Pathophysiology of the Cardiovascular System and Neonatal Hypotension

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The purpose of this article is to review the cardiovascular pathophysiology of blood pressure and discuss the potential causes of hypotension in the term and preterm neonate.

Accepted for publication October 2014.

Abstract

Hypotension is common in low birth weight neonates and less common in term newborns and is associated with significant morbidity and mortality. Determining an adequate blood pressure in neonates remains challenging for the neonatal nurse because of the lack of agreed-upon norms. Values for determining norms for blood pressure at varying gestational and postnatal ages are based on empirical data. Understanding cardiovascular pathophysiology, potential causes of hypotension, and assessment of adequate perfusion in the neonatal population is important and can assist the neonatal nurse in the evaluation of effective blood pressure. This article reviews cardiovascular pathophysiology as it relates to blood pressure and discusses potential causes of hypotension in the term and preterm neonate. Variation in management of hypotension across centers is discussed. Underlying causes and pathophysiology of hypotension in the neonate are described.

Keywords: neonatal hypotension; definition; physiology; cardiovascular system; preterm; management; assessment; cerebral; autoregulation; blood pressure

Maintaining effective blood pressure for adequate tissue and organ perfusion in the neonate is critical for optimum outcomes and is dependent on several physiologic mechanisms which may be compromised in the ill or premature neonate. To have an understanding of the complexities of the neonatal cardiovascular system and the potential causes of hypotension, it is essential to review the circulatory changes that occur during the transition from intrauterine to extrauterine life, the many mechanisms that control blood pressure in the body, and the differences in the term and preterm neonate.

PHYSIOLOGY OF BLOOD PRESSURE CONTROL

Cardiac Output

Blood pressure is the amount of blood ejected from the heart and is the product of cardiac output (the amount of blood ejected from the left ventricle) and systemic vascular resistance (the forces acting against blood flow from the heart). Maintaining adequate organ perfusion is dependent on cardiac output and systemic vascular resistance. Cardiac output, or systemic blood flow, is determined by the heart rate and stroke volume. Heart rate is influenced by stimulation of the heart's conduction system and the autonomic nervous system, both of which determine the intrinsic rate of the heart. The higher the heart rate, the greater the cardiac output. Stroke volume is the amount of blood ejected from the heart with each contraction. Stroke volume is determined by the amount of preload, afterload, and contractility of the heart.[1]

Preload is the volume of blood in the ventricles prior to contraction at the end of diastole when the ventricle has filled. Preload can be reduced in ill or premature infants as a result of an elevated heart rate or low circulating blood volume.[2] Afterload is the pressure against which the heart must pump during systole and is influenced by systemic

http://dx.doi.org/10.1891/0730-0832.34.1.31

vascular resistance.[1] Systemic vascular resistance is the resistance of the systemic circulation against blood flow from the heart and is determined by vessel diameter and blood viscosity. Blood vessel diameter is influenced by blood vessel vasodilation and vasoconstriction. The greater the blood vessel diameter, the less the systemic vascular resistance, and the smaller the blood vessel diameter, the greater the systemic vascular resistance. Blood viscosity increases when the blood contains a greater amount of red blood cells versus plasma (polycythemia), therefore increasing the systemic vascular resistance. Afterload is influenced in the newborn at birth by increased pulmonary vascular resistance and elimination of the low-resistance placental circulation, which is replaced by a higher-resistance systemic circulation.

Contractility is the force of contraction of the heart or inotropy.[3] Contractility can be reduced in the premature neonate because of fewer cardiac muscle fibers and an immature myocardium.[2] Cardiac output is increased in the mature heart by increasing heart rate and stroke volume. Neonates lack the ability to increase stroke volume and rely primarily on increased heart rate to compensate for low cardiac output.[4]

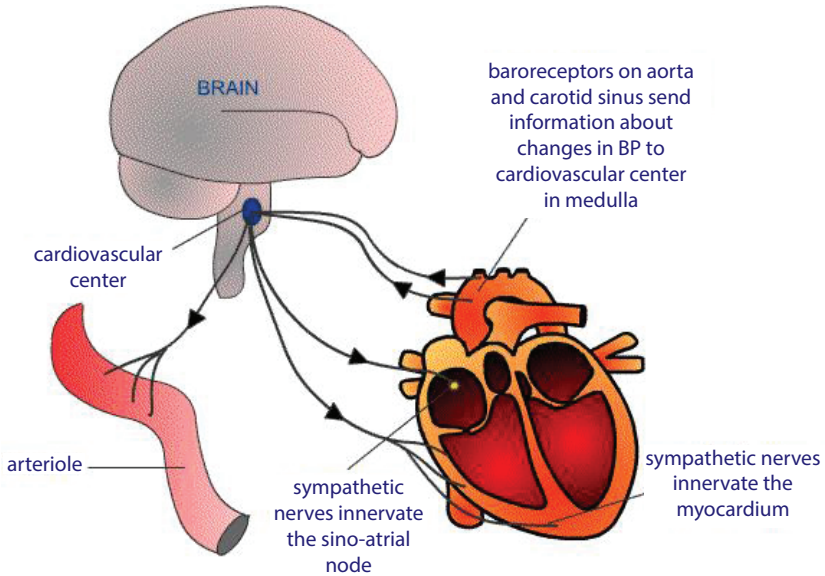
Neural Control

The autonomic system consists of the sympathetic and parasympathetic nervous systems which stimulate the heart to regulate heart rate and contractility. The sympathetic nervous system acts on the contractile filaments of the heart to increase or decrease the force of contraction of the heart muscle separately from preload and afterload.[1]

The autonomic nervous system responds quickly to hypotension by acting on the baroreceptors to maintain blood pressure. Baroreceptors are nerve endings located in the carotid arteries and the aortic arch. Baroreceptors send impulses to the brain which stimulates the sympathetic nervous system to vasoconstrict or vasodilate arteries to alter blood flow in response to stretch of the arterial walls or a fall in blood pressure (Figure 1).[3] Baroreflex sensitivity is impaired in newborns and to a greater extent in premature newborns because of immaturity of the vagal system which can contribute to cardiovascular instability.[5] Baroreflex sensitivity improves with increasing postmenstrual age.[6]

After blood is ejected from the heart, there are long- and short-term mechanisms that control arterial blood pressure in the body. Blood pressure regulation is maintained by neural mechanisms of the autonomic nervous system and humoral mechanisms of the kidneys and pituitary gland consisting mainly of the renin-angiotensin system and vasopressin.[1] Neural mechanisms providing short-term control of arterial blood pressure include the sympathetic and parasympathetic nervous systems. The sympathetic nervous system consists of nerve fibers located on each side of the spinal column that extend into the blood vessels and the heart. The sympathetic nervous system controls blood pressure by causing constriction of the arteries and arterioles. Constriction of the arteries and arterioles increases peripheral vascular resistance, which raises the amount of blood flow to the heart and consequently causes a temporary rise in arterial blood pressure. A significant fall in blood pressure is immediately followed by autonomic nervous system signals that increase the rate and contractility of the heart and contraction of systemic vessels, which increases the amount of blood flow back to the heart. Conversely, a temporary decrease in blood pressure

FIGURE 1 ■ In response to a drop in blood pressure, the autonomic nervous system acts on baroreceptors to send impulses to the brain which stimulates the sympathetic nervous system to vasoconstrict or vasodilate to alter blood flow.



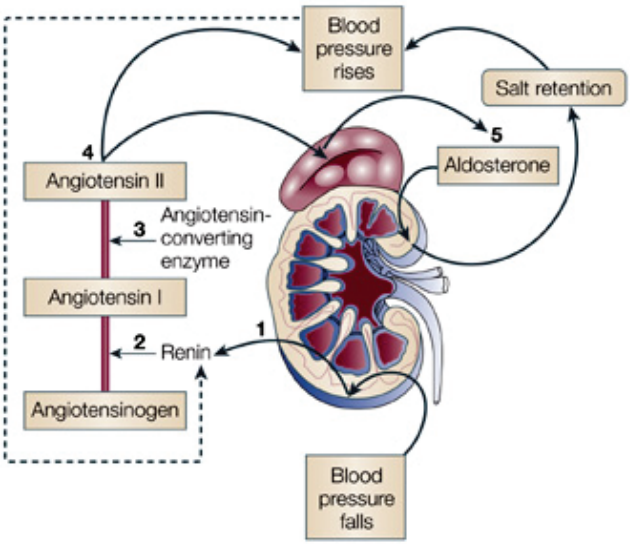
Abbreviation: BP = blood pressure.

can be caused by parasympathetic stimulation of the vagus nerve, which contains nerve fibers that extend into the heart. Parasympathetic vagal stimulation of the heart reduces the heart rate and slightly decreases muscle contractility, consequently causing a temporary decline in blood pressure.[3]

Humoral Control

The mechanism for short-term regulation, as occurs in response to a sudden drop in blood pressure or a sudden increase in physical activity, responds quickly but is ineffective at maintaining blood pressure over a longer period. The kidneys play a role in the long-term control of blood pressure with the renin-angiotensin-aldosterone system. The kidneys respond to low blood pressure after a period of hours or days by secreting renin. Renin stimulates the release of angiotensin I from the kidneys which is converted to angiotensin II in the lungs. Angiotensin I has an initial mild vasoconstrictive effect which facilitates blood return to the heart. Angiotensin II is the active hormone that regulates blood pressure by stimulating the kidneys to release aldosterone. Angiotensin II and aldosterone stimulate the kidneys to reabsorb sodium along with water back into the bloodstream, thereby increasing plasma blood volume and consequently increasing blood pressure (Figure 2). Vasopressin, or antidiuretic hormone, regulates water retention and vasoconstricts blood vessels. Vasopressin is released by the posterior pituitary gland in response to inadequate blood volume. Vasopressin increases blood pressure by decreasing water excretion by the kidneys and acting as a potent vasoconstrictor of arterioles throughout the body.[3]

FIGURE 2 ■ Control of blood pressure by renin-angiotensin-aldosterone system.



The kidneys secrete renin in response to low blood pressure. Renin stimulates the release of angiotensin I from the kidneys, which is converted to angiotensin II in the lungs. The kidneys release aldosterone in response to angiotensin II. Angiotensin II and aldosterone stimulate the kidneys to reabsorb water and sodium into the bloodstream.

Autoregulation

The local nutrient needs of the body tissues drive the amount of blood flow they receive. In response to the tissue needs, cardiac output increases to some degree but is not able to meet high tissue demands for nutrients. High tissue demands occur with strenuous activity which in the term infant can occur with crying.[3] Increased tissue demands can occur in preterm infants during the transitional period of low systemic flow prior to the fetal shunts closing. A state of shock can occur in the term or preterm infant in response to sepsis or hemorrhage which can also drive an increased need for blood flow to the tissues.[7] In addition to increasing cardiac output to increase blood flow to tissues, local blood vessels dilate and constrict in response to sympathetic nervous system stimulation to control blood flow and meet tissue needs. This process is referred to as *autoregulation*, which is the ability of local tissues to control blood flow despite variations in the arterial pressure.[3]

There are two theories proposed to explain the physiology of autoregulation of local blood flow that are relevant in both the term and preterm newborn: the metabolic and myogenic theories. The *metabolic theory* suggests that, with an increased arterial pressure, the increase in nutrients to the tissues greater than the demand causes vasoconstriction of local blood vessels, which lowers blood flow despite the rise in arterial pressure. This theory would apply in the term or preterm newborn during a period of crying. The *myogenic theory* suggests autoregulation of local blood flow occurs after the vessels stretch secondary to a rise in arterial pressure, which may also occur during crying. The vessel stretch causes the vessels to constrict and reduce blood flow to normal despite the high arterial pressure[3] (see definitions provided in Table 1).

There has been a long-standing concern that preterm infants may have a decreased ability to autoregulate cerebral blood flow. The vulnerability of the neonate's brain secondary to autoregulatory deficits has been studied, and findings are varied related to whether or not cerebral blood flow is maintained during episodes of hypotension or low systemic blood flow and the association between hypotension and neurologic morbidity in premature infants.[8–12] Kluckow and Evans[11] measured superior vena cava blood flow, as a marker of systemic blood flow, using Doppler echocardiography in 126 neonates with gestational ages of 23–29 weeks. They found a strong association between low systemic blood flow and intraventricular hemorrhage. They also observed that low systemic blood flow did not correlate with low systemic blood pressure, suggesting that low systemic blood pressure may not be an indicator of low systemic blood flow. Martens and associates[10] studied the association between hypotension and neurologic morbidity in 266 preterm neonates <32 weeks gestational age, and they found that a mean blood pressure of <30 mmHg was a major risk factor for neurologic

TABLE 1 ■ Physiology of Blood Pressure Control Mechanisms

Mechanism of Blood Pressure Control	Definition
Cardiac system	The heart regulates cardiac output by altering heart rate and stroke volume. Determinants of stroke volume: • Preload—volume of blood in the filled ventricles prior to contraction • Afterload—pressure against which the heart must pump (systemic vascular resistance) • Contractility—force of contraction of the heart
Neural control	The autonomic nervous system stimulates the heart to increase the force of contraction and sends impulses to vasodilate or vasoconstrict for short-term regulation of blood flow.
Humoral control	The renin-angiotensin-aldosterone system of the kidneys regulates long-term control of blood pressure by altering blood volume.
Autoregulation	The ability of the local tissues to regulate consistent blood flow despite changes in arterial blood pressure Local control of blood flow at the tissue level: • Metabolic theory—Local blood vessels vasoconstrict in response to a rise in blood pressure when blood flow is greater than tissue needs. • Myogenic theory—Following a rise in blood pressure, vessels stretch is followed by vessel constriction to reduce excess blood flow to tissues.

morbidity. Munro and colleagues[9] studied the relationship between cerebral blood flow and mean arterial blood pressure in 17 infants with a mean gestation of 26 weeks. They found that cerebral autoregulation was present with a normal mean blood pressure but was lost at a mean blood pressure <30 mmHg. They also found that none of the hypotensive newborns in this study had neurologic morbidities. More recently, Børch and colleagues[8] examined the relationship between white matter blood flow and mean blood pressure in 13 infants with a gestational age of 26–32 weeks. They found that blood flow to white matter was reduced at a mean blood pressure <29 mmHg. A recent large study of 1,024 extremely low gestational age newborns (ELGANs) born prior to 28 weeks gestation found little evidence to support an association between hypotension and neurologic morbidity.[12] The authors suggested that prior studies that found an association between hypotension and neurologic morbidity had small sample sizes. They concluded that the small sample sizes could increase the likelihood that the neurologic morbidity was associated with factors other than hypotension.

Chemical Factors

Chemical factors may impact vascular resistance by changing the diameter of the arteries, which causes changes in blood flow. These chemical factors include partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and partial pressure of oxygen (PaO_2). Hypocapnia and hypoxia both cause vasodilation. Oxygen and hypercapnia are vasoconstrictive. Changes in $PaCO_2$ have a greater effect on cerebral blood flow than blood flow to other organs which helps to maintain oxygen delivery to the brain during hypoxic and hypercapnic episodes.[13]

NEWBORN TRANSITION: CIRCULATORY CHANGES

Many circulatory changes must occur at birth for the successful transition from intrauterine to extrauterine life, some of which may not happen normally in the premature newborn and can affect blood pressure. At birth, the lower vascular resistance system of the placental circulation is eliminated which increases the newborn's systemic vascular resistance. The immature myocardium of premature newborns has less contractile myofibrils, less fatty acid energy stores, and fewer mitochondria. These developmental differences may limit the ability of the heart to overcome the increased systemic vascular resistance, resulting in low systemic blood flow.[14] The newborn initiates breathing, and there is a decrease in pulmonary vascular resistance. Normally, there is functional closure of the ductus arteriosus and ductus venosus in most term infants within 12–15 hours of life or up to three days. Blood flow transitions through shunts from right to left in utero to left to right which results in the functional closure of the foramen ovale and eventually ductus arteriosus.[15] Premature infants may have difficulty effectively transitioning from intrauterine to extrauterine circulation. Low systemic blood flow is common in the first day of life in premature newborns born <30 weeks gestation.[14] Premature newborns commonly have a persistent ductus arteriosus because of an immature duct that is less muscular, more sensitive to circulating prostaglandins, and less sensitive to the vasoconstrictive effects of oxygen than term newborns.[16] Premature newborns also have a delayed drop in pulmonary vascular resistance and as a result a delayed rise in cardiac output, all of which contribute to low systemic blood flow. The cause of the delayed drop in pulmonary vascular resistance in premature newborns is unknown but may be related to immaturity of the vasculature. Further impairments of systemic blood flow in premature newborns occur with increased intrathoracic pressure during positive pressure ventilation. The increased intrathoracic pressure compresses the heart and decreases venous return.[14]

DEFINITION OF HYPOTENSION

Several definitions of neonatal hypotension are found in the literature. Seri defines hypotension as a blood pressure at which there is a loss of autoregulation of organ blood flow that can result in tissue ischemia and organ damage.[17] The importance of using this definition for hypotension is that it describes the pathology that occurs, which allows clinicians to measure indicators of hypotension rather than numerical values. Some

authors define hypotension using measurements. Hypotension in the first few days of life is defined as a mean blood pressure of less than 1–2 mmHg higher than gestational age or a value less than the 10th percentile for gestational age.[18] Using this criteria, a mean blood pressure of <28 mmHg would be considered hypotensive in a neonate with a gestational age of 26 weeks. Other definitions include a mean arterial blood pressure of <30 mmHg, which is more commonly found to be associated with poor outcomes.[19] Determination of a minimum blood pressure that maintains adequate cardiovascular function in the neonate remains challenging because of the complexities of immaturity, illness, and transition from intrauterine to extrauterine circulation and has yet to be determined.

Blood pressure increases with advancing gestational age, postnatal age, and increasing birth weight.[20] Published nomograms exist for normal blood pressure ranges in infants based on gestational and postnatal age as determined by continuous arterial monitoring of neonates at each gestational age group during the first 72 hours of life (Figure 3). According to Nuntnarumit and associates, mean blood pressure is lower in extremely premature newborns and rises significantly with advancing gestational age.[21] Nuntnarumit and colleagues also found that the tenth percentile for mean blood pressure is at least 30 mmHg by three days of life for infants born at all gestational ages.[21] A mean blood pressure of less than the neonate's gestational age is commonly used as an indication to treat hypotension.[22]

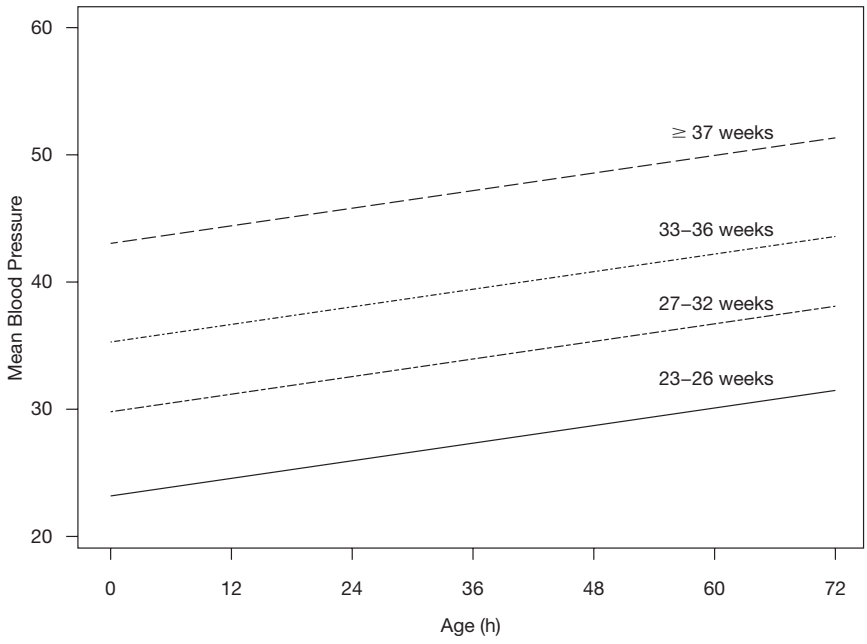
Causes of Hypotension

Delayed transition from intrauterine to extrauterine life
Immature myocardium (decreased contractility)
PDA
Chorioamnionitis
Perinatal depression/asphyxia
Immature HPA axis system
Relative adrenal insufficiency
Sepsis
NEC
Hypovolemia

CAUSES OF HYPOTENSION

There are several potential causes of neonatal hypotension (see sidebar). Hypotension and low systemic blood flow commonly occur on the first day of life in premature neonates because of the delays in circulatory transition from intrauterine to extrauterine life and an immature myocardium.[15] The immature myocardium of premature neonates has a lesser number of mitochondria, which provide energy to the cells, and less energy stores than the term infant which negatively impacts the ability of the premature heart to adapt to the stresses of the transition from intrauterine to extrauterine circulation.[23] Low systemic blood flow is common in premature

FIGURE 3 ■ Mean blood pressure in neonates.



Nomogram for mean blood pressure (BP) in neonates with gestational ages 23 to 43 weeks, derived from continuous arterial BP measurements obtained from 103 infants admitted to the NICU. The graph shows the predicted mean BP of neonates of different gestational ages during the first 72 hours of life. Each line represents the lower limit of 80 percent confidence interval (two-tail) of mean BP for each gestational age group; 90 percent of infants for each gestational age group will be expected to have a mean BP value equal to or greater than the value indicated by the corresponding line, the lower limit of the confidence interval.

From Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. *Clin Perinatol*. 1999;26(4):981-996. Copyright Elsevier (1999). Reprinted with permission.

infants in the first two days of life and less common by 48 hours of age secondary to increasing systemic vascular resistance and improved myocardial contractility.[14,22,24]

Peripheral vasodilation can occur on the first day of life in neonates born to mothers with chorioamnionitis.[17] Chorioamnionitis is inflammation of the fetal membranes caused by bacterial infection and is associated with release of cytokines called tumor necrosis factor (TNF) and interleukin-1 (IL-1). Release of TNF and IL-1 in response to inflammation causes vasodilation of blood vessels and increased capillary permeability.[25] Capillary permeability secondary to damage to the epithelium allows plasma to leak out of the vasculature. Vasodilation of the blood vessels and increased capillary permeability are thought to be the causes of hypotension.[3] Researchers found that chorioamnionitis is strongly associated with hypotension in very low birth weight infants that develops on DOL 1.[25]

Myocardial dysfunction may cause hypotension on the first day of life in term and preterm infants secondary to perinatal depression.[17] Perinatal asphyxia causes the fetal myocardial tissue to be deprived of blood flow and oxygen. Histamine is then released by the tissues secondary to damage to the myocardium from a lack of nutrients. Histamine causes generalized vasodilation and increased capillary permeability allowing plasma to leak from the vascular circulation into the tissues.[3]

After the first day of life, hypotension in the very low birth weight infant can also be caused by a patent ductus arteriosus (PDA), relative adrenal insufficiency, or the inflammatory response associated with sepsis or necrotizing enterocolitis (NEC).[17] If a PDA persists after pulmonary vascular resistance falls and systemic vascular resistance becomes higher than pulmonary vascular resistance, blood shunts from the left side of the heart to the right side of the heart through the PDA and into the pulmonary artery. If the ductus remains open during both systole and diastole, blood flows continuously away from the systemic circulation and into the pulmonary artery.[15] A hemodynamically significant PDA can cause systemic hypotension and reduced blood flow to the organs.[17] Symptoms of a PDA include bounding pulses, widened pulse pressure, active precordium, and a harsh, continuous murmur.[26]

The hypothalamic-pituitary-adrenal (HPA) axis system is a feedback loop between the endocrine glands (hypothalamus, pituitary, and adrenal) that regulates many body functions and controls the response to stress and illness. The HPA system releases cortisol in response to illness and stress.[27] Cortisol release by the adrenal glands occurs when response to stress or inflammation is critical for survival. Premature neonates have an immature HPA system.[28] They may be able to produce enough cortisol for growth and development but are unable to increase production in response to stress or illness.[27] Relative adrenal insufficiency occurs when cortisol is produced in amounts sufficient for homeostasis and growth but not in amounts sufficient for the stressed or ill neonate.[27,29] Relative adrenal insufficiency may cause hypotension after the first day of life.[17]

Sepsis is also an important cause of hypotension in the term and preterm infant.[17] In response to sepsis, mediators that play a complex role in controlling the inflammatory response are released by damaged epithelium. These mediators, which are similar to those described here in response to chorioamnionitis, as well as bacterial endotoxins, increase vascular permeability and cause vasodilation. Increased vascular permeability and vasodilation results in plasma leaking out of blood vessels and into interstitial spaces, resulting in hypovolemia and hypotension.[1] In the case of septic shock, cortisol insufficiency prevents the body from decreasing the inflammatory response which also can lead to capillary leak and decreased myocardial contractility resulting in hypotension.[27] Hypovolemia is an uncommon cause of hypotension in term and preterm newborns and should be suspected in a pale infant with tachycardia and a history of blood loss or tight nuchal cord.[22]

ASSESSMENT OF ADEQUATE PERFUSION

Because of the complexities of cardiac output and systemic vascular resistance in the maintenance of blood pressure and organ perfusion and the lack of ability to determine a minimum blood pressure required to maintain adequate perfusion, assessment findings should be used in addition to blood pressure measurements when determining adequate perfusion (see sidebar). Neonatal nurses should avoid using numerical data in isolation when determining if a neonate is hypotensive and should use assessment findings and clinical history when evaluating effective blood pressure.

Assessment of perfusion in neonates during the first day of life should start with a review of maternal and clinical history for factors that may predispose them to hypotension including, but not limited to, gestational age, chorioamnionitis, perinatal depression, or signs of blood loss. Physical assessment findings that may indicate hypotension include tachycardia and prolonged capillary refill time.[30] A capillary refill time of greater than three seconds may occur secondary to a low cardiac output. Tachycardia, heart rate ≥160 bpm, is a compensatory mechanism for decreased cardiac output. Weak pulses may also indicate decreased cardiac output. Mottling, a spider web appearance of the skin, may occur from vasoconstriction as blood is shunted from the skin to vital organs in response to decreased perfusion.[31]

Signs of Inadequate Perfusion

- Capillary refill time >3 seconds
- Tachycardia
- Weak pulses
- Mottled skin
- Oliguria
- Metabolic acidosis
- Lethargy

Oliguria and metabolic acidosis can occur as a result of inadequate organ blood flow. Decreased blood flow to the organs results in anaerobic metabolism, which causes metabolic acidosis, and can be an indicator of inadequate perfusion. Biochemical indicators of metabolic acidosis include a low serum bicarbonate level and an increased anion gap.[15] Urine output may not always be helpful in determining adequate organ perfusion in the premature neonate because of the inability of premature infants to concentrate urine and reduce urine output in response to decreased organ perfusion[23] but is still recommended as one indicator of effective organ perfusion. After the cardiopulmonary transition from intrauterine to extrauterine circulation, which occurs over the first two to three days of life, the causes of hypotension are generally related to pathophysiologic processes including sepsis, PDA, or NEC. Assessment findings with these conditions include lethargy, tachycardia, prolonged capillary refill time, metabolic acidosis, and decreased urine output.[2]

TREATMENT OF HYPOTENSION

Initial management of hypotension should be focused on assessment and treatment of suspected causes. Treatment should be planned with the goal of maintaining adequate blood flow to the organs. Despite the fact that studies have demonstrated an inconsistent correlation between low arterial blood pressure, cerebral blood flow,[8,12,32,33] and systemic perfusion,[34] arterial blood pressure remains the standard assessment of circulatory function. Several studies have found wide variations in the treatment of hypotension in low birth weight infants among neonatal units.[35–37] Al-Aweel and colleagues studied the differences in the prevalence of hypotension and management using vasopressor and volume in several NICUs for infants with a birth weight <1,500 g.[36] They found a threefold difference in occurrence of hypotension among units and a ninefold difference in management with vasopressor and volume support. The researchers concluded that the differences in prevalence of hypotension were not related to birth weight or illness severity but may be related to differences in monitoring, documentation, or local medical practices. They also concluded that differences in vasopressor use among units may be related to different management practices (prophylactic use vs actual treatment of hypotension).

Laughton and associates studied factors related to treatment of hypotension in ELGANs born between 23 and 27 weeks and found that treatment of hypotension correlated with decreased gestational age, low birth weight, male gender, and high illness severity. They also found significant variation in management among centers. In addition, the researchers found that blood pressures remained lower in treated infants compared with untreated infants, which they thought may be related to the goal of treatment being to improve urine output and perfusion rather than to raise mean arterial blood pressure.[38]

In the absence of strong evidence examining the causes of inadequate circulation in preterm infants and the effects of treatment, it has been suggested that management of hypotension be based both on signs and symptoms of decreased circulation as well as treatment of suspected causes of circulatory dysfunction rather than just numerical values.[2] The common approaches to treatment of hypotension have not been found to be associated with improved outcomes and may be harmful,[37] which suggests the approach to management should be cautious and clinical trials are needed. The National Association of Neonatal Nurses published evidence-based recommendations for management of hypotension in premature infants in the first few days of life (Table 2).[39] The guideline was developed based on a systematic review of available evidence and was endorsed by the American Academy of Pediatrics.[40] The authors of the guideline support the recommendation to treat hypotension based on clinical indications and potential causes of hypotension rather than a numerical value alone. Treatment of hypotension with dopamine was recommended if the potential cause of the hypotension was suspected to be infection or chorioamnionitis or was unknown,[39] and has been found in a Cochrane Review to be more effective than dobutamine for short-term treatment of hypotension in preterm infants. The Cochrane Review highlighted the paucity of evidence supporting any benefit to treatment of systemic hypotension and the long-term outcomes of preterm infants treated with dopamine versus dobutamine.[41] Dopamine is associated with a greater improvement in blood pressure and cerebral

TABLE 2 ■ Treatment of Hypotension in the Very Low Birth Weight Infant During the First Three Postnatal Days of Life

Hypovolemia or Acute Blood Loss	Myocardial Dysfunction	Sepsis or Chorioamnionitis	Unknown Cause
Volume expander 10 mL/kg: normal saline, blood, lactated ringers. Repeat as needed.	Dobutamine titrated to effect.	Dopamine titrated to effect.	Dopamine titrated to effect.
Dopamine titrated to effect.	Consider adding low-dose dopamine. If persistent, consider epinephrine and discontinue dopamine.	Consider adding epinephrine titrated to effect. For refractory hypotension, consider hydrocortisone.	Consider adding dobutamine titrated to effect. If ineffective, consider epinephrine and discontinue dobutamine. For refractory hypotension, consider hydrocortisone.

Adapted from Vargo L, Seri, I. *The Management of Hypotension in the Very-Low-Birth-Weight Infant: Guideline for Practice.* Glenview, IL: National Association of Neonatal Nurses; 2011.

blood flow in hypotensive preterm infants than other therapies.[42] Dopamine has a dose-dependent effect on stimulation of alpha- and beta-adrenergic receptors, which consequently increase systemic vascular resistance and myocardial contractility and raise blood pressure and cardiac output. It is thought that some premature neonates are resistant to the effects of dopamine because of immaturity of the cardiovascular adrenergic receptors.[43] Dobutamine is recommended as treatment of hypotension related to myocardial dysfunction. Treatment with a volume expander is recommended for signs of acute blood loss or hypovolemia.[39] Several authors recommend epinephrine for treatment of symptomatic infants with refractory hypotension unresponsive to dopamine or dobutamine.[2,39]

Corticosteroids are effective in management of premature newborns with hypotension refractory to other treatments, but, because of the lack of data on safety of use and the concern for development of cerebral palsy, they are not recommended as a routine treatment for hypotension.[44,45] Researchers investigated the usefulness of measuring cortisol levels prior to treatment with hydrocortisone in ill newborns with refractory hypotension to determine adrenal insufficiency and predict response. They found that cortisol levels did not correlate with gestational age or response to corticosteroid treatment.[46]

CONCLUSION

Hypotension continues to be a problem in premature infants and is associated with morbidity and mortality. The lack of standardized values for defining neonatal hypotension at varying gestational and postnatal ages highlights the importance of careful assessment of perfusion, in conjunction with knowledge of the pathophysiology of blood pressure and the unique challenges commonly presenting in premature and ill infants that contribute to low blood pressure. The neonatal nurse plays an important role in the assessment of neonatal perfusion and must be aware of risk factors and signs and symptoms of hypotension to facilitate prompt initiation of treatment when indicated to reduce morbidity and mortality.

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