Hemodynamic Instability in Hypoxic Ischemic Encephalopathy: More Than Just Brain Injury—Understanding Physiology, Assessment, and Management

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The purpose of this article is to explore the underlying pathophysiology of hemodynamic instability in the neonate following perinatal asphyxia, describe how to recognize hemodynamic compromise, and discuss management strategies to improve hemodynamics and potentially improve outcomes.

***Funding**. The author(s) received no specific grant or financial support for the research, authorship, and/or publication of this article.*

Accepted for publication
January 31, 2020

Abstract

Hypoxic-ischemic encephalopathy (HIE) can have both transient and long-lasting effects on the neonate, including neurologic, renal, cardiac, hepatic, and hematologic. Both the disease process and the treatment option of therapeutic hypothermia can result in hemodynamic instability. Understanding the effects of HIE on the neonatal myocardium, pulmonary vascular bed, and the cardiac dysfunction that can occur is key to managing infants with HIE. This article focuses on causes of hemodynamic instability in neonates following perinatal asphyxia and how to recognize hemodynamic compromise. It reviews the underlying pathophysiology and associated management strategies to improve hemodynamics and potentially improve outcomes.

Keywords: cardiovascular status; hypoxic-ischemic encephalopathy (HIE); hemodynamics; neurology

The peripartum period is full of risk. Transition from intrauterine to extrauterine life can be complicated by periods of hypoxia or ischemia resulting in long-lasting sequelae and multiorgan impairment. Hypoxic-ischemic encephalopathy (HIE) is present when the following criteria are met: metabolic changes (arterial umbilical cord pH <7.00 or base deficit ≥12 mmol/L, or both), persistence of an Apgar score of 0–3 at five minutes of extrauterine life, clinical and neurologic sequelae in the immediate neonatal period, and clinical and chemical evidence of multiorgan failure in the early neonatal period. HIE occurs in the perinatal period due to a variety of causes, including maternal medical conditions, in utero events, intrapartum events, and fetal factors.[1]

Asphyxiated neonates represent an extremely vulnerable population, with potential for significant end-organ dysfunction which may potentiate neurologic injury. Neonates with HIE can suffer neurologic, renal, cardiac, hepatic, and hematologic side effects. While therapeutic interventions to reduce cerebral metabolic demands and prevent secondary injury exist, these same protective interventions, such as therapeutic hypothermia (TH), can also have significant impact on neonatal hemodynamics. The neurologic impact is the hardest to predict and usually has the most long-term effect on the

http://dx.doi.org/10.1891/0730-0832.39.3.129

neonate and the family. During the acute phase of HIE, managing and supporting all the affected organs is critical to the survival of the neonate.

The ability to recognize hemodynamic instability in this population is compromised by the effects of treatment but remains fundamental to improving both short- and long-term outcomes. Once identified, appropriate management strategies can stabilize cardiac output (CO) and improve end-organ perfusion, ultimately making TH better tolerated and serving to prevent further end-organ injury. This article focuses on the etiology of hemodynamic instability in neonates following perinatal asphyxia, and how to recognize hemodynamic compromise.

PATHOPHYSIOLOGY

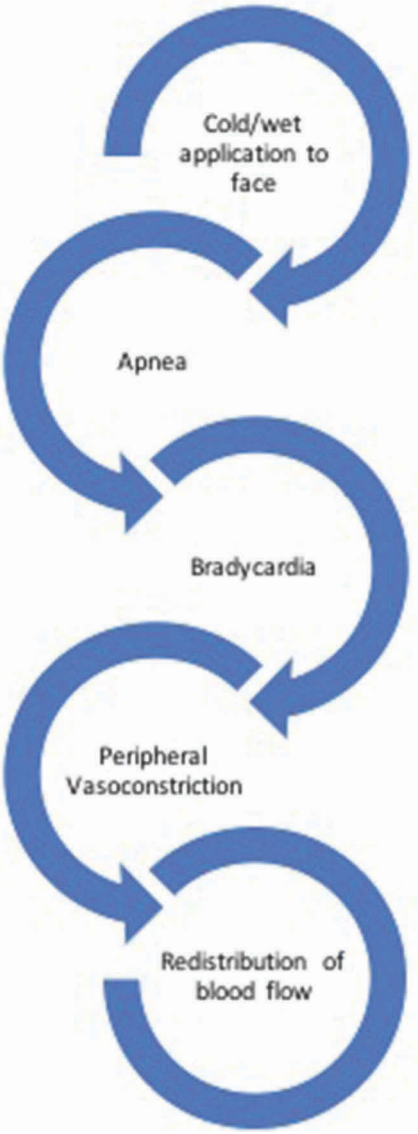
Dive Reflex

All mammals, including humans, have an intrinsic mechanism intended to preserve oxygen stores, known as the mammalian diving response.[2] This reflex is typically provoked with cessation of respiration secondary to complete underwater submersion of the face.[2] As respiration becomes impossible, it becomes essential to conserve oxygen necessary for aerobic metabolism.[2] Sensory information from the trigeminal nerve travels along the afferent pathway to the brain stem, which results in efferent signals via the vagus nerve causing the desired effects in target organs.[3] In the heart this translates to bradycardia and in the vascular musculature results in increased peripheral vascular resistance.[3] This change in vascular resistance allows a redistribution of blood flow to the central nervous system, heart, and adrenal glands.[4] The drop in partial pressure of oxygen in the lungs sensed by the carotid bodies also causes afferent signaling via the glossopharyngeal nerve to cause efferent brain-stem signaling to sympathetic nerves that cause further peripheral vasoconstriction.[3]

The diving response, or reflex, is commonly studied in birds as well as mammals; however, differences between avian, mammalian, and neonatal responses exist. Once provoked in humans, a drop in CO is not always seen, but peripheral vasoconstriction occurs and can ultimately lead to a dramatic increase in blood pressure.[5] Periods of hypoxia or ischemia readily trigger the physiologic processes associated with mammalian diving in neonates. Interestingly, this response is most readily elicited in infancy. The vigorous response, while preserved, becomes less intense with age.[3]

In periods of reduced blood flow or oxygen deprivation, as in HIE, the diving response results in shunting of blood away from inactive muscle groups to preserve supply to the brain and heart. This shunting is achieved through increases in peripheral vascular resistance that can ultimately impact cardiac function and output. Reflexive bradycardia also serves to reduce oxygen consumption of the heart.[3] Asphyxia, as well as TH, also impairs the fall in pulmonary vascular resistance (PVR) normally seen after birth, leading to increased afterload to the right heart. Together these changes can lead to compromised cardiac function and output (Figure 1).

FIGURE 1 ■ Dive reflex.



The Neonatal Myocardium and HIE-Related Cardiac Dysfunction

Cardiac output is a product of heart rate and stroke volume. When compared to adults, neonates possess a limited ability to increase CO by increasing stroke volume and are significantly dependent on heart rate. The neonatal myocardium is still developing at the time of birth. While able to function fully, its composition and characteristics differ from the adult heart and will undergo changes over time.[6] The neonatal myocardial cells are disorganized, with reduced contractile tissue. Adult hearts have 60 percent contractile tissue, while the neonatal myocardium contains only 30 percent contractile tissue.[7–9] With reduced numbers of mitochondria and overall energy stores, the neonatal heart is less able to cope with increased stress or changes in afterload.[7–9]

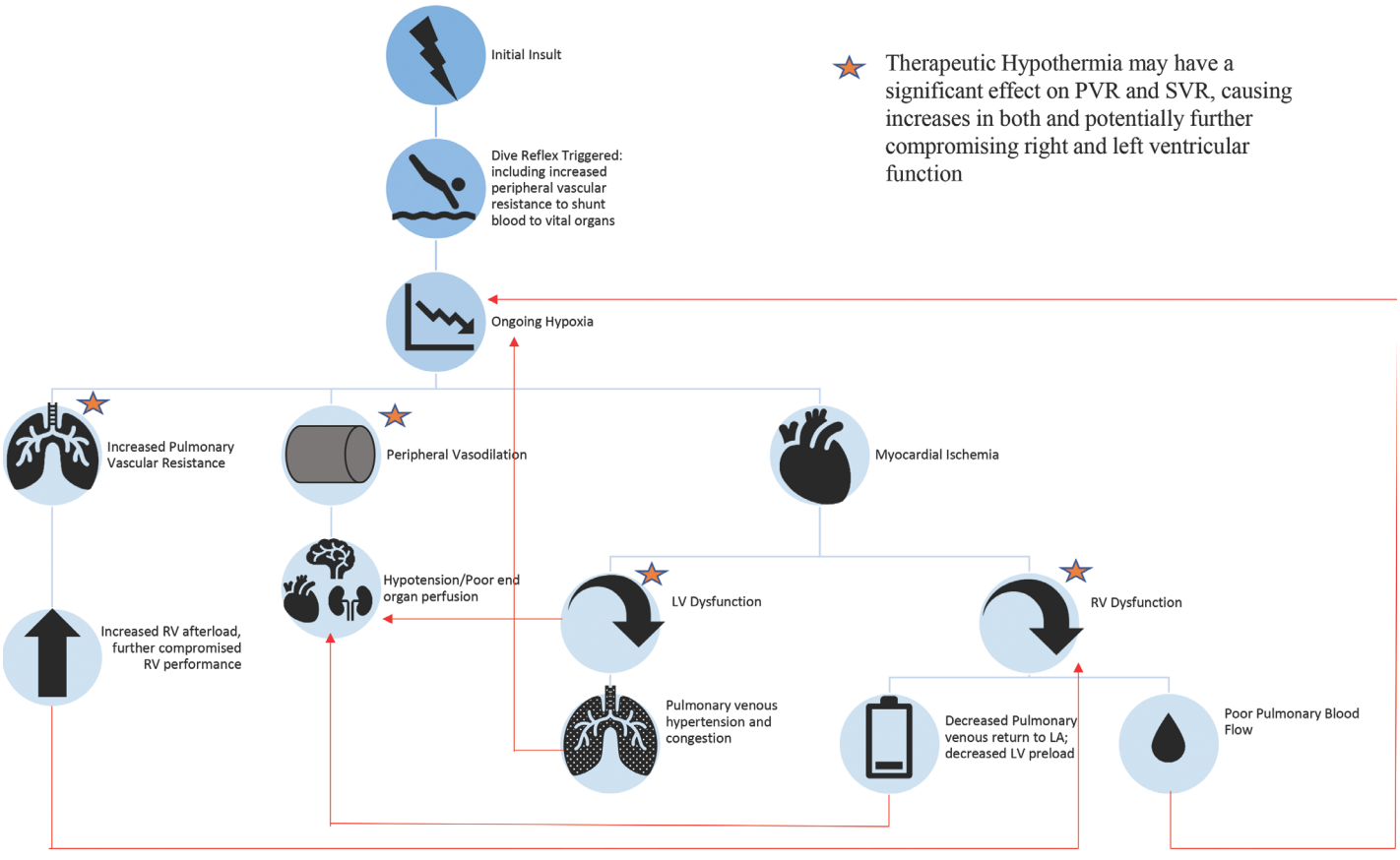
Hypoxia upregulates molecular pathways that can decrease myocardial contractility and impair overall cardiac performance.[3] In fact, up to one-third of asphyxiated neonates will have transient myocardial ischemia.[3] If unrecognized, or inadequately managed, cardiac dysfunction or altered CO can potentially exacerbate initial neurologic injury, lead to poor tolerance of TH, and will impact survival.[7] As the diving reflex directs blood flow to the vital organs such as the brain and heart, these altered patterns of blood flow can also lead to poor perfusion of the myocardium and papillary muscles as well as subendocardial tissues, resulting in myocardial ischemia as the blood flow to the myocardium may still be inadequate.[7] The diving reflex does not ensure adequate blood flow to each vital organ equally. Although the initial response to hypoxia or ischemia is peripheral vasoconstriction, as seen in the dive reflex, prolonged hypoxia triggers systemic arteries to dilate in an effort to improve delivery of blood, albeit reduced in oxygen content, to the tissues.[10] Initially, increased systemic vascular resistance results in increased afterload on the left ventricle (LV), which may already be compromised because of the initial insult. Ongoing hypoxia and subsequent vasodilation may manifest as hypotension. This coupling of poor cardiac function and vasodilation significantly compromises end-organ perfusion.

HIE and the Impact on the Pulmonary Vascular Bed

The fetus exists in a state of elevated PVR allowing preferential blood flow of placental-oxygenated blood to the low-resistance systemic circulation. This elevated PVR is maintained through compression from fluid-filled alveoli on pulmonary vessels, lack of lung distention, narrowing of the vascular lumen by cuboidal endothelial cell arrangement, and most importantly from hypoxic vasoconstriction resulting from a low alveolar oxygen tension.[11] While remaining sensitive to oxygen levels, there is a steady rise in PVR as the pulmonary bed develops.[12]

For neonates delivered at term, increased alveolar oxygen concentrations following the initiation of breathing result in a dramatic fall in PVR after birth.[12] Neonates born with hypoxia have a persistent elevation in PVR as a direct result of insufficient oxygen delivery and oxygen sensitivity of the pulmonary vasculature. Hypoxia results in pulmonary artery constriction, pulmonary vasoconstriction and a decrease in systemic vascular resistance.[10] In cases of sustained hypoxia, PVR does not decrease, leading to development of persistent

FIGURE 2 ■ Hemodynamic changes related to perinatal hypoxic/ischemic insult and therapeutic hypothermia.



Abbreviations: LA = left atrium; LV = left ventricle; PVR = pulmonary vascular resistance; RV = right ventricle; SVR = systemic vascular resistance.

pulmonary hypertension of the newborn (PPHN). PPHN can also cause further strain on the right ventricle (RV) already affected by myocardial ischemia. This sustained increased RV afterload can cause dysfunction and contribute to worsening pulmonary blood flow, ultimately leading to decreased left ventricular preload. Clinically, this may manifest as hypotension or further evidence of poor end-organ perfusion. Increased PVR in this clinical situation is a reversible, non-pulmonary, cause of PPHN and can be managed with timely recognition and appropriate intervention.[13] Figure 2 summarizes the hemodynamic changes seen in HIE and TH.

CLINICAL EVALUATION OF HEMODYNAMICS

For most neonates, transient myocardial ischemia is asymptomatic and improves over time. Clinical assessment of hemodynamics in neonates undergoing TH is complicated by the effect of temperature. Resting bradycardia is a well-established finding secondary to TH, with estimates of a reduction in heart rate of 14–45 beats per minute #(bpm).[14] This bradycardia may be beneficial at reducing the overall substrate requirement of the heart.[8] The clinician should be concerned at a finding of a normal or elevated heart rate despite TH, as this can indicate an effort to increase CO and be cause for concern of hypoperfusion.[8]

Other clinical and biochemical markers may be helpful in detecting overall impaired cardiac performance; however, they may also be difficult to interpret. Reliance on clinical assessment of color and perfusion can be affected by peripheral vasoconstriction secondary to TH. Metabolic acidosis and lactic acidosis can be unreliable values because they may reflect the initial injury and be persistently abnormal for hours to days, making it difficult to discern if these values reflect low CO.[7] Urine output as a measure of CO and adequate renal perfusion may also be unreliable because acute kidney injury (AKI) in the setting of the ischemic insult, which is estimated to occur in 50 to 70 percent of asphyxiated neonates, may be the cause of low urinary output.[15]

An electrocardiogram (ECG) and measurement of cardiac enzymes are used to evaluate myocardial ischemia in adults. In a study by Barberi and colleagues, published in 1999, neonates with transient myocardial ischemia due to HIE were found to have ECG changes and cardiac enzyme elevation.[16] ECG changes were categorized from grade I to IV and included measuring changes in the T, ST, and Q waves from a 12-lead ECG. In this study, neonates with severe HIE had grade III to IV changes on ECG and this was considered a specific marker of severe myocardial involvement.[16] These authors recommended that ECG evaluation be completed on day of life (DOL) 2 to avoid "innocent" repolarization changes that are routinely present on DOL 1.[16] Other biochemical markers may also be useful in assessing the severity of end-organ impairment, such as evaluating creatine kinase-MB isozyme (CK-MB). This enzyme was noted to be significantly elevated in neonates who had moderate or severe HIE, with increases in levels beginning at about four to eight hours after injury.[17] Furthermore, troponin I and troponin T have been significantly elevated in neonates with severe asphyxia and may be used to help assess the severity of the insult.[17]

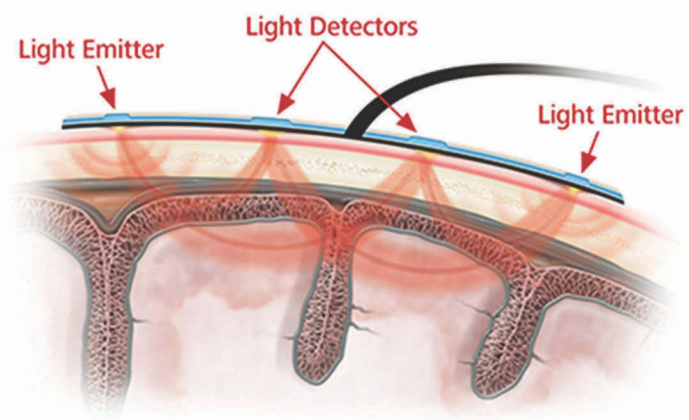
Arterial blood pressure is commonly used to evaluate hemodynamic state, but this measurement can also be difficult to interpret. Evidence supporting acceptable norms for blood pressure measurements in neonates during the first few days of life is significantly lacking; the impact of transition from fetal to neonatal life should also be considered. Neonates undergoing TH generally maintain an appropriate diastolic pressure, given the peripheral vasoconstriction from hypothermia. Systolic pressure is commonly low normal but is likely adequate in maintaining sufficient end-organ perfusion. Clinicians should be cautious about treating hypotension without clinical concern of inadequate perfusion—that is, hypotension based solely on numerical values—because an elevation in systolic blood pressure could increase the risk of reperfusion hemorrhage.[7]

Ventricular dysfunction may present as hypotension with or without hypoxemia. Left ventricular dysfunction causing reduced stroke volume may result in hypotension, with a clinical examination reflecting poor CO. Right ventricular impairment, on the other hand, may present as low blood pressure secondary to poor LV preload and thus output, or, if there are significantly elevated pulmonary pressures (PPHN) and RV dysfunction, hypoxemia secondary to poor pulmonary flow may be the most concerning clinical finding.[7] It would be important for the clinician to also recognize that significant LV dysfunction may result in pulmonary venous hypertension, which presents as respiratory insufficiency and hypoxemia.[7] A chest radiograph can be consistent with pulmonary edema. If hypoxia is thought to be secondary to PPHN, typical management strategies to reduce PVR may actually worsen the neonate's clinical status. In this setting, LV output may be critically low, and may require augmented systemic blood flow via mechanisms to increase right-to-left shunting at the ductus, rather than strategies to reduce PVR, which would ultimately reverse ductal shunting and possibly further compromise systemic blood flow.

Targeted Neonatal Echocardiography

An exceptionally helpful bedside tool to assess hemodynamics and guide therapy is targeted neonatal echocardiography (TnEcho). TnEcho is helpful in identifying the pathophysiology of hemodynamic instability, rather than relying solely on clinical information, which could be difficult to interpret in the context of TH. Furthermore, TnEcho offers the ability for ongoing assessment of evolving cardiovascular status and aids in determining responses to therapies.[7] Neonates can develop cardiac dysfunction or reduced myocardial contractility after the initial injury. TnEcho assesses LV and RV function along with evaluation for pulmonary artery hypertension. The CO of neonates with HIE receiving TH is two-thirds of their output during a normothermic state. It is postulated that a lower CO is well tolerated by

FIGURE 3 ■ Near-infrared spectroscopy (NIRS) monitoring.



these neonates because it is sufficient to meet the metabolic demands of a cooled, asphyxiated neonate.[7,18] Generally, there is an improvement in CO and systolic blood pressure with a reduction in the systemic vascular resistance during the rewarming phase after completion of TH.[7,18]

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) monitoring can provide an immediate, noninvasive, bedside measurement of regional cerebral and somatic oxygenation in neonates.[19] Near-infrared technology utilizes light that passes through the neonate's underlying skin and tissue and is partially absorbed by oxygenated and deoxygenated hemoglobin before being measured by a detector on the same sensor (Figure 3).[19] NIRS allows for a tissue saturation level to be calculated and reflects the ratio of arterial to venous blood flow, and the balance between oxygen delivery and consumption in the underlying tissues.[19] A two-site monitoring of simultaneous cerebral and somatic NIRS measures is recommended because hemodynamic compromise often results in a reduction of somatic oxygenation prior to changes in cerebral oxygenation because of cerebral blood flow preservation with cerebral autoregulation mechanisms.[19] Normative values for cerebral oxygenation measurements have been established at approximately 40 to 56 percent just after birth, increasing to 78 percent in the first 48 hours after birth.[20] These values slowly stabilize during the first three to six weeks of life with normal expected values of 55 to 85 percent.[20] Evidence of neurologic injury has been demonstrated with sustained cerebral levels below 40 percent.[19] Neonates with adverse outcomes from HIE, have a higher regional cerebral oxygenation measurement on DOL 1 when compared to neonates with HIE who have favorable outcomes; however, these neonates then have declining levels after 24 hours.[19] This can be explained by low energy metabolism following severe brain injury with low oxygen utilization, cerebral hyperperfusion, and impaired autoregulation.[19,20] In neonates with a favorable outcome, the fractional tissue oxygen extraction remains stable.[19] Implementation of NIRS neuromonitoring may prompt assessments of potential causes of decreased cerebral oxygenation, including hypotension or hemodynamic instability.[19,20]

Near-infrared spectroscopy technology is not without its limitations. There are significant variances in the functionality and tissue penetration among commercial NIRS devices. There are variabilities in the absolute saturation measures which support the argument that NIRS is better suited for trend monitoring. Hair, dark skin, and interfering light from other sources such as phototherapy devices, as well as certain conditions such as subdural edema or hematoma below the sensor, can interfere with the absorption of the near-infrared light which will render NIRS monitoring inaccurate.[19,20] There has also been a lack of evidence around the interpretation of NIRS monitoring. Despite these limitations, NIRS monitoring may still be a useful adjunct to improve the care of neonates at high risk of hemodynamic instability and impaired end-organ oxygenation.

APPROACH TO MANAGEMENT

The approach to supportive cardiovascular care in HIE requires the clinician to be aware of the dynamic of the fetal–neonatal transition over the course of the hypoxic event and eventual recovery and the interaction of hemodynamics with concomitant therapies such as ventilatory support and the provision of TH.[7,21] Cautious fluid resuscitation, with a fluid bolus or blood transfusion, should be considered for neonates with hemorrhagic hypovolemia (e.g., HIE secondary to placental abruption) or for neonates who have evidence of reduced preload or underfilling on echocardiogram.[21] Although hypoxia and reoxygenation injury can increase the peripheral microvascular permeability and exacerbate fluid shifts, it is important to assess intravascular volumes prior to providing fluid boluses.[21]

Myocardial ischemia can impact both ventricles or have a unilateral impact on the LV or RV as previously described. The etiology of poor CO or hypotension should be identified to direct appropriate pharmacotherapy. This may be challenging without echocardiogram information because clinical presentation may not be quickly or readily understood by all clinicians, resulting in misdirected treatment.

Pharmacologic Therapies

There are a variety of pharmacologic therapies that can be helpful in managing the hemodynamic instability in neonates with HIE. However, determining which therapy to utilize requires an understanding of its properties and effects on the neonatal myocardium. There is also a lack of clarity among clinicians with regard to thresholds for initiating therapies. Table 1 lists pharmacologic agents commonly used in the treatment of hemodynamic instability. There may be additional drugs utilized in various centers, based on clinician experience and expertise. This table is not exhaustive but seeks to identify agents well-supported by the literature for their use in the neonate.

Dopamine, an endogenous catecholamine and a precursor for norepinephrine synthesis, is a commonly used antihypotensive agent in neonates. It provides dose-dependent stimulation of the alpha- and beta-adrenergic as well as dopaminergic receptors, although there is substantial variability among neonates when determining the effective dose needed to stimulate each receptor.[22] Dopamine can increase cardiac contractility and heart rate at moderate doses of about 5–10 mcg/kg/minute.[22] Dopamine also indirectly stimulates dopamine-2 receptors to release norepinephrine stored in peripheral sympathetic nerve endings. There are limited norepinephrine stores in neonates; thus, dopamine may lose effectiveness as the indirect inotropic pathway becomes depleted. There is high variability with the response to dopamine, especially in critically ill neonates with ischemia.[21] Furthermore, use of high-dose dopamine may increase pulmonary arterial pressures, leading to increased ventricular afterload and right-to-left shunting at the level of the ductus arteriosus, which can aggravate hypoxemia.[21] Given the lack of reliable response to dopamine and its ability to cause excessive vasoconstriction and potentiate pulmonary hypertension, dopamine may not be a suitable first choice for neonates with HIE.

Dobutamine, a synthetic catecholamine with direct adrenoreceptor agonism, is an appropriate first-line agent for low systolic blood pressure and concerns for hypoperfusion or echocardiographic evidence of decreased CO. Dobutamine improves cardiac contractility and increases stroke volume and CO. Dobutamine may restore myocardial contractility and lower the SVR, resulting in restoration of tissue perfusion.[23] It should be noted, however, that in the presence of tachycardia, dobutamine can increase oxygen consumption in the myocardium, which can potentially exacerbate cardiac dysfunction in the context of ongoing poor oxygen delivery.[8,21]

Epinephrine is an endogenous catecholamine, that at low doses in neonates, acts on the beta-1 and beta-2 adrenoreceptors. It can be appropriate therapy for hypotension in neonates with HIE with concern for decreased CO and decreased systemic vascular resistance. Epinephrine at low doses stimulates beta receptors, enhances myocardial contractility, and causes peripheral vasodilation. Epinephrine, however, is associated with hyperglycemia and elevated serum lactate levels because it causes disturbances in the metabolism of carbohydrates and lactate.[21,24]

Norepinephrine, an endogenous sympathomimetic amine, acts on myocardial and vascular alpha-1 receptors with mild to minimal beta-adrenergic stimulation. Norepinephrine can cause excessive systemic vasoconstriction, which can aggravate impaired ventricular contractility and increase myocardial oxygen requirements in the asphyxiated neonate.[21] In the context of pulmonary hypertension treated with inhaled nitric oxide (iNO), norepinephrine has been shown to decrease the

TABLE 1 ■ Inotropic Support[7,8]

Drug	SVR	PVR	Receptor Activity
Dopamine	++	+++	α; variable effects related to dose and individual variability in response
Dobutamine	–	No significant effect	β_1, β_2, and α_1 (net vascular effect neutral; little effect on blood pressure and afterload)
Epinephrine	+++	++	α and β_1 and β_2
Norepinephrine	+++	– or No significant effect	α some β_1
Vasopressin	+++	–	V_1, V_2 receptors in kidney

Abbreviations: α = alpha; β_1, β_2 = beta; PVR = peripheral vascular resistance; SVR = systemic vascular resistance; V_1, V_2 = vasopressin.
+ indicates increased; – indicates decreased.

oxygen requirement and improve blood flow to the lungs by increasing CO without causing peripheral ischemia.[22] There is limited evidence for the use of norepinephrine in the context of a neonate with HIE undergoing TH. Norepinephrine is not an appropriate first-line therapy, given the side effect of systemic vasoconstriction, but it could be useful in the neonate with HIE and right-heart failure with severe pulmonary hypertension.[21]

Vasopressin causes vasoconstriction in vascular smooth muscle, whereas in the pulmonary vasculature, it activates the nitric oxide pathway and leads to vasodilation. When hypotension is caused by either vasodilation or elevated pulmonary pressures, use of vasopressin can be advantageous. An awareness that vasopressin has been associated with remarkable hyponatremia and a transient decrease in the platelet count is important for those considering its use.[7,21]

Adrenal insufficiency or adrenal hemorrhage has also been reported with HIE. In situations where hypotension is refractory to catecholamine therapy, hydrocortisone should be considered. Hydrocortisone could also be beneficial in neonates with impaired adrenal function.[7] Corticosteroids can decrease the breakdown of catecholamines, increase calcium levels within myocardial cells, and upregulate adrenergic receptors.[22] Close monitoring of blood pressure and glucose values is recommended with hydrocortisone use.

Although there is no evidence to support the need for sedation in neonates undergoing TH, it is a common practice.[25] The use of sedation can have hemodynamic consequences. Studies show an accumulation of opioids and benzodiazepines in neonates undergoing TH, which can lead to hypotension, further complicating the hemodynamic status.[14,24,25]

In addition to inotropic or vasopressor support, other strategies can aid in improving cardiac stability. In cases of severe RV dysfunction, afterload reduction may be required. Milrinone, a selective phosphodiesterase III inhibitor, has been shown to readily reduce PVR and has been seen as a useful drug in managing PPHN in neonates with secondary RV dysfunction.[26] This may need to be considered carefully, as there is significantly reduced milrinone clearance with TH, and with poor drug clearance there is a risk of significant hypotension from systemic vasodilation.[7]

Inhaled nitric oxide, a first-line drug for pulmonary vasodilation in persistent pulmonary hypertension, may be suggested if therapies such as sedation or ventilation are not adequate. Caution should always be used when administering both iNO and mechanical ventilation. Vigilant weaning of mean airway pressure must occur to prevent additional respiratory sequelae. High mean airway pressure should be avoided as this can worsen pulmonary venous return and it should be considered a cause of hypotension in neonates requiring high ventilation parameters.[7]

SEQUELAE

Perinatal hypoxic-ischemic injury is frequently accompanied by multiorgan involvement. The risk of neurologic injury is often thought of as the most concerning consequence of HIE; however, it is equally important to consider the risk of myocardial dysfunction because it can also contribute to postnatal neurologic impairment and exacerbate multiorgan injury.[7] The complexity of the perinatal period and the transition to the extrauterine environment pose unique challenges for neonates with HIE, particularly with the addition of acute hemodynamic instability. Although neuroprotective hypothermia has transformed the care of this vulnerable population and resulted in improved neurocognitive outcomes, a comprehensive understanding of and refinement in the management of hemodynamic instability may provide additional benefits.

Early evidence of myocardial dysfunction in neonates with HIE following the initial perinatal hypoxic-ischemic injury may be a marker for greater risk of adverse neurologic injury.[7] Right ventricular dysfunction at 24 hours of age is an independent predictor of an abnormal brain magnetic resonance imaging (MRI) or death, even after adjusting for the severity of the insult.[7] In a study by Mohammad and associates, in neonates with HIE, hemodynamic instability requiring inotropes in the first 72 hours of life was also associated with an increased risk of death or neurologic injury detected by MRI.[27] Research on nonsurviving, asphyxiated neonates has shown several cardiac abnormalities, including RV dilation, ventricular hypertrophy, and papillary muscle necrosis.[28] Although there have been several studies documenting the long-term neurologic outcomes for perinatal asphyxia, information regarding cardiac outcomes for neonates with HIE are not often reported.[28]

CONCLUSION

Improvement in myocardial function is critical to restoring CO and oxygen delivery to essential end-organ systems, such as the brain. The pathophysiology of hemodynamic compromise in neonates with HIE is complex and an individualized, thoughtful approach to therapy is essential. A comprehensive understanding of the physiologic mechanisms of neonatal hypoxic-ischemic injury and therapy, particularly the impact on neonatal hemodynamics, is vital to providing comprehensive care to the asphyxiated neonate. The invaluable bedside assessments to support decision-making and individualize treatment strategies may present an opportunity for improved neurologic outcomes.

REFERENCES

1. Schmolzer GM, Rehan VK. Delivery room management. In: *Avery's Neonatology: Pathophysiology and Management of the Newborn*. Philidelphia, PA: Lippincott Williams & Wilkins; 2016:228–230.
2. Panneton WM. The mammalian diving response: An enigmatic reflex to preserve life? *Physiology*. 2013;28:284–297. https://doi.org/10.1152/physiol.00020.2013
3. Godek D, Freeman AM. *Physiology, Diving Reflex. V*. Treasure Island, FL: StatPearls Publishing; 2019.
4. 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):1325–1331. https://doi.org/10.1016/0002-9378(90)90046-a

5. Baranova TI, Berlov DN, Glotov OS, et al. Genetic determination of the vascular reactions in humans in response to the diving reflex. *Am J Physiol Heart Circ Physiol.* 2017;312:11622–11631. https://doi.org/10.1152/ajpheart.00080.2016
6. Wolf AR, Humphrey AT. Limitations and vulnerabilities of the neonatal cardiovascular system: Consderiations for anesthetic management. *Pediatr Anaesth.* 2014;24:5–9. https://doi.org/10.1111/pan.12290
7. Giesinger RE, Bailey LJ, Deshpande P, et al. Hypoxic-ischemic encephalopathy and therapeutic hypothermia: The hemodynamic perspective. *J Pediatr.* 2017;180:22–30.e22. https://doi.org/10.1016/j.jpeds.2016.09.009
8. Giesinger RE, McNamara PJ. Hemodynamic instability in the critically ill neonate: An approache to cardiovascular support based on disease pathophysiology. *Semin Perinatol.* January 14, 2016;40:174–188. https://doi.org/10.1053/j.semperi.2015.12.005.
9. Kluckow M. The pathophysiology of low systemic blood flow in the preterm infant. *Front Pediatr.* 2018;6:29. Mini Review. https://doi.org/10.3389/fped.2018.00029.
10. Waypa GB, Schumacker PT. Hypoxia-induced changes in pulmonary and systemic vascular resistance: Where is the O2 sensor? *Respir Physiol Neurobiol.* 2010;174:201–211. https://doi.org/10.1016/j.resp.2010.08.007.
11. Mathew B, Lakshminrusimha S. Persistent pulmonary hypertension in the newborn. *Children (Basel).* July 28, 2017;4. https://doi.org/10.3390/children4080063.
12. Lakshminrusimha S, Saugstad OD. The fetal circulation, pahtophysiology of hypoxemic respiratory failure and pulmonary hypertension in neonates, and the role of oxygen therapy. *J Perinatol.* 2016;36:S3–S11. https://doi.org/10.1038/jp.2016.43.
13. Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: Advances in diagnosis and treatment. *Semin Fetal Neonatal Med.* 2015;20:262–271. Review. https://doi.org/10.1016/j.siny.2015.03.001
14. Zanelli S, Fairchild K. Physiologic and pharmacologic considerations for hypothermia therapy in neonates. *J Perinatol.* 2011;31:377–386. https://doi.org/10.1038/jp.2010.146
15. Sweetman DU, Riordan M, Molloy EJ. Management of renal dysfunction following term perinatal hypoxia-ischaemia. *Acta Paediatr.* 2013;102:233–241. Research Support, Non-U.S. Gov't Review. https://dx.doi.org/10.1111/apa.12116.
16. Barberi I, Calabro MP, Cordaro S, et al. Myocardial ischaemia in neonates with perinatal asphyxia: Electrocardiographic, echocardiogaphic and enzymatic correlations. *Eur J Pediatr.* 1999;158:742–747. https://doi.org/10.1007/s004310051192
17. Armstrong K, Franklin O, Sweetman D, et al. Cardiovascular dysfunction in infants witah neonatal encephalopathy. *Arch Dis Child.* 2012;97:372–375. https://doi.org/10.1136/adc.2011.214205
18. Gebauer CM, Knuepfer M, Robel-Tillig E, et al. Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. *Pediatrics.* 2006;117:843–850. https://doi.org/10.1542/peds.2004-1587
19. Chock VY, Variane GFT, Netto A, et al. NIRS improves hemodynamic monitoring and detection of risk for cerebral injury: Cases in the neonatal intensive care nursery. *J Maternal-Fetal Neonatal Med.* October 2018;29:1–9. https://doi.org/10.1080/14767058.2018.1528223.
20. Dix LML, van Bel F, Lemmers PMA. Monitoring cerebral oxygenation in neonates: An update. *Front Pediatr.* 2017;5. https://doi.org/10.3389/fped.2017.00046.
21. Joynt C, Cheung PY. Cardiovascular supportive therapies for neonates with asphyxia—A literature review of pre-clinical and clinical studies. *Front Pediatr.* 2018;6:363. https://doi.org/10.3389/fped.2018.00363.
22. Ruoss JL, McPherson C, DiNardo J. Inotrope and vasopressor support in neonates. *NeoReviews.* 2015;16:e351–e361. https://doi.org/10.1542/neo.16–6-e351
23. Noori S, Friedlich P, Seri I. The use of dobutamine in the treatment of neonatal cardiovascular compromise. *NeoReviews.* 2004;5:e22–e26. https://doi.org/10.1542/neo.5-1-e22
24. Sahni M, Jain S. Hypotension in neonates. *NeoReviews.* 2016;17:e579–e587. https://doi.org/10.1542/neo.17-10-e579
25. Natarajan G, Shankaran S, Laptook AR, et al. Association between sedation-analgesia and neurodevelopmental outcomes in neonatal hypoxic-ischemic encephalopathy. *J Perinatol.* 2018;38:1060–1067. https://doi.org/10.1038/s41372-018-0126-7
26. McNamara PJ, Laique F, Muang-In S, et al. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. *J Crit Care.* 2006;21:217–223. https://doi.org/10.1016/j.jcrc.2006.01.001
27. Mohammad K, Hicks M, Buchhalter J, et al. Hemodynamic instablility associated with inacreased risk of death or brain injury in neonates with hypoxic ischemic encephalopathy. *J Neonatal-Perinatal Med.* 2017;10:363-370. https://doi.org/10.3233/NPM-1816162.
28. LaRosa DA, Ellery SJ, Walker DW, et al. Understanding the full spectrum of organ injury following intrapartum asphyxia. *Front Pediatr.* February 17, 2017;5:16. https://doi.org/10.3389/fped.2017.00016.

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