Evaluation and Treatment of Hypotension in the Preterm Infant

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Despite our limited understanding of the pathophysiology of hypotension and the benefits of therapeutic intervention in the preterm infant, a significant number of preterm newborns receive cardiovascular support.1 The proportion of extremely preterm infants receiving intervention varies greatly among neonatal intensive care units (NICUs), ranging from 29% to 98% in a recent study.2 Although some of this variation may reflect different population characteristics, much is solely related to differing patterns of practice.1 The current review addresses issues regarding cardiovascular support in this unique population of patients: (1) definition of hypotension and shock in the preterm infant, (2) clinical assessment of hypotension and shock, (3) the short- and long-term consequences of hypotension, and (4) the therapeutic options available.

DEFINITION OF HYPOTENSION AND SHOCK IN THE PRETERM INFANT

The definition of hypotension in the preterm infant is contentious. Hypotension could be defined as a “statistically low blood pressure.” This assumes that normative data have been derived from a population of patients and that if the value decreases lower than a certain percentile (eg, third, fifth, tenth percentile), the patient is deemed to be hypotensive. Many normative blood pressure reference ranges exist based on birth weight, gestational age, and postnatal age criteria.3–8 Considerable variation exists among these reference ranges because of frequent methodologic flaws: retrospective data collection, small numbers of patients, collection of only a few data points and averaging over wide time ranges, combined invasive and noninvasive measurements, and inclusion of small for dates and appropriate for gestational age infants. Many

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studies have a priori excluded infants who were thought to require treatment with pressor agents, have included data obtained while they were receiving such agents, or have excluded data from those with poor outcomes, which tends to exclude the most immature infants and sometimes leads to tiny sample sizes. Other normal ranges have been generated that, although demonstrating the postnatal increases in blood pressure, have lumped all preterm infants together.

Other normal values have been generated and widely applied without any empiric validation. The most popular criterion for diagnosing hypotension seems to be the Joint Working Group of the British Association of Perinatal Medicine recommendation that the mean arterial blood pressure in millimeters of mercury should be maintained at or greater than the mean gestational age in weeks. Despite a complete lack of published evidence to support this recommendation, it has been used as the primary entry criterion by several recent randomized therapeutic intervention trials. It is essential that any statistical definition of hypotension that is based on empiric observation integrates the known increases with increasing postnatal and gestational age and is preferably derived from a population of preterm infants with minimal exclusions apart from treatments designed to change the blood pressure.

The question of how to define what is a “normal” blood pressure is difficult. It may be preferable to define hypotension by a blood pressure value lower than which there is a statistically increased risk for adverse outcome (ie, “unsafe blood pressure”) if such a threshold exists and can be defined. The authors attempted to answer this question in a large database from very low birth weight (VLBW) infants and identified a statistically worse outcome with decreasing mean blood pressure thresholds. The incidence of adverse outcome (defined as grade 3 or 4 intraventricular hemorrhage [IVH]) increased from 21% to 31% when the definition of hypotension was reduced from 20 to 15 mm Hg in all patients less than 28 weeks of age. These definitions (20 and 15 mm Hg) accounted for only 7.1% and 1.2%, respectively, of the overall population of infants less than 28 weeks of age, however. When less extreme definitions of hypotension were applied, the increase in risk for severe IVH associated with hypotension was small. Even if we could define a threshold lower than which there is an increased chance of adverse outcome, this does not necessarily mean that intervention is going to result in improved outcome at such a value.

The ideal definition would be a threshold blood pressure lower than which intervention results in improved outcome (ie, operational threshold). This value is unlikely to be a single value; it would have to be patient specific and would depend on several factors, including gestation, birth weight, and postnatal age, and perhaps the cause of the hypotension. Such a threshold currently remains elusive.

Hypotension and Shock

Shock is a pathologic state characterized by inadequate tissue oxygen delivery to meet demand. There is little or no correlation between systemic blood flow and blood pressure in the preterm infant; extremely low systemic perfusion, shock, can occur with normal blood pressure. Conversely, preterm infants with blood pressure lower than average often have no biochemical or clinical signs of shock, presumably have adequate tissue oxygen delivery, and probably do not require treatment. We have called this approach “permissive hypotension.”

When systemic oxygen delivery decreases, there are several initial compensatory responses that occur to maintain perfusion and oxygen delivery to the most vital organs, including peripheral vasoconstriction, which maintains blood pressure (ie, shock without hypotension). Progression to the uncompensated phase is characterized by signs of poor perfusion accompanied by low blood pressure (ie, shock with
hypotension), ultimately leading to the irreversible stage if appropriate therapy is not instituted. In contrast to the permissive hypotension approach mentioned previously, intervention to improve perfusion may be warranted in infants with shock despite normal blood pressure.

RECOGNITION OF HYPOTENSION AND SHOCK IN THE PRETERM INFANT

Clinical Signs

Currently, there is no validated clinical scoring system available to diagnose shock, and the assessment of adequate end organ blood flow in the preterm infant is subjective. Bedside evaluation includes assessment of capillary refill time, color, heart rate, blood pressure, and urine output. None of these parameters in isolation is specific in identifying poor perfusion. Capillary refill time values exist for the term neonate, but there are limited data on capillary refill times in the preterm neonate. Osborn and colleagues showed a weak association between capillary refill time and systemic blood flow. Wodey and colleagues have shown a significant relation between cardiac index and capillary refill time in preterm neonates. The authors recently confirmed a limited relation between capillary refill values obtained in the forehead, sternum, and foot and simultaneously obtained superior vena cava (SVC) flow measurements.

The relation between skin color and illness severity in the newborn has been evaluated using an objective measurement tool. Colorimeter values were found to be significantly different in the high-illness severity group, particularly in the blue-yellow axis; however, no data on blood pressure or cardiac function were given. Further investigations of whether an objective measurement of when an infant is “off color” might help with diagnosis of shock are warranted.

Heart rates are extremely variable, vary with gestational and postnatal age, and correlate with oxygen consumption; however, neither absolute heart rate nor trend analysis of heart rate is validated as a way to assess cardiac function. Urine output is low and variable in the first 24 hours; however, good urine output is somewhat re-assuring. Although the positive predictive value (PPV) of each of these individual measures for identifying poor perfusion is unknown and likely to be low, it does seem that clinical assessment using a combination of signs allows one to identify patients with poor outcomes.

Central venous pressure (CVP) monitoring is commonly performed in adult and pediatric intensive care, in which it is often used to guide fluid management. Normal values for CVP in preterm infants have a wide range (2.8–13.9 mm Hg), and there are numerous technical difficulties in obtaining CVP measurements. It is unclear if CVP correlates with circulating blood volume in the preterm infant; in any case, most preterm infants with lower blood pressure in the first few days are not hypovolemic. Thus, CVP monitoring is of limited use in the NICU. Mixed venous saturation monitoring is frequently used in adult and pediatric intensive care units, but its role in the preterm neonate is limited by the interatrial shunting and technical difficulties encountered in safely obtaining a value.

Serum Lactate Values

Serial lactate measurements are useful in critically ill adults as a manifestation of poor tissue oxygen delivery. Lactate values have been analyzed in several clinical situations in the preterm infant, including sepsis and necrotizing enterocolitis. Values obtained during the first day of postnatal life can predict outcome. Deshpande and Platt showed a worse outcome when lactate concentrations remained...
persistently elevated in sick ventilated newborns (23–40 weeks of gestation). Mortality was 57% if two lactate values were greater than 5.6 mmol/L, highlighting the importance of serial lactate assessments. Groenendaal and colleagues estimated the PPV and negative predictive value (NPV) of arterial lactate within 3 hours after birth in a cohort of preterm babies and found that with a cutoff value of 5.7 mmol/L, the PPV was 0.47 and NPV was 0.92 for a combined adverse outcome (death or poor neurodevelopmental outcome).

Data are limited on the use of serum lactate values specifically in hypotensive newborns. Only one previous study has evaluated the role of lactate in assessment of perfusion. Wardle and colleagues, in an assessment of peripheral oxygenation, found no difference in lactate levels between normotensive and hypotensive preterm infants. In the authors’ cohort of VLBW infants, they identified a weak negative correlation between lactate values and SVC flow. A combined lactate value of more than 4 mmol and prolonged capillary refill times of more than 4 seconds in the foot resulted in a PPV of 80% and a NPV of 88% for identifying low SVC flow, highlighting the value of combining clinical and biochemical parameters.

**Objective Assessment of Flow**

The peripheral perfusion index (PPI) is readily obtained from some bedside pulse oximeter devices. It is essentially a relative measure of the pulse strength and may permit a continuous noninvasive estimate of peripheral perfusion. Its role has recently been reviewed in the adult intensive care unit. In the neonatal acute care setting, a low PPI has been shown to correlate with illness severity and may be useful to detect left obstructive heart lesions in term newborns. PPI monitoring warrants further evaluation in the assessment of perfusion in the preterm infant.

Functional echocardiography may have an important role to play in assessing the adequacy of circulatory status in the preterm infant. It provides an objective assessment of cardiac function and output and permits assessment of response to therapeutic interventions. In the preterm infant, circulatory shunting complicates the measurement of systemic blood flow: left ventricular output is equal to pulmonary blood flow minus any left-to-right shunting across a foramen ovale, and right ventricular output is equal to systemic blood flow plus left-to-right foraminal shunting. In comparison, SVC flow provides a shunt-independent assessment of blood flow to the upper body. Low SVC blood flow has been associated with adverse short- and long-term outcomes. Functional echocardiography is rational and noninvasive. It gives useful information about hemodynamics; however, the PPV of low SVC flow measurement for adverse outcome is low, and therapy aimed at preventing low flow has not yet been shown to be beneficial.

Near-infrared spectroscopy (NIRS) has been used to assess the adequacy of peripheral oxygenation and cerebral oxygenation in the preterm infant. Wardle and colleagues evaluated oxygen delivery and consumption in the forearm of 30 preterm babies, 15 of whom were hypotensive by Watkins’ criteria. They identified lower oxygen delivery and oxygen consumption in the hypotensive babies, with no difference in fractional oxygen extraction (FOE). There was no difference in NIRS-measured variables (oxygen delivery, oxygen consumption, and FOE) in patients who had an adverse outcome compared with those who had a normal outcome. NIRS has yet to demonstrate that its use results in improved outcome in the preterm infant, and its use in the NICU as a clinical monitor has recently been questioned. Future randomized trials of cardiovascular support could incorporate functional echocardiography and NIRS to identify patients who may benefit from cardiovascular support.
**Intramucosal pH or PCO2**

Using gastric tonometry, the intramucosal pH or PCO2 of the stomach can be calculated and used as an index of local perfusion. Because splanchnic blood flow decreases early during compensated shock states, it can be used as an index of adequate overall oxygen delivery. Its use in the neonatal population is limited to a study of 38 VLBW infants in whom recurrent low intramucosal pH was significantly associated with an increase in gastrointestinal complications. There was no statistically significant association between intramucosal pH and death. Its role has yet to be evaluated in assessment of cardiovascular stability in the preterm infant.

**SHOULD WE WORRY ABOUT HYPOTENSION?**

The authors recently performed a systematic review to determine if there was a blood pressure threshold that accurately discriminated between preterm infants with a good outcome and those with an adverse outcome. They identified 18 studies in total, none of which were methodologically robust. The overall assessment of the data was that there is some association between having a lower blood pressure and having a worse outcome; however, there are several potential confounding factors that preclude the elucidation of strong inferences from this association. The definition of hypotension varied substantially across the studies. One definition that has been used is a single mean blood pressure value less than 30 mm Hg. Such a definition may result in an artifactual association between hypotension and adverse outcome because the more immature babies, at greatest risk for IVH, are much more likely to be hypotensive by this rule.

The authors identified four studies that met the greatest proportion of their inclusion criteria. Using continuous invasive blood pressure monitoring, Miall-Allen and colleagues identified an excess of IVH in preterm newborns with a mean blood pressure less than 30 mm Hg. Bada and colleagues showed that infants who developed moderate to severe IVH had lower blood pressure values for their postnatal ages than matched control infants who did not develop IVH. Watkins and colleagues, having taken postnatal age and birth weight into account, identified an association between a lower blood pressure (less than tenth percentile from self-constructed tables) and the frequency of severe IVH. The exact timing and duration of hypotension were not taken into account. Each of these studies was confounded by the fact that pressors were used and not accounted for in the analyses. More recently, Cunningham and colleagues found no association between the development of severe IVH and a prolonged period with a mean blood pressure less than gestational age in weeks. Data collected from the Canadian Neonatal Network have shown that those infants who had a lowest blood pressure less than their gestational age, or a blood pressure less than the tenth percentile using Watkins’ criteria, were statistically slightly more likely to have severe IVH. This minor increase in risk was no longer apparent when pressor use was accounted for, however. Infants in the database who were not hypotensive and yet received inotropes were more likely to have a worse outcome than hypotensive patients who had not received such treatment. This finding could be interpreted in many different ways, one of which is that the adverse outcomes attributed in the past to hypotension are actually caused by the treatment of hypotension. An alternative explanation is as follows: physicians sometimes give cardiovascular support to infants who are unwell and poorly perfused despite an acceptable blood pressure (compensated shock), and such infants do poorly despite treatment. In contrast, the authors sometimes do not treat infants who have a statistically lower blood pressure but who appear to be well perfused, and such infants do well. Either of these
explanations calls into question the common practice of routinely treating infants according to simplistic blood pressure thresholds.

**CURRENT THERAPIES**

Many different therapeutic algorithms exist for treatment of hypotension.\(^53,54\) These typically consist of volume expansion, followed by inotropic support (often dopamine as a first line) and, more recently, corticosteroids. The authors recently surveyed Canadian neonatologists concerning their approach to the diagnosis and treatment of hypotension in the VLBW infant.\(^9\) Three predominant regimens currently exist in practice; each consists of volume, followed by dopamine (91%), with the subsequent addition of steroid, epinephrine, or dobutamine. There is little evidence to support this current approach.

**Volume**

The initial approach by most clinicians to hypotension in the preterm infant is volume replacement. There is no physiologic rationale for this approach and no reliable evidence to support it; most infants who are hypotensive have normal circulating blood volumes.\(^55–57\) Furthermore, an increasing volume of fluid administered during the first few days of life is associated with an increasing prevalence of bronchopulmonary dysplasia (BPD).\(^58,59\) This correlation was confirmed by a prospective controlled trial that demonstrated improved survival and decreased BPD rates in preterm babies who were randomized to low fluid intakes versus those given a more liberal fluid intake.\(^60\) Goldberg and colleagues\(^61\) found an increase in the incidence of IVH in preterm infants receiving rapid volume expansion, and adverse neurologic outcome\(^62\) has been reported in VLBW infants who had received colloid boluses. The relative lack of response to volume administration is also evidence that hypotensive preterm infants are rarely hypovolemic.\(^63–65\) There is therefore no empiric evidence to support the use of fluid boluses as therapy of hypotension, with observational data supporting adverse cardiovascular, pulmonary, and neurologic outcomes.

**Inotropes**

There are several randomized controlled trials\(^66–70\) comparing the effects of various different catecholamine agents in systemic hypotension. Dopamine reliably increases blood pressure but seems to do so largely by increasing vascular resistance\(^71\) and often leads to a decrease in systemic perfusion. Dobutamine does not reliably increase blood pressure but usually is associated with an increase in left ventricular output\(^69\) and SVC flow.\(^72\) Epinephrine increases blood pressure\(^11\) and may increase systemic flows, but limited data are available.\(^73,74\) The greatest concern remains the paucity of evidence that clinically important outcomes are improved by the use of any of these catecholamine pressor agents.

**Glucocorticoids**

There are a several prospective randomized trials addressing corticosteroid use for prevention\(^75,76\) and treatment of hypotension\(^12,77–80\) in the newborn. In one of the prophylactic studies, a reduction in the amount of inotrope required was noted, and in the second, there was no difference in inotrope use. No data are provided on long-term follow-up in either of these studies. There was an increase in the number of adverse effects, however, including hyperglycemia necessitating insulin infusion and gastric perforation in the treated group. In the treatment of hypotension trials, there was variation across the studies with respect to increase in blood pressure and reduction in
inotrope use. No advantage of steroids has been documented for any clinically relevant outcomes (death or IVH rate), and no long-term outcome data are provided in any of the trials. The use of glucocorticoids for the prevention and treatment of hypotension cannot be recommended until clinically important benefits are demonstrated in future trials.

SUMMARY

The definition and subsequent appropriate treatment of hypotension and the clinical diagnosis of shock remain elusive, as evidenced by the continued wide variation in practices across NICUs. Currently, many infants receive potentially toxic therapies based solely on simplistic criteria, such as a mean blood pressure less than the gestational age in weeks, in the absence of any evidence that such an approach is beneficial. An approach to treatment that includes blood pressure values but also clinical signs and biochemical values before deciding to initiate therapy markedly reduces the number of infants who receive therapy and is associated with good outcomes. Good clinical practice requires a careful assessment of the risks and benefits of an intervention before starting it. The available evidence suggests that an infant who is clinically well perfused despite a numerically low blood pressure is at low risk and may not benefit from intervention. The frequency of treatment can be reduced by a clinically selective approach to as few as 11% of VLBW infants with no evidence of adverse results. It is incumbent on those promoting a more interventionist approach to perform the requisite randomized controlled trials to prove that clinical outcomes are improved.

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