes of this phenomenon include massive hemorrhage with hypovolemia and severe fetal bradycardia or asystole. (9,16,17) These infants are usually extremely depressed at birth, with a one-minute Apgar score of 0 or 1 indicating impaired circulation.

Asphyxia with intrauterine resuscitation and recovery

An infant may suffer severe asphyxia during labor, followed by intrauterine resuscitation. (18) The infant may then be born with a normal or near-normal acid-base status, albeit with a recent brain injury. Examples include maternal hypotension, uterine tachysystole, and umbilical cord compression.

"Maternal hypotension may be caused by the administration of conduction anesthesia or maternal supine position in labor and can result in significant fetal hypoxia and ischemia. The hypotension can be corrected with intravenous infusions and changing the maternal position. Similarly, uterine hypertonicity may result in decreased or absent maternal-fetal oxygen exchange and severe fetal hypoxia."

Maternal hypotension may be caused by the administration of conduction anesthesia or maternal supine position in labor and can result in significant fetal hypoxia and ischemia. The hypotension can be corrected with intravenous infusions and changing the maternal position. Similarly, uterine hypertonicity may result in decreased or absent maternal-fetal oxygen exchange and severe fetal hypoxia. This can be relieved with changes in maternal position, administration of supplemental oxygen to the mother, decreasing or stopping oxytocin administration, and the use of tocolysis. (18) Finally, umbilical cord occlusion can lead to fetal hypoxia and asphyxia. Intrauterine resuscitation may include changing the maternal position or amnioinfusion. In each of these examples, the infant may experience brain-damaging asphyxia during the labor but be born following intrauterine resuscitation and with a normal or nearly-normal UA acid-base status.

Birth trauma and head compression

Infants can develop traumatic brain damage following any difficult delivery. Volpe states, "potential overlap between mechanical trauma and hypoxic-ischemic cerebral injury is important to recognize because perinatal mechanical insults may also result in hypoxic-ischemic cerebral injury, perhaps secondary to disturbances of disturbances of placental or cerebral blood flow." (19) The damages are usually detected on neuro-imaging with a cerebral contusion, intracranial hemorrhages, skull fractures, and scalp hemorrhages. While the brains of these traumatized infants may produce a modest amount of metabolic acid, if the placenta is functioning adequately and umbilical cord blood flow is maintained, acid does not accumulate in the fetal circulation.

Prolonged or excessive pressure on the fetal head has been associated with brain ischemia. (19,20) Common causes of this phenomenon include cephalopelvic disproportion, prolonged labor, uterine tachysystole (hyperstimulation), head presentation anomalies, and cranial compression from vacuums and/or forceps. The external pressure on the infant skull results in decreased cerebral perfusion. There may also be a decrease in venous drainage, contributing to further cerebral ischemia. Additionally, compressions of the fetal skull can cause intracranial hemorrhage that results in further brain hypoxia and ischemia. And as with other forms of traumatic brain injury, any acid produced by the fetal brain can be cleared if the placenta and cord are functioning adequately, explaining why these infants are commonly born with normal acid-base status.

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Post-natal hypoxia

Infants with mild or moderate asphyxia may be born with a normal acid-base status but develop brain-damaging complications of the asphyxiation after birth. Potential complications of asphyxia commonly causing brain damage include necrotizing enterocolitis, (21) meconium aspiration syndrome, (22) tension pneumothorax, and persistent pulmonary hypertension (PPHN) (23). The most common cause of PPHN is birth asphyxia. (24) Heritage reviewed 71 cases of PPHN and found that 36 (51%) were due to birth asphyxia. (25) PPHN can cause brain damage due to relentless hypoxia. (26,27)

One treatment of PPHN is the use of hyperventilation with associated hypocarbia. However, this therapy exposes the infant to the additional risk of cerebral ischemia caused by hypocarbia. (28,29) Cerebral blood flow in the newborn depends on the infant's pCO_2. Studies in lambs demonstrated abrupt decreases in cerebral blood flow almost immediately upon the onset of hypocarbia. (30) Every decrease of pCO_2 of 1 mmHg caused an approximate 3% decrease in cerebral blood flow – an effect that could exacerbate the cerebral ischemia of birth asphyxia. The decreased cerebral blood flow associated with hypocarbia became less prominent over time (30); however, after the hypocarbia was terminated, there was a sudden increase in cerebral blood flow to greater than baseline levels. If this occurs in the human newborn, it could result in cerebral hyperemia, an increased risk of intracranial hemorrhage, and reperfusion injury. Studies of human newborns who had PPHN demonstrated worse outcomes in those who had longer periods of hyperventilation and hypocarbia (23,31), although it remains possible that the brain injury was due more to severe PPHN than to the prolonged hypocarbia.

	Venous Blood Normal Range (Mean ± 2 SD)	Arterial Blood Normal Range (Mean ± 2 SD)
pH	7.25 – 7.45	7.18 – 7.38
pCO_2 (mmHg)	26.8 – 49.2	32.2 – 65.8
pO_2 (mmHg)	17.2 – 40.8	5.6 – 30.8
HCO_3^- (mmol/L)	15.8 – 24.2	17 – 27
Base excess	-8 to 0	-8 to 0

*Table 1: Normal Umbilical Cord Blood Gases**

** From the data of Yeomans (8) as modified by Pomerance (9)*

Asphyxiated newborns are frequently hypotensive after birth because of either acute blood loss with hypovolemia or post-asphyxial cardiomyopathy. (3) In either case, the asphyxiated infant may have lost his or her ability to autoregulate cerebral blood flow across a range of blood pressures. (32, 33) Thus, any degree of hypotension in the post-asphyxial stabilization period can contribute to a newborn's cerebral ischemia and brain injury.

Approximately 80-90% of infants with brain-damaging asphyxia will demonstrate findings of encephalopathy with seizure activity. (3-6) Although asphyxiated infants with seizures have worse outcomes than asphyxiated infants without seizures, it remains controversial whether the seizures *per se* result in additional brain injury. Numerous animal studies have demonstrated brain injury following prolonged or recurrent seizures (34,35,36), but methodological considerations prevent a clear understanding of the harm of seizures *per se* in the human newborn.

Synergism

There are situations where two processes occur together, and while neither alone would be of sufficient severity to cause brain damage, the two processes combined result in brain damage. At least three such situations may arise in the asphyxiated newborn – asphyxia acting synergistically with intrauterine infections, hyperbilirubinemia, and hypoglycemia.

Combined exposure to infection and intrapartum asphyxia exert synergistic harmful effects on the fetal brain. (37) Neonates exposed to intrauterine infection who also had potentially asphyxiating obstetric complications are at a much greater risk of cerebral palsy than those with only the obstetric complications. (37-40) Nelson and Grether found that combined exposure to infection and intrapartum hypoxia dramatically increased the risk for spastic cerebral palsy (odd ratio = 78) compared to hypoxia alone.

normal acid-base determination at birth

Technical

1. Failure to sample the umbilical artery
2. Air bubbles in the sample

Pathophysiologic

3. Complete umbilical cord occlusion
4. Circulatory collapse and impaired tissue perfusion
5. Birth trauma/head compression
6. Synergism
   - chorioamnionitis
   - hypoglycemia
   - hyperbilirubinemia
7. Intrauterine resuscitation
   - maternal hypotension
   - uterine hypertonicity
   - cord compression or occlusion
8. Post-asphyxial hypoxia
   - necrotizing enterocolitis
   - meconium aspiration syndrome
   - tension pneumothorax
   - persistent pulmonary hypertension
   - hypocarbia
   - hypotension
   - ? seizures

Table 2: Explanations for an acute asphyxial brain injury associated with a normal or near-

(40) Sameshima and Ikenoue found that intrauterine infection was capable of causing brain damage in preterm infants, but that intrauterine infection only caused brain damage in term infants when it was associated with intrauterine hypoxia. (41)

"Hypoglycemia is a common complication of birth asphyxia due to depleted glycogen stores and hyperinsulinemia. "

Severe hyperbilirubinemia can cause neonatal encephalopathy and kernicterus. The risk of kernicterus increases as free bilirubin crosses the blood-brain barrier resulting in neuro-toxicity. Asphyxia and fetal hypoxia are known to dislodge bilirubin from albumen, creating increased amounts of free bilirubin and disrupting the blood-brain barrier, allowing easier entry of the free bilirubin into and impairing bilirubin clearance from the brain. (42,43) Thus asphyxia of only mild or moderate degree and with a normal acid-base balance at birth can be a significant contributing factor to the development of kernicterus and cerebral palsy.

Hypoglycemia is a common complication of birth asphyxia due to depleted glycogen stores and hyperinsulinemia. (44) Hypoglycemia is known to increase an asphyxiated infant's risk of brain injury. (45) This has been demonstrated in hypoxic newborn rats (46), asphyxiated newborn dogs (47), asphyxiated newborn lambs (48), and ischemic newborn dogs. (49) Studies from human newborns (50,51) also support the belief that hypoglycemia combined with hypoxia may result in brain injury, even when either condition alone might not have resulted in brain damage.

Summary:

Most babies who suffer brain damage from birth asphyxia will have a UA pH of less than 7.0. (7) As the pH falls progressively below 7.0, the risks of adverse outcomes increase. (52,53) But the fact that an individual's risks increase as the UA pH falls progressively below 7.0 does not eliminate the presence of risk when the UA pH is 7.0 or more. As demonstrated in this paper, there are multiple technical and pathophysiologic explanations for brain-damaging birth asphyxia with a normal or near-normal umbilical acid-base analysis. If the remaining facts of the case indicate that the likely time of the insult was in the peripartum period, the report of a normal or near-normal UA pH should not preclude one from attributing an infant's neonatal encephalopathy or long-term brain damage to birth asphyxia

Clinicians are encouraged to obtain samples from the UA and UV for complete acid-base analysis. The blood gases should then be analyzed in light of all the clinical events of the pregnancy, labor, delivery, and newborn period.

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