

# Fetal Asphyxia: Pathogenic Mechanisms and Consequences

*Hypoxia* is defined as a reduced or insufficient level of oxygen in the body's tissues. In clinical and physiologic usage, the term is generally reserved for more substantial degrees of reduced O<sub>2</sub> availability, such as occurs at moderately high altitude when a person notices the O<sub>2</sub> limitation. When one travels from sea level up to 10,000 feet, mild forms of discomfort may be noted such as tachypnea, tachycardia, exercise intolerance, and headache, and in general, the higher the altitude, the greater the discomfort. Hypoxia in both adults and fetuses is thus a continuum from normoxia, to easily tolerated reduced O<sub>2</sub>, to a reduction requiring physiologic adaptation such as tachypnea, to reduced function, to tissue damage, and finally to death. These and other terms are defined in **Table 5-1**.

**Table 5-1** Definition of Terms Related to Hypoxia

Acidemia	Increased concentration of hydrogen ions in the blood
Acidosis	Increased concentration of hydrogen ions in the tissues of the body
Aerobic metabolism	Metabolism of glucose using oxygen; aerobic metabolism generates 38 molecules of adenosine triphosphate (ATP) per each glucose molecule for energy use
Anaerobic metabolism	Metabolism of glucose without the use of oxygen; anaerobic metabolism generates 2 molecules of ATP per each glucose molecule for energy use
Asphyxia	Comes from the Greek word for "pulseless"; a decrease in O <sub>2</sub> and increase in CO <sub>2</sub> due to an interference with gas exchange; asphyxia is a continuum described by degrees of acidosis
Base	A substance that is capable of accepting hydrogen ions and thereby decreasing acidity
Base excess (BE)	The amount of base or HCO <sub>3</sub> <sup>-</sup> that is available for buffering; as metabolic acidosis increases, the base excess decreases
Bicarbonate (HCO <sub>3</sub> <sup>-</sup> )	HCO <sub>3</sub> <sup>-</sup> (often referred to as bicarb) is the base or hydrogen acceptor that is part of the primary buffering system within the blood
Buffer	A buffer is a chemical substance that is both a weak acid and salt, and can absorb or give up hydrogen ions, thereby maintaining a constant pH value; the primary buffer involved in fetal oxygenation is HCO <sub>3</sub> <sup>-</sup>
Hypercarbia	Excessive carbon dioxide in blood; sometimes referred to as hypercapnia
Hypoxia	Decreased oxygen in tissue
Hypoxemia	Decreased oxygen content in blood
Hypoxemia-ischemia	Reduced amount of oxygen and inadequate volume of blood delivered to tissues; can cause brain injury if delivery of oxygen and glucose falls below critical levels
Metabolic acidemia	Low bicarbonate (negative base excess)
Mixed acidosis	Low pH that reflects both increased carbon dioxide and decreased base excess (i.e., increased lactic acid)
pH	pH refers to the concentration of hydrogen ions in blood and refers to "puissance hydrogen," which is French for strength (or power) of hydrogen; a pH of 7.0 = 0.0000001 (which is 10 <sup>-7</sup> ) moles per liter of hydrogen ions
Respiratory acidemia	High PCO <sub>2</sub>

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In the fetus, the continuum of hypoxia is mostly caused by a reduction of either maternal placental (i.e., intervillous) blood flow, or reduced umbilical blood flow. Both of these factors result in reduced exchange of the respiratory gases, so in addition to hypoxia there is also a buildup of carbon dioxide, resulting in what is called a *respiratory acidosis*. At more severe degrees of reduction of these two blood flows, and therefore more severe hypoxia, the cells of the body will convert from aerobic to anaerobic metabolism for energy production, of which the end product is lactic acid. This results in reduction of bicarbonate, and therefore a *metabolic acidosis* (Figure 5-1).

*Hypoxemia* is used to describe a reduced level or concentration of  $O_2$  in the blood. The direct measurement of hypoxia in tissues is rarely possible, so measurements of oxygen in the blood are used as surrogates.

*Hypoxia-ischemia* describes reduced amount of oxygen and inadequate blood flow in tissue. The combination of hypoxia and ischemia can cause brain damage when oxygen and glucose delivery fall below critical levels.

*Asphyxia* has the pathologic meaning of insufficiency or absence of exchange of the respiratory gases, though etymologically it comes from the Greek word meaning pulseless. Although the word asphyxia strictly could be applied to any change in respiratory gas levels from normal, by common usage it is generally reserved for the more severe degrees, where compensatory mechanisms are required for tolerance, or tissue damage or death occurs.

The severity of hypoxia or asphyxia is described in terms of acidemia, hypercarbia, hypoxemia, and base excess. In this text, we use the terms hypoxia and asphyxia to denote the moderate or more severe degrees when the fetus uses physiologic alterations to tolerate the condition.

There are basically three common means by which the human fetus can become hypoxic or asphyxiated: (1) insufficiency of uterine blood flow<sup>1</sup>; (2) insufficiency of umbilical blood flow<sup>2</sup>; or (3) a decrease in maternal arterial oxygen content.<sup>3</sup> Each of these mechanisms converges into a common pathway that involves the fetal response to reduction of available oxygen. In addition, the

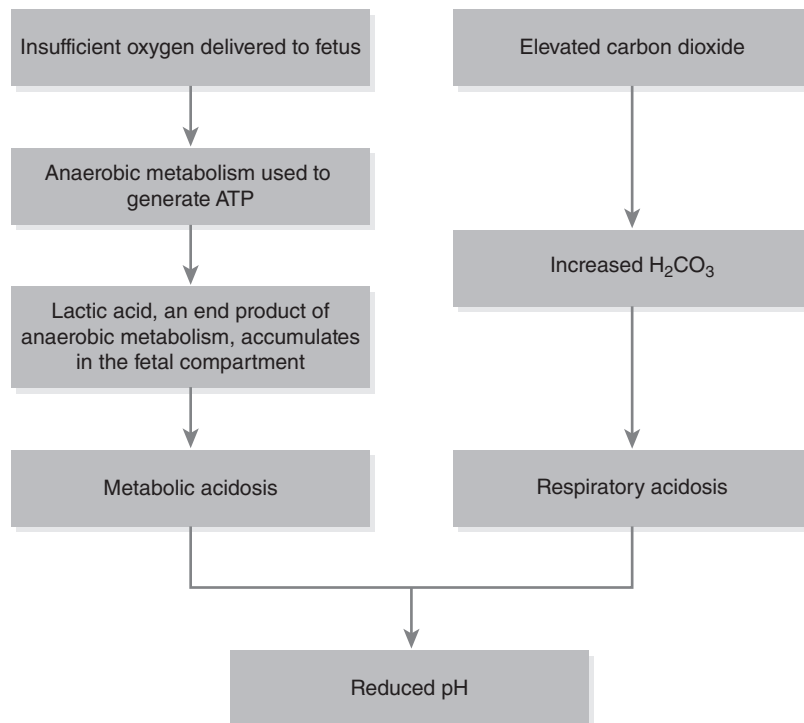


Figure 5-1 Consequences of insufficiency of exchange of respiratory gases.

fetus has higher oxygen needs during pyrexia, which may play a role in the known increased risk for newborn neurologic damage following chorioamnionitis.<sup>4,5</sup> Other mechanisms, such as fetal anemia, are relatively rare in clinical practice.

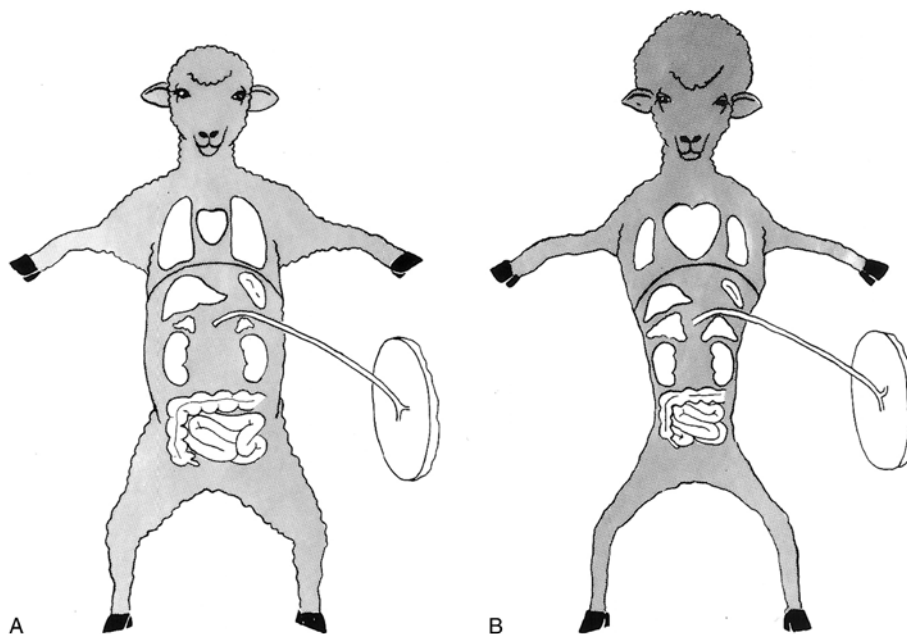
The two organ systems that have the most critical roles in the fetal response to hypoxia are the cardiorespiratory and central nervous systems. In both, the initial response involves a series of physiologic changes that devolve to pathologic responses when asphyxia persists. Similarly, in both systems the response to acute hypoxial stress is different than the response to chronic hypoxia. The sections that follow address physiologic and pathologic responses to acute hypoxia first followed by the effects of chronic hypoxia.

## I. FETAL CARDIORESPIRATORY RESPONSES TO HYPOXIA

In the previously normoxic fetus, a number of compensatory mechanisms occur during acute hypoxia including redistribution of blood flow, bradycardia, a drop in oxygen consumption, and a shift to anaerobic metabolism. This series of responses may be thought of as temporary compensatory mechanisms that enable the fetus to survive moderate periods of limited oxygen supply without decompensation of vital organs, particularly the brain and heart. Carbohydrate stores may also play a role. These mechanisms are physiologic and not associated with irreversible damage if the degree of hyperoxia is moderate and intermittently engaged. When asphyxia worsens, myocardial dysfunction occurs, which leads to general decompensation.

### A. Redistribution of Blood Flow

Blood flow is redistributed during hypoxia favoring certain vital organs, such as the heart, brain, and adrenal glands, and there is a concomitant decrease in blood flow to the gut, spleen, kidneys, and musculoskeletal regions (**Figure 5-2**).<sup>6</sup> Blood flow to the placenta is maintained. In studies



**Figure 5-2** A schematic illustration of the redistribution of blood flow that occurs during fetal hypoxia. The size of the organs and other regions of the fetus are in proportion to the quantity of blood flow. The head, heart, and adrenal glands are larger, and the placental size remains unchanged. Other organs and the body are smaller. **A.** Normoxia. **B.** Hypoxia. Courtesy of Dr. M. Lynne Reuss.

of hypoxic lamb fetuses, cerebral oxygen consumption was constant over a wide range of arterial oxygen contents because the decrease in arteriovenous oxygen content accompanying hypoxia was compensated for by the increase in cerebral blood flow (CBF). This initial response is presumed to be advantageous to a fetus in the same way the diving reflex is advantageous in an adult seal, in that the blood containing the available oxygen and other nutrients is supplied preferentially to vital organs, i.e., those organs with a high metabolic demand, and a high utilization to storage ratio. These changes have been extensively studied in the fetal sheep and there is correlative data from human studies particularly with respect to this brain-sparing effect.<sup>7,8</sup>

Increased alpha-adrenergic activity is important in determining regional distribution of blood flow in hypoxic fetal sheep by selective vasoconstriction. In studies of alpha-adrenergic blockade, the hypertension and increased peripheral vascular resistance observed during fetal hypoxia was reversed.<sup>9</sup> These changes were due to an increase in the resistance in the gut, spleen, lungs, and probably musculoskeletal areas, which shows the participation of the alpha-adrenergic system in the vasoconstriction of those areas.<sup>9</sup>

The local endothelium also has an effect on regional blood flow distribution. The endothelium releases vasoactive agents such as reactive oxygen species and nitric oxide. Nitric oxide acts locally on vascular smooth muscle to oppose peripheral constriction,<sup>10</sup> but superoxide reacts with nitric oxide to counter this effect. Thus, local factors affect vascular tone during hypoxia. Antioxidants may be useful in countering the effects of acute hypoxia and are currently the subject of research for such use.

## **B. Bradycardia**

Fetal bradycardia is triggered by the carotid chemoreflex as described in Chapter 3. This slows the speed of cardiac filling, which facilitates myocardial oxygen extraction and also increases end-diastolic volume.<sup>11</sup> The increase in end-diastolic volume initiates the Frank–Starling mechanism and increases stroke volume to the degree available in the fetal heart. Thus, the cardiac output is maintained despite the lower heart rate, although there is a limit to this.

## **C. Reduction in Oxygen Consumption**

Overall, fetal oxygen consumption decreases during hypoxia, likely as a result of decreased movement, change to a more quiescent state, and reduction of metabolic synthesis, such as growth. In one study, fetal oxygen consumption decreased to values as low as 60% of control from approximately 8 mL per minute per kg to 5 mL per minute per kg during fetal hypoxia in the chronically instrumented fetal sheep at an arterial oxygen tension of 10 mmHg.<sup>12</sup> This decrease was rapidly instituted, stable for periods up to 45 minutes, proportional to the degree of hypoxia, and rapidly reversible upon cessation of maternal hypoxia. It is accompanied by a fetal bradycardia of about 30 beats per min (bpm) below control and an increase in fetal arterial blood pressure.

Oxygen uptake in the heart and brain increases during hypoxia. In both organs it has been shown that the increase in blood flow matches the decrease in arteriovenous oxygen concentration differences across the organ so as to maintain the oxygen uptake by that organ.

## **D. Anaerobic Metabolism**

It is known that the fetus depends partially on anaerobic metabolism for energy needs during oxygen insufficiency.<sup>13,14</sup> As noted in Chapter 4, the efficiency of anaerobic metabolism is much less than that of aerobic metabolism. The end result of anaerobic metabolism is an accumulation of lactate primarily in the partially vasoconstricted beds where oxygen is inadequate for basic needs. Because lactate leaves the fetal circulation relatively slowly, the result is a decrease in the base excess in the fetal compartment over time. If this process continues unabated, the metabolic acidosis can

depress myocardial function, which leads to hypotension and then ischemia in the heart and other essential organs.

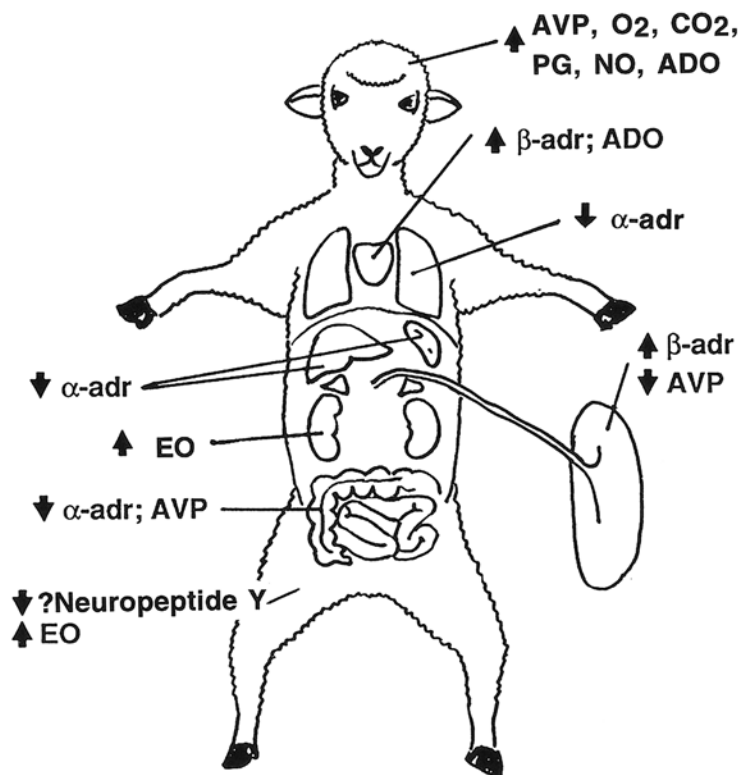
### E. Role of Carbohydrate Stores

It is likely that carbohydrate availability is critical in supplying substrates for anaerobic metabolism at more severe degrees of hypoxia. It has also been shown in experimental animals that a newborn's ability to tolerate asphyxia depends on cardiac carbohydrate reserves. This probably also applies to a human fetus, and clinical observations support the view that carbohydrate-depleted fetuses and newborns succumb more readily to hypoxia than do those with normal reserves. The clinical correlate of this observation is that a nutritionally growth-restricted fetus is thus more susceptible to intrauterine hypoxia than is a normally grown fetus.

### F. Mechanism of Cardiorespiratory Responses

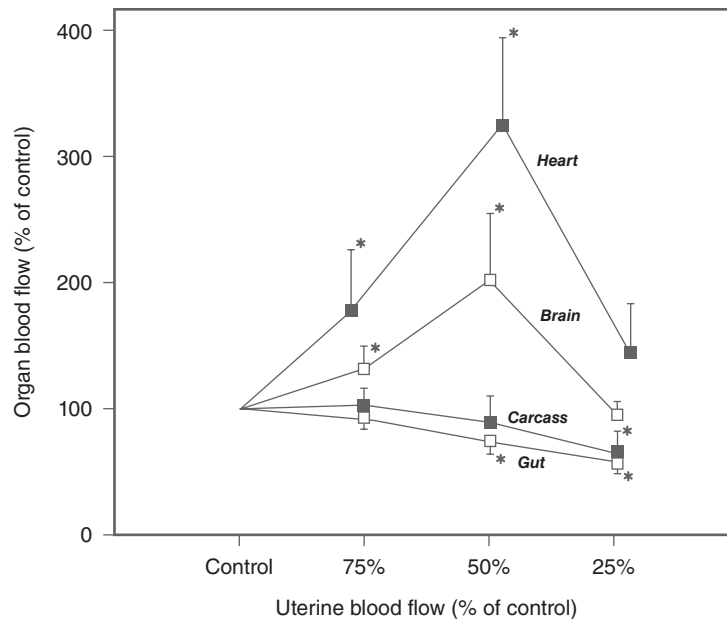
The cardiovascular responses to hypoxia are instituted rapidly and are mediated by both neural and humoral mechanisms (Figure 5-3). The close matching of blood flow to oxygen availability to achieve a constancy of oxygen consumption has been demonstrated in the fetal cerebral circulation,<sup>15</sup> and in the fetal myocardium.<sup>11</sup>

Although the tonic influence of the autonomic nervous system on heart rate, blood pressure, and the umbilical circulation in a normoxic fetus is quantitatively minor, the autonomic activity during hypoxia is significantly increased. In studies using total pharmacologic blockade, it has been demonstrated that during hypoxia, parasympathetic activity is augmented three- to five-fold and beta-adrenergic activity doubles when measured by heart rate response.<sup>16</sup> The net result of these changes is a decrease in FHR during hypoxia. Augmented beta-adrenergic activity also may



**Figure 5-3** Summary of the mechanisms that are known to participate in the regulation of blood flow due to changes in vascular resistance in different organs and tissues during hypoxia in the fetal sheep.

Abbreviations: ADO, adenosine; α-adr, alpha-adrenergic; AVP, arginine vasopressin; β-adr, beta-adrenergic; CO<sub>2</sub>, carbon dioxide; EO, endogenous opioids; NO, nitric oxide; O<sub>2</sub>, oxygen; PG, prostaglandins.



**Figure 5-4** The effect of graded reductions in uterine blood flow on blood flow redistribution in the sheep fetus. When uterine blood flow is reduced to 75% of control, blood flow is preferentially redistributed to the heart and brain at the expense of other tissues or organs (e.g., carcass and gut). This redistribution is more pronounced when uterine blood flow is reduced to 50% of control value. However, when further reduced to 25% of control, the resultant severe asphyxia results in a partial “breakdown” of the blood flow redistribution mechanism. It is suggested that this leads to a reduction of myocardial and/or cerebral oxygen consumption (see text). Based on Yaffe H, Parer JT, Block BS, Llanos AJ. Cardiorespiratory responses to graded reductions of uterine blood flow in the sheep fetus. *J Dev Physiol.* 1987; 9:325-336.<sup>1</sup>

be important in maintaining cardiac output and umbilical blood flow during hypoxia, probably because of the increased inotropic effect on the heart.

Plasma concentrations of catecholamines, arginine vasopressin,  $\beta$ -endorphin, and atrial natriuretic factor increase during hypoxia in the fetus. The contributions of catecholamines to the circulatory responses to hypoxia have been described. Vasopressin contributes to the increase in blood pressure observed during hypoxia by decreasing umbilical and gut blood flows. Beta-endorphin and probably other endogenous opioids also participate in the response to hypoxia. A blockade of endorphin receptors with naloxone has been shown to further increase the hypertensive response by increasing vasoconstriction in the kidneys and carcass. During hypoxia, a decrease in the fetal blood volume has been described. Atrial natriuretic factor may play a role in this response. In addition, nitric oxide, prostaglandins, and adenosine have all been implicated in regulation of the fetal circulation during hypoxia.

Most of these results have been observed from studies of chronically catheterized fetal sheep. The relative contribution of these and other mediators to the cardiovascular response to hypoxia in a human fetus continues to be explored; however, it is clear that the redistribution of blood flow is a powerful mechanism for protection of essential fetal organs from asphyxial damage during periods of oxygen insufficiency.

During more severe asphyxia or sustained hypoxemia, these responses are no longer maintained and a decrease in the cardiac output, arterial blood pressure, and blood flow to the brain and heart occurs (**Figure 5-4**).<sup>1</sup> These changes may be considered to be a stage of decompensation after which tissue damage and even fetal death may follow.

## G. Myocardial Dysfunction Following Profound Hypoxia

During profound asphyxia, hypotension may occur partly from loss of peripheral vasoconstriction, but hypotension is primarily related to asphyxia impairment of myocardial contractility. Asphyxia that is severe and long enough in duration to deplete glycogen stores in the heart seems to be the

main cause of myocardial dysfunction. “Cardiac stunning,” a term applied to reversible cardiac failure without histological change, is thought to be the first manifestation of myocardial dysfunction that is followed by irreversible myocardial failure if asphyxia is not resolved.<sup>17</sup> Preterm fetuses have more glycogen stores than do term fetuses; this may be part of the reason the preterm fetus can withstand acute asphyxia longer than a term fetus.<sup>18,19</sup>

## H. Fetal Response to Chronic Hypoxia

Intrauterine growth restriction, which can be due to placental dysfunction and chronic insufficient supply of nutrient or oxygen, is known to be associated with an increased risk for cardiovascular disease later in postnatal life. The mechanism underlying this relationship is the subject of current animal studies and results are still preliminary. In brief, it appears that intrauterine chronic hypoxia may affect both morphology and function of the heart in ways that increase vulnerability to cardiovascular related disorders in adulthood.<sup>20</sup>

Chronic hypoglycemia and hypoxemia are associated with elevated levels of circulating catecholamines. The catecholamines appear to play a role in blunting pancreatic insulin secretion, which results in less glycogen synthesis. Growth restriction occurs as a result of decreased oxygen consumption. Redistribution of blood flow remains present over the course of chronic hypoxia and decreased renal blood flow may explain the development of oligohydramnios. Shifts in blood flow contribute to the “brain-sparing” response as oxygenated blood continues to be preferentially delivered to the brain. Activation of the hypothalamic–pituitary–adrenal (HPA) axis results in elevated cortisol levels, which are also theorized to play a role in some of the long-term postnatal vulnerabilities of cardiovascular disorders. One important short-term clinical correlate is that the intrauterine growth restricted fetus is more vulnerable to acute hypoxia. Obstetric management of intrauterine growth restriction (IUGR) is reviewed in more detail in Chapter 10.

## II. CENTRAL NERVOUS SYSTEM RESPONSE TO HYPOXIA

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The response to cerebral hypoxia in the fetus is initially protective during mild hypoxia, and involves substantial compensatory mechanisms during moderate hypoxia. However, these compensatory mechanisms break down in the presence of severe asphyxia and damage then ensues.

### A. Cerebral Blood Flow and Oxygen Metabolism During Acute Hypoxia

When the fetus is initially subjected to hypoxemia severe enough to stimulate the chemoreceptors and the brain stem autonomic center, the heart rate decreases by parasympathetic nerve stimulation. This is usually accompanied by an increase in the arterial blood pressure probably from sympathetic nerve stimulation. CBF thereby increases quite quickly by means of hypertension and a decrease of cerebrovascular resistance. There is some redistribution of blood flow within the central nervous system as well.<sup>8</sup> This mechanism of cerebral autoregulation is essential for maintaining oxygen delivery to the central nervous system during physiologic variations in blood pressure and other factors. In response to these changes, fetal breathing and fetal movement cease, oxygen consumption is reduced, and cerebral metabolism slows.<sup>21</sup>

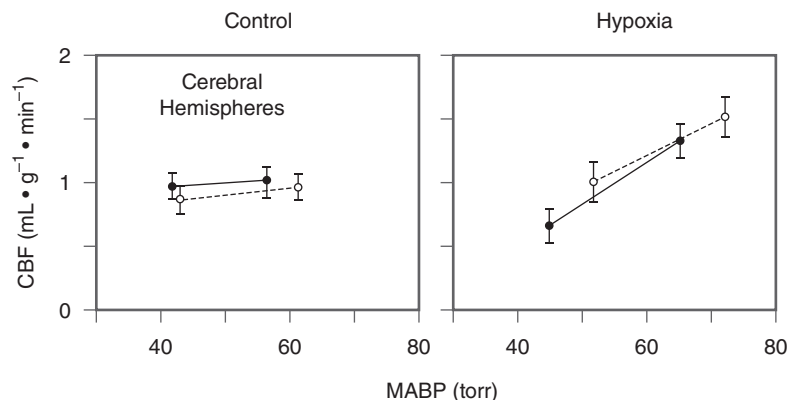
During acute hypoxia or asphyxia produced in the fetal sheep by various techniques, there is an initial decrease in cerebral vascular resistance and an increase in CBF.<sup>6,15,22,23</sup> The increase in blood flow is such that oxygen consumption in the cerebral hemispheres remains constant over the range of ascending aortic oxygen tensions of 14 to 36 mmHg.<sup>15</sup> This cerebral autoregulation is maintained during mild transient mild hypoxia. Arterial oxygen content has the best overall correlation with CBF during hypoxia.

Carbon dioxide tension is also involved in vasodilation of the cerebral vascular bed during asphyxia.<sup>24</sup> The CBF is directly proportional to carbon dioxide tension, but this may not result in increased oxygen consumption by the brain. The response may teleologically be thought of as a mechanism for reducing elevated brain carbon dioxide.

Carbon dioxide has an independent effect, which may alter the brain's ability to tolerate hypoxia, because as carbon dioxide falls, CBF also falls; therefore, in order to maintain oxygen consumption, oxygen extraction must increase. This is of less importance in the fetus because during asphyxia in utero, carbon dioxide almost invariably rises, unless there is extreme maternal hyperventilation.

CBF autoregulation in the fetus is dependent on adequate arterial oxygen because during more severe degrees of hypoxia, CBF becomes pressure dependent (**Figure 5-5**).<sup>25</sup> Under conditions of severe asphyxia when uterine blood flow was 25% of control, it was found that sufficient augmentation of the CBF was no longer maintained, and CBF decreased to control values (Figure 5-4).<sup>1</sup> There was a doubling of the vascular resistance in the cerebral vasculature compared to normoxic control values, and a further increase in arterial blood pressure. This decrease in blood flow, coupled with a decreased arteriovenous oxygen difference during more profound hypoxemia, results in a decrease in cerebral oxygen consumption to as much as half of normal.<sup>26</sup> This reduced consumption appears to be proportional to the degree of hypoxemia as measured by arterial oxygen content and is due to the fact that cerebral vascular resistance does not decrease further in response to and in proportion to the increasing hypoxemia. Thus, CBF can no longer be augmented below a certain level of hypoxemia, and with the progressive obligatory reduction in arteriovenous oxygen difference, the uptake of oxygen falls. The reduction in cerebral oxygen consumption appears to occur when ascending aorta oxygen content is below 1 mM. The inability of the fetus to maintain sufficient oxygen delivery to the brain had previously been predicted on the basis of the increased fraction of cardiac output (25–50%) required to be directed toward the heart and central nervous system. On the basis of mathematical modeling it was suggested that when ascending aortic oxygen content was reduced from 1 to 0.5 mmol/L<sup>-1</sup> such a compensation could not take place, and the cardiovascular system may begin to fail in delivering adequate amounts of oxygen to at least some parts of the central nervous system.

There are several possible mechanisms for the variations in CBF during hypoxia; one possibility (extrapolating from adult studies) is a direct action of oxygen tension in smooth muscle. Oxygenases have been suggested as oxygen sensors in mediating the responses. Release of the vasodilator



**Figure 5-5** CBF related to fetal mean arterial blood pressure. Under control conditions there is autoregulation with constancy of CBF at varying pressures. This constancy (or autoregulation) is lost under hypoxic conditions. Arrows show the direction of experimental change in pressure.

Abbreviations: CBF, cerebral blood flow; MABP, mean arterial blood pressure

Reproduced with permission from Tweed WA, Cote J, Pash M, Lou H. Arterial oxygenation determines autoregulation of cerebral blood flow in the fetal lamb. *Pediatr Res.* 1983;17:246-249.<sup>25</sup>



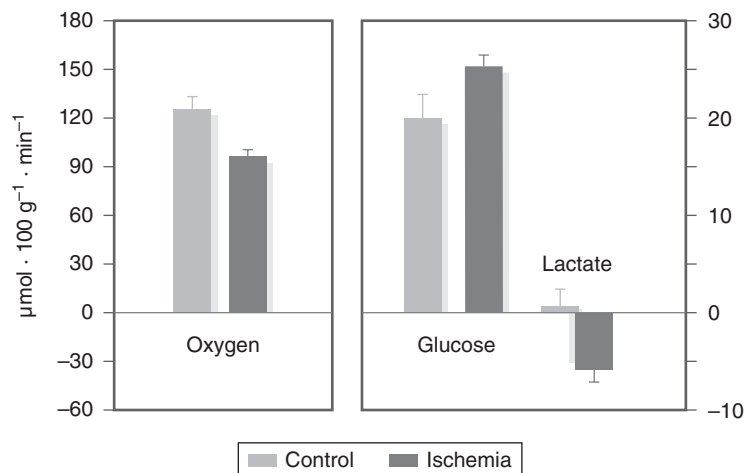
adenosine may be one such mechanism. It has been shown that brain vascular resistance increases and CBF decreases during hypoxia in fetal sheep in response to arginine vasopressin, prostaglandin, and nitric oxide blockade,<sup>27</sup> thus demonstrating a role for these substances. There may also be other as yet unidentified substances and mechanisms.

## B. Cerebral Carbohydrate Metabolism During Hypoxia

The presence of adequate brain carbohydrate stores is an important determinant of tolerance to asphyxia. During hypoxia of moderate to severe degrees, the circulating glucose concentration rises by approximately 50% in fetal sheep. Similarly, there is development of a metabolic acidosis, most of which can be explained by increased lactate levels that are due to anaerobic metabolism.<sup>28</sup>

The glucose and lactate flux across the brain has been studied in the fetal sheep during cerebral ischemia produced by partial occlusion of the brachiocephalic artery.<sup>29</sup> Hypoxia triggers an increase in circulating glucose. This increase may be potentiated by decreased peripheral use of glucose, increased hepatic production of glucose, and release of glucose from glycogen stores secondary to the catecholamine response. During severe ischemia, brain oxygen consumption decreases by approximately 26%, and glucose uptake is increased by approximately 25% (Figure 5-6). This is considerably more glucose than can be accounted for by the corresponding fall in oxygen uptake. The brain lost lactate during brachiocephalic artery occlusion, but not as much as would be expected. The authors concluded that lactate accumulated in the brain tissue because of inability of the blood–brain barrier to transport it, and that this may contribute to brain injury, in which elevated lactate levels have been previously implicated in adult and premature fetuses.<sup>29</sup> During combined hypoxemia and cerebral ischemia, however, the same group of authors could not detect a net lactate flux out of the central nervous system. They suggested that this may be due to a concomitant increase in both cerebral and systemic lactate concentration.

In a similar model, it was shown that a glucose infusion tended to maintain electroencephalographic (EEG) amplitude during cerebral ischemia, thus suggesting glucose had a protective effect. In further studies, fetal glucose levels were reduced 33% by insulin infusion, which did not produce any short-term reduction in cerebral oxygen or glucose consumption.<sup>30</sup>

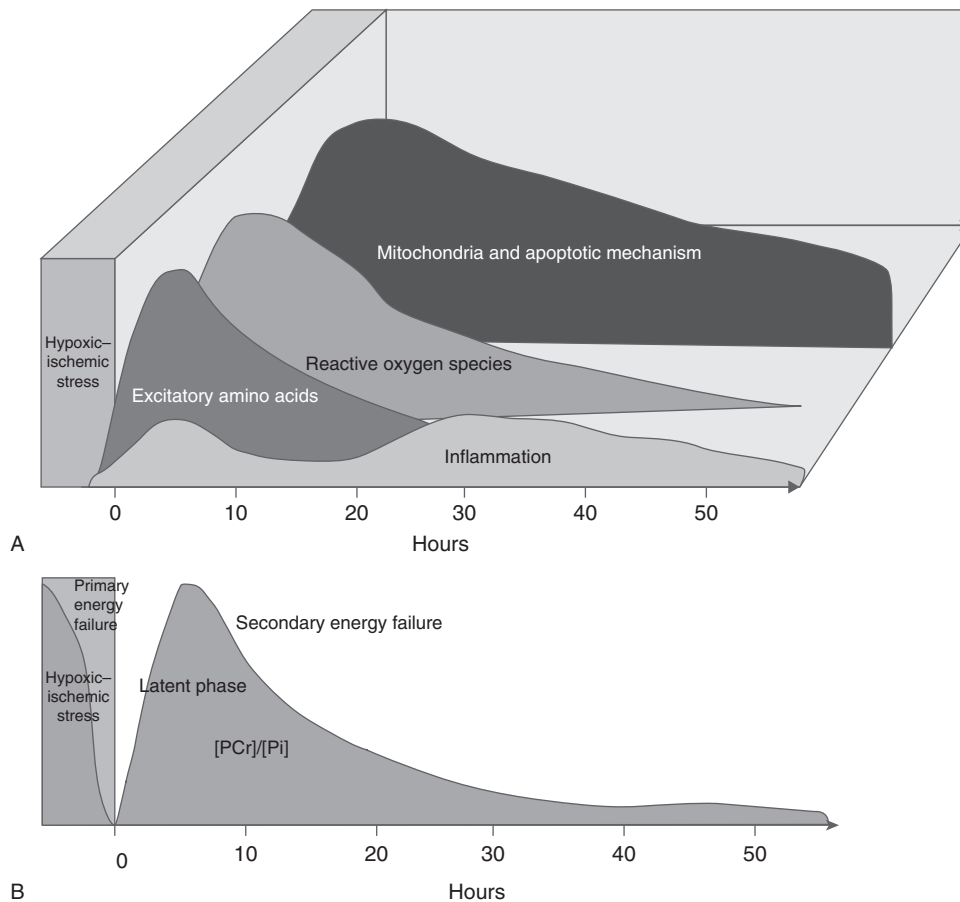


**Figure 5-6** Net fluxes of oxygen, glucose, and lactate during experimental cerebral ischemia in fetal sheep. There is a decrease in oxygen uptake, an increase in glucose uptake, and an increase in lactate output by the brain during ischemia. Reproduced with permission from Chao CR, Hohimer AR, Bissonnette JM. Cerebral carbohydrate metabolism during severe ischemia in fetal sheep. *J Cerebral Blood Flow Metab.* 1989;9:53-57.<sup>29</sup> Copyright © 1989 by SAGE Publications, Ltd. Reprinted by permission of SAGE Publications, Ltd.

### C. Hypoxic–Ischemic Injury

When systemic hypotension occurs following myocardial dysfunction, autoregulation of CBF and cerebral perfusion fail and the brain becomes ischemic.<sup>31,32</sup> Tissue oxygen deficiency occurs from both hypoxemia and ischemia, and the areas of fetal brain most vulnerable are those that experience the lowest perfusion pressure, which are the watershed areas between vascular nets within the brain,<sup>33</sup> and the areas that are the most metabolically active under normal conditions such as the sensorimotor cortex, thalamus, cerebellum, and brain stem.

During acute hypoxic deterioration, high-energy metabolites are depleted, and an evolution of the brain damage ensues. The first stage of energy depletion is called “primary energy failure” and corresponds to severe cytotoxic edema and cell swelling. Following the primary energy failure, a recovery period called the “latent phase” occurs in which reperfusion restores oxygen and glucose. During this phase, recovery of high-energy reserves such as phosphocreatine are reattained and electroencephalographic parameters recover as well. After the “latent phase,” a “secondary energy failure” follows and brain cells die many hours or even days later. The gradual drop change in phosphocreatine levels affected by asphyxial insults is shown in **Figure 5-7**.<sup>34</sup> Immediately after the insult, phosphocreatine recovers to the pre-insult value. The phosphocreatine level decreases again 5 to 6 hours after the insult and remains at a low



**Figure 5-7** A. Time course of four important of molecular mechanisms of brain injury following hypoxic–ischemia. B. Change in cerebral [PCr]/[Pi] after hypoxic–ischemia. The primary and secondary decreases of this high-energy phosphate reserve correspond with primary and secondary energy failure.

Abbreviations: PCr, phosphocreatine concentration; Pi, inorganic orthophosphate concentration.

level. This secondary deterioration in high-energy reserves energy and cerebral energy failure usually occurs approximately 6 to 15 hours after birth. Subsequently, a longer-term tertiary phase occurs that may inhibit repair and reorganization.

### Primary Energy Failure

Insufficient adenosine triphosphate (ATP) sets off the chain of events that results in cellular death (Figure 5-8).<sup>35-37</sup> The sodium-potassium pump that maintains sodium in the extracellular space and potassium in the intracellular space fails; this leads to cellular edema and depolarization of the cell membrane, which results in necrotic cell death.<sup>38,39</sup> Excitatory neurotransmitters such as glutamate accumulate in the synaptic space due to a failure of

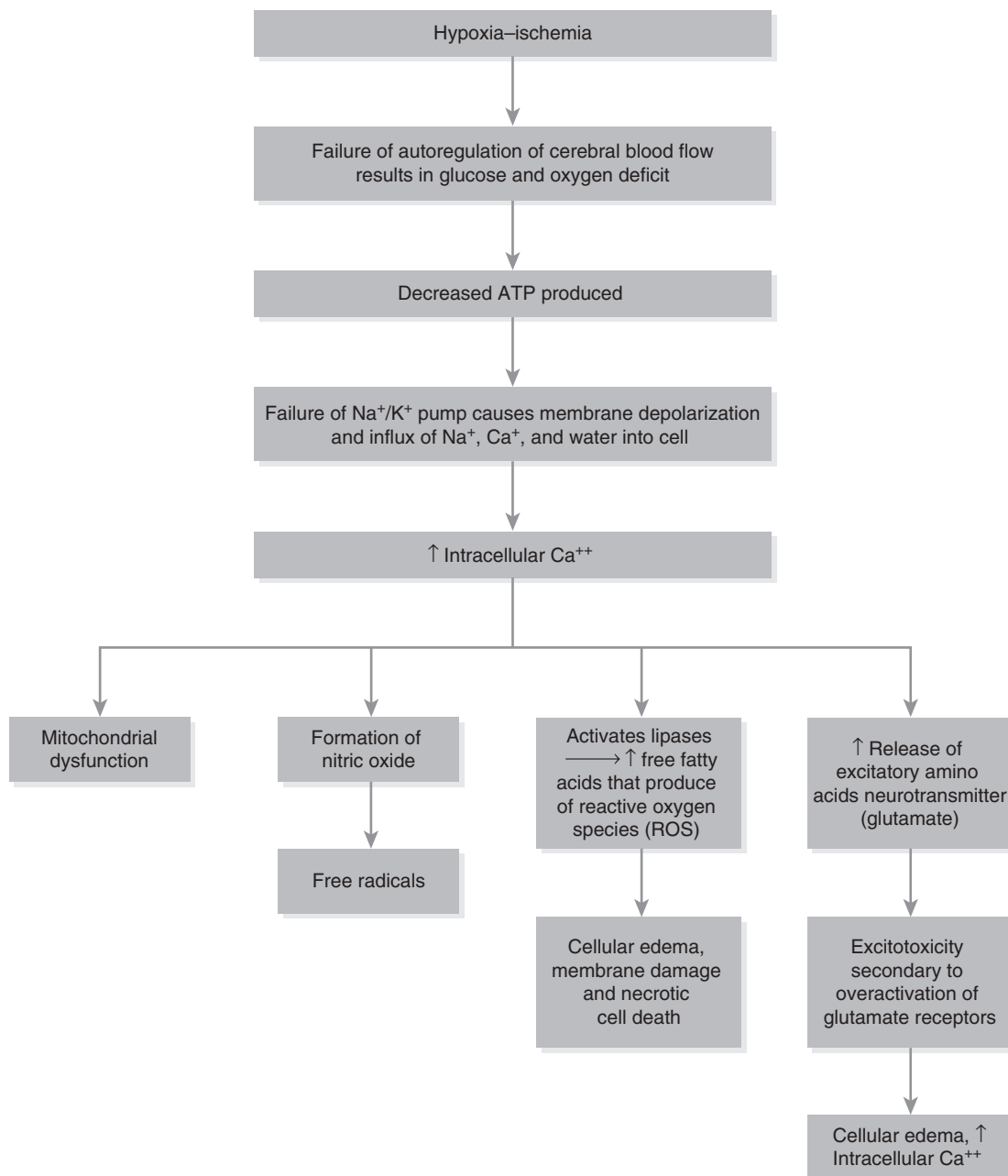


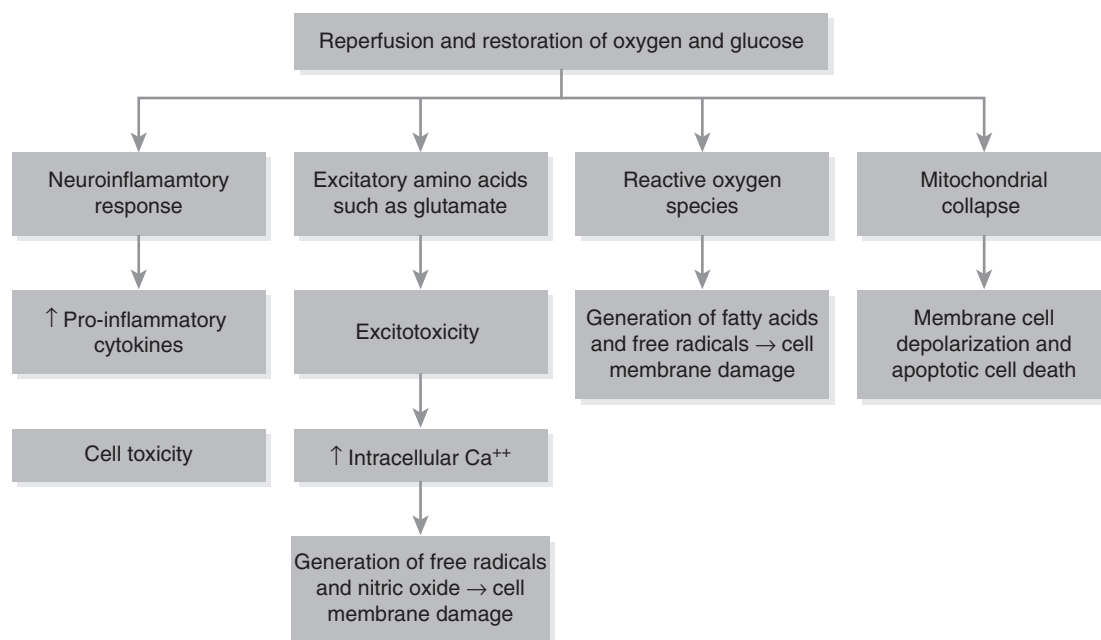
Figure 5-8 Primary energy failure: mechanism of hypoxic-ischemic injury.

the normal reuptake mechanisms. The excess glutamate overstimulates glutamate receptors including the N-methyl-D-aspartate (NMDA) glutamate receptor in the postsynaptic neurons, which results in an intracellular biochemical cascade due to an influx of calcium into the intracellular space.<sup>38</sup> Calcium in the cytoplasm then instigates a chain reaction of enzymatic processes, which result in the production of several compounds that further damage the cell including nitric oxide and other free oxygen radicals.<sup>31,36,40,41</sup> In addition, the results of this process include microvascular damage with resultant necrosis and apoptosis.

## Secondary Energy Failure

Some of the products of cellular metabolism that are produced in the absence of glucose and oxygen become more dangerous during reperfusion when the asphyxia subsides and oxygenation is restored. Thus, reperfusion exacerbates the injury to brain neurons and initiates a secondary process of cell death. The region of the brain affected by these events is dependent upon the gestational age of the fetus, development of the neurons involved, and the severity of the insult.<sup>41</sup>

Many studies have demonstrated that this evolution of brain energy deterioration involves four different mechanisms: (1) excitatory amino acids such as glutamate; (2) mitochondrial deterioration and apoptotic mechanisms; (3) reactive oxygen species; and (4) inflammation (Figure 5-9).<sup>31,41-43</sup> It is important to take into consideration when and how much these four mechanisms contribute to the pathophysiology in the context of primary and secondary energy failure. Glutamate has a toxic effect on the central nervous system through excitotoxicity. Excessive activation of the post-synaptic NMDA receptor by glutamate leads to neuronal death. Mitochondrial dysfunction leads to an upregulation of apoptosis, which is believed to play a more important role in brain damage in the developing fetus compared with that of adult. Reactive oxygen species generated during the initial insult react with lipids and proteins to further disrupt the stability of neuronal cell membranes. Finally immuno-inflammatory cells such as microglia and macrophages are activated, resulting in several adverse effects including additional production of reactive oxygen species and production of proinflammatory cytokines.



**Figure 5-9** Secondary energy failure: mechanism of hypoxic-ischemic injury.

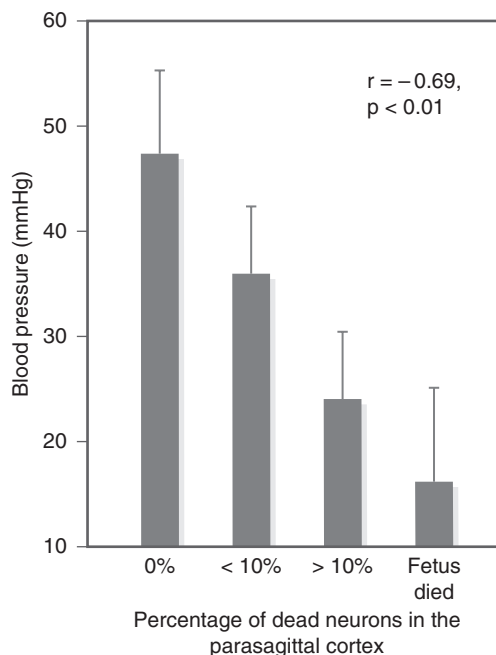
## D. Mechanism of Perinatal Brain Damage: Animal Studies

In clinical practice, the severity, pattern, and timing of asphyxia are usually unknown. Therefore, animal studies are used to initially identify the pathophysiology of fetal asphyxia and correlate the type of hypoxic–ischemic stress to the type of brain damage.

Ronald E. Myers was the pioneer of animal experiments that researched mechanisms of fetal brain damage with a series of studies of fetal monkeys that demonstrated how both respiratory and metabolic acidosis occurred rapidly following complete cessation of oxygen delivery.<sup>44</sup> Blood was sampled for 13 minutes from the femoral artery through a catheter placed before birth. The pH fell at 0.04 units per minute, the carbon dioxide tension increased 6 mmHg per minute, and the base excess fell slightly more than 1 mEq/L per minute. The oxygen tension fell to about 6 mmHg in about 2 minutes, and stabilized at that level. Intact survival generally did not occur after 10 minutes of complete oxygen lack. Survivors generally had brain stem lesions, although the patterns of damage were variable. Myers and coworkers also studied prolonged partial asphyxia in sheep and monkeys as chronic hypoxia is more common than acute sentinel events.<sup>45</sup> Similar to their findings following brief complete asphyxia they found a variable pattern of response to partial asphyxia. Survivors generally had neurologic deficits due to cortical lesions, in contrast to those subjected to complete oxygen cessation wherein the lesions were usually in the brain stem.<sup>45</sup>

### Importance of Hypotension and Cerebral Hypoperfusion

The animal experiments of fetal and neonatal hypoxic–ischemic brain damage can be divided into those that have induced “total (global) acute stress” and those that have induced “partial subacute stress.” Total acute stress is often introduced by interrupting blood flow to the uteroplacental region or to the umbilical cord. Gunn et al. found that neuronal damage following induced asphyxia via uterine artery occlusion in fetal sheep was strongly associated with the minimum blood pressure during the insult but not with the degree of hypoxia (**Figure 5-10**).<sup>28</sup> In a subsequent study by Mallard et al., severe umbilical cord occlusion for 10 minutes in near-term fetal sheep produced



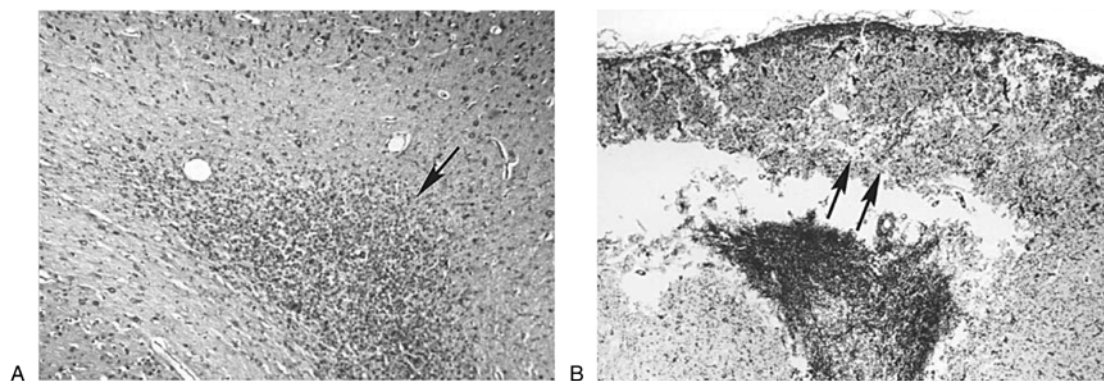
**Figure 5-10** Relationship between minimum blood pressure during severe asphyxia and percentage of dead neurons in the parasagittal cortex at 72 hours in fetal sheep.

Based on Gunn AJ, Parer JT, Mallard EC, Williams CE, Gluckman PD. Cerebral histologic and electrocorticographic changes after asphyxia in fetal sheep. *Pediatr Res.* 1992;31:486-491.<sup>28</sup>

neuronal cell loss in the hippocampus.<sup>46</sup> Although the duration was short, severe asphyxia, hypoxemia, bradycardia, and electrocorticographic suppression were present for up to 5 hours following the intervention. Three of 17 animals did not survive the asphyxia. Hippocampus, cerebellum, basal ganglia, and thalamus as well as the brain stem were mainly injured. The metabolism during asphyxia was not quantitated but it was most likely severely depressed. These studies also demonstrated the critical importance of hypotension and/or brain hypoperfusion during total acute asphyxia.<sup>28,46</sup> Neuronal damage is strongly associated with the minimum blood pressure during the insult but not with the degree of hypoxia. These data are consistent with the suggestion that impairment of cerebral perfusion and hypotension is a critical event in causing cerebral damage during perinatal asphyxia.

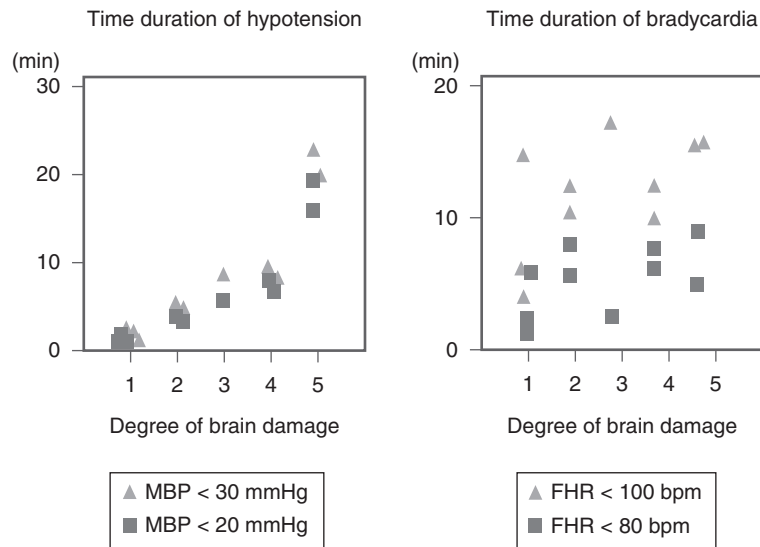
The experimental study of partial subacute stress has also revealed the importance of hypotension on severity of brain damage. Ikeda et al. produced relative prolonged partial asphyxia via umbilical cord occlusion for approximately 60 minutes in chronically instrumented near-term fetal lambs until the fetal arterial pH was less than 6.9 and base excess was 20 mEq/L or less.<sup>47</sup> Although the asphyxia protocol was strictly applied, neuropathologic changes varied from case to case, ranging from almost total infarction of cortical and subcortical structures to extremely subtle and patchy white matter alterations (**Figure 5-11**). This variation enabled the authors to evaluate the relationship between physiologic and histologic parameters. The histopathologic changes were categorized into five grades that ranged from mild to severe histologic damage. The severity of change in pH, base excess, PCO<sub>2</sub>, PO<sub>2</sub>, and oxygen content did not correlate with the extent of histologic damage. The duration of hypotension (defined as < 20 mmHg mean blood pressure and < 30 mmHg) did show a significant correlation with histologic grade (**Figure 5-12**), but the duration of bradycardia (defined as < 80 bpm and < 100 bpm) did not. Recovery time for electrocorticographic amplitude, presence of convulsions, and blood lactate level at 24 hours after asphyxia were well correlated with the severity of fetal brain damage.

Ball et al. produced seizures after umbilical cord occlusion of less severity and longer duration.<sup>48</sup> It has been shown that a change in electrocorticographic activity from low voltage/high frequency to high voltage/low frequency is associated with a similar decrease in oxygen uptake.<sup>49</sup> The degree of hypoxemia seen in the moderately asphyxiated fetuses is associated with such an EEG change from low to high voltage; this alone may explain the decrease in cerebral oxygen consumption that occurs during high-voltage EEG compared to low-voltage EEG. We do not have data on the exact



**Figure 5-11** A. Photomicrograph of cerebral cortical white matter of an asphyxiated fetal lamb brain following 60-minute umbilical partial occlusion that shows increased cellularity (arrow) confined to junction of cerebral cortex and white matter (Hematoxylin-eosin stain, original magnification  $\times 98$ ). B. Another fetal lamb in the same severity of asphyxia showed almost total infarction with necrosis of gray matter (arrows) and separation of white matter (Luxol fast blue-cresyl violet stain, original magnification  $\times 49$ ).

Reproduced with permission from Ikeda T, Murata Y, Quilligan EJ, et al. Physiologic and histologic changes in near-term fetal lambs exposed to asphyxia by partial umbilical cord occlusion. *Am J Obstet Gynecol.* 1998;178(1 pt 1):24-32.<sup>47</sup> Copyright 1998, with permission from Elsevier.



**Figure 5-12** Correlation between duration of hypotension and bradycardia and histologic grade of fetal brain damage. Duration of hypotension correlated significantly with histologic grade.

Abbreviations: bpm, beats per minute; FHR, fetal heart rate; MBP, mean blood pressure.

Reproduced with permission from Ikeda T, Murata Y, Quilligan EJ, et al. Physiologic and histologic changes in near-term fetal lambs exposed to asphyxia by partial umbilical cord occlusion. *Am J Obstet Gynecol.* 1998;178(1 pt 1):24-32.<sup>47</sup> Copyright 1998, with permission from Elsevier.

threshold of reduction in oxygen consumption that causes damage to the fetal brain. It seems likely however that a 15% reduction would be tolerable.

In summary, severe intrapartum asphyxia causes injury to the fetal brain via the combination of hypoxia and ischemia. Because the fetus has remarkable compensatory mechanisms, most survivors of nonfatal asphyxial insults have no sequelae. In newborns wherein the insult was severe but sublethal, neurologic impairment due to hypoxic–ischemic encephalopathy results. These studies have some important clinical implications. They show the remarkable conservation strategies available to the fetus despite quite substantial hypoxemia, mainly due to the fetal capacity for augmenting CBF. This may explain why intact survival is frequently seen in the human fetus despite severe documented asphyxia at birth. With profound asphyxia, however, there is decompensation of these mechanisms and such fetuses may subsequently develop hypoxic neuronal damage or die.

### III. FETAL ASPHYXIA AND NEWBORN MORBIDITY

The degree of damage to any individual fetus following intrauterine asphyxia is quite variable. Some fetuses may not survive the episode in utero, others will have central nervous system damage that results in neurologic defects, and still others will survive without apparent deficits. Multiple factors influence the outcomes of intrauterine asphyxia including gestational age, exacerbating conditions such as infection, and duration and degree of the hypoxia, to name only a few. Studies of umbilical artery blood gas acid–base values, neonatal encephalopathy, cerebral palsy etiologies, and more recently, MRI analysis of perinatal brain lesions are just beginning to help determine the threshold values that predict neurologic impairment.

#### A. Blood Gas Markers of Fetal Asphyxia

Umbilical artery blood gas values represent the acid base status of the newborn just prior to birth. In view of the fact that the state of asphyxia spans a continuum from “physiologic” to “terminal,” and

that pathologic brain damage has not been rigidly defined in terms of acid–base state at birth, it is not yet possible to assign a particular umbilical artery pH or base excess value or set of values that can be used to identify clinically significant asphyxia in the newborn. The duration and extent of metabolic acidosis and hypoxia that will result in neurologic damage to the human fetus are not known.

Low and colleagues approached this problem under the premise that severity of asphyxia should be correlated with severity of organ disorders: brain (encephalopathy), cardiovascular, respiratory, and renal complications. The authors compared the newborn outcomes in a cohort of infants with no acidosis ( $n = 59$ ), respiratory acidosis ( $n = 51$ ), and metabolic acidosis ( $n = 59$ ). They first found that respiratory acidosis without a metabolic component, detected in umbilical artery cord gas analysis, had no harmful effect on short-term or long-term outcome in newborns (Table 5-2).<sup>50,51</sup> In a subsequent study, these authors determined the threshold of metabolic acidosis that is associated with newborn complications by categorizing newborn complications into four different degrees of umbilical artery base deficit.<sup>51</sup> Table 5-3 shows the relationship between moderate and severe organ complications in each of the four different groups of the umbilical arterial base deficit. The newborns with an umbilical artery base deficit more than 12 mmol/L were most likely to have organ dysfunction, especially within the central nervous system.

Gilstrap et al. evaluated the umbilical cord gases and newborn outcomes of 2738 women with a singleton pregnancy in cephalic presentation.<sup>52</sup> These authors found that newborns are at low risk for immediate complications following intrapartum asphyxia unless the umbilical artery pH is less than 7 and Apgar scores are 3 or less at both 1 minute and 5 minutes. Goodwin and coworkers reviewed the course of 129 term nonanomalous singleton infants with umbilical arterial pH below 7 and concluded that a pH below 6.8 with marked hypercarbia (carbon dioxide tension usually above 100 mmHg) and metabolic acidosis (base excess usually below  $-15$  mEq/L) is the acid–base status at birth that relates best to neonatal death or major

**Table 5-2 Classification of Intrapartum Fetal Asphyxia**

Asphyxia	Metabolic Acidosis at Delivery <sup>a</sup>	Encephalopathy	Cardiovascular, Respiratory, and Renal Complications
Mild	Present	Minor: present or absent	Minor: present or absent
Moderate	Present	Moderate: present	Severe: present or absent
Severe	Present	Severe: present	Severe: present

<sup>a</sup> Defined as umbilical artery base deficit greater than or equal to 12 mmol/L.

Reproduced with permission from Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. *Am J Obstet Gynecol.* 1994;170(4):1081-1087.<sup>50</sup> Copyright 1994, with permission from Elsevier.

**Table 5-3 Threshold of Metabolic Acidosis in the Term Newborn**

Moderate or Severe Newborn Complications	Umbilical Artery Base Deficit			
	4–8 mmol/L <sup>a</sup>	8–12 mmol/L <sup>a</sup>	12–16 mmol/L <sup>a</sup>	> 16 mmol/L <sup>a</sup>
Central nervous system	2	0	5	24
Respiratory	0	3	9	8
Cardiovascular	0	1	1	18
Renal	0	1	2	8

<sup>a</sup>  $n = 58$ .

Based on Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. *Am J Obstet Gynecol.* 1997;177(6):1391-1394.<sup>52</sup>



neurologic dysfunction.<sup>53</sup> Goldaber et al. expanded on the previous studies in their review of 3506 term newborns with an umbilical arterial pH of less than 7.20.<sup>54</sup> The newborns were categorized into five groups based on umbilical artery pH: (1) less than 7.0; (2) pH of 7.0 to 7.04; (3) pH of 7.05 to 7.09; (4) pH of 7.10 to 7.14; and (5) pH of 7.15 to 7.19. Two-thirds of the newborns with an umbilical artery pH less than 7.0 also had a metabolic component to the acidemia. The incidence of neonatal intensive care admission, Apgar score of 3 or less at 5 minutes, and need for intubation was significantly increased in the group that had an umbilical artery pH of less than 7.0. On the basis of this work, the authors defined a *pathologic fetal acidemia* as an umbilical artery pH of less than 7.0.

More recently Malin et al. conducted a meta-analysis of these studies and others.<sup>55</sup> They identified 51 articles that included 481,753 infants and the meta-analysis confirmed that low umbilical artery pH is significantly associated with neonatal mortality (OR, 16.9; 95% CI, 9.7–29.5), hypoxic–ischemic encephalopathy (OR, 13.8; 95% CI, 6.6–28.9), and cerebral palsy (OR, 2.3; 95% CI, 1.3–4.2).

These studies have clearly shown that an umbilical artery pH of less than 7.0 and a base deficit of more than 12 mmol/L are the threshold values most reliably associated with newborn morbidity and mortality. However, most infants with metabolic acidosis at birth do not have short-term or long-term complications. Furthermore, there are many reasons in addition to intrapartum hypoxia that can cause newborn morbidity. Thus, these studies provide limited predictive utility with regard to the relationship between umbilical artery values at birth and long-term outcome. We therefore believe that the term *asphyxia* should not be used to denote a specific pathologic state but rather should be used to define simply what it is, that is, elevated carbon dioxide and reduced oxygen, with a metabolic component. The term *asphyxia* should simply be used as a preceding descriptor for the acid–base features of umbilical arterial blood and the weakness of these values as a predictor of fetal damage should be implied.

## B. Neonatal Encephalopathy

Neonatal encephalopathy is a clinically defined syndrome that includes:

- Disturbed neurologic function in the earliest days of life in an infant born or at 35 weeks' gestation.
- A subnormal level of consciousness or seizures and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes.<sup>56</sup>

Neonatal encephalopathy occurs in approximately 2 per 1000 live births. Hypoxic–ischemic brain injury is a subset of neonatal encephalopathy and is only one of many etiologies of neonatal encephalopathy. Because neither hypoxia nor ischemia can be assumed to have been the unique initiating causal mechanism for a specific individual with neurologic impairment, ACOG has recommended that the term hypoxic–ischemic encephalopathy be replaced by neonatal encephalopathy.<sup>56</sup>

In 1976, Sarnat and Sarnat developed a scoring system that subcategorizes infants with neonatal encephalopathy into mild, moderate, and severe encephalopathy on the basis of multiple physical signs such as level of consciousness, neuromuscular control, reflexes, and autonomic function.<sup>57</sup> Although these three categories are well correlated with long-term neurological outcome, Sarnats' system is not suited to determine immediate management after birth, because the criteria are not assigned until after the first 24 hours of life.<sup>57</sup>

The Thompson score, introduced in 1997, is therefore used for making immediate decisions about newborn management. This score consists of six categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro), and autonomic nervous system (pupils, heart rate, or respiration).<sup>58</sup> The Thompson score can be used to initiate interventions such as hypothermia.

**Table 5-4 Common Cerebral Lesions Observed in Neonatal Encephalopathy**

Term	Description
Basal ganglia–thalamus (BGT) pattern	Striatum and ventrolateral thalamus: most common, 25–75%; severe partial insult of prolonged duration or a combined partial with profound terminal insult
Watershed or border zone predominant pattern	Parasagittal cortical neuronal necrosis at regions between the major cerebral vessels: watershed: 15–45%; hypotension, maternal fever
White matter injury	Periventricular leukomalacia or white matter injury: mainly preterm infant, milder noncystic forms seen in 10–20% in term infant; hypotension, infection/inflammation
Vascular lesion	Focal arterial distribution infarct: 5–10% in term infant; ischemic infarction

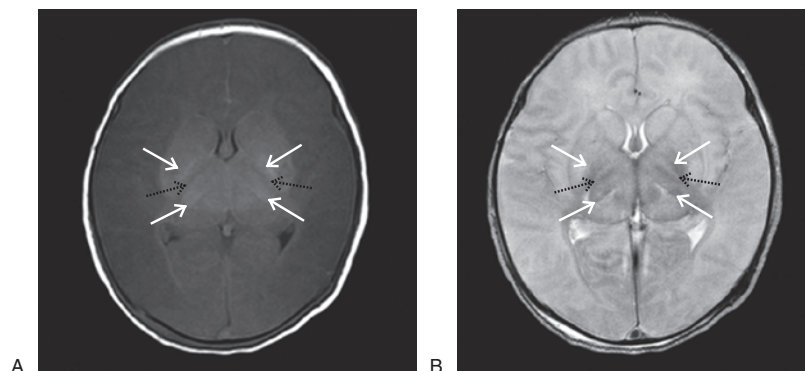
Based on American College of Obstetricians and Gynecologists (ACOG) Task Force on Neonatal Encephalopathy. *Neonatal Encephalopathy and Neurologic Outcome*. 2nd ed. Washington, DC: ACOG; 2014.<sup>56</sup>

### C. Neonatal Brain Damage Following Fetal Asphyxia

Recent progress in imaging techniques, especially magnetic resonance imaging (MRI), has enabled us to evaluate and study the evolution of perinatal brain damage in living fetuses and neonates. It is valuable to speculate on the severity, pattern, and timing of hypoxic and/or ischemic insult. **Table 5-4** summarizes the four common cerebral lesions observed in perinatal brain damage identified via magnetic resonance imaging. The selective vulnerability of specific brain regions appears to be based on factors such as metabolic demand, density of glutamate receptors, and extent of vascularization.

#### Basal Ganglia–Thalamus Pattern: Acute Hypoxic–Ischemic Injury

The most frequently observed brain damage in survivors of acute asphyxia is centered in the deep nuclear brain matter and includes the basal ganglia, striatum, and thalamus (**Figure 5-13**).<sup>59</sup> These injuries are especially common in cases that involve an acute hypoxic–ischemic insult such as occurs following placental abruption or uterine rupture. Conventional MRI cannot usually detect brain abnormalities until 24 to 48 hours after a hypoxic–ischemic insult occurs.



**Figure 5-13** An infant at 37 weeks' gestation born after cord prolapse with Apgar score 0 at 5 minutes. Spontaneous heart beat was recovered 40 minutes after the birth. MRI was taken on 5 days of life. The infant received hypothermic therapy for 72 hours from 4 hours after birth. **A.** T1-weighted image shows high-signal intensity lesions on both basal ganglia and ventrolateral thalamus (solid arrows). Posterior limbs of internal capsules are changed to low intensity from normal high intensity (dashed arrows).

**B.** Low-signal intensity lesions are observed in corresponding areas on T2-weighted images.

Images courtesy of Dr. Tomohiko Nakamura, neonatologist of Nagano Children's Hospital.

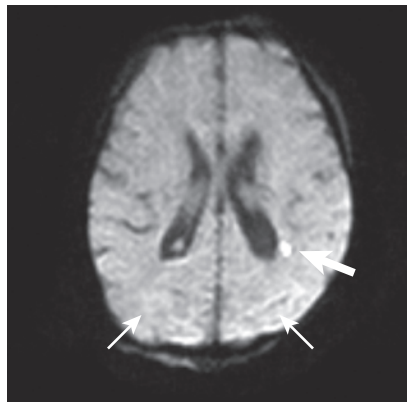
In the basal ganglia–thalamus (BGT) pattern, characteristic bilateral high-signal intensity is observed in the putamen and ventrolateral thalamus in the T1 weighted image. Lesions of the posterior limb of the internal capsule (PLIC) manifest low-signal intensity, whereas the normal term infant shows high-signal intensity in the PLIC. The PLIC represents one of earliest myelination areas within the pyramidal tracts. In term infants, the BGT area is one of the highest energy-demanding parts of the brain and contains a high number of glutamate receptors, which contributes to the vulnerability of this section of the brain to hypoxic-ischemic insult. Human research in this area corresponds to results of animal data that found severe prolonged asphyxia such as 5 minutes of complete carotid occlusion repeated three times resulted in striatal lesions while 30 minutes of partial carotid occlusion resulted in parasagittal cortex lesions.<sup>60</sup>

### Watershed Injury: Chronic Asphyxia

Watershed cortical damage including parasagittal cortex is mainly seen following chronic ischemic insult (**Figure 5-14**).<sup>61</sup> Watershed injury affects mainly the white matter and, in more severely affected infants, the overlying cortex in the vascular watershed zones (anterior-middle cerebral artery and posterior-middle cerebral artery). These lesions can be unilateral or bilateral and predominantly posterior and anterior. Although loss of the cortical ribbon and, therefore, the gray-white matter differentiation, can be seen on conventional MRI, diffusion-weighted imaging highlights the abnormalities and is especially helpful in making an early diagnosis. A repeat MRI may show cystic evolution, but more often atrophy and gliotic changes will be recognized.

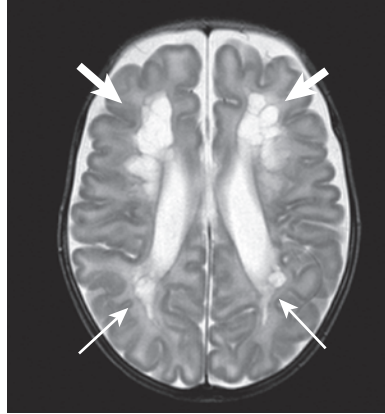
### White Matter Injury: Premature Fetus/Newborn

Injury to the white matter in the dorsal and lateral sections of the ventricles is more common in preterm newborns compared to term newborns, and more common following severe asphyxial insults (**Figure 5-15**). The white matter in the dorsal and lateral sections of the ventricles is vulnerable to ischemia and hypotension (not necessarily accompanied with hypoxia) for a three-fold reason; compared to term fetuses, the preterm fetus has (1) fewer anastomoses between ventrofugal arteries (arteries extending from brain parenchymal outward) and ventropetal arteries (arteries extending from brain surface inward); (2) more pre-myelinating oligodendrocytes (preOLs) that are especially



**Figure 5-14** A 2723-gram asphyxiated infant was born at 39 weeks' gestation with 1- and 5-minute Apgar scores of 2 and 3, respectively. Diffusion weighted image MRI at 7 days of life revealed high intensity cystic region in the left periventricular zone (thick arrow). Rather high intensity areas are seen in both occipital lobes (thin arrows), compatible with watershed areas between middle and posterior cerebral arteries.

Image courtesy of Dr. Tomohiko Nakamura, neonatologist of Nagano Children's Hospital.



**Figure 5-15** This infant was born at 26 weeks' gestation with a birth weight of 614 grams. Cystic lesions are seen in both paraventricular regions, frontal lobes (thick arrows) and occipital lobes (thin arrows), corresponding watershed area in T2-weighted image MRI obtained at 3 months of life. Image courtesy of Dr. Tomohiko Nakamura, neonatologist of Nagano Children's Hospital.

vulnerable to reactive oxygen species; and (3) poor autoregulation in response to hypotension. In addition to ischemia, another important cause of white matter injury is infection and/or inflammation, which frequently accompanies premature birth. Recently given advances in perinatal and neonatal care, the typical cystic paraventricular leukomalacia (PVL) is rarely seen, while diffuse white matter injury manifesting as decreased volume of white matter is seen more often.<sup>62</sup>

## Vascular Lesions: Stroke

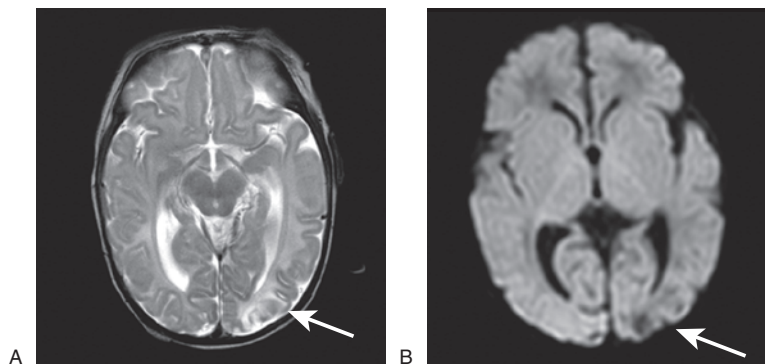
The National Institute of Neurological Disorders and Stroke workshop defines perinatal ischemic stroke as “a group of heterogeneous conditions in which there is focal disruption of CBF due to arterial or cerebral venous thrombosis or embolism, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies.”<sup>63</sup> Recent advancements in MRI imaging have facilitated the diagnosis and classification of these conditions (**Figure 5-16**). The four perinatal ischemic stroke classifications are: (1) symptomatic neonatal arterial ischemic stroke; (2) symptomatic neonatal cerebral sinovenous thrombosis; (3) presumed perinatal ischemic stroke; and (4) periventricular venous infarction. Although the potential causes of stroke include thrombophilia, placental thrombosis, infection, cardiac anomalies, and maternal drug use (e.g., cocaine), in most cases, no specific causes are identified. Neonatal arterial ischemic stroke is usually associated with the worst prognosis including congenital hemiplegia, deficits in language, vision, cognition, behavior, and other higher brain functions. Venous infarction has better prognosis.

## D. Cerebral Palsy

Cerebral palsy is a syndrome characterized by:

- Abnormalities of muscle tone, posture, and movement that can range in severity.
- Cerebral palsy is the result of a cerebral abnormality, originating early in development. The cerebral abnormality can occur during fetal development or in a neonate up to 28 days of life.
- The condition is not progressive or degenerative but the clinical presentation may vary as the individual matures.

The etiology of cerebral palsy is considered to be multifactorial because the developing fetal brain is vulnerable to damage from many different insults including infection, inflammation, and



**Figure 5-16** An infant at 40 weeks' gestation with a history of exsanguination from umbilical cord rupture before delivery. MRI was taken at 28 days of life. **A.** T2-weighted image. High intensity area is observed in the left occipital region (arrow). **B.** Apparent diffusion coefficient map confirming recent infarction (restricted diffusion) in the same area (arrow). Images courtesy of Dr. Tomohiko Nakamura, neonatologist of Nagano Children's Hospital.

**Table 5-5 MacLennan Criteria to Define an Acute Intrapartum Hypoxic Event**

Essential Criteria <sup>a</sup>	Criteria That Together Suggest an Intrapartum Timing but by Themselves Are Nonspecific <sup>b</sup>
<ol style="list-style-type: none"> <li>1. Evidence of a metabolic acidosis in intrapartum fetal, umbilical arterial cord, or very early neonatal blood samples as defined by pH &lt; 7.00 and base deficit <math>\geq</math> 12 mmol/L</li> <li>2. Early onset of severe or moderate neonatal encephalopathy in infants <math>\geq</math> 34 weeks' gestation</li> <li>3. Cerebral palsy of the spastic quadriplegic or dyskinetic type</li> </ol>	<ol style="list-style-type: none"> <li>4. A sentinel (signal) hypoxic event occurring immediately before or during labor</li> <li>5. A sudden, rapid, and sustained deterioration of the fetal heart rate pattern usually following the hypoxic sentinel event</li> <li>6. Apgar scores of 0–6 for &gt; 5 minutes</li> <li>7. Early evidence of multisystem involvement</li> <li>8. Early imaging evidence of acute cerebral abnormality</li> </ol>

<sup>a</sup> All three of the essential criteria are necessary before an intrapartum hypoxia can be considered the etiology of cerebral palsy.

<sup>b</sup> If evidence for some of the 4–8 criteria is missing or contradictory, the timing of the neuropathology becomes increasingly in doubt.

Based on MacLennan AH. A template for defining a causal relationship between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ*. 1999;319(7216):1054-1059.<sup>64</sup>

asphyxia. Although cerebral palsy is not progressive, the clinical presentation can change as the brain develops and matures. This disorder is often accompanied by other consequences of cerebral dysfunction such as intellectual disability, speech, or hearing impairment.

Many authorities have attempted to define criteria to establish a causal link between intrapartum events and subsequent cerebral palsy. In 1999, MacLennan published criteria to define the cerebral palsy cases caused by acute intrapartum hypoxic events (**Table 5-5**).<sup>64</sup> This consensus committee established criteria for the association on two levels: essential criteria and supportive findings. This concept was subsequently enlarged by a task force of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics that has identified neonatal signs sufficient to cause neonatal encephalopathy that is likely to have been caused by peripartum or intrapartum hypoxia–ischemia (**Table 5-6**).<sup>56</sup> Although these signs suggest that a neonate has sustained a hypoxic–ischemic insult, it is not yet possible to definitively determine when the injury occurred.

**Table 5-6 Acute Peripartum or Intrapartum Events Sufficient to Cause Neonatal Encephalopathy**

Neonatal Characteristic	Description
Apgar score	< 5 minutes at 5 and 10 minutes after birth
Umbilical artery acidemia	pH < 7.0 and/or base deficit $\geq$ 12 mmol/L
Magnetic resonance imaging	MRI imaging abnormalities that appear after 24 hours of life; MRI obtained between 24–96 hours is the most sensitive for determining the timing of cerebral injury; conventional qualitative MRI findings: diffusion abnormalities, deep nuclear gray matter, or watershed cortical injury are most likely to indicate hypoxic–ischemic injury
Multisystem organ failure	Can include renal injury, hepatic injury, hematologic abnormalities, gastrointestinal injury, cardiac dysfunction, metabolic derangements, or a combination of these abnormalities
Sentinel hypoxic or ischemic event	A sentinel hypoxic or ischemic event that occurred immediately before or during labor and delivery (e.g., ruptured uterus, placental abruption, vasa previa, and amniotic fluid embolism)
Fetal heart rate patterns	Category II tracing identified on presentation or for longer than 60 minutes that includes minimal/absent variability and no accelerations suggests a previously compromised fetus; Category I FHR pattern that develops into a Category III pattern over the course of labor; additional FHR patterns consistent with hypoxic–ischemic events include tachycardia with recurrent decelerations and persistent minimal variability with recurrent decelerations
Other proximal or distal factors	No evidence of other proximal or distal factors that could contribute to neonatal encephalopathy

Based on American College of Obstetricians and Gynecologists (ACOG) Task Force on Neonatal Encephalopathy. *Neonatal Encephalopathy and Neurologic Outcome*. 2nd ed. Washington, DC: ACOG; 2014.<sup>56</sup>

## IV. FACTORS THAT MODIFY FETAL VULNERABILITY TO ASPHYXIA

Several factors are known to increase fetal vulnerability to central nervous system damage following an asphyxial insult. In clinical practice, prematurity and infection/inflammation are the most common problems encountered. Intrauterine growth restriction and uteroplacental insufficiency are also likely to increase fetal vulnerability to injury from an asphyxial insult. To make matters more complicated, the relationship between premature labor, infection/inflammation, and hypoxia/asphyxia is highly interrelated. Infection may sensitize the fetal brain to damage to hypoxial damage.<sup>65</sup> Although many of the pathologic mechanisms underlying these relationships have been identified, the etiologic cascade and relative importance of individual players has not been fully elucidated and is the subject of ongoing research.

### A. Prematurity

The a priori vulnerability of preterm fetuses to brain injury has been attributed to factors such as fragile capillaries, immature cardiovascular responses, and increased vulnerability to free radical toxicity. Interestingly, premature fetal sheep behaved surprisingly similar to term fetal sheep when subjected to asphyxia with regard to heart rate, blood pressure, and CBF. However, the premature fetal lamb of 0.6 gestational age survived up to 30 minutes of complete cord occlusion without brain damage. This was in contrast to the fact that 10-minute cord occlusion

ensured brain damage.<sup>47</sup> The ability of the premature fetus to tolerate prolonged periods of asphyxia longer than a term fetus is attributed to the fact that preterm fetuses have more anaerobic capacity in the brain and more myocardial glycogen stores.<sup>18,66</sup> The low requirement for oxygen during asphyxia may also play a role. Thus, the increased tolerance to asphyxial insults may subject the preterm fetus to longer exposure to asphyxia; the prolonged exposure is then ultimately responsible for the increased risk to injury and widespread neuronal damage noted in survivors.

## B. Infection and Inflammation

Multiple epidemiologic studies have documented a strong relationship between infection/inflammation and cerebral palsy. In a meta-analysis of this body of work, Wu and Colford found clinical chorioamnionitis strongly associated with cerebral palsy in term infants (RR 4.7; 95% CI 1.3–16.2) and in preterm infants (RR, 1.9; 95% CI, 1.4–2.5) although the relationship is somewhat weaker in preterm infants.<sup>67</sup> The authors subsequently evaluated the risk factors for cerebral palsy that were not determined to be of postnatal origin in a population-based cohort and found chorioamnionitis is an independent risk factor for cerebral palsy in term infants (OR, 4.1; 95% CI, 1.6–10.1).<sup>68</sup>

Animal studies using rodent and sheep models have facilitated our understanding about the relationship between infection/inflammation and brain damage. The major culprit appears to be upregulation of cytokine and chemokines that induce an inflammatory response. TNF alpha, IL 1-beta, IL-6, and IL-8 have been reported to damage brain cells, especially pre-oligodendroglia and oligodendroglia, thereby hampering myelination.<sup>69</sup> This work has also shown that fetal exposure to specific inflammatory mediators induced hypotension in preterm fetuses that resulted in white matter damage whereas term fetuses did not respond with profound hypotension.<sup>70</sup>

## Infection/Inflammation and Preterm Birth

There is now a strong and persuasive body of evidence from animal experiments and human data demonstrating that intrauterine and extrauterine infection/inflammation cause preterm labor and preterm birth via the actions of pro-inflammatory cytokines. Intrauterine infection is commonly the result of ascent of lower genital tract microorganisms leading initially to choriodecidual activation and inflammation, and subsequently membrane inflammation, amniotic fluid invasion, and then fetal systemic infection from inhalation and/or ingestion of contaminated amniotic fluid. The fetal response is characterized by migration of fetal leucocytes from fetal vessels in the chorionic plate and into the Wharton's jelly of the umbilical cord, so-called funisitis. There may be a more generalized fetal inflammation—the fetal systemic inflammatory response syndrome (FSIRS)<sup>71</sup>—probably mediated in part by widespread endothelial injury.<sup>72</sup> FSIRS is associated with hypotension, neonatal seizures, need for intubation, meconium aspiration syndrome, multiorgan dysfunction, chorioamnionitis, preterm delivery, hypoxic-ischemic encephalopathy or neonatal encephalopathy,<sup>73-75</sup> intraventricular hemorrhage,<sup>76</sup> white matter damage, periventricular leukomalacia, bronchopulmonary dysplasia, and cerebral palsy in the term and near-term infant.<sup>77</sup> It is probably the most common antecedent of low Apgar scores and other indicators of neonatal depression.<sup>75,78</sup> Fetal demise from overwhelming sepsis or growth restriction may also occur.<sup>79</sup> It has been suggested that intrauterine exposure to infection causes fetal overproduction of cytokines, leading to cellular damage in the fetal brain. One study found increased levels of inflammatory cytokines in the amniotic fluid of infants with white matter lesions and these cytokines were overexpressed in the brains of infants who have periventricular leukomalacia.<sup>80</sup>

## Infection/Inflammation and Hypoxia/Asphyxia

Several animal and human studies suggest that infection/inflammation increases the magnitude of hypoxia/asphyxial brain damage.<sup>43,65</sup> Sameshima et al. analyzed 139 cases following clinical chorioamnionitis and the highest odds ratio for brain damage was fetal tachycardia and prematurity. In premature neonates, infection/inflammation per se can be the cause of brain damage especially white matter injury; however, in the term/near-term neonates, infection/inflammation is often a prerequisite for hypoxic brain damage.<sup>81</sup>

In contrast, some studies on premature rodent fetuses have found that inflammatory mediators induce preconditioning, which then protects or attenuates the effects of subsequent hypoxia.<sup>82,83</sup>

Definitive conclusions about the effect of infection/inflammation in preterm and term human fetuses are difficult to reach until more is known about several other modulating factors including dose and duration of exposure, the fetal response to different bacterial endotoxins, and the role of the immune system cascade.

## C. Uteroplacental Insufficiency and Intrauterine Growth Restriction

If exposed to acute hypoxic insults such as uterine contractions during labor, a fetus experiencing chronically hypoxemic condition will deteriorate more rapidly than will a well-oxygenated fetus.<sup>84-86</sup> Westgate et al. imposed asphyxia by cord occlusion on two cohorts of fetal lambs, one group exposed to chronic hypoxia and the other was a nonhypoxemic group. The hypoxemic group became hypotensive and acidemic more rapidly than did the nonhypoxemic group with statistical significance.<sup>87</sup> Other studies have replicated these results.<sup>88</sup> Overall it appears that hypoxemic fetuses have less reserve of anaerobic capacity and less glycogen storage in the heart than nonhypoxemic fetuses, which increases their vulnerability to subsequent acute hypoxial stressors.<sup>89,90</sup>

## D. Intrauterine Tachysystole

One of the most common problems during the intrapartum period is uterine tachysystole or hypertonus, which in clinical practice is often due to oxytocin administered for labor induction or augmentation. Uterine contractions decrease blood flow in the uterine artery with uterine end-diastolic velocity reaching zero when the intrauterine pressure exceeds approximately 35 mmHg.<sup>91,92</sup> It is well established that fetal cerebral oxygenation is decreased during or immediately following a uterine contraction and an inter-contraction interval of approximately 60 seconds or more is optimal for exchange of respiratory gases.<sup>93,94</sup> Furthermore, placental perfusion may be reduced to a greater degree when exogenous oxytocin is used to stimulate uterine contractions although Doppler studies assessing the effect of induced uterine contractions on placental blood flow are preliminary.<sup>95</sup>

Episodes of tachysystole are relatively common during labor and the large majority of fetuses have sufficient reserve to tolerate short periods of tachysystole. However, case control studies of newborns with metabolic acidemia at birth have found these infants were likely to have experienced more periods of tachysystole that were associated with more FHR decelerations and deeper FHR decelerations when compared to newborns without metabolic acidemia.<sup>96,97</sup> Thus, the clinical correlate is clear to maternity care providers. Clinical management must be directed toward prevention of tachysystole when possible.



## V. TREATMENTS FOR NEWBORNS WITH NEONATAL ENCEPHALOPATHY

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### A. Therapeutic Hypothermia

Therapeutic hypothermia is a milestone therapy for neonatal asphyxia in this millennium. Several animal studies have confirmed that therapeutic hypothermia effectively prevented or mitigated brain damage in the fetus and newborn with hypoxic–ischemic encephalopathy.<sup>56</sup> Following therapeutic findings in animal research, hypothermia has been applied to human neonates. Almost all clinical trials have been carried out using a similar protocol, i.e., inclusion criteria of more than 35 weeks of gestational age, evidence of asphyxia, and neonatal encephalopathy. Cooling to between 33.5 and 34.5°C core temperature is started within 6 hours of life, which implies that the cooling is instituted before the second energy failure begins, and is continued for 72 hours. A Cochrane meta-analysis of 11 randomized clinical trials ( $n = 1505$  infants) found that therapeutic hypothermia was associated with a significant reduction in neonatal mortality (RR 0.75; 95% CI 0.64–0.88) and neurodevelopmental disability in survivors (RR 0.77; 95% CI 0.63–0.94).<sup>98</sup> The adverse effects included sinus bradycardia, skin and scalp reddening and hardening, subcutaneous fat necrosis, coagulopathy, sepsis, and thrombocytopenia.<sup>98</sup> Because a certain number of candidates for therapeutic hypothermia are born in hospitals that do not have access to a neonatal intensive care unit, a passive hypothermia strategy, i.e., avoiding pyrexia, should be applied until these infants can be transferred to an institution that can institute cooling.

The mechanism by which cooling is effective includes decreasing metabolism and suppressing several of the pathologic cascades that lead to cell death such as relief of excitatory amino acid, oxidative stress, apoptosis, and the inflammation process.<sup>99</sup> Infants who have received hypothermic therapy have shown delayed change in MRI evolution compared to those without hypothermia, which indicates that hypothermia widens the therapeutic window.<sup>100</sup>

### B. New Adjuvant Therapy

Although therapeutic hypothermia has become the routine therapeutic modality for infants with hypoxic–ischemic neonatal encephalopathy, almost 40% of infants who receive therapeutic hypothermia have an adverse neurologic disability. New adjuvant therapies that provide neuroprotection for these infants is needed and current research is assessing treatments such as melatonin, xenon, erythropoietin, anticonvulsants, and stem cell therapy.

## VI. CONCLUSION

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Numerous studies have evaluated the relationship between FHR patterns and subsequent newborn acidemia, neonatal encephalopathy, and/or cerebral palsy. The identification of intrapartum events and newborn umbilical artery indices that suggest cerebral palsy is related to intrapartum asphyxia, provides some criteria for subscribing an etiology once cerebral palsy has occurred.<sup>56</sup> However, maternity care clinicians need to know what intrapartum indices are prospectively predictive and this information is not yet available.

To illustrate the problem, the magnitude of damage following fetal asphyxia is shown in **Table 5-7**. The “overprediction” of newborn morbidity from FHR deceleration patterns is striking, as abnormal FHR patterns are 100-fold more common than severe metabolic acidosis at birth. Even FHR patterns with diminished or absent variability do not consistently predict immediate morbidity by approximately 10-fold. Newborn umbilical artery pH of less than 7.0 occurs in approximately 3 to 4 per 1000 births. Although a pH of less than 7.0 and a

**Table 5-7 Fetal Heart Rate Monitoring and Newborn Outcome**

	Incidence <i>n</i> /1000 Live Births
<b>Intrapartum FHR</b>	
Variant patterns	300/1000
Variant patterns with decreased variability	30/1000
<b>Immediate newborn outcome</b>	
Umbilical artery pH $\leq$ 7.0	3.4/1000
Newborn seizures	3.1/1000
<b>Long-term outcome</b>	
Cerebral palsy due to all causes	2.5/1000
Cerebral palsy due to intrapartum asphyxia	0.25/1000

base deficit of more than 12 mmol/L are the best threshold values positively associated with newborn morbidity, the absolute number of infants with metabolic acidosis at birth who have neurologic impairment is quite small and the majority of newborns with these values will have normal outcomes. Perhaps most importantly, the factors that increase vulnerability for brain damage such as infection and premature gestational age have been identified but the quantitative contribution of these factors to the incidence of brain damage following asphyxia has not been determined.

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