Pathophysiology of Birth Asphyxia

Matthew A. Rainaldi, MD*, Jeffrey M. Perlman, MB ChB

KEYWORDS

• Neonate • Birth asphyxia • Perinatal • Fetal acidemia
• Hypoxic–ischemic encephalopathy • Cerebral palsy

KEY POINTS

- The pathophysiology of birth asphyxia centers on the interruption of placental blood flow.
- The goal of the fetus is to preserve blood flow to the brain, heart, and adrenal glands during asphyxia.
- Blood flow to noncritical organs is sacrificed to preserve critical organ blood flow.
- Circulatory and noncirculatory adaptive mechanisms allow the fetus to cope with interruption of placental blood flow.
- The most severe consequence of asphyxia is permanent brain injury. Cerebral injury begins with an initial insult and continues during the reperfusion period.

INTRODUCTION

The term asphyxia can be defined as a condition of impaired gas exchange in a subject, which leads to progressive hypoxia, hypercarbia, and acidosis depending on the extent and duration of this interruption. Birth asphyxia, or impaired gas exchange during the perinatal period, does not have precise biochemical criteria. As such, caution must be exercised in labeling a neonate with "asphyxia." Unfortunately, this term is often inappropriately linked with poor neurodevelopmental outcome, commonly referred to as cerebral palsy. Before a potential causal relationship between an acute intrapartum interruption of placental blood flow and a later case of cerebral palsy can be established, the American Congress of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy require 4 essential criteria[1]: (1) evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH <7.00 and base deficit $\geq$ 12 mmol/L), (2) early onset of severe or moderate neonatal encephalopathy in infants born at 34 weeks or more of

The authors have nothing to disclose.
Division of Newborn Medicine, Komansky Center for Children's Health, New York Presbyterian Hospital, Weill Cornell Medicine, 525 East 68th Street, N-506, New York, NY 10065, USA
* Corresponding author.
E-mail address: Mar9198@med.cornell.edu

Clin Perinatol 43 (2016) 409–422
http://dx.doi.org/10.1016/j.clp.2016.04.002 **perinatology.theclinics.com**
0095-5108/16/$ – see front matter

gestation, (3) cerebral palsy of the spastic quadriplegic or dyskinetic type, and (4) exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

Asphyxia may occur before, during, or after delivery. Its pathophysiology is extremely complex and can be a result of factors related to the mother, the placenta, and/or the fetus and neonate. This section focuses predominantly on the interruption of placental blood flow and the fetal adaptive mechanisms that occur around the time of birth.

The goals of this article are to (1) review the fetal and neonatal circulations and how transition can be disrupted with asphyxia, (2) describe the adaptive responses, both circulatory and noncirculatory that are protective against asphyxia, (3) review the biochemical processes regulating gas exchange in the placenta, and (4) define the mechanisms of cell death after asphyxia and discuss pathologic brain injury as it relates to the asphyxial insult.

NORMAL FETAL CIRCULATION

The human fetus exists in a hypoxemic, but not a pathologically hypoxic state. A number of remarkable mechanisms allow the fetus to thrive under these conditions. Oxygen diffuses readily from the maternal to fetal circulation to bind high-affinity fetal hemoglobin. This blood from the placenta returns through the umbilical vein to the fetus and the majority enters the ductus venosus. The blood has a P_{O_2} of approximately 40 to 50 mm Hg[2] before joining less oxygenated blood from the inferior vena cava en route to the right atrium. Interestingly, the more oxygenated blood from the umbilical vein is directed through the foramen ovale to the left side of the heart. This blood goes on to exit the left ventricle via the aorta to the carotid and coronary arteries.[3] Thus, the fetus preferentially supplies more oxygenated blood to the brain and heart. Less oxygenated blood from the inferior vena cava remains in the right side of the heart to exit via the pulmonary trunk. The majority of this blood bypasses the lungs via the ductus arteriosus[3] and enters the aorta distal to the carotid and coronary pathways. This mixture of blood has a P_{O_2} of 15 to 25 mm Hg,[3] and a portion travels out the umbilical arteries to the placenta.

Additional factors unique to the fetus ensure adequate oxygen delivery to meet tissue demand. Hemoglobin levels are higher in the fetus compared with adults and children.[4] Fetal hemoglobin has a high affinity for oxygen and shifts the oxygen–hemoglobin dissociation curve to the left. This facilitates transfer of oxygen from the mother to the fetus across a smaller concentration gradient. These factors increase the oxygen-carrying capacity of fetal blood. The rate of tissue perfusion is higher in the fetus than the adult.[3] Thus, increased delivery of blood counteracts relatively low oxygen saturation. Additionally, the fetus expends less energy on thermoregulation and respiratory effort than the neonate.

CIRCULATORY CHANGES DURING LABOR AND NEONATAL TRANSITION

Uterine contractions lead to decreased uterine arterial blood flow[5] and decreased flow into the intervillous spaces. Transplacental gas exchange may be impaired transiently,[6] but this is generally inconsequential during normal labor.[7] When the fetal side of the circulation is examined, uterine contractions do not seem to affect umbilical blood flow. This was shown by Malcus and colleagues,[8] who measured umbilical artery flow velocity waveforms via Doppler ultrasonography and found no differences before or during contractions. However, it was noted that fetuses with an arterial

pH of 7.1 or less were more likely to have increased resistance to arterial flow during contractions.

Significant circulatory changes occur with the transition to ex utero life. Many of these changes happen simultaneously. In an infant that cries immediately after birth, the lungs rapidly expand and pulmonary vascular resistance drops. Pulmonary blood flow increases significantly. Right-to-left shunting at the ductus arteriosus decreases and eventually reverses as pulmonary artery pressure decreases below systemic blood pressure. Increases in Pa_{O_2} stimulate ductal closure. The pulmonary venous system then returns more blood to the left atrium than in fetal life. Left atrial pressure exceeding right atrial pressure causes the foramen ovale to functionally close. In the systemic circulation, the low resistance placenta is removed from the circulation when the umbilical cord is clamped. An increase in systemic vascular resistance leads to an increase in systemic blood pressure, aiding in reversal of the ductal shunt. An adult circulation pattern is established.

CAUSES OF PERINATAL ASPHYXIA

Impaired gas exchange can occur before, during, or after delivery. This process, including recovery, may be entirely isolated to fetal life. It may occur during labor and delivery, and result in abnormal circulatory transition. Asphyxia may also develop in the immediate neonatal period if an infant cannot support his or her own gas exchange without the placenta.[3]

During fetal life as well as labor and delivery, interruption of the placental blood flow is the most common final pathway leading to asphyxia. Factors leading to interruption of blood flow come in many forms (**Table 1**). Maternal diseases such as diabetes, hypertension, or preeclampsia may alter placental vasculature and decrease blood flow. Hypotension in the mother can be translated to the fetal circulation (eg, medication effect, maternal disease, spinal anesthesia, etc). Placental factors such as abruption, fetomaternal hemorrhage, or inflammation may compromise blood flow. Chorioamnionitis and funisitis are strongly linked to placental compromise and asphyxia.[9] The umbilical cord may be compressed extrinsically, as is seen with a nuchal cord or cord prolapse. Factors solely related to the neonate may also be responsible for asphyxia. For example, congenital airway anomalies may not allow for adequate pulmonary gas exchange once the placental circulation ceases. Neurologically abnormal neonates may not have appropriate respiratory drive to effectively ventilate. This may be intrinsic to the neonate (ie, central nervous system anomaly, spinal cord injury) or owing to extrinsic effects of medications.

Table 1
Selected causes of perinatal asphyxia

Maternal	Placental/Umbilical Cord	Neonatal
Diabetes mellitus	Placental abruption	Airway anomalies
Hypertension	Fetomaternal hemorrhage	Neurologic disorders
Preeclampsia	Umbilical cord compression (prolapse, nuchal cord, knot, etc)	Severe cardiopulmonary disease
Hypotension/shock	Infection/inflammation	Severe circulatory compromise (blood loss)
Uterine rupture	Velamentous cord insertion	Infection
Severe anemia	—	Medication effect
Infection	—	—

ADAPTIVE MECHANISMS AFTER ASPHYXIA

The disruption of placental blood flow initiates important adaptive mechanisms in the fetus that are both circulatory and noncirculatory in nature. Circulatory changes involve redistribution of cardiac output and "centralization" of blood flow to vital organs. Noncirculatory responses aim to preserve cell viability. With a severe or prolonged interruption of placental blood flow, these adaptations are overwhelmed, increasing the risk of end-organ injury.

Circulatory Changes After Asphyxia

When placental blood flow is compromised, the fetus aims to redistribute cardiac output to protect more vital organs (eg, brain, myocardium, and adrenal glands). Known as the "diving reflex," this alteration of blood flow is at the expense of decreased flow to less vital organs, such as the kidney, intestine, skin, and muscle. A number of factors contribute to this reflex. Hypoxemia is sensed by carotid artery chemoreceptors, leading to catecholamine release.[10] This surge of catecholamines, in turn, causes peripheral vasoconstriction and centralization of blood flow. Hypoxemia also causes constriction of the pulmonary vasculature, with a resultant decrease in pulmonary blood flow, left atrial blood return, and left atrial pressure.[11,12] Right-to-left shunting across the foramen ovale increases in an effort to deliver even more oxygenated blood to the left heart (preferentially directed to the brain and myocardium). In addition, adaptive mechanisms within the cerebral circulation facilitate this process. Thus, cerebral vascular resistance decreases in the presence of hypoxemia. Experimental studies indicate that resistance can decrease by as much as 50%, increasing cerebral blood flow, and compensating for decreased blood oxygen content during initial asphyxia.[13–15]

Preservation of critical organ blood flow comes at the expense of decreased flow to "noncritical" organs (**Fig. 1**). When systemic blood pressure drops low enough, compensatory mechanisms fail. This critical threshold is at a point below which the cerebral circulation can no longer dilate to maintain flow.[16] Cerebral oxygen delivery is superseded by demand and brain injury occurs.

Although the diving reflex represents the ideal pathway to preserve critical organ function, not all neonates seem to exhibit these protective adaptive mechanisms consistently.[17,18] Phelan and colleagues[18] described 14 cases of hypoxic–ischemic encephalopathy (HIE) in which multiorgan dysfunction did not occur. All of these infants developed cerebral palsy. It was postulated that the mechanisms contributing to asphyxia in these cases did not allow sufficient time to centralize fetal blood flow (eg, uterine rupture, prolonged fetal heart rate deceleration). Studies in both humans and animals have suggested that intermittent asphyxia for less than 1 hour is unlikely to lead to brain injury, but severe "total" asphyxia can cause brain injury much sooner.[19–21] The adaptations of the diving reflex may be overwhelmed in extreme cases. Shah and colleagues[17] reviewed records of infants with HIE for a 10-year period. They found no differences when comparing multiorgan dysfunction of infants with severe adverse outcome to those with good outcome, suggesting a variable activation of the diving reflex.

Respiratory Responses to Asphyxia

In addition to the cardiovascular changes that occur with asphyxia, characteristic changes in breathing patterns occur. Critical to understanding the relationship between respiratory and circulatory changes is the work of Dawes and colleagues.[22] Using rhesus monkeys, these investigators initiated asphyxia by ligating the umbilical cord and covering the head with a small bag of warm saline. A characteristic series of changes

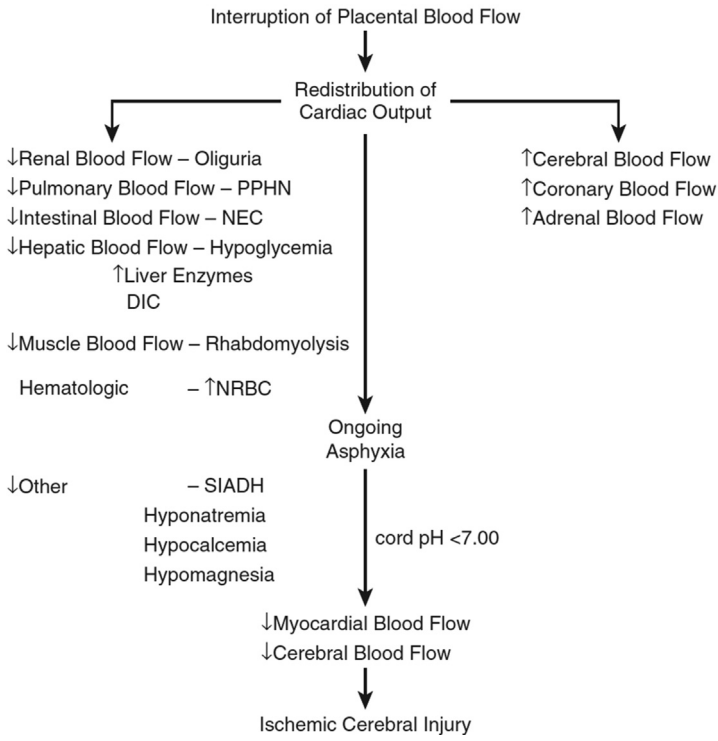

Fig. 1. Adaptive mechanisms and systemic consequences of interruption of placental blood flow. DIC, disseminated intravascular coagulation; NEC, necrotizing enterocolitis; NRBC, nucleated red blood cells; PPHN, persistent pulmonary hypertension of the newborn; SIADH, syndrome of inappropriate antidiuretic hormone release.

were seen. Within 30 seconds of total asphyxia, a brief period of rapid rhythmic respiratory effort occurred. This culminated in apnea (primary) and bradycardia, which lasted for approximately 30 to 60 seconds (**Fig. 2**). The animal then began to have gasping respirations, but spontaneous regular respiration could be induced via prompt physical stimulation. If no intervention was performed, the gasping lasted for approximately 4 minutes. It gradually became weaker until a terminal "last gasp" occurred. This was deemed secondary apnea and, unless resuscitation was initiated, death followed.

Noncirculatory Responses to Asphyxia

Several biologic factors aid in preserving critical organ viability during and after asphyxia. The cerebral metabolic rate is lower in the fetus versus the term infant or adult, creating a more favorable ratio of energy supply and demand.[23] Additionally, the neonatal brain has the capacity to use alternate energy sources when needed.[24] In situations of relative oxygen and glucose depletion, energy substrates such as lactate and ketones become critical for cerebral metabolism.[23,25] The fetal and neonatal myocardium is more resistant to hypoxia–ischemia than the adult myocardium.[26] In addition to the brain and heart, protective effects of fetal hemoglobin may also allow for a greater tolerance to a hypoxic environment.[27] Importantly, at low oxygen tensions (ie, below a "crossover P_{O_2}"), a left-shifted fetal hemoglobin–oxygen dissociation curve may be advantageous in delivering more oxygen to tissues.[28–30] During acute acidosis, the affinity of oxygen for hemoglobin immediately decreases via the Bohr effect.[28] This

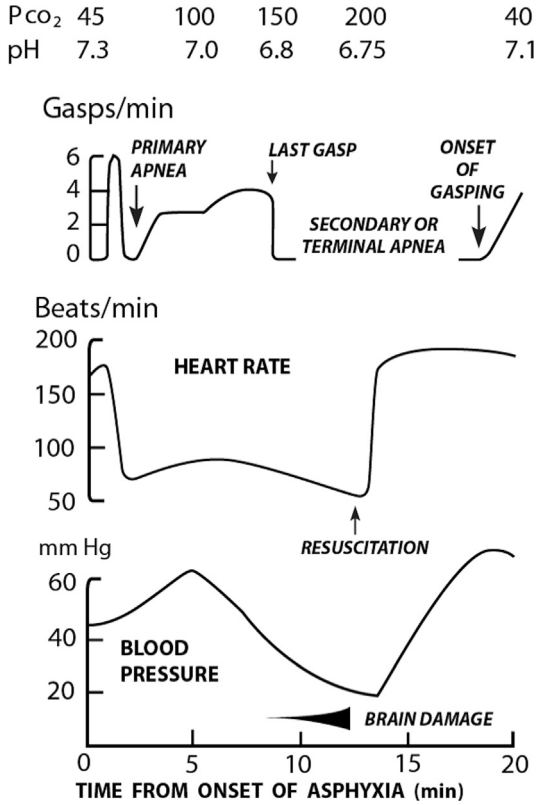

Fig. 2. Relationship between respiration, heart rate, blood pressure, and acidosis in rhesus monkeys during asphyxia and resuscitation. (*Adapted from* Dawes G, Jacobson H, Mott JC, et al. The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. J Physiol 1963;169(1):174.)

decrease allows for an easier unloading of oxygen to tissues during acidosis, as is seen in perinatal asphyxia.

IMPAIRED GAS EXCHANGE AND ACIDOSIS

Diminished oxygen and carbon dioxide gas exchange across the placenta is the hallmark of perinatal asphyxia. Both gases move down a partial pressure gradient via simple diffusion. Impaired exchange of each gas contributes to acidosis.

As stated, the fetus is able to thrive at relatively low oxygen tensions. The maternal uterine artery delivers oxygenated blood to the placenta via spiral arteries. This blood enters the relatively large intervillous space (mixing with deoxygenated blood) and interfaces with chorionic villi containing fetal vessels. Oxygen is transported via simple diffusion in a passive, non–energy-dependent manner. The principal factors that dictate placental oxygen transfer are shown in **Table 2**. When fetal oxygen demand exceeds placental oxygen delivery, cells resort to anaerobic respiration to combat energy needs. Via the anaerobic pathway, lactic acid accumulates, and pH decreases.

Carbon dioxide is produced by the fetus and transported in the blood in 3 forms: (1) in the red blood cell as bicarbonate, (2) by hemoglobin as carbamate, and (3) as

Table 2
Major factors affecting placental oxygen transfer

Factor	Components
Placental membrane diffusing capacity	Surface area, thickness, oxygen solubility, diffusivity of tissues
Maternal arterial P_{O_2}	Inspired P_{O_2}, alveolar ventilation, mixed venous P_{O_2}, pulmonary blood flow, pulmonary diffusing capacity
Fetal arterial P_{O_2}	Maternal arterial P_{O_2}, maternal placental Hb flow, placental diffusing capacity, umbilical venous P_{O_2}, fetal O_2 consumption, fetal peripheral blood flow
Maternal and fetal Hb-O_2 affinities (P_{50})	pH, temperature, P_{CO_2}, 2,3-diphosphoglycerate concentration, CO concentration
Maternal placental blood flow	Arterial pressure, placental resistance to blood flow, venous pressure
Fetal placental blood flow	Umbilical artery blood pressure, umbilical venous blood pressure, placental resistance to blood flow
Spatial relationship between maternal and fetal blood flow	Vascular architecture
Amount of CO_2 exchange	—

Abbreviations: CO, carbon monoxide; Hb, hemoglobin.
Adapted from Longo LD, Hill EP, Power GG. Theoretical analysis of factors affecting placental O 2 transfer. Am J Physiol 1972;222(3):730–9.

dissolved gas. Although dissolved CO_2 gas accounts for a smaller proportion of blood CO_2 content than bicarbonate and carbamate, it is responsible for the majority of placental transfer.[31] In fact, CO_2 diffuses quite quickly, approximately 20 times faster than oxygen. Because of this, carbon dioxide transfer is predominantly dependent on blood flow, that is, intact uteroplacental and fetoplacental circulations.[31] CO_2 moves from a higher fetal to a lower maternal concentration and is ultimately eliminated by the maternal lungs. As such, the maternal pH is slightly higher (approximately 0.1 units) than the fetal pH. Two interesting phenomena, the Bohr and Haldane effects, aid in gas exchange across the placenta. The Bohr effect refers to the enhanced oxygen transfer as influenced by pH and P_{CO_2}. As maternal blood accepts CO_2 and becomes more acidotic, its oxygen–hemoglobin dissociation curve shifts to the right. This decreases oxygen affinity and facilitates unloading of oxygen. At the same time, the fetal circulation loses CO_2 and becomes more alkalotic, shifting the curve to the left, and promoting oxygen uptake. The Haldane effect refers to a complementary process by which CO_2 transport by hemoglobin is influenced by oxygen. Binding of oxygen to hemoglobin increases unloading of CO_2 on the fetal side. Thus, more fetal CO_2 becomes available in the placenta for transport to the maternal circulation. Analogously, when hemoglobin is deoxygenated, greater amounts of CO_2 can bind, which assists maternal circulation in CO_2 removal.

Fetal acidemia, or accumulation of acid occurs via 3 pathways: (1) excess carbon dioxide and in turn carbonic acid, (2) excess noncarbonic or metabolic acid (eg, lactic, uric, or keto acids), or (3) both carbonic and noncarbonic acids.[19,32] As stated, carbon dioxide quickly diffuses across the placenta and is excreted by the maternal lungs.[33] Thus, alterations in fetal pH owing to carbon dioxide accumulation can occur

and resolve quickly. In contrast, noncarbonic acids only slowly diffuse across the placenta into the maternal circulation. The primary noncarbonic acid, lactic acid, accumulates as a result of oxygen deprivation and anaerobic glycolysis and does so more slowly than carbonic acid. This process results in a more sustained acidemia, the degree of which may relate to both the severity and duration of the hypoxic–ischemic insult.[19]

Because metabolic acids diffuse slowly into the maternal circulation for excretion by the maternal kidneys, some degree of acidemia may be seen in maternal conditions, such as diabetes, preeclampsia, and chronic hypertension, which may result in a more acidic pH in the umbilical artery not necessarily owing to fetal asphyxia.

The degree of acidosis or umbilical arterial pH that best defines asphyxia remains imprecise. Traditionally, asphyxia was defined as a cord umbilical arterial pH of less than 7.20.[34] Severe fetal acidemia, or an umbilical arterial pH of less than 7.00 reflects a degree of acidemia where the risk of adverse neurologic sequelae is increased.[34,35] However, even with this degree of acidemia, the likelihood of subsequent brain injury remains low. The majority of these infants (>60%) have an uneventful delivery, remain in the well nursery, and are discharged home without complication.[36] Even when infants with severe fetal acidemia are admitted to intensive care (usually because of respiratory difficulties) about 80% to 90% exhibit a benign neurologic course and it is only a small percentage present with encephalopathy.[37–39] In 1 study, 8 of 47 infants (12%) with severe fetal acidemia admitted to the intensive care unit developed HIE, including seizures.[37] In this study, infants with seizures were 234 times more likely to require cardiopulmonary resuscitation in the delivery room versus those without seizures.[37] Therefore, the presence of severe fetal acidemia, although a distinct marker of stress, does not equate necessarily with the inability of the fetus to maintain cerebral perfusion. However, when severe acidemia is seen in the context of a bradycardic neonate requiring intensive delivery room resuscitation, a significant intrapartum insult is more likely. It is in this case that cerebral perfusion and oxygen delivery were compromised. The resistance of the brain to asphyxia, even when profound, is extraordinary and is in part based on the ability of the fetus to adapt to interruption of placental blood flow to preserve cerebral perfusion and oxygen delivery (as described previously).

NEURONAL CELL DEATH AFTER ASPHYXIA

When compensatory mechanisms are overwhelmed and cerebral blood flow can no longer meet demand, a cascade of biochemical events begins. These events are complex, interrelated, and ultimately lead to cell death without intervention. This section focuses on the cellular pathophysiology of hypoxic–ischemic brain injury, as is seen with asphyxia.

In the asphyxiated fetus or neonate, oxygen delivery is reduced, anaerobic glycolysis takes over, and high-energy phosphate compounds decrease (ie, adenosine triphosphate and phosphocreatinine). Lactic acid accumulates and membrane ion pumps fail (Na^+/K^+ adenosine triphosphatase and Na^+/Ca^{2+} exchanger). With membrane pump failure, sodium and water influx into cells, leading to cell swelling. Calcium also flows into cells, which initiates release of excitatory amino acids such as glutamate into the extracellular space. This overexcitation leads to more calcium influx, fostering an excitotoxic cycle.[40] Further consequences include formation of free radicals, production of nitric oxide, and lipid peroxidation of cell membranes (**Fig. 3**).

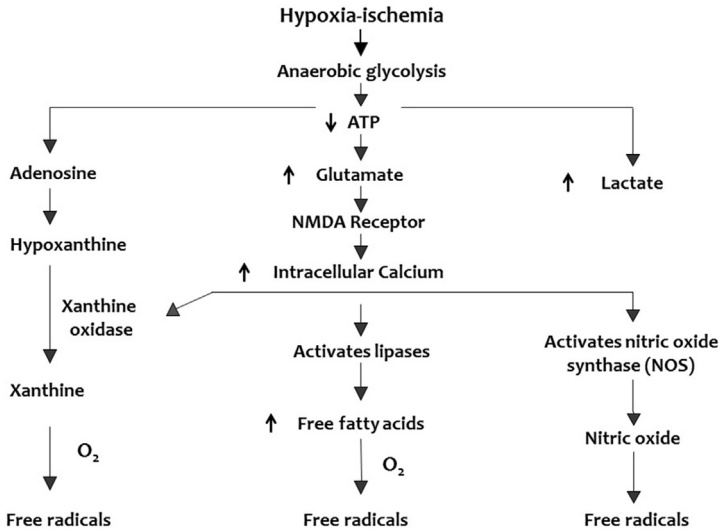

Fig. 3. Potential biochemical mechanisms of hypoxic–ischemic brain injury. ATP, adenosine triphosphate.

The endpoint of cell death is described classically to occur via necrosis or apoptosis (programmed cell death). Necrosis is defined by cell swelling, disruption of organelles, and loss of phospholipid membrane integrity with cell lysis. It represents a rapid and severe breakdown of cellular function that occurs with the primary hypoxic–ischemic insult.[41] After resuscitation, cerebral perfusion and oxygenation are restored, along with partial restoration of energy sources. However, there is a subsequent progressive decrease in high-energy phosphates 24 to 48 hours later, that is, a secondary energy failure.[42]

During secondary energy failure, reperfusion injury occurs owing to extended reactions from the primary insult. This injury is characterized by inflammation, generation of reactive oxygen species and free radicals, and importantly cell death via apoptosis.[43] When apoptotic pathways are initiated, adenosine triphosphate is used to actively dismantle cells into consumable components.[41] Cells shrink, chromatin condenses, and nuclei become pyknotic. Apoptosis may be induced through caspase-dependent or gene transcription (caspase-independent) processes.[40] Caspase-3 is the most abundant effector caspase in the developing brain[44] and there is a direct correlation between the activation of caspase-3 and the degree of injury after hypoxia–ischemia.[45] Because of its delayed nature, apoptosis has become an enticing target for potential therapies for HIE.[46] Recently, hybrid forms of neuronal death have gained attention, filling in the gaps between necrosis and apoptosis along a continuum of cell death.[41]

PATHOLOGIC BRAIN INJURY AFTER PERINATAL ASPHYXIA

Brain injury after asphyxia is hypoxic–ischemic in nature and occurs in characteristic locations on MRI or at autopsy. The injured region can vary depending on the type and duration of insult, gestational age, and whether the infant was treated with hypothermia.[47,48] The classic patterns of neuropathologic injury from HIE include (1) selective

neuronal necrosis, (2) parasagittal cerebral injury, (3) periventricular leukomalacia, and (4) focal ischemic necrosis.

Selective neuronal necrosis is the most common type of brain injury. It generally has 3 patterns: diffuse, cortical–deep nuclear, and deep nuclear–brain stem. Parasagittal cerebral injury occurs in the end-arterial watershed area of the parietooccipital cortex and subcortical white matter. Periventricular leukomalacia refers to a classic white matter necrosis and gliosis of preterm infants, although it can be identified in term infants after hypoxia–ischemia. Focal ischemic necrosis pertains to arterial stroke and can be identified in vascular distributions of 1 or more cerebral arteries. Heterogeneous patterns are common, because elements of more than 1 of these patterns are frequently appreciated. Partial lesions may also be found, as described in a recent study where 10 infants that were treated with therapeutic hypothermia had isolated hippocampal injury.[48] MRI findings associated with poor outcome include involvement of the basal ganglia and thalamus, posterior limb of the internal capsule, and loss of gray–white matter differentiation.[19,49]

TIMING AND DURATION OF PERINATAL ASPHYXIA

The precise time at which an asphyxial event occurred is often a focus of intense scrutiny by the obstetrician, neonatologist, and parents. This may be obvious in cases with profound sentinel events, that is, change in fetal heart rate tracing (absent variability or decelerations), uterine rupture, placental abruption, cord prolapse, or trauma. But, in some cases, this remains elusive. In this sense, the asphyxial insult can be classified as acute or subacute.

A classic example of an acute asphyxial insult is that of a “megacode,” where a full resuscitation occurs.[50] An abrupt change in fetal heart rate may have been appreciated, and the neonate presented with poor Apgar scores and severe acidosis. Renal and other end-organ dysfunction is often seen along with encephalopathy.

A subset of asphyxiated infants may not present with significant circulatory collapse at birth. In these cases, the insult likely occurred in a subacute fashion, allowing the fetus to “self-resuscitate” in utero. Labor is often uncomplicated and the neonate does not require serious intervention at delivery. As a result, severe acidemia is not apparent, but encephalopathy may be present. Some of these infants may go unrecognized initially, then develop a syndrome of encephalopathy and seizures within 12 to 24 hours.[51] A distinctly different presentation was described in a recent study of term infants treated with hypothermia. Seven infants with subacute insults based on intrapartum characteristics presented with more severe encephalopathy at birth and were less likely to require intensive resuscitation as compared with 26 with acute insults (eg, uterine rupture).[52] With either presentation systemic organ injury is common, particularly renal dysfunction, along with evidence of brain injury on MRI. In these cases, timing of the injury is often difficult. Subtle clues from the maternal history may be valuable (ie, decreased fetal movement), as well as characteristic MRI findings. Injury on MRI may evolve throughout the reperfusion period and the interpretation of an MRI should take this into account.[53] For instance, diffusion and metabolic changes worsen until day 4 or 5 and then begin to normalize.[54]

Certain injury patterns can offer suggestions as to the duration of asphyxia. The most severe and prolonged insults often result in diffuse neuronal injury.[19] Moderate to severe prolonged insults tend to lead to cortical and deep nuclear (basal ganglia and thalamic) neuronal injury (**Fig. 4**). Hypoxia–ischemia that is severe and abrupt predominantly causes deep nuclear–brain stem injury.

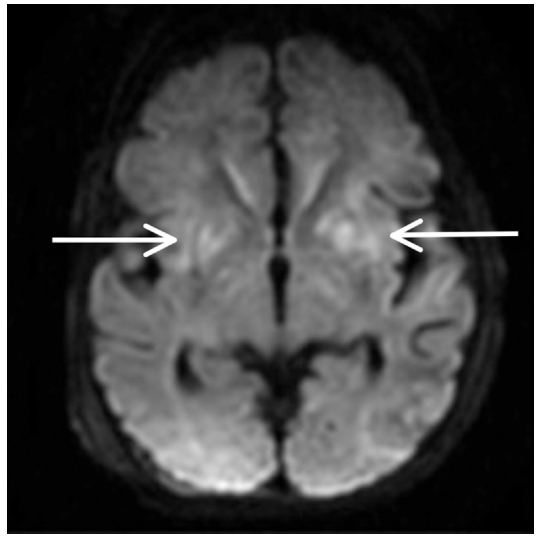

Fig. 4. Diffusion-weighted MRI (axial) image showing basal ganglia injury (*arrows*).

SUMMARY

The fetal circulation is remarkable in its ability to adequately deliver oxygen in a hypoxemic environment. The pathophysiology of perinatal asphyxia centers around the interruption of placental blood flow. Although there are many adaptive mechanisms that aim to prevent adverse consequences of asphyxia, these mechanisms can be overwhelmed. When compensatory mechanisms can no longer keep up with blood flow demand, acidosis and ultimately cell death occur. A comprehensive understanding of the pathophysiology of asphyxia is crucial to effective management of these infants.

REFERENCES

1. American Congress of Obstetricians and Gynecologists (ACOG). Committee Opinion. Number 326. Inappropriate use of the terms fetal distress and birth asphyxia. Obstet Gynecol 2005;106:1469–70.
2. Nicolaides K, Economides D, Soothill P. Blood gases, pH, and lactate in appropriate-and small-for-gestational-age fetuses. Am J Obstet Gynecol 1989; 161(4):996–1001.
3. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant. 9th edition. Philadelphia: Saunders/Elsevier; 2011.
4. Walker J, Turnbull EN. Haemoglobin and red cells in the human foetus and their relation to the oxygen content of the blood in the vessels of the umbilical cord. Lancet 1953;262(6781):312–8.
5. Li H, Gudmundsson S, Olofsson P. Clinical significance of uterine artery blood flow velocity waveforms during provoked uterine contractions in high-risk pregnancy. Ultrasound Obstet Gynecol 2004;24(4):429–34.
6. Boylan PC, Parisi VM. Fetal acid–base balance. In: Creasy RK, Resnik R, editors. Maternal–Fetal Medicine. 3rd edition. Philadelphia: Saunders; 1994. p. 349–58.
7. Stuart B, Drumm J, Fitzgerald D, et al. Fetal blood velocity waveforms in uncomplicated labour. BJOG 1981;88(9):865–9.

8. Malcus P, Gudmundsson S, Marsal K, et al. Umbilical artery Doppler velocimetry as a labor admission test. Obstet Gynecol 1991;77(1):10–6.
9. Mir IN, Johnson-Welch SF, Nelson DB, et al. Placental pathology is associated with severity of neonatal encephalopathy and adverse developmental outcomes following hypothermia. Am J Obstet Gynecol 2015;213(6):849.e1-7.
10. Kara T, Narkiewicz K, Somers VK. Chemoreflexes–physiology and clinical implications. Acta Physiol Scand 2003;177(3):377–84.
11. Rudolph AM, Heymann MA. The circulation of the fetus in utero methods for studying distribution of blood flow, cardiac output and organ blood flow. Circ Res 1967;21(2):163–84.
12. Rudolph A, Yuan S. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. J Clin Invest 1966;45(3):399.
13. Koehler RC, Jones M, Traystman RJ. Cerebral circulatory response to carbon monoxide and hypoxic hypoxia in the lamb. Am J Physiol 1982;243(1):H27–32.
14. Jones M, Sheldon RE, Peeters LL, et al. Regulation of cerebral blood flow in the ovine fetus. Am J Physiol 1978;235(2):H162–6.
15. Ashwal S, Dale PS, Longo LD. Regional cerebral blood flow: studies in the fetal lamb during hypoxia, hypercapnia, addosis, and hypotension. Pediatr Res 1984;18(12):1309–16.
16. Block BS, Schlafer DH, Wentworth RA, et al. Intrauterine asphyxia and the breakdown of physiologic circulatory compensation in fetal sheep. Am J Obstet Gynecol 1990;162(5):1325–31.
17. Shah P, Riphagen S, Beyene J, et al. Multiorgan dysfunction in infants with post-asphyxial hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2004;89(2):F152–5.
18. Phelan JP, Alen MO, Korst L, et al. Intrapartum fetal asphyxial brain injury with absent multiorgan system dysfunction. J Matern Fetal Med 1998;7(1):19–22.
19. Volpe JJ. Neurology of the newborn. 5th edition. Philadelphia: Saunders/Elsevier; 2008.
20. Low JA, Galbraith R, Muir D, et al. Factors associated with motor and cognitive deficits in children after intrapartum fetal hypoxia. Am J Obstet Gynecol 1984; 148(5):533.
21. Pasternak JF, Gorey MT. The syndrome of acute near-total intrauterine asphyxia in the term infant. Pediatr Neurol 1998;18(5):391–8.
22. Dawes G, Jacobson H, Mott JC, et al. The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. J Physiol 1963;169(1):167–84.
23. Cremer JE. Substrate utilization and brain development. J Cereb Blood Flow Metab 1982;2(4):394–407.
24. Vannucci RC, Yager JY. Glucose, lactic acid, and perinatal hypoxic-ischemic brain damage. Pediatr Neurol 1992;8(1):3–12.
25. Yager JY, Heitjan DF, Towfighi J, et al. Effect of insulin-induced and fasting hypoglycemia on perinatal hypoxic-ischemic brain damage. Pediatr Res 1992;31(2): 138–42.
26. Dawes G, Mott JC, Shelley HJ. The importance of cardiac glycogen for the maintenance of life in foetal lambs and new-born animals during anoxia. J Physiol 1959;146(3):516–38.
27. Oski FA. The unique fetal red cell and its function. E. Mead Johnson Award address. Pediatrics 1973;51(3):494–500.
28. Wimberley P. A review of oxygen and delivery in the neonate. Scand J Clin Lab Invest 1982;160(Suppl):114–8.

29. Aberman A. Crossover PO2, a measure of the variable effect of increased P50 on mixed venous PO2 1. Am Rev Respir Dis 1977;115(1):173–5.
30. Woodson RD. Physiological significance of oxygen dissociation curve shifts. Crit Care Med 1979;7(9):368–73.
31. Cowett RM. Principles of perinatal-neonatal metabolism. New York: Springer Science & Business Media; 2012.
32. Wyka KA, Mathews PJ, Rutkowski JA. Foundations of respiratory care. Clifton Park, NY: Delmar Publishing; 2011.
33. Thorp JA, Rushing RS. Umbilical cord blood gas analysis. Obstet Gynecol Clin North Am 1999;26(4):695–709.
34. Goldaber K, Gilstrap L III, Leveno K, et al. Pathologic fetal acidemia. Obstet Gynecol 1991;78(6):1103–7.
35. Sehdev HM, Stamilio DM, Macones GA, et al. Predictive factors for neonatal morbidity in neonates with an umbilical arterial cord pH less than 7.00. Am J Obstet Gynecol 1997;177(5):1030–4.
36. King TA, Jackson GL, Josey AS, et al. The effect of profound umbilical artery acidemia in term neonates admitted to a newborn nursery. J Pediatr 1998; 132(4):624–9.
37. Perlman JM, Risser R. Severe fetal acidemia: neonatal neurologic features and short-term outcome. Pediatr Neurol 1993;9(4):277–82.
38. Goodwin TM, Belai I, Hernandez P, et al. Asphyxial complications in the term newborn with severe umbilical acidemia. Am J Obstet Gynecol 1992;167(6): 1506–12.
39. Fee SC, Malee K, Deddish R, et al. Severe acidosis and subsequent neurologic status. Am J Obstet Gynecol 1990;162(3):802–6.
40. Calvert JW, Zhang JH. Pathophysiology of an hypoxic–ischemic insult during the perinatal period. Neurol Res 2005;27(3):246–60.
41. Northington FJ, Chavez-Valdez R, Martin LJ. Neuronal cell death in neonatal hypoxia-ischemia. Ann Neurol 2011;69(5):743–58.
42. Vannucci RC, Towfighi J, Vannucci SJ. Secondary energy failure after cerebral hypoxia-ischemia in the immature rat. J Cereb Blood Flow Metab 2004;24(10): 1090–7.
43. Vannucci RC. Hypoxic-ischemic encephalopathy. Am J Perinatol 2000;17(3): 113–20.
44. Sakahira H, Enari M, Nagata S. Cleavage of CAD inhibitor in CAD activation and DNA degradation during apoptosis. Nature 1998;391(6662):96–9.
45. Zhu C, Wang X, Xu F, et al. The influence of age on apoptotic and other mechanisms of cell death after cerebral hypoxia-ischemia. Cell Death Differ 2005;12(2): 162–76.
46. Dixon BJ, Reis C, Ho WM, et al. Neuroprotective strategies after neonatal hypoxic ischemic encephalopathy. Int J Mol Sci 2015;16(9):22368–401.
47. Sie LT, van der Knaap MS, Oosting J, et al. MR patterns of hypoxic-ischemic brain damage after prenatal, perinatal or postnatal asphyxia. Neuropediatrics 2000; 31(3):128–36.
48. Kasdorf E, Engel M, Heier L, et al. Therapeutic hypothermia in neonates and selective hippocampal injury on diffusion-weighted magnetic resonance imaging. Pediatr Neurol 2014;51(1):104–8.
49. Rutherford MA, Pennock JM, Counsell SJ, et al. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. Pediatrics 1998;102(2):323–8.

50. Wyckoff MH, Aziz K, Escobedo MB, et al. Part 13: neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132(18 Suppl 2):S543–60.
51. Perlman JM. Intrapartum asphyxia and cerebral palsy: is there a link? Clin Perinatol 2006;33(2):335–53.
52. Kasdorf E, Grunebaum A, Perlman JM. Subacute hypoxia-ischemia and the timing of injury in treatment with therapeutic hypothermia. Pediatr Neurol 2015; 53(5):417–21.
53. Rutherford M, Counsell S, Allsop J, et al. Diffusion-weighted magnetic resonance imaging in term perinatal brain injury: a comparison with site of lesion and time from birth. Pediatrics 2004;114(4):1004–14.
54. Barkovich A, Miller S, Bartha A, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. AJNR Am J Neuroradiol 2006;27(3):533–47.