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Recognition and Management of Cardiovascular Insufficiency in the Very Low Birth Weight Newborn

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The measurement of blood pressure in the very low birth weight newborn infant is not simple and may be erroneous because of numerous factors. Assessment of cardiovascular insufficiency in this population should be based on multiple parameters and not only on numeric blood pressure readings. The decision to treat cardiovascular insufficiency should be made after considering the potential complications of such treatment. There are numerous potential strategies to avoid or mitigate hypoperfusion states in the very low birth weight infant.

FOREWORD

The original guideline, "The Management of Hypotension in the Very-Low-Birth-Weight Infant: Guideline for Practice," was published in 2011 by the National Association of Neonatal Nurses (NANN) with the objective, "To provide an evidence-based clinical guideline for the management of systemic hypotension in very low birth weight infants during the first 3 days of postnatal life." At the time of revision, it was determined that a collaborative effort between NANN and the Committee on Fetus and Newborn of the American Academy of Pediatrics would best function to create the foundation for an updated, relevant clinical report that would serve all neonatal providers. There are similarities throughout this report to the original NANN publication. However, this clinical report addresses recent updates in research and evidence-based practice in relation to caring for the neonate with hypotension.

INTRODUCTION

Identification and management of clinically significant systemic hypoperfusion in the infant born weighing less than 1500 g (ie, very low birth weight [VLBW] infant) during the first week of postnatal life

abstract

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is challenging. The objectives are to recognize cardiovascular insufficiency (ie, insufficient cardiac output to meet metabolic needs and provide adequate end-organ tissue perfusion), which can clinically present as hypotension, delayed capillary refill, oliguria, and/or metabolic acidosis, to determine when to intervene, and to decide which appropriate evidence-based strategy to use.[1,2] There is no consensus that a specific blood pressure (BP) threshold in VLBW infants predicts pathology. In addition, the threshold values that potentially warrant intervention are probably different for newborn infants of the same gestational age and weight and will also change for the same neonate during successive postnatal days. Moreover, the literature is conflicting regarding the range of BP values that may influence outcomes such as morbidity, mortality, and neurodevelopmental outcomes in this population.[1,3,4] Frequently used numeric thresholds, such as a BP measurement that is below a mean arterial pressure (MAP) of 30 mm Hg, or a MAP value that is less than the infant's gestational age in weeks, are arbitrary and not supported by high-level evidence. Moreover, there are many difficulties in obtaining valid BP values, either by invasive intraarterial measurements or by noninvasive cuff technology, in this population.[5] Published arbitrary values that reflect population "norms" will vary by gestational age, postnatal age, and weight and do not necessarily correlate with inherent physiologic responses or cardiovascular insufficiency in the patient. However, deleterious consequences of hypoperfusion include a reduction in the delivery of oxygen and other nutrients to the cells, anaerobic metabolism, lactic acidosis, and cell death.[1,5,6] The management of hypotension in the VLBW infant should include an understanding of the infant's presenting diagnosis; the physiologic consequences of the conversion from fetal to neonatal circulation; the significance of shunting through the foramen ovale and ductus arteriosus; recent pH, carbon dioxide, oxygen tensions, and base deficit and how they may alter cerebral hemodynamics; and systemic vasodilation, vasoconstriction, and cardiac function. Additionally, an understanding of how cerebral hemodynamics are influenced by systemic hemodynamics is necessary when making decisions on how to manage hypotension; systemic hypoperfusion depends on the complex interaction among these various factors, especially cardiac output, systemic vascular resistance, and MAP.[4]

This clinical report reviews transitional physiology of the VLBW infant, current and emerging methods for assessing BP and end-organ perfusion, and current treatment practices aimed at minimizing morbidity and mortality in VLBW infants with cardiovascular insufficiency.[6,7]

TRANSITIONAL PHYSIOLOGY OF THE VLBW INFANT

The immaturity of the fetal cardiovascular and pulmonary systems in VLBW infants affects the transitional physiology from fetal to neonatal life. When transition is abnormal, perfusion may be compromised because of factors associated with hypovolemia, immature myocardium and the structural persistence of fetal channels (ie, patent ductus arteriosus), adrenal insufficiency and immaturity of the sympathetic and parasympathetic responses, and peripheral baroreceptors and chemoreceptors. Hypovolemia may result from intrapartum fetal blood loss or a decrease in placental transfusion secondary to apnea at birth. Additional risk factors for low blood volume may include emergency cesarean delivery, low Apgar scores, the need for mechanical ventilation, and multiple births.[8] Decreased preload attributable to absolute hypovolemia or vasodilatory shock attributable to an abnormally elevated blood vessel capacitance will result in decreased cardiac output and hypoperfusion. Although there is no evidence that correlates the presence of hypotension in preterm newborn infants with hypovolemia, a meta-analysis comparing delayed versus immediate umbilical cord clamping in preterm infants demonstrated improved hemodynamics, higher hematocrits, less need for transfusion, and lower hospital mortality rate in infants in the delayed cord clamping cohort.[9]

The VLBW newborn infant has more difficulty than the term neonate adapting to the changes that occur at birth, including the rapid increase in systemic vascular resistance (SVR).[10] This difficulty adapting to the increase in SVR may lead to decreased cardiac output resulting from an increase in left ventricular afterload.[11] The VLBW infant is at increased risk for hemodynamic instability because of immature cardiac myocytes. The autonomic nervous system is less responsive to stimuli, resulting in reduced ventricular contractility, making the heart less able to distend and, therefore, decreasing preload. Increased vascular resistance is a compensatory mechanism to maintain normal BP; however, poor cardiac contractility reduces cardiac output that manifests as hypotension. The premature myocardium has decreased energy stores, fewer mitochondria and

contractile elements, higher water content, and underdeveloped smooth muscle. Contractility is highly dependent on extracellular calcium, an important vulnerability because VLBW infants are at risk for hypocalcemia. These disadvantages, which may affect cardiac output and systemic blood flow, are exacerbated by hypoxia and acidosis.[10] Usual changes in pulmonary vascular resistance and SVR at birth, which result in alteration of the fetal shunts (foramen ovale and ductus arteriosus), may not occur in the VLBW neonate, thus allowing those shunts to remain patent. Perinatal asphyxia and sepsis may also contribute to myocardial dysfunction in the VLBW infant. Moreover, the characteristics of the immature myocardium make it relatively unresponsive to inotropic treatment.[11]

The immature endocrine responses of the VLBW infant also contribute to a higher risk of hypoperfusion. Acute hypoxemia in the term newborn infant is associated with increases in vasopressin, glucocorticoids, epinephrine, norepinephrine, and adrenocorticotropic hormone and results in redistribution of blood flow to vital organs. These responses are blunted in the VLBW infant. Immaturity of the adrenal glands may limit the VLBW infant's ability to maintain cortisol production in the event of a sustained stress. Because of immaturity of the sympathetic and parasympathetic systems and the presence of chemoreceptors and baroreceptors in the aortic arch and carotid sinus, the compromised VLBW infant may have difficulty maintaining adequate perfusion pressure. In addition, the dysfunction of the autoregulatory system puts the compromised VLBW neonate at increased risk of developing reperfusion injury.[12]

CONSEQUENCES OF INADEQUATE END-ORGAN TISSUE PERFUSION

When deciding to treat hypotension in VLBW infants, the objective is to maintain adequate systemic blood flow, thereby ensuring perfusion and oxygen delivery to all organs and tissues. Specifically, special emphasis is focused on sustaining cerebral blood flow and oxygen delivery.[12] Some research has been able to associate hypotension, however defined, with low systemic blood flow (LSBF) or decreased effective circulating blood volume, which reduces the volume of blood reaching organs and tissues. LSBF results in reduced oxygen transport to the organs and can lead to shock, diminished cerebral blood flow, and increased risk for unfavorable neurodevelopmental outcomes.[8,12–16] Numeric hypotension in the first several days of life in a VLBW infant raises concerns for adequate brain perfusion.[7,8,12,13,17–22] Significant numeric hypotension with associated clinical manifestations during the first 24 hours of life has been associated with adverse outcomes in VLBW infants <29 weeks' gestation, including intraventricular hemorrhage (IVH), periventricular leukomalacia, bronchopulmonary dysplasia, the potential for intestinal injury, and death.[3,8]

St Peter et al[22] reported that the incidence of death and severe IVH were significantly higher in 24- to 28-weeks' gestational age neonates born with hypotension, which was classified as a MAP <30 mm Hg or less than the corresponding gestational age. In addition, they found a threefold increased incidence of severe IVH (grade 3 or 4) and a significantly increased incidence of retinopathy of prematurity in infants with MAP <30 mm Hg versus ≥30 mm Hg. No differences in outcomes of necrotizing enterocolitis and bronchopulmonary dysplasia were noted by this numeric definition of hypotension. Infants who received vasopressors had higher rates of death and severe IVH in this study.[22] Some studies suggest that the neuroprotective mechanism of cerebral autoregulation is compromised below a MAP of 30 mm Hg.[23,24] The reduction in blood flow to white matter in the preterm infant brain raises the concern that a mean BP threshold of 30 mm Hg may be clinically important, resulting in an increased incidence of periventricular/intraventricular hemorrhage when this value is not maintained.[25] Conversely, other studies have shown no relationship between MAP and cerebral blood flow.[26] Specifically, a large observational study of newborn infants of extremely low gestational age (born before 28 weeks' gestation) found that hypotension defined by traditional measurements in this population was not associated with an increased incidence of brain injury.[27] These contradictory findings suggest a mechanism for regulating cerebral blood flow in these neonates at levels below generally accepted norms of BP. However, many factors other than BP can determine clinically meaningful outcomes.[12,20,26] In addition, there is some evidence that autoregulatory mechanisms that protect circulation to the vascular bed of the forebrain in VLBW infants may be immature so that stress at delivery may result in vasoconstriction of forebrain vessels. Thus, VLBW infants may have decreased total cerebral blood flow despite measured "normal" BP values.[12,28] Other evidence suggests that perfusion to the brain is

significantly increased from the date of birth to the day after birth regardless of gestational age in preterm neonates born at less than 34 weeks' gestation.[29]

EVALUATION OF ORGAN BLOOD FLOW

Evidence substantiating the assessment of organ perfusion in relation to systemic blood flow is complex and adequate perfusion cannot be achieved simply by the maintenance of a "normal" BP. The relationship among BP, systemic blood flow, SVR, and blood flow regulation of various organs during the transition to extrauterine life in the extremely preterm neonate is multifactorial. Evaluating the hemodynamics that affect organ perfusion in the VLBW infant is dependent on knowledge of blood flow in the superior vena cava (SVC), blood flow in the pulmonary bed, resistance in peripheral and pulmonary circulations, blood flow in the ductus arteriosus, output from the right ventricle, adequacy of myocardial function from existing pathology or congenital abnormalities, tissue oxygenation, and hypo- or hypercapnia, among others.[6,28,30] Unfortunately, many of these factors are not easily monitored in a noninvasive manner. Studies have not demonstrated convincing evidence that intervening at a specific threshold BP in extremely preterm infants results in less mortality or adverse neurodevelopmental outcomes.[31] Furthermore, at least 2 studies imply that treatment with inotropic agents and/or volume administration may be associated with an increase in morbidities such as intraventricular hemorrhage.[32,33] Studies by Eriksen et al that attempted to demonstrate that treatment of numeric hypotension with dopamine resulted in decreased cerebral autoregulation have shown mixed results in newborn piglets.[34] Other retrospective studies have reported that treatment of hypotension in this population was associated with an increase in adverse outcomes compared with matched infants who were not treated.[3,19,35] However, one should view these findings with caution, because treatment in these retrospective studies may indicate more severe clinical hypotension. Limitations include the possibility that intervention for hypotension could be related to a more vulnerable patient population or that ineffective or late initiation of treatment was not identified as part of the findings. In either case, hypotension in these studied populations could lead to critical cerebral hypoperfusion resulting in long-term neurodevelopmental disability. The discrepant findings demonstrate the need for additional randomized control trials to evaluate "permissive hypotension" (ie, allowing blood pressures to fall a certain percentage below accepted norms) and associated outcomes in an extremely preterm animal model. Noori et al have suggested several levels of hypoperfusion, including a functional BP threshold (a value several mm Hg less than the numeric threshold at which cerebral function may become compromised) and an ischemic BP threshold (a value approximating 50% of normal cerebral blood flow, which compromises the structural integrity of the brain).[12]

MONITORING LOW SYSTEMIC BLOOD FLOW

Effective monitoring of LSBF is a critical assessment component for the clinician to be able to effectively manage hypoperfusion in the extremely preterm infant.[6,12] However, this assessment is confounded by the ability of current technologies to effectively measure LSBF on extremely small infants. Given the limitations of our current understanding of measuring neonatal BP, the hemodynamic status of the VLBW newborn infant should be assessed by an evaluation of all systems involved in maintaining organ perfusion, which includes assessment of cardiac function, respiratory function, renal and hepatic function, oxygenation, hemoglobin level, presence of adrenal sufficiency, and autoregulation of blood flow.[5] The goal should not be to avoid numeric hypotension but to prevent the consequences of shock.[4] Although several parameters are used to define and treat hypoperfusion in VLBW infants, these standards are subjective and not based on strong evidence. Additional assessment findings representing decreased organ perfusion (eg, oliguria) can serve to inform the provider when determining whether there is a need for intervention in the presence of numeric hypotension. Other clinical indications include abnormal physical examination, tachycardia, metabolic and lactic acidosis, and prolonged capillary refill time. However, some of these signs (particularly decreased urine output) may occur late in the course of the hypoperfusion.[31]

Physical Examination and Clinical Signs

Preterm infants' heart rates are variable, with a "normal range" of 120 to 160 beats per minute.[36] Cardiac output is the product of stroke volume and heart rate. Clinicians often interpret tachycardia as a response to low cardiac output and unstable hemodynamic status. However, other factors, such as gestational age, central nervous system function, degree of illness, pain, and temperature can affect an infant's heart rate, making it difficult to use this parameter in isolation when determining perfusion status. However, sustained tachycardia that

is not explained by fever or pain is suggestive of hypovolemia.

Commonly, oxygen saturation is continuously monitored by pulse oximetry in unstable VLBW infants, and, although a late sign of hypoperfusion, oxygen saturation can inform clinicians about the fractional saturation of oxygen in preductal or postductal arterial hemoglobin being transported to tissues and vital organs.[33,37,38]

Using typical oxygen saturation probes and monitors, perfusion index (PI) can be calculated.[38] PI is derived from the percent difference of infrared signal ratio between pulsatile (ie, arterial blood flow) and nonpulsatile (ie, tissue, bone, organ) absorbers and correlates with peripheral perfusion, SVC blood flow, cardiac output, and stroke volume in newborn infants.[38] An observational study of more than 300 preterm infants with gestational ages less than 32 weeks found that PI varied with certain clinical factors (ie, lower PI readings were found during dopamine infusion and mechanical ventilation, and higher PI readings were correlated with female sex, increasing gestational age, and wide pulse pressure). Good correlation between PI and regional cerebral oxygenation ($rSco_2$) was also demonstrated between 24 and 72 hours of life.[39] It has been suggested that a combination of PI, functional echocardiography, amplitude-integrated electroencephalography (aEEG), and near-infrared spectroscopy (NIRS) may provide a method for noninvasive, continuous monitoring of the hemodynamics and perfusion in neonates during transition, but more research is needed.[12]

Capillary refill time (CRT) is a common clinical tool used to assess the hemodynamic status in preterm infants, with the chest as the site used most often.[41] Normal CRT in newborn infants is reported as less than 4 seconds but varies widely and has inconsistent correlation with SVC flow.[41] CRT values greater than 4 seconds may be a sign of poor perfusion.[41]

Urinary output (UO) has been used to assess organ perfusion status but is confounded in newborn infants because of transitional physiology and the resultant prediuretic phase followed by a diuretic phase.[32] Moreover, UO is calculated and expressed as milliliters per killigram per hour (mL/kg/hour) and may not fall into an abnormal range until hours after a hypoperfusion episode. Because fluid intakes in the first 24 hours vary greatly, comparison of UO to total fluid intake may be more meaningful to assessing kidney perfusion in an individual patient. After the first day of age, UO should stabilize and reflect the infant's fluid balance.[32] UO of less than 1.5 mL/kg/hour accompanied by other signs of hypoperfusion after 24 hours of age should be investigated.[42] Accurate UO can be challenging to measure in neonates without indwelling urinary catheters, although the use of such catheters carries inherent risks.

Laboratory Values

Serum lactate is frequently used in the evaluation of hypoperfusion in VLBW infants, although few studies in this population have correlated high serum lactate concentrations with adverse outcomes[43,44] or have correlated serum lactate concentrations with end-organ perfusion or blood flow.[32] In addition, in the circumstance of poor perfusion, lactate can accumulate but not circulate until perfusion has improved. Use of serum lactate concentration as a measurement of anaerobic metabolism attributable to hypoperfusion can be confounded by the presence of liver abnormalities, inborn errors of metabolism, or medications.[32]

Blood Pressure Measurement

The most common definitions of hypoperfusion in the neonate, during the transition, are (1) a BP measurement that falls below a MAP of 30 mm Hg, or (2) a MAP that is less than the gestational age (in weeks) of the infant.[45] The Management of Hypotension in the Preterm Extremely Low Gestational Age Newborn (HIP) Trial defined hypotension as a MAP "1 mm Hg below a MAP value equivalent to gestational age that persisted over a 15-minute period."[2] Because 90% or more of extremely preterm infants born between 23 and 26 weeks' gestation will maintain a MAP of 30 mm Hg or greater after 3 postnatal days,[46] many investigators, including the HIP Trial group, used this definition to specify hypotension in the first 72 hours of life.[2] After the transitional period, shunting from the patent ductus arteriosus and foramen ovale is less likely to be the etiology of symptomatic hypotension,[46] which may need to be considered along with other clinical and laboratory findings for the management of hypotension beyond the third day of life. However, these simplistic and mostly nonevidence-based definitions of hypotension in the first 72 hours of life are largely based on principles of developmental cardiovascular physiology and interpretation of factors that constitute hypoperfusion, which can result in clinically relevant negative consequences to the VLBW neonate.

The standard measurement of MAP is through the use of an arterial catheter, either peripherally inserted through the radial artery or centrally inserted through the umbilical artery.[47] This method

provides direct measurement but is subject to numerous problems. Because of the small size of the catheters, miniscule bubbles can lead to inaccurate BP readings.[48] The absence or distortion of the dichrotic notch should suggest dampening of the waveform and erroneous readings. In addition, risks such as painful insertion (with a peripheral arterial line), infection, the introduction of emboli, and formation of thrombus are considerations when using these lines.

The accuracy of noninvasive cuff BP readings can be confounded by the size and fit of the cuff on the infant's limb, the infant's position (prone or supine), and the infant's state of arousal.[49] Moreover, cuff BP readings are not continuous.

Newer and Future Methods of Assessing Perfusion

Point-of-care ultrasonography is a broad term that refers to the use of portable ultrasonography technology and offers clinicians the opportunity to assess the neonate at the bedside with minimal disruption.[50] Functional echocardiography, also known as targeted neonatal echocardiography (TNE), is the use of point-of-care ultrasonography technology to perform focused evaluation of the neonate's cardiovascular function, providing information about ventricular systolic function, direction and severity of atrial and ductus arteriosus shunting, and estimations of right ventricular and pulmonary arterial pressures.[2] The goal for TNE is to monitor the hemodynamic status with associated pathophysiology and the response to treatment, preferably after structural anomalies and arrhythmias have been ruled out.[51] Clinical scenarios in which TNE may be useful in this context in the VLBW neonate during the first 72 hours of life include suspected patent ductus arteriosus, evaluation of cardiac function with potential perinatal asphyxia, and abnormal cardiovascular adaptation presenting with numeric hypotension, lactic acidosis, oliguria, or other signs of low systemic blood flow states.[51] The use of TNE as an assessment tool for hypoperfusion in VLBW infants is not considered a standard of care at this time for many reasons, including a relative lack of expertise in the use of the technology by noncardiologists in the NICU, timely access to the equipment, lack of evidence-based clinical practice guidelines related to the management of hypoperfusion in VLBW infants,[51] support from radiology colleagues, and legal concerns.[52]

Transcutaneous Doppler ultrasonography is a continuous-wave device that is less expensive than typical ultrasonography equipment. Using this technique, blood flow velocity across pulmonary and/or aortic valves is measured and cardiac output can be calculated.[53] Although this technique provides useful information via a relatively easy technique, there is high interuser variability.[53] When evaluating the superior vena cava, systemic blood flow is low in many extremely preterm infants during the first 6 to 12 hours of life, often without a corresponding low BP value.[7] The immature myocardium of the VLBW infant exhibits decreased ability to direct blood flow against the increased SVR that results after separation from the low-resistance placental circuit and may result in decreased systemic blood flow.[7] As the transition progresses over the first 36 hours of postnatal life, LSBF usually improves and the systemic blood flow (ie, SVC flow) normalizes.[7,54] However, using SVC blood flow as a surrogate for systemic blood flow in VLBW infants has limitations, as does the measurement of left ventricular output by evaluating the velocity of blood flow distal to the aortic valve using Doppler ultrasonography.[55] As described in the 2011 NANN guideline "The Management of Hypotension in the Very-Low-Birth-Weight Infant: Guideline for Practice," left-to-right ductal shunting during the first few postnatal days limits the efficacy of this technique. Right ventricular output, as measured by echocardiography, during the first 24 hours of life is believed to be a relatively more accurate measure of systemic blood flow at this time. Low right ventricular output measured before 48 hours of life in VLBW infants has been correlated with low aEEG activity in these infants, and low mean BP has been correlated with excessive discontinuity of electroencephalography (EEG).[56] Low cerebral blood flow (CBF) in very preterm infants has been associated with abnormal electroencephalography and increased risk of poor long-term outcome.[56]

Near-Infrared Spectroscopy

Current investigations to assess organ blood flow in VLBW neonates are being conducted by using NIRS.[12] By measuring certain oxygen-dependent compounds that selectively absorb near-infrared light during passage through blood vessels, this technique may help evaluate blood flow to vital organs including the brain. Oxygenation indices can be calculated from the measurement of the oxygen-dependent compounds.[12] Using the Fick principle and assuming certain constants, CBF can also be measured.[39] Using NIRS, the $rSco_2$, a measure of cerebral hemodynamics,

can be calculated and monitored, utilizing $rSco_2$ and cerebral fractional tissue oxygen extraction reference curves.[57] NIRS monitoring holds promise, but several problems prevent its widespread clinical use at this time, including a lack of validation studies and nonstandardization of mathematical models between different NIRS programs.[57]

Integrated Evaluation of Hemodynamics

The inability to effectively monitor hemodynamic changes at the tissue level and blood flow to specific organs hampers the understanding of what constitutes hypotension in VLBW infants. Although BP can be measured both invasively and noninvasively and treated to achieve currently accepted "normal" ranges, it has become evident that BP is only one of many components that determine overall tissue perfusion and, thus, oxygen delivery to specific organs in VLBW infants.[12] Several reviews suggest that evaluation of hemodynamics should be accomplished by using an integrated approach that considers all systems involved in maintaining organ perfusion and integrates the assessment of cardiac function, respiratory function, oxygenation, hemoglobin, presence of adrenal insufficiency, and autoregulation of blood flow.[1,4,5,12,20,30,35] This approach could provide for more individualized assessment and management of hypoperfusion in this vulnerable population.

Future Considerations

Currently, other methods to assess perfusion in VLBW infants are being evaluated. Measures of cerebral function, such as EEG and aEEG, may be useful adjuncts in assessing the functional impact of perfusion changes in the brain. aEEG, which can be readily applied at the bedside by trained nurses, can provide basic level bedside evaluation of cerebral electrical activity. More commonly used to assess brain function and diagnose seizures in association with hypoxic ischemic encephalopathy in term and near-term infants, aEEG studies in VLBW neonates have examined the relationship between bedside readings, cardiovascular hemodynamics during the postnatal transition period, and neurodevelopmental outcomes.[12,58,59] Impedance electrical cardiometry, also referred to as thoracic electrical bioimpedance, noninvasively assesses beat-to-beat cardiac output using echocardiographic measurements of cardiac output and may be useful as a trending tool.[12,53] However, results may not be accurate in infants with high cardiac output or who are on high-frequency ventilation,[60] and more studies are needed. Other emerging technologies and methods to measure cardiac output in preterm infants include visible light technology, indicator dilution techniques, and arterial pulse contour analysis.[12,53]

STRATEGIES TO MITIGATE INADEQUATE TISSUE PERFUSION

As has been discussed previously, the management of hypotension in the VLBW infant is complex, depending on the assessment of many clinical and laboratory factors. This issue will require continued scrutiny and well-developed research in the future. The definitions of hypotension used by different clinicians vary widely and thus will affect treatment strategies until evidence provides clear parameters for this diagnosis. Several interventions are used to treat low BP in this vulnerable population. Treatments currently used include volume expansion, vasopressor-inotropes, lusitropes, and corticosteroids.

Volume Expansion

The provision of adequate circulating blood volume begins at birth. Recent editions of *The Textbook of Neonatal Resuscitation* (seventh and eighth editions) recommend delayed cord clamping for 30 to 60 seconds in the vigorous preterm newborn infant with intact placental circulation.[45] Hypovolemia or ineffective circulating blood volume is not a common cause of numeric hypotension in the VLBW infant in the first 72 hours of life unless there is evidence of intrapartum asphyxia, tight nuchal cord or fetal blood loss attributable to fetal-maternal hemorrhage, antepartum hemorrhage, twin-to-twin transfusion syndrome, vasa previa, or cord accidents.[61,62] Antenatal steroids, delayed cord clamping, and not requiring mechanical ventilation are associated with a higher postnatal BP.[63]

Substrates used for volume expansion to treat low BP include normal saline, lactated Ringer solution, type O Rh-negative blood, and albumin. Since 2005, the Neonatal Resuscitation Program has recommended isotonic saline or packed red blood cells in preference to albumin when volume expansion is indicated. A trend toward increased mortality when albumin was used compared with normal saline for volume expansion was demonstrated by Oca et al.[64] However, this finding has not been supported by randomized controlled trials.[65,66] The primary rationale for the preferential use of normal saline rather than albumin as a volume expander is that crystalloid is as

effective, less expensive, and readily available.[67]

Inotropic Support

Inotropes have the primary pharmacologic action of increasing myocardial contractility, lusitropes increase the rate of myocardial relaxation, vasopressors increase vascular tone, and corticosteroids act by up-regulating cardiovascular adrenergic receptor expression.[68,69] Consideration should be given to the neonate's underlying cause of hypotension and the pharmacologic actions of the drug being prescribed.

Although dopamine may increase renal perfusion at low doses, higher-dose dopamine therapy may result in decreased end-organ perfusion, possibly because dopamine decreases left ventricular output. Thus, despite improved BP measurements, high-dose dopamine therapy may lead to strain on the myocardium and decreased oxygen delivery. Dopamine can also lead to dangerously elevated levels of CBF through previously ischemic tissue, resulting in reperfusion injury and IVH.[12,22,69–71] Other potential risks of dopamine therapy include cardiac arrhythmias; extravasation injury; increased pulmonary arterial pressure, which, in turn, may worsen pulmonary hypertension if present; inhibition of thyrotropin leading to transient hypopituitarism; and inhibition of growth hormone and gonadotropins.[72–76]

Low- to moderate-dose epinephrine has been used as an alternative to dopamine for the treatment of hypotension in VLBW infants, but there are knowledge gaps concerning epinephrine's effect on systemic blood flow in this population. Low-dose epinephrine has active β-adrenergic effects, but its α-adrenergic effects are weaker. Despite producing some vasodilation, administration usually results in increased cardiac output and BP.[63] However, higher doses of epinephrine result in increased vascular resistance and decreased cardiac output secondary to increased peripheral vascular resistance, increasing the risk of decreased end-organ perfusion. Short-term adverse effects of epinephrine include significant increases in heart rate, higher lactate concentrations, lower bicarbonate concentrations, and hyperglycemia, which may require insulin.[77] Careful small increases in epinephrine dosage in hypotensive VLBW infants have not been reported to result in abnormal neurologic events, or long-term adverse outcomes such as death, cerebral palsy, or profound neurodevelopmental delay.[63,77]

Dobutamine produces predominantly β-adrenergic effects yielding increased myocardial contractility and decreased pulmonary and systemic vascular resistance.[78] At moderate to high doses (5 mcg/kg per minute to 20 μg/kg per minute), dobutamine will increase cardiac output and BP.[69,79] When compared with dopamine, dobutamine increases SVC flow and right and left ventricular output more effectively, which may result in improved end-organ perfusion.[12,79]

Hydrocortisone

Hydrocortisone is as effective as inotropes such as dopamine for improving hypotension in VLBW infants. However, the data on the long-term safety of corticosteroids used for this purpose is limited.[80] Studies have shown that hydrocortisone increases BP, increases tissue perfusion, and prevents ischemic tissue injury as a standalone therapy or in conjunction with volume and inotropic therapies.[81] The studies on the use of hydrocortisone for the treatment or prevention of bronchopulmonary dysplasia are controversial, but infants with serum cortisol concentrations below the median who were treated with hydrocortisone had increased survival without bronchopulmonary dysplasia when compared with those who did not receive this therapy.[81] Although the neurodevelopmental effects are unclear, in a 2-year follow-up study of extremely preterm infants randomly assigned to receive early hydrocortisone to prevent bronchopulmonary dysplasia, the group receiving hydrocortisone had a statistically significant improvement in developmental outcome in neonates born at 24 to 25 weeks' gestation but not those born at 26 to 27 weeks' gestation.[82] Moreover, in a study of vasopressor-resistant preterm infants with borderline hypotension, a low-dose regimen of hydrocortisone had no effect on CBF.[83]

Milrinone

Milrinone is a selective phosphodiesterase III inhibitor used to improve cardiac output by improving ventricular contractility, enhancing diastolic relaxation, and decreasing peripheral vascular resistance. A study of the effectiveness of milrinone versus placebo in hypotensive VLBW infants in a double-blind randomized controlled trial demonstrated that milrinone did not prevent LSBF in these infants. No adverse effects of milrinone were demonstrated in this study.[84] Currently, there is no strong evidence to support the use of milrinone for the treatment of hypotension in VLBW infants.

Titration of Therapy

All treatments of hypotension in the VLBW population have potential adverse effects and should be carefully considered. It is recommended that each therapy or drug used have careful titration with cautious stepwise increases in dosage to reach the desired effect. Moreover, the provider may increase inotropic drug dosage approximately every 3 to 5 minutes to achieve the desired result, if the drug is being delivered with correct line priming and the infusion pump has been properly set up and calibrated.[63,68,69,71]

SUMMARY AND RECOMMENDATIONS

Continued research efforts should be encouraged to ensure the most recent evidence-based treatment options are used to manage BP in VLBW neonates and to clearly define what constitutes hypotension in this population. All parameters of effective circulating blood volume should be considered before deciding on specific interventions for treatment. This report suggests a cautious and conservative approach that is based on known physiology in this population. However, the knowledge gaps on transitional cardiovascular physiology and pathophysiology in VLBW infants makes it difficult to establish any specific guidelines on the treatment of hypotension in this population. At the current time, clinical trials addressing this question have been unable to provide the appropriate information and lacked the power to give specific guidance on the management of neonatal hypotension in clinical practice.[63] One recently concluded study, The Hypotension in Preterm Infants (HIP) randomized trial in newborn infants born before 28 weeks' gestation with mean BP less than gestational age in the first 72 hours of life, was terminated early due to problems with enrollment. Although the study lacked power, it failed to demonstrate significant differences in clinical outcomes at 36 weeks postmenstrual age between the treatment group (saline bolus/dopamine) and restrictive management group (5% dextrose infusion only).[85] Future trials that use clinically relevant outcome measures to define hypotension in VLBW infants are needed to establish reasonable BP values and treatment modes in this population. Ongoing large randomized controlled trials such as the NEO-CIRC project (http://www.neocirculation.eu) may provide some additional evidenced--based recommendations. At the present time, the following recommendations can be made:

- The diagnosis of cardiac insufficiency in the VLBW infant should not be based on a threshold BP value alone. The measurement of BP in this population is not simple and may be erroneous.
- Assessment of BP should be based on multiple parameters including gestational age, weight, and postnatal age using standardized tables that recognize values >2 standard deviations below the mean. The diagnosis of cardiac insufficiency that warrants treatment should consider other factors including physical findings, such as hypotonia, tachycardia, and poor capillary refill, clinical findings, such as poor urine output, laboratory studies, such as metabolic acidosis and increased lactate concentrations, and bedside evaluation using technology such as functional echocardiography (when available).
- The treatment of cardiac insufficiency is not without hazard, and the decision to treat should consider the potential complications of such treatment.
- Delayed cord clamping, decreased blood sampling, appropriate ventilatory management (ie, avoiding excessive mean airway pressure and hypocarbia), and other attempts to avoid hypovolemia, anemia, and decreased cardiac output may have an important role in avoiding or mitigating hypoperfusion states in the VLBW infant.

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ABBREVIATIONS

aEEG: amplitude-integrated electroencephalography
BP: blood pressure
CBF: cerebral blood flow
CRT: capillary refill time
IVH: intraventricular hemorrhage
LSBF: low systemic blood flow
MAP: mean arterial pressure
NANN: National Association of Neonatal Nurses
NIRS: near-infrared spectroscopy
PI: perfusion index
$rSco_2$: regional cerebral oxygenation
SVC: superior vena cava
SVR: systemic vascular resistance
TNE: targeted neonatal echocardiography
UO: urinary output
VLBW: very low birth weight

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