Asphyxia, Therapeutic Hypothermia, and Pulmonary Hypertension

Regan Geisinger, MD[a,†], Danielle R. Rios, MD, MS[a], Patrick J. McNamara, MB, BCh, BAO, DCH, MSc, MRCP, MRCPCH[a], Philip T. Levy, MD[b,*]

KEYWORDS

• Hypoxic ischemic encephalopathy • Therapeutic hypothermia
• Acute pulmonary hypertension • Echocardiography

KEY POINTS

- Neonates with a perinatal hypoxic event and subsequent neonatal encephalopathy are at risk of acute pulmonary hypertension (aPH) in the transitional period.
- The hypoxic insult to cardiopulmonary performance that clinically manifests as aPH may further exacerbate organ damage and contribute to the short-term and long-term neurologic sequelae.
- The phenotypic contributors to aPH following perinatal asphyxia include a combination of parenchymal lung disease (in some cases), hypoxic vasoconstriction of the pulmonary vascular bed, right ventricular dysfunction, and occasionally left heart dysfunction.
- The process of aPH in neonatal encephalopathy is dynamic, evolving with the disease course impacted by the intervention of therapeutic hypothermia during both the cooling and rewarming phases.
- Despite the increased recognition of the risk for aPH, there remains a lack of clarity regarding thresholds for hemodynamic screening, diagnosis, and intervention for aPH in neonatal encephalopathy.

INTRODUCTION

Neonates with a perinatal hypoxic event and subsequent neonatal encephalopathy are at risk of developing acute pulmonary hypertension (aPH) in the early neonatal

[a] Division of Neonatology, Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242, USA; [b] Division of Newborn Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Hunnewell 436, Boston, MA 02115, USA
[†] In memory, with gratitude.
* Corresponding author.
E-mail address: philip.levy@childrens.harvard.edu

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period.[1] Clinicians are most often concerned with the hypoxic cerebral injury that results from the lack of adequate blood flow and/or gas exchange immediately before, during, or after delivery, also known as perinatal asphyxia. The injurious processes of perinatal asphyxia may extend to cardiopulmonary performance, which in some patients may clinically manifest as aPH, and further exacerbate organ damage that contributes to the short-term and long-term neurologic sequelae.[2–5] In addition, mortality is higher in infants with combined features of hypoxic ischemic encephalopathy (HIE) and aPH when compared with infants with aPH alone.[6] Accordingly, a high index of suspicion for aPH and its consequences in the immediate postnatal period is important to consider in neonates following a hypoxic ischemic event.

During the past 2 decades, therapeutic hypothermia has become the standard of care for cases where a hypoxic ischemic insult causes moderate or severe encephalopathy.[7] Although perinatal asphyxia may have a negative impact on heart rate, loading conditions, myocardial performance, and vascular interactions, therapeutic hypothermia itself may subsequently modify cardiac performance and pulmonary hemodynamics, exacerbate the aPH, and complicate mechanistic delineation in this high-risk population. Because the biological processes of aPH in neonatal encephalopathy are dynamic and further influenced by both the cooling and rewarming phases of therapeutic hypothermia, the integration of hemodynamic (clinical, biochemical, and echocardiographic) features must be considered to allow for a better assessment of the immediate risk and long-term prognosis. Echocardiography evaluation of cardiac performance and pulmonary vascular hemodynamics may help elucidate cardiopulmonary compromise earlier, enable a more precise approach to therapeutic intervention, monitor treatment response throughout the initial insult and phases of therapeutic hypothermia, and improve overall outcomes.[3,4] This article discusses the impact of perinatal asphyxia on myocardial performance and the pulmonary vascular system, including the causes, risk factors, and hemodynamic assessment of associated aPH. In addition, we discuss the interaction between asphyxia and aPH during each phase of therapeutic hypothermia and highlight important hemodynamic considerations unique to these patients. We provide a physiology-based approach for management of aPH based on recent discoveries and emerging diagnostic methods and therapies.

TERMINOLOGY

Persistent pulmonary hypertension (PPHN) is the terminology typically used for pulmonary hypertension that presents in the immediate postnatal period secondary to abnormal transition of the pulmonary circulation. Although the term “PPHN” may be applicable to patients with hypoxic vasoconstriction of the pulmonary vascular bed and maladaptive pulmonary vasculature leading to failure of the normal postnatal decline in pulmonary vascular resistance (PVR), it misrepresents those cases of pulmonary hypertension that are associated with right[3,4,8] and left heart dysfunction[9,10] in neonates following a perinatal hypoxic event. As such, the phrase “acute pulmonary hypertension” is more suitable in the transitional period because it reflects disturbances of elevated mean pulmonary artery pressure (mPAP) due to a broad range of diseases including right ventricle (RV) or left ventricle (LV) dysfunction, as well as hypoxic pulmonary vasoconstriction, which may result from the perinatal hypoxic insult.[11]

EPIDEMIOLOGY AND RISK FACTORS

HIE affects approximately 1 to 2 per 1000 live births in developed countries and 26 per 1000 in low-resource countries.[12] The incidence of aPH ranges from 13% to 29%

among infants with HIE,[5,6,13–17] which is higher than the incidence of aPH (0.43–6 per thousand live born term infants) in the general population.[18] Acute pulmonary hypertension is more commonly associated with moderate-to-severe HIE.[6] Several reports have investigated the prevalence of aPH since the introduction of therapeutic hypothermia (TH) as standard of care for treatment of moderate/severe HIE.[6,16,19,20] The original trials of TH did not show a higher overall incidence of hypoxemic respiratory failure with presumed pulmonary hypertension.[19] Lakshminrusimha and colleagues[6] reported no difference in the rates of aPH between neonates receiving TH (33.5°C) and those with normothermia in the Neonatal Research Network (National Institute of Child Health and Human Development [NICHD]-NRN) clinical trials. NICHD-NRN optimizing cooling trial showed higher incidence of aPH and extracorporeal membrane oxygenation (ECMO) need with deeper cooling to 32°C.[14] On the contrary, Joanna and colleagues[16] found that aPH was 2.5 times higher in neonates who received TH, and echocardiographic evidence of increased PVR was reported after TH in the observational study by Seghal and colleagues.[20] There is overlap in maternal, fetal, and postnatal risk factors between the phenotypical presentations of neonatal aPH. Maternal and fetal risk factors can affect the development of pulmonary vasculature (eg, maternal diabetes, presence of fetal hypoxemia,[16] maternal age,[5] and outborn status[5]) and how it adapts to extrauterine life (**Table 1**). Additional in utero conditions (eg, placental insufficiency and oligohydramnios) can result in excessive pulmonary vascular muscularization and pulmonary hypoplasia, respectively, which further increase the risk of altered transition and HIE. Perinatal risk factors can lead to injury to the lung parenchyma (eg, respiratory distress syndrome, meconium aspiration,[5,6,16] sepsis,[5] and pulmonary hemorrhage[16]) and affect the molecular pathways responsible for pulmonary vasomotor tone and lead to aPH.[21] Joanna and colleagues[16] found an association between aPH and HIE with several postnatal factors before the initiation of TH, including severe acidosis (presence of hypercarbia on the first postnatal gas) use of medications during delivery room resuscitation, and higher baseline fraction of inspired oxygen (Fio_2; **Fig. 1**). Infants with aPH were more likely to require longer duration of inotropic support[5] and had lower cardiac output,[16] highlighting that the perinatal insult may also cause ventricular dysfunction.[5]

IMPACT OF PERINATAL ASPHYXIA ON PULMONARY VASCULAR VASOREACTIVITY

There are several mechanisms by which perinatal asphyxia and subsequent hypoxia and acidosis prevent the normal relaxation of the pulmonary vascular bed. There is

Table 1
Risk factors for acute pulmonary hypertension in neonates with perinatal asphyxia

Maternal	Fetal	Neonatal
Maternal diabetes	Fetal hypoxemia	Outborn status
Advanced maternal age	Oligohydramnios	Severe acidosis (hypercarbia)
Placental insufficiency		Need for delivery room resuscitation with pharmacologic agents
Maternal drugs (eg, SSRIs) NSAIDs		Myocardial dysfunction
Congenital infections		Meconium aspiration syndrome
		Respiratory distress syndrome
		Pulmonary hemorrhage
		Sepsis
		Polycythemia

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

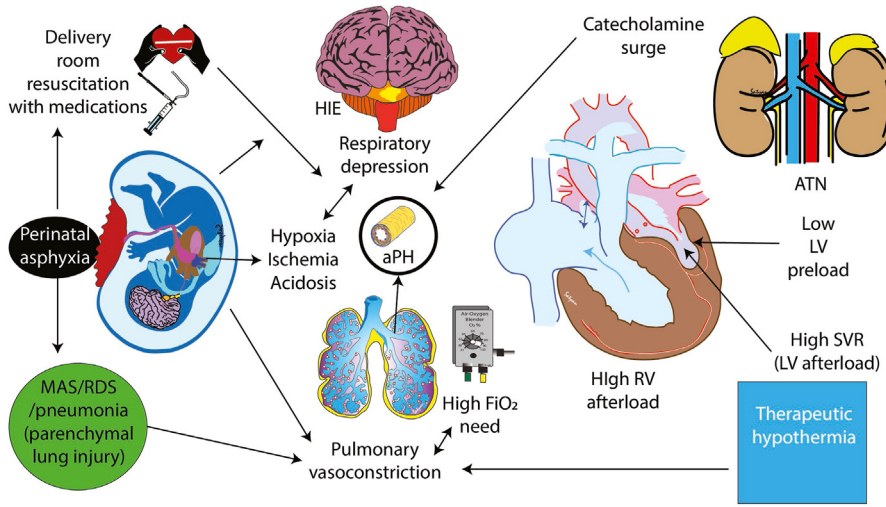

Fig. 1. Pathophysiology of aPH in neonates following perinatal asphyxia. Asphyxia is often associated with parenchymal lung disease such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), or pneumonia or idiopathic aPH contributing to hypoxic pulmonary vasoconstriction. The use of medications (epinephrine) during delivery room resuscitation increases the risk of HIE associated with aPH. ATN, acute tubular necrosis; LV, left ventricle; SVR, systemic vascular resistance. (Image Courtesy of Dr. Satyan Lakshminrusimha.)

an imbalance in favor of production of endothelin 1 with reduced production of nitric oxide that leads to elevated PVR causing deoxygenated blood to be shunted to the systemic vasculature.[22] A "surge of catecholamines" from the adrenal glands produces pulmonary and peripheral vasoconstriction that concentrates blood flow to the brain and further contributes to hypoxemia.[1] Subsequent respiratory depression with late clearance of fluid from the lungs can also increase PVR and reduce the cardiac output to the lungs. As the PVR increases and the aPH worsens, the impairment in oxygenation and pulmonary venous return further compromises the already reduced systemic blood flow from the HIE-induced cardiac injury.[23]

IMPACT OF PERINATAL ASPHYXIA ON MYOCARDIAL PERFORMANCE

Perinatal asphyxia can lead to a specific type of neonatal cardiomyopathy in the anatomically normal heart characterized by ventricular pump failure and dilated heart muscle[9] (**Table 2**). Heart failure has been documented in 30% to 82% of neonates with severe HIE.[9,24,25] Compared with children and adults, the neonatal myocardium is composed of less-developed contractile mechanisms with disorganized myofibrils, immature calcium handling system, and inadequately compliant collagen (**Fig. 2**).[9] This places the immature myocardium at increased susceptibility to afterload and extremes of heart rate changes (force–frequency relationship). The etiology of an acquired hypoxic-ischemic myocardial insult is either from the perinatal or coronary insult (stenosis, abnormal origin, or in utero compromise).[26] At the cellular level, hypoxia and acidosis disturbs the physiologic cardiomyocyte metabolism that switches almost completely from glycolytic pathways to oxidation of fatty acids.[27] Redistribution of blood flow with perinatal asphyxia can also lead to decreased perfusion and myocardial ischemia. The myocardial perfusion may be further compromised from the high intramural myocardial pressure secondary to elevated ventricular filling pressures and the low

Table 2
Impact of asphyxia and therapeutic hypothermia on cardiopulmonary status

	Therapeutic Hypothermia	
Hypoxic ischemic insult	Cooling phase	Rewarming phase
Vascular Vasoconstriction of the pulmonary vascular bed	Vascular Pulmonary vasoconstriction: ↑ PVR Systemic vasoconstriction: ↑ SVR Decreased cerebral blood flow Redistribution of LVO to brain Cerebral redistribution	Vascular Pulmonary vascular vasodilation: ↓ PVR Systemic vasodilation: ↓ SVR Persistent cerebral redistribution
Myocardial RV dysfunction LV dysfunction	Myocardial Decreased preload Decreased RV contractility Altered RV–pulmonary vascular coupling Decreased cardiac output Autonomic Sinus bradycardia Increased influence of the parasympathetic system Other Altered net inotropic response, clearance, and drug metabolism	Myocardial Normalization of preload Increased contractility Improved RV – pulmonary vascular coupling Increased LVO/RVO/cardiac output Autonomic Increased heart rate Other Mobilization (exaggerated) effect of inotropes

Abbreviations: LV, left ventricle; LVO, left ventricle output; PVR, pulmonary vascular resistance; RV, right ventricle; RVO, right ventricle output; SVR, systemic vascular resistance.

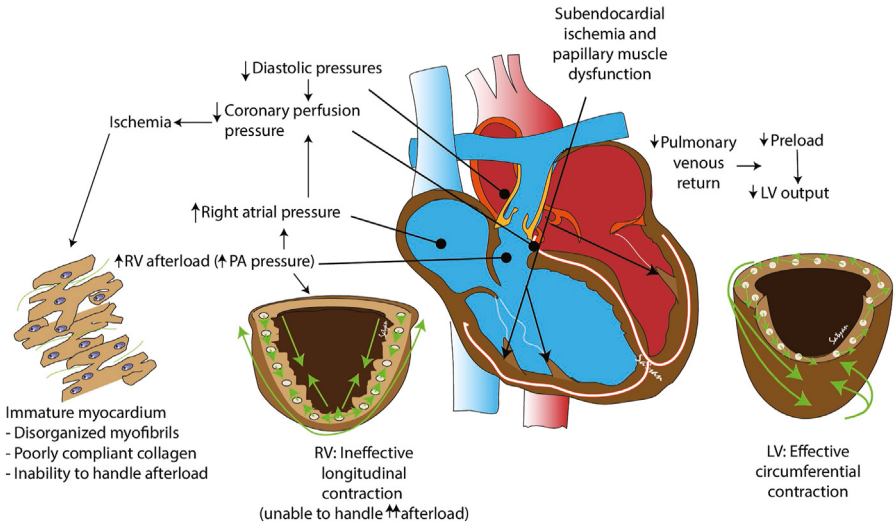

Fig. 2. Impact of asphyxia and TH on cardiac function. Perinatal asphyxia is associated with low diastolic pressure. Acute PH is associated with high right ventricular (RV) and PA pressure in turn leading to increased right atrial pressure. A combination of low diastolic pressure and high right atrial pressure results in low coronary perfusion pressure leading to myocardial ischemia. The RV with longitudinal contraction is less effective in dealing with increased afterload compared with LV with more effective circumferential contraction. Reduced pulmonary venous return due to aPH and deviation of the interventricular septum to the left results in low LV preload. (Image Courtesy of Dr. Satyan Lakshminrusimha.)

systemic diastolic pressure. Morphologically, perinatal asphyxia leads to a dilated cardiomyopathy where the cavity is enlarged with normal or thin wall thickness.[9] The heart can be affected on all levels but there is a preference/tendency for dysfunction at the papillary muscles and subendocardial regions.[26,28] Collectively, these factors predispose the myocardium to diastolic dysfunction and altered compliance with the following impact on the heart: (1) lacking the reserve to cope with reduced preload from low pulmonary venous return, blood loss, and capillary leak and/or (2) not tolerating the abrupt increase in afterload from a combination of hypoxia, sepsis, sedation, adrenal failure, and induced autonomic dysfunction. After the initial perinatal hypoxic insult, myocardial contractility increases and the heart works to enhance blood flow and protect against systemic hypoxia.[29] Myocardial injury will ultimately develop when this "compensation mechanism" fails.[30] Cardiac dysfunction will further worsen following reperfusion injury secondary to reactive oxygen species. Both inflammatory and oxidative stress eventually reduce the contractile responsiveness of the myocardium, causing a significant reduction in cardiac output,[31] hypotension, and further impairment of cerebral blood flow and perfusion of other organs.[29] Differences between RV and LV are outlined in later discussion. In preterm infants with a perinatal asphyxia, the rate of myocardial injury may be higher with known risk factors for diastolic dysfunction and decreased response to altered loading conditions.[32]

PHENOTYPIC ETIOPATHOLOGIES OF ACUTE PULMONARY HYPERTENSION IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

The spectrum of phenotypical presentation for aPH in neonates with HIE is best determined from contributions of PVR, pulmonary blood flow (PBF), and pulmonary capillary

wedge pressure (PCWP) on mPAPs by the equation: mPAP = (PVR × PBF) + PCWP.[33] There are 3 potential contributors to aPH that have been observed in neonates with a perinatal hypoxic insult: (1) Hypoxic pulmonary vasoconstriction and elevated PVR[6]; (2) Alterations in right heart performance with altered PBF[3,4]; and (3) Depressed left heart function impacting PCWP.[10] Awareness of the spectrum of these different phenotypes can facilitate appropriate monitoring and management (Fig. 3).

Hypoxic Pulmonary Vasoconstriction

In neonates with HIE, the pulmonary vasculature can maladapt after delivery due to either intraparenchymal lung disease processes (eg, meconium aspiration and air leak syndromes) or extraparenchymal disorders (eg, acidosis and sepsis) that affect oxygenation, ventilation, and lung recruitment.[33] The hypoxic vasoconstriction of the pulmonary vasculature leads to elevated PVR. With this phenotype, the pulmonary vasculature is structurally normal but with abnormal vasoreactivity due to mediators promoting vasoconstriction and negating vasodilation, which affect the transitional reduction of RV afterload and the relationship of PVR to systemic vascular resistance (SVR).[34] This phenotype presents with hypoxia and occasionally parenchymal lung disease. For example, meconium aspiration syndrome can interfere with gas exchange, alter lung compliance, and result in raised PVR. In addition, the neonate with HIE may not be able to initiate respirations on their own and is reliant on less-effective positive pressure breaths that can interfere with establishing functional residual capacity. As such, even in the absence of identified lung pathologic condition, proper clearance of fetal lung fluid may be impaired without establishment of pressure gradient for fetal lung fluid to be absorbed (see Fig. 1).

Right Heart Disease

Normal RV performance is critical for adequate PBF. The right heart disease that manifests in neonates with HIE may originate from a primary insult to the RV during the initial and reperfusion injury, in addition to its dual response to elevated PVR with hypoxic pulmonary vasoconstriction or ventriculo-ventricular interactions with LV disease.[8] Giesinger and colleagues[3] demonstrated that echocardiographic evidence of RV dysfunction at 24 hours of age in neonates with HIE undergoing TH was an independent

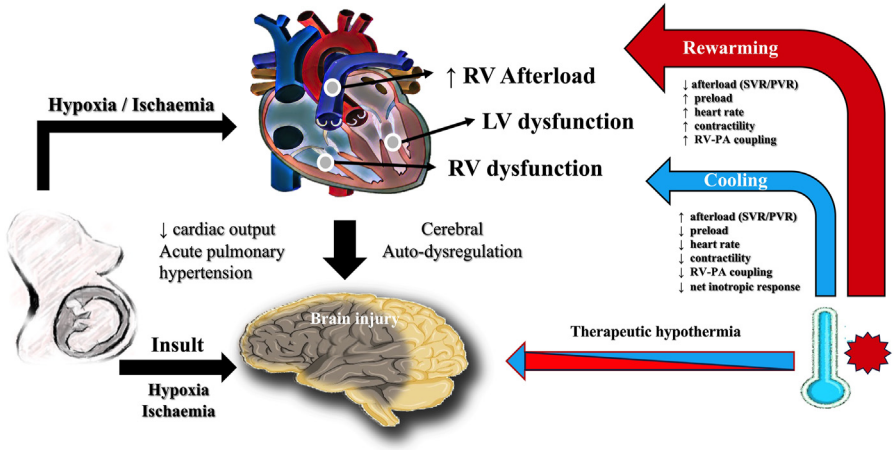

Fig. 3. Phenotypic contributors to aPH following perinatal asphyxia.

predictor of death or abnormal brain MRI in the short term and adverse neurodevelopment into early infancy,[4] even after adjusting for severity of the insult and subsequent disease burden with preserved LV functional parameters and the pseudonormalization of pulmonary hemodynamics.[3] It is plausible that primary RV dysfunction alone has the potential to lead to biventricular enlargement, dilated cardiomyopathy, and further impairment to systemic circulation and end-organ perfusion.[9] The developmental biology of the RV affects how it responds to a primary hypoxic injury during the perinatal transition and aids in classification and management of neonatal aPH.[35] The RV is a thin-walled structure with coarse trabeculations that provide the substrate for the RV to accommodate increases in volume and afterload. Unlike the LV, that has its own unique circumferential fiber pattern to provide the major contributions to stroke volume and enhance cardiac output, the RV relies primarily on a deep longitudinal fiber layer that does not allow for robust responses to changes in afterload (according to the force–frequency relationship) compared with its neighboring LV. The RV experiences greater wall stress for a similar degree of afterload as compared with the LV. In addition, the RV coronary circulation is negatively affected by high right heart pressure and low aortic root pressure seen with impaired pulmonary venous return following perinatal asphyxia. The RV loses its dominance during transition with redistribution of postnatal blood flow, and this leads to increased metabolic demands on the right heart that may not respond favorably to hypoxia and acidosis. As such, the RV becomes dependent on preload with a weakened response to augment cardiac output according to the RV Frank–Starling relationship. Although both the LV and RV may be equally affected by the initial hypoxic insult and reperfusion injury, the cumulative effect may be less well tolerated by the RV due its unique morphology and its immature ability to respond to changes in loading conditions. The RV disease tends to be worse in the first postnatal days and typically resolves during the first week of age.[3,4]

Left Heart Disease

In some neonates with HIE, the LV may also be impacted by the initial perinatal insult.[36] The abnormal LV performance manifests as reduced stroke volume and altered parameters of systolic and diastolic function leading to decreased cardiac output.[1] As mentioned, reactive oxygen species are also present during the reperfusion injury and may reduce contractile responsiveness and lead to further reduction in cardiac output. Severe LV failure with impaired compliance increases left heart preload, according to the Frank–Starling curve, and the overstretched left heart and high PCWP may lead to pulmonary venous congestion and increased pressures in the pulmonary artery.[37] Because of the increased RV afterload, secondary right heart failure may ensue and worsen the aPH. Neonates with HIE and severe LV failure present with hypoxemia, respiratory failure, low cardiac output, and can ultimately progress to cardiogenic shock with failure of compensatory mechanisms. The pulmonary venous congestion and left heart components of this aPH phenotype are usually not responsive to pulmonary vasodilators (eg, inhaled nitric oxide, iNO) because the primary insult is not on the pulmonary arterial (PA) circulation. Diagnostic clues include pulmonary edema on radiograph and persistent left-to-right shunting at the atrial level (indicative of higher left atrial pressure) with simultaneous right-to-left shunting through the patent ductus arteriosus (PDA). In the setting of severe LV failure, infants may have critically low cardiac output; therefore, the systemic circulation is exclusively dependent on right-to-left flow across the PDA and selective pulmonary vasodilators would be harmful. Finally, LV diastolic dysfunction and subsequent increases in PCWP are associated with a higher risk for invasive ventilation and pulmonary disease in infants[38] and are directly correlated with abnormal coupling of the RV to its afterload during the

transitional period.[39] The reduced left heart function is often transient, with the most severe cardiovascular abnormalities typically occurring 48 to 72 hours after the initial insult, followed by gradual recovery.[40]

HEMODYNAMICS OF ACUTE PULMONARY HYPERTENSION IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

Perinatal asphyxia–induced aPH results in a "constellation of hemodynamic consequences that manifest as oxygenation failure with cyanosis, severe ventilation perfusion mismatch, low cardiac output in severe cases, and unstable vasoreactivity that leads to instability with handling and agitation."[21] Acute pulmonary hypertension associated with hypoxic pulmonary vasoconstriction (and elevated PVR) and pulmonary venous congestion from left heart dysfunction (elevated PCWP) may both result in a direct increase in RV afterload but require careful delineation because the approach to management is divergent. The challenge for the RV is to remain hemodynamically coupled to the pulmonary circulation in the setting of elevated RV afterload. The RV to pulmonary vasculature coupling is maintained by RV adaptation to increasing pulmonary vascular load by enhancing contractility to maintain PBF.[41] Muscle hypertrophy is a crucial adaptive mechanism that enhances the contractile capabilities of the RV. Prolonged exposure to increased afterload and progressive pressure loading on the RV can lead to maladaptive ventricular remodeling, in which the RV dilates and results in decreased stroke volume followed by an increase in heart rate to maintain cardiac output.[41] This response to high afterload is associated with an increase in RV myocyte stress, dilation, and septal bowing, which further impairs RV function and decreases PBF. In situations where there is an additional primary insult on the RV, the PBF is decreased. RV dysfunction will serve as the catalyst for a cascade of downstream events and "self-perpetuating cycle of declining cardiovascular wellbeing" if untreated.[21] Varying degrees of LV dysfunction can ensue due to the initial perinatal hypoxic insult or "inter-ventricular dependence from LV compaction caused by RV dilation and septal bowing and decreased LV filling from decreased PBF."[33] Ultimately, the neonatal myocardium will not be able to handle complex hemodynamic changes, and the RV uncouples from high afterload, leading to decreased RV performance and overt RV failure.[42]

IMPACT OF THERAPEUTIC HYPOTHERMIA ON ACUTE PULMONARY HYPERTENSION

TH is considered standard of care for neonates suffering from perinatal asphyxia and moderate or severe HIE.[7] The known adverse impact of TH on the cardiopulmonary system is well documented[43,44] with ongoing hemodynamic instability related either to the primary insult, the effects of TH (cooling and/or rewarming), or even the approach to intervention. Although each adverse effect may compromise vital organ perfusion and metabolism and potentially decrease the effectiveness of neuroprotective strategies,[1,45] the risks are outweighed by the benefits to survival and neurodevelopmental outcome.[13] As such, cardiac performance depends on the interaction among preload, afterload, intrinsic myocardial contractility, and heart rate. Therefore, it is important to characterize the hemodynamic changes that can occur during both the cooling and rewarming phases of TH to understand the overall contribution to aPH in this high-risk population (see **Table 2**).

Cooling

The expected physiologic effects during cooling include increased systemic and PVR, reduced cardiac contractility with altered inotropic responses, reduced preload, lower heart rate, and ultimately reduced cardiac output.[43,44]

Increased pulmonary vascular resistance

Hypothermia causes pulmonary vascular constriction and potentially modulates PVR through neuronal mechanisms[46] but this may not be clinically significant in every case.[47] In a lamb model cooled to 30°C, pulmonary artery pressure increased by approximately 50%[48] and in a rodent model, PVR increased 1% per 1°C decrease in body temperature.[48] Increase in blood velocity[49] and catecholamine responses[50] to hypothermia temperatures may also contribute to higher PVR in infants in the cooling phase. Oxygen requirements may increase in patients with aPH due to hypoxic pulmonary vasoconstriction and increased PVR. However, evidences from the original TH studies have not shown a significant increase in aPH.[13] In the only observational human study, Vasquez and Geisinger and colleagues[51] demonstrated that in neonates with HIE, the cooling phase of TH is associated with increased mPAP and worsening pulmonary hemodynamics on echocardiography but RV function was not affected. It is likely that the magnitude by which cooling changes PVR varies by temperature range as observational studies have demonstrated increases in Fio_2 requirement in some but not all neonates with HIE.[43] In addition, experts suggest that initiation of cooling may still modulate the risk of aPH (or exacerbate aPH that is already present) in some patients; therefore, caution is advised in neonates who already display clinical signs of aPH.[4,8,11,36]

Increased systemic vascular resistance

At delivery, the sympathetic system is not yet fully functional because the resting peripheral vascular tone remains high but with decreased beta-adrenergic receptors. Cooling further increases the alpha-adrenergic receptors but blunts the beta-adrenergic effect and affects the intolerance of the myocardial contractility to respond to an increased systemic or PVR (afterload). Ultimately, these processes lead to a reduced net inotropic effect of cardiotropic medications.

Reduced preload

The reduction in preload is multifactorial. The initial perinatal hypoxic insult can increase hydrostatic pressure and lead to increased capillary permeability. The total fluid goal is also restricted when HIE is suspected to minimize metabolic demands and due to coexisting renal dysfunction due to acute tubular necrosis. There is also increased blood sampling during the early cooling phase of TH. A primary insult to RV or a secondary response of the RV to elevated PVR can both lead to reduced stroke capacity, reduced pulmonary venous return, and inferior filling of the LV. Accordingly, stroke volume and cardiac output will be low during the cooling phase based on the Frank–Starling relationship.

Impaired contractility

Cooled neonates have reduced heart function during treatment,[10,52,53] probably to a similar degree as seen in noncooled neonates.[10] Although heart function is reduced during TH, plasma lactate levels that are often high at the start of treatment[10,54] usually improve during cooling,[10] due to reduced metabolic demands at low body temperature. The impairment in contractility results from intolerance to increased afterload, immaturity of the cardiomyocytes, and a blunted beta-adrenergic effect. As such, there is often an altered inotropic response and caution must be used when initiating and titrating certain medications while in the cooling period.[55] For example, neonates with hypoxic respiratory failure and HIE who have undergone TH and are treated with milrinone to augment contractility and reduce pulmonary afterload developed profound reduction of diastolic blood pressure that required escalation of additional cardiotropic support.[55] These effects are postulated to relate to milrinone toxicity secondary to impaired renal clearance.

Lower heart rate

Sinus bradycardia is common during the cooling phase with slow repolarization of the sinoatrial node by reduced intracellular calcium release but does not usually require medical treatment.[13] The decreased effect of the parasympathetic system on the heart during TH also induces moderate bradycardia and leads to decreased stroke volume and reduced metabolic demand on the myocardium.

Altered right ventricle–pulmonary artery coupling

RV function depends on its afterload. With increasing PAP, there is a proportional response in RV systolic function, which is governed by the stress–velocity relationship (ie, RV–PA coupling). The challenge in aPH is for the RV to remain hemodynamically coupled to a compliant pulmonary artery circulation with the degree of RV failure in the first 24 hours directly linked to poor outcomes beyond the neonatal period.[4] Evidence also shows in addition to the initial insult, the cooling phase leads to abnormal RV–PA interactions.[3] This has relevance because when RV–PA coupling is normal, treatment to lower PVR may also enhance RV performance and normalize RV function.

Rewarming

The second phase of TH has its own unique impact on hemodynamics with progressive vasodilation of the systemic and pulmonary vasculature, increases in preload, heart rate, and cardiac output. Although less is known about the hemodynamic impact of rewarming on the brain, observational studies have shown that most intraventricular hemorrhage occurs during the rewarming period and was associated with significant hemodynamic lability.[45] "Rewarming hemodynamics" and how to actively adjust the cardiovascular specific medications throughout the warming period requires further study.[1]

Decreased pulmonary vascular resistance

Rewarming leads to pulmonary vasculature dilation and decreased PVR.[56]

Decreased systemic vascular resistance

Rewarming leads to progressive systemic vasodilation with a decrease in SVR. This is clinically reflected by a lower diastolic component of the blood pressure. As such, the mean blood pressure may actually remain unchanged or decline.[46] Rewarming may be associated with seizures requiring additional antiepileptic medications that may also contribute to hypotension. The lower diastolic blood pressure may affect pharmacologic clearance and metabolism of cardiotropic medications. The mean blood pressure may drop but studies have shown that the redistribution of blood flow to the brain remains constant,[57] with nonsignificant clinical changes in stroke volume and mean blood pressure.[56]

Increased preload

Rewarming results in progressive vasodilation of the systemic and pulmonary vasculature with increased PBF. The total fluids are also slowly increased while some infants are also able to tolerate some enteral nutrition.

Contractility

Rewarming hemodynamics leads to improved cardiac contractility, increased metabolic rate, and cardiac output that are predominately heart rate dependent.[58,59] As such, there may be an "exaggerated" effect of inotropes.

Increased heart rate

Rewarming physiologically raises the heart rate and leads to enhanced stroke volume.[60] Cardiac output actually increases more due to heart rate than stroke volume.[61]

Right ventricle–pulmonary artery coupling

Recent evidence shows infants with more severe HIE show an increase in coupling during the rewarming phase.[3] Interestingly, Geisinger and colleagues[3] also showed that in neonates that underwent TH with normal outcomes, novel echocardiographic measures of coupling were actually preserved. The authors suggest that changes outside of afterload (eg, primary insult on RV performance) may affect RV function in neonates with poor outcomes.[3]

CARDIOPULMONARY ASSESSMENT AND DIAGNOSTIC APPROACH TO ACUTE PULMONARY HYPERTENSION IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

Screening for Acute Pulmonary Hypertension in Hypoxic Ischemic Encephalopathy

There are no consensus guidelines on when to screen for aPH in neonates with HIE, which leads to management variation.[1,62] The diagnosis of aPH in neonates with HIE relies on the assessment of various clinical parameters, biochemical markers, and the use of noninvasive imaging tools. Although the gold standard for diagnosis of PH is cardiac catheterization, its invasive nature makes it a less than ideal modality to screen and monitor aPH in neonates with HIE.[63] Infants with HIE receive a comprehensive laboratory and neurologic evaluation but only some centers routinely perform a complete hemodynamic assessment that includes cardiac biomarkers and echocardiography.[1,62] Unfortunately, the clinical signs of myocardial injury and aPH, as well as electrocardiographic and radiographic findings, are all nonspecific and often insensitive.[64] Specifically, the conventional cardiovascular markers of heart rate and blood pressure are late markers of insufficient cardiac performance. In addition, arterial blood pressure is not reflective of RV function and/or abnormal brain tissue oxygen delivery.[65] Urinary output and plasma lactate are influenced by the primary hypoxic-ischemic insult so they are a less reliable indicator of the adequacy of systemic perfusion. Skin perfusion is modified significantly during TH. Biochemical markers (eg, troponin and creatine kinase-MB) of cardiac injury have been explored in newborns with neonatal encephalopathy and have potential prognostic significance concerning mortality and outcome.[31,64,66–76] However, other than providing insight into contractility, they do not provide real-time information regarding the other major determinants of cardiac performance (eg, loading conditions, heart rate, or morphology). As such, echocardiography remains the primary choice for diagnostic evaluation, follow-up, and analysis of treatment results in neonates with cardiomyopathy associated with perinatal asphyxia. Until recently, echocardiography was only considered in the presence of clinical cardiovascular compromise and/or elevation of biomarkers but recent expert consensus suggests that advanced hemodynamic assessment should be performed early for all infants with HIE treated with TH.[77] Others suggest that a baseline echocardiogram should be obtained at minimum when cardiovascular agents are initiated and/or Fio_2 requirement is greater than 30% but also in moderate to severely impaired infants before or at 24 hours to identify myocardial dysfunction that may not be clinically obvious given the wide variety of competing problems in this high-risk population.[1,23,62]

Echocardiographic Assessment

Echocardiography is used to evaluate myocardial performance and pulmonary hemodynamics and delineate the phenotypes and hemodynamic profile of aPH.[33,78] The characterization of aPH by echocardiography is based on 3 broad categories: (1) evaluation of the severity of PH with indirect assessment of elevated RV afterload and estimation of pulmonary hemodynamics, (2) evaluation of measures of right and left ventricular performance, and (3) appraisal of shunts[78] (**Table 3**). This approach provides

Table 3
Comprehensive evaluation of acute neonatal pulmonary hypertension by echocardiography

Categories	Characteristics
Severity of PH	
Interventricular septal wall configuration[a]	Degree of septal wall flattening in end-systole estimates RVSP in response to changes in RV afterload. Flattening at end-systole suggests >50% systemic RVSP. Posterior systolic bowing into LV suggests suprasystemic RVSP
Eccentricity index (EI)[b]	Ratio of the LV dimensions parallel and perpendicular to the septum in systole and diastole. Elevated PAP if >1.3
Doppler integration of the tricuspid valve (TRJV)	Quantitative estimate of RVSP by the modified Bernoulli equation Quantitative estimate of PVR by the Abbas formula (TRJV:VTI) RVSP estimates PADP
Doppler integration of the pulmonary valve (RVET/PAAT)	Provides reliable non-invasive estimate of mPAP, PVR, and compliance.[c] Normal RVET: PAAT <4
Shunt direction (PDA, ASD, and ventricular septal defect [VSD]: see later discussion)	Size and direction of the flow
Pulmonary/systemic hemodynamics	
Left ventricular output	Normal Range 150–300 mL/min/kg
Right ventricular output	Normal Range 150–300 mL/min/kg
End-organ flow evaluation (MCA, celiac artery Doppler)	Absent or reversed diastolic flow suggestive of high-volume systemic shunts
RV performance[d]	
Morphology	4-chamber view of outflow tracts and linear dimensions of cavity, wall thickness, end-systolic and end-diastolic areas
Fractional area of change (FAC)	Change in cavity dimensions (estimate of RV ejection fraction). Normal RV FAC >35%
Tricuspid annular plane systolic excursion (TAPSE)	Provides an estimate of longitudinal myocardial shortening and RV systolic performance Normal TAPSE >8.5
Tissue Doppler imaging (DI)	Provides quantitative measures of RV systolic (S′) and diastolic (E′ and A′) function
Strain and strain rate	Assessment of RV systolic function (strain), diastolic function (diastolic strain rate), and contractility (systolic strain rate)
RV velocity time integral (VTI)	Estimate of RV stroke volume, reflecting the cumulative inflow of deoxygenated blood and venous return (in the absence of a PDA)
RV-PA coupling (TAPSE/PAAT and Strain/PAAT)	Reliable estimate of invasive coupling hemodynamics
LV Performance	
Morphology	4 chamber view of outflow tracts and linear dimensions of cavity, wall thickness, end-systolic and end-diastolic areas

(*continued on next page*)

Table 3
(*continued*)

Categories	Characteristics
Ejection fraction/shortening fraction	Assess LV systolic function Normal EF >55%
Mitral annular plane systolic excursion	Provides an estimate of longitudinal myocardial shortening and LV systolic performance
Tissue DI	Provides quantitative measures of RV systolic (S′) and diastolic (E′ and A′) function.
Strain and strain rate	Assessment of LV systolic function (strain), diastolic function (diastolic strain rate), and contractility (systolic strain rate)
LV VTI	Marker of systemic blood flow
Pulmonary vein Doppler	Assess LV preload
Appraisal of shunt (size and direction of flow)	
PDA	Estimate PASP from systemic pressure, ductal size, characterize restriction patterns
Atrial level shunt (PFO/ASD)	Estimation of RA to LA pressure (direction: right to left shunt indicates right atrial hypertension, left to right shunt indicates higher left atrial pressure)
VSD	Estimate RVSP and PASP from systemic pressure (if applicable)

Abbreviations: FAC, fractional area change; PAAT, pulmonary artery acceleration time; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PFO/ASD, patent foramen ovale/atrial septal defect; RVET, RV ejection time; RVSP, RV systolic pressure; TRJV, tricuspid regurgitant jet velocity.

[a] The degree of septal wall flattening in end-systole provides an estimate of RVSP.

[b] Diastolic LV EI is a reflective marker of RV volume overload and systolic EI reflects RV pressure overload. A pressure-loaded RV in cPH will deviate the septum in systole and reduce the perpendicular dimension resulting with an end-systolic LV EI $\geq$ 1.3.

[c] Visual inspection of the Doppler flow envelope across the RV outflow tract has been shown to be a sensitive predictor of altered pulmonary hemodynamics in neonates with PH. The characteristic midsystolic notch (the "flying W") and its different patterns integrate all the indicators of pulmonary vascular load and RV function and have been used to detect a decline in the RV afterload during the early transitional period in healthy term infants.

[d] RV FAC, TAPSE, tissue DI, and Deformation have all been validated in term and preterm infants with emerging reference patterns in health and disease states.

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comprehensive information regarding disease severity, responsiveness to therapy, and the relative contributions of pulmonary vascular injury, left heart, and right heart disease in neonates with HIE.[23] All phenotypes may result in exposure of the RV to sustained high afterload that can lead to dilated cardiomyopathy with depressed global function and performance. Recent advances in quantitative echocardiography permit a more comprehensive assessment of myocardial performance in neonatal encephalopathy that could not be previously obtained with conventional imaging.[3,4,9,10,36,40,52,53]

MANAGEMENT OF ACUTE PULMONARY HYPERTENSION IN NEONATES WITH PERINATAL ASPHYXIA

Management of aPH in neonates with perinatal asphyxia requires attention to the phenotypic presentation with an aim to provide sufficient PBF to increase oxygenation

and reduce secondary consequences of increased afterload on RV mechanics.[33] The clinical evaluation for aPH begins with a rapid multifaceted approach to identify risk factors, recognize symptoms, and anticipate potential illness. The management consists of 4 principal concepts: (1) supportive cardiorespiratory care (ventilator support, correction of metabolic derangements, sedation and pain management, consideration for surfactant replacement therapy, and treatment of infection), (2) use of pulmonary vasodilators to decrease afterload, (3) cardiotropic support for impaired RV and LV systolic performance, and (4) ECMO if needed[79] (**Table 4**). It is important to note that the selection of pulmonary vasodilators and cardiotropic medications should be based on the suspected underlying phenotype coupled with the degree of impairment of systemic hemodynamics, ventricular dysfunction, and degree of parenchymal disease (**Table 5**). Intravenous dobutamine (2.5–10 mcg/kg/min) is the recommended first-line treatment of RV dysfunction. Nonresponders should be transitioned to low-dose epinephrine (0.03–0.05 mg/kg/min) because higher doses of dobutamine are unlikely to benefit and may induce deleterious tachycardia. The selection of

Table 4
Management of acute pulmonary hypertension in neonates with perinatal asphyxia

Principle Concepts	Mechanism
Supportive cardiorespiratory care	Correction of metabolic derangements that can alter afterload Maintenance of adequate oxygenation Lung recruitment optimization (enhanced ventilation strategies) Cardiovascular support with fluid resuscitation, inotropic agents, or selective systemic vasopressors based on the phenotype[a] Sedation therapies (conservative and pharmacologic) Other[b]
PH targeted therapy (promote pulmonary vasodilation)	NO-cGMP pathway (eg, iNO, sildenafil) Prostacyclin-cAMP pathway (eg, prostacyclin agonist)
Optimization of RV support	Enhanced preload: cautious volume resuscitation Afterload reduction: iNO and PgE1 (if ductus arteriosus is closing or closed to offload RV) Augment RV function: inotropic agents (dobutamine and epinephrine) [c]
Optimization of LV support	Enhanced preload: cautious volume resuscitation Afterload reduction: dobutamine (weak vasodilator) Augment RV function: inotropic agents (dobutamine and epinephrine)
ECMO	VV ECMO: hypoxic respiratory failure without hemodynamic compromise VA ECMO: hypoxic respiratory failure with hemodynamic compromise

[a] Steroid treatment to stabilize blood pressure in inotropic-resistant environments may also be necessary.
[b] Additional therapies to promote pulmonary vasodilation, improve oxygenation, and minimize pulmonary vasoconstriction in specific circumstances include the following: (1) antibiotics (eg, pneumonia and sepsis); (2) red blood cell transfusion for optimization of oxygen delivery; and (3) surfactant replacement therapy (eg, respiratory distress syndrome and meconium aspiration).
[c] Cautious use of milrinone with inotropic support.
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Table 5
Physiology-based treatment strategies: choice of inotropes in hypoxic ischemic encephalopathy and therapeutic hypothermia

Pathophysiology	Mechanism	Treatment
Hypoxic respiratory failure	aPH ± parenchymal disease	Lung recruitment optimization Surfactant replacement therapy (RDS) Selective pulmonary vasodilators (iNO) Caution with milrinone
Impaired systemic hemodynamics	aPH with hypotension	
	Isolated systolic hypotension	Dobutamine, epinephrine
	Refractory hypotension	Hydrocortisone
	If TnECHO available	Vasopressin, Norepinephrine
	Normal function	Epinephrine, Fluid bolus, PGE
	Severe RV dysfunction	Evaluate coronary, myocarditis
	Severe LV disease/Normal RV function	

Addition of PGE to support the systemic circulation in the setting of severe RV dysfunction, increasing lactate, and evidence of poor end-organ perfusion.

Abbreviations: aPH, acute pulmonary hypertension; iNO, inhaled nitric oxide; LV, left ventricle; PGE, prostaglandins; RDS, respiratory distress syndrome; RV, right ventricle; TnECHO, targetted neonatal echocardiography.

vasopressor support in patients with low diastolic or mean arterial pressure is another important consideration. Intravenous vasopressin or norepinephrine may be appropriate in the setting of preserved LV function with low diastolic blood pressure and aPH. Cautious adjustment of these medications during the rewarming phase should be considered with the known physiologic changes to loading conditions, heart rate, and contractility. Pathophysiology-based approaches will dictate the appropriate therapy. For example, an infant with meconium aspiration and hypoxic pulmonary vasoconstriction may benefit from iNO to decrease the PVR; however, a neonate with isolated moderate-severe LV systolic dysfunction is at risk of deterioration following the initiation of iNO due to the need to maintain a right–left ductal shunt to support systemic blood flow. However, if the LV dysfunction is due to severe RV dysfunction (from a primary insult to the RV or secondary to high PVR), then iNO may still be beneficial. In general, the choice of therapy must be balanced against the goal of optimizing SVR, PVR, and cardiac function. The use of cardiotonic drugs, and the specific agent to use, should be tailored to the individual and based on consideration of the pathophysiologic findings related to end-organ perfusion, loading conditions, and heart function.

Extracorporeal Membrane Oxygenation Utilization

The incidence of ECMO utilization in neonates with HIE and aPH has been reported between 4% and 9%.[14,15] The use of ECMO in these high-risk neonates has been shown to be safe with good survival,[80] although the choice of venovenous (VV) or venoarterial (VA) ECMO may lead to differences in mortality or intracranial hemorrhages.[81] Both VV ECMO and VA ECMO are used for neonatal respiratory failure following perinatal asphyxia but no randomized controlled trial has been done to compare these modalities in this patient population.[82] Interestingly, despite a survey in 2009 that showed that close to 50% of responders from active neonatal centers with ECMO would not offer it as a rescue modality to neonates with moderate-severe HIE,[83] the actual number of neonates with a perinatal insult and aPH that have received ECMO has increased

during the past decade.[84] Most outcome data have focused on mortality and/or development of intracranial bleeding but are limited to case reports, small case series, or nested cases in large registries. With the recognition that ECMO may not confer the same risk of intracranial hemorrhage and mortality as one perceived,[84–86] it is no longer contraindicated in neonates with progressive aPH and myocardial dysfunction and should be considered as a rescue therapy. As such, we suggest that when an HIE infant undergoing TH has severe aPH that requires ECMO, the TH should (1) not be discontinued in lieu of avoiding ECMO and (2) continued and managed through the ECMO circuit for the entire period of cooling and rewarming.

SUMMARY

Acute neonatal pulmonary hypertension is a common consequence of perinatal hypoxia that is even more pronounced in neonates with moderate-to-severe HIE. The pathogenesis of the association between perinatal asphyxia and aPH is multifactorial and results from a combination of hypoxic vasoconstriction of the pulmonary vascular bed and primary insults to right or left ventricular performance or other pathophysiologic disorder. The diagnosis of aPH requires clinical awareness of risk factors, recognition of hemodynamic changes, and understanding of the different imaging modalities to provide comprehensive information regarding phenotypes, disease severity, and the influences of pulmonary vascular disease and cardiac dysfunction. Longitudinal assessment can offer valuable physiologic insights into disease progression and response to therapies.

Best Practices

What is the current practice?

- Infants with perinatal asphyxia and associated lung disease are closely monitored for hemodynamic instability with consideration for echocardiographic evaluation for diagnosis, follow-up, and analysis of treatment results for acute pulmonary hypertension (aPH), but it is not considered standard of practice at every institution.

Best Practice

- Neonates with hypoxic ischemic encephalopathy (HIE) associated aPH may have multiple underlying etiologies that need to be recognized. The approach to management may differ according to the initial insult and during each phase of therapeutic hypothermia (cooling and rewarming).
- Blood pressure is not a reliable predictor of cardiovascular well-being and underlying heart dysfunction.
- Comprehensive assessment of the hemodynamic profiles of aPH include a thorough clinical exam and comprehensive quantitative echocardiography to help guide therapeutic intervention.
- The initial insult, therapeutic hypothermia, and rewarming modulate the major determinants of cardiac performance, afterload, preload, contractility, heart rate, and even morphology. Therefore, careful adjustment of cardiotropic agents and pulmonary vasodilators is recommended in neonates with aPH and myocardial dysfunction.

What changes in current practice are likely to improve outcomes?

- In depth understanding of underlying risk factors and etiopathologies that contribute to the disease phenotype and utilization of non-invasive tools and clinical assessment to guide patient-targeted therapies based on hemodynamic profiles during the cooling and rewarming phases of therapeutic hypothermia.

- Early hemodynamic screening with echocardiography to delineate the contribution of hypoxic pulmonary vasoconstriction from right ventricle (RV) or left ventricle (LV) dysfunction to the clinical manifestation of aPH seen following perinatal asphyxia.
- aPH is often exacerbated by TH leading to increased RV afterload and reduced LV preload.

Is there a clinical algorithm?

- Although there is increased recognition of the impact of aPH in neonates with HIE on short- and long – term neurological outcomes, there is no universal algorithm for screening, diagnosis, or the approach to intervention based on phenotypic presentation.

Major recommendations

- A high index of suspicion for cardiopulmonary dysfunction and aPH is important in the neonate with clinical and biochemical evidence of a hypoxic ischemic insult.
- Neonates with a perinatal hypoxic event at risk for aPH should have screening, and if clinically indicated, serial echocardiograms should be performed to assess severity and response to treatment following the initial hypoxic insult and during both the cooling and rewarming phases of therapeutic hypothermia.
- Therapeutic hypothermia and rewarming modify loading conditions and blood flow and careful adjustment of inotropic agents is recommended with avoidance of those that contribute to increased pulmonary artery pressures as able.
- A combination of pulmonary vasodilators to reduce RV afterload and inotropes supporting ventricular function and vasoactive agents supporting SVR is needed to optimize hemodynamics in aPH during TH. Caution must be exercised while using pulmonary vasodilators in the presence of LV dysfunction.

Summary statement

- It is important to understand the underlying etiopathologies, unique hemodynamic profiles of different endotypes, and novel assessments in order to guide targeted management and improve outcomes in neonates following perinatal hypoxic event and risk for aPH.

DISCLOSURE

The authors have nothing to disclose.

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