The diagnosis and management of hypotension in neonates

Ryan Farrugia*, Hector Rojas and Heike Rabe

Neonatal & Paediatric Intensive Care Unit, Department of Paediatrics, Mater Dei Hospital, Malta

Academic Department of Paediatrics, Brighton and Sussex Medical School, Royal Alexandra Children’s Hospital, Brighton, BN2 5BE, UK

*Author for correspondence: ryan.farrugia@gov.mt

The diagnosis and management of hypotension in neonates is a frequently encountered issue in the intensive care setting. There is an ongoing debate as to the appropriateness of blood pressure monitoring as an indicator of organ perfusion and tissue hypoxia. These ultimately determine morbidity and mortality in the sick newborn. This article explores the methods available for the assessment of organ perfusion and speculates on other means that may become available in the future. Different modalities of treatment currently in use are discussed, with the aim of using information gained from perfusion monitoring techniques to determine the optimal choice of therapy.

Hypotension is a commonly encountered problem in the field of neonatology. At least half of extremely low-birth weight babies will have at least one hypotensive episode throughout their early life [1]. The figure varies according to gestational age, degree of growth restriction and postnatal age. Lower and upper limits of gestational age-adjusted physiological blood pressure values for both term and preterm infants have not been determined [2,3]. In term newborns, hypotension is commonly considered to be a mean blood pressure that is lower than the tenth percentile for age [4,5]. Similar definitions have been extrapolated to the preterm population using data gathered from a cohort of healthy preterm babies. The critical condition of most extremely preterm babies in the first week of life has not been appropriately defined frequently and need to be kept at the level of the heart. Dampening of transduced waveforms leads to inaccurate measurements and is a frequently encountered problem [12].

Blood pressure monitoring is an established parameter in the field of neonatology, frequently being assumed to be a proxy measurement for the degree of organ perfusion and therefore as a marker for shock and circulatory compromise. Systemic hypotension in preterm neonates is known to be associated with organ damage resulting from organ hypoperfusion. A strong link with adverse neurological outcomes following hypotensive episodes has long been demonstrated [7-8]. The duration as well as severity of hypotension has also been shown to correlate with the degree of neurological impairment at 2 years of age in extremely low-birth weight infants [8,9].

Accurate measurement of systemic blood pressure (SBP) in sick neonates can prove challenging. The accuracy of noninvasive oscillometric techniques in comparison with invasive techniques is still under debate. Studies carried out in the 1980s and 1990s claim that noninvasive oscillometric techniques tend to overestimate SBP, especially at the lower reaches, and therefore tend to underestimate hypotension [10]. More recent studies claim that there is good correlation between the two techniques [11]. This may be a reflection of improvements in technology that have taken place in the interim years. Both techniques require rigorous methodology in order to yield accurate results. Appropriately sized cuffs are required for noninvasive blood pressure monitoring. Blood pressure transducers used for invasive monitoring need to be calibrated frequently and need to be kept at the level of the heart. Dampening of transduced waveforms leads to inaccurate measurements and is a frequently encountered problem [12].

Systemic arterial blood pressure itself has been shown to be poorly correlated with systemic blood flow in preterm neonates [15]. Systemic hypotension is therefore not a reliable marker of systemic hypoperfusion in preterm neonates. Surprisingly, no internationally accepted consensus exists on the definition of shock in newborns [14].

Several treatment strategies have been used to provide cardiovascular support to hypotensive newborns; these include volume expansion, inotropes and corticosteroids. All have been extensively studied with mixed results. All have
been shown to raise blood pressures and all carry potential risks of adverse effects. It would therefore be logical to advocate a rational use of antihypotensive interventions and to give preference to treatment strategies that best target the etiology of the hypotension. Such a decision would require two prerequisites: a consensus as to what constitutes an abnormally low blood pressure and/or circulatory failure requiring treatment and the availability of alternate markers that may point towards the etiology of circulatory failure, thereby facilitating the selection of an appropriate treatment strategy. Indeed, one could argue that a critical appraisal is warranted as to whether blood pressure monitoring is the most appropriate strategy for the early detection of shock in sick newborns.

**Neonatal physiology & the etiology of circulatory failure**

SBP is the product of cardiac output and systemic vascular resistance. Cardiac output, in turn, is dependent on heart rate, preload, afterload and myocardial contractility. Any of these factors can act independently or in combination to result in a reduction in SBP. The neonatal circulatory system differs from the adult in that it is undergoing a state of adaptation from extratutine life. Duct-dependent congenital heart disease needs to be excluded in all newborns with persistent hypotension. Rapid infusion of fluids in a neonate with a patent ductus arteriosus may cause left-to-right shunting and congestive heart failure, induced by volume overload.

A significant number of hypotensive newborns have been reported to have a normal or high cardiac output. It therefore follows that in a significant number of cases, hypotension may be the result of reduced vascular resistance, secondary to abnormal vasomotor tone or to significant shunting [15,16].

A significant proportion of hypotensive newborns will be receiving invasive ventilation due to respiratory distress. This, together with the degree of prematurity, increases the risks of tension pneumothorax and pneumopericardium, which could impair venous return and cardiac contractility, and which should be actively excluded.

**A practical approach to the assessment of organ perfusion**

The ultimate aim for the neonatologist treating a sick neonate is survival without morbidity, with a special emphasis on neuroprotection. Published evidence enforces the belief of the need for an adequate perfusion of vital tissues. Perfusion of vital organs is dependent on SBP, but measured SBP may itself be a poor marker of organ perfusion, particularly in the first 48 h of life.

Traditional methods of assessing tissue and organ perfusion have depended on indirect and subjective assessments of tissue function.

**Skin & superficial tissue perfusion**

In low cardiac output states, blood supply to the skin is diverted to vital organs. Skin perfusion can be assessed by timing capillary refill and measuring central–peripheral temperature gap. Both of these assessments are affected by the thermal environment [17]. Capillary refill time (CRT) needs to be measured centrally and correlates poorly with hypovolemia in children [18]. In preterm and very low-birth weight babies in the first days of life, vasomotor tone is not yet well established. In these patients, skin perfusion assessment is an unreliable marker of tissue perfusion [19].

White light spectroscopic techniques are in development for the noninvasive measurement of tissue hemoglobin in newborns [20]. These techniques work on the principle that oxyhemoglobin and deoxyhemoglobin absorb light at specific wavelengths. Scatter of nonabsorbed light gives tissues a specific wavelength profile, which can be measured at the skin surface.
Orthogonal polarization spectral imaging utilizes linearly polarized light with a specific wavelength for hemoglobin and allows visualization of small blood vessels in the extremities [21].

Laser Doppler flowmetry is being researched as a noninvasive technique to quantify blood flow in human tissues such as skin and could likewise hold promise in assessing tissue perfusion in neonates (Box 1) [22].

Cerebral perfusion

The measurement of cerebral perfusion is a much sought-after parameter in the ambit of neuroprotection, especially since it has been shown that cerebral perfusion is independent of mean arterial blood pressure in preterm newborns [23].

Near infrared spectroscopy has been a promising development in this field. Near infrared spectroscopy takes advantage of the high degree of transparency of brain tissue to light in the near infrared spectrum and allows real-time noninvasive measurement of regional oxygen saturation and hemoglobin concentration, both through the skin and the intact skull. Its use in preterm and term neonates has been validated [24,25], but the technique is not yet in routine use. The SafeBoostC study group is currently evaluating this method further [101].

Echocardiography

The use of echocardiography as a tool for bedside hemodynamic measurements in the neonatal intensive care unit is gaining impetus. Echocardiography is being increasingly considered an integral component of the assessment of the critically ill newborn [26-27]. The increasing availability of ultrasound equipment in neonatal units has rendered these assessments logistically feasible.

Transesophageal echocardiography on critically ill neonates allows the exclusion of structural congenital heart disease, which is frequently the unexpected cause of hemodynamic instability.

Assessment of cardiac contractility by measurement of shortening fractions and left ventricular stroke distance may be helpful in the choice of inotropic support. Left ventricular output has the limitation of being an unreliable indicator of perfusion in the presence of a patent ductus arteriosus or intracardiac shunts, a common scenario in newborns with a transitional circulation.

Measurement of inferior vena cava diameter allows the operator to gain an indication of preload and therefore the adequacy of vascular filling. Inferior vena cava diameter may, however, be increased in cardiac failure states and in children ventilated with high pressures.

Echographic measurement of the flow through the superior vena cava (SVC) reflects venous return from the brain and upper body, which is not biased by ductal or intracardiac shunts. It gives a better reflection of cerebral blood flow than cerebral artery Doppler measures [28]. A correlation has been demonstrated between poor upper body blood flow in the first day of life and an increase in mortality, risk of necrotizing enterocolitis (NEC), peri-/intra-ventricular hemorrhage (P/IVH) and adverse neurodevelopmental outcomes in infants born at less than 30 weeks gestation [29,30].

Common carotid flow has been validated in a population of term and preterm infants, but has not been sufficiently studied in extremely low-birth weight infants [31]. The common carotids account for the majority of cerebral blood flow and therefore allow for an accurate assessment of cerebral perfusion.

The superior mesenteric artery (SMA) supplies the gut from the duodenum to the transverse colon. Poor SMA flow may play a key role in the etiology of NEC. Measurements and clinical correlations of SMA flow are still awaiting validation and may, in the near future, offer an insight into the relationship between intestinal perfusion and pathologies, such as feed intolerance and NEC [32,33].

Lactate

Lactic acid accumulates as a result of anaerobic metabolism resulting from decreased tissue perfusion, sepsis or inborn errors of metabolism. A strong linear correlation has been demonstrated between arterial and capillary lactate levels [34]. Capillary measurements are therefore frequently used in newborns in whom arterial samples may

---

**Box 1. Currently used noninvasive methods for the assessment of circulation.**

- Clinical examination: capillary refill time, pulses, skin color, blood pressure and urine output
- Echocardiography and Doppler: enables measurement of cardiac output and superior vena cava flow, but requires considerable expertise, and does not provide real-time data
- Near infrared spectroscopy: real-time noninvasive measurement of regional perfusion and oxygenation
- Laser Doppler: quantification of blood flow in capillaries
- White light spectroscopy: measurement of hemoglobin in superficial tissues using absorption and scatter algorithms, providing real-time data on perfusion
- Orthogonal polarization spectral imaging: visualization of small peripheral blood vessels using polarized light
- Pulse oximetry: real-time oxygenation and perfusion
be difficult to obtain. Serial measurements can provide useful indicators of tissue hypoxia with values of more than 3 mmol/l at birth being abnormal [35]. Combining serum lactate levels with CRT improves positive and negative predictive values. A serum lactate level >4 mmol/l and CRT >4 s correlates with a 97% probability of detecting a low SVC flow (Box 2) [36].

Renal perfusion
Urine output is measured as a surrogate for renal perfusion. Changes in urine output, especially in the uncatheterized newborn, are a late and relatively insensitive marker of tissue perfusion, and only occur once a drop in blood pressure has occurred [57].

Treatment strategies

Volume expansion
A meta-analysis published as part of a Cochrane review in 2009 by Osborn and Evans cited five trials that compared volume therapy versus no treatment in very preterm infants and found that mortality was similar for infants who received volume compared with those who received no treatment [38]. Two of these studies also examined neurological outcomes in terms of P/IVH. The NNNI 1996 compared 519 infants who received gelatine-based plasma substitutes with infants receiving fresh frozen plasma and established no clear benefit in survival rates and long-term neurological outcome. This study, however, found a significant reduction in the incidence of NEC and an increase in the incidence of sepsis in the treated group [41].

NNNI 1996 compared 519 infants who received gelatine-based plasma substitutes with those who received no treatment and found no significant differences in severe disability or mortality. This study, however, found a significant reduction in the incidence of NEC and an increase in the incidence of sepsis in the treated group [41].

Box 2. Biomarkers for assessment of circulatory status.

- Serum lactate: strong correlation between rising lactate and falling superior vena cava flow especially when combined with other observations, such as capillary refill time
- IL-8: early-phase marker for sepsis, with high sensitivity and specificity for likelihood of survival when used in septic shock
- Fetal blood IL-6, urinary β2-microglobulin: described as indicators of fetal inflammatory response in preterms of less than 30 weeks gestation
- Serum cortisol: positive correlation between rising cortisol levels and scores for predicting sepsis

Data taken from [64,69–72].
significantly increased risk of NEC in infants receiving gelatine-based plasma substitutes and an increased risk of sepsis in those receiving fresh frozen plasma.

No studies comparing outcomes in neonates treated with packed red blood cell transfusions with those receiving no treatment have been found.

**Volume therapy in the prevention of hypotension**

Significant interest has been expressed in the utilization of blood contained within the placental circulation to augment neonatal blood volume. Up to two-thirds of a newborn’s circulating blood volume may reside within the placental circulation at birth.

Upon delivery of a baby, blood continues to flow through the placental circulation for a short period of time, resulting in a transfer of blood from the placental circulation to the neonate. Such transfer, also referred to as placental transfusion, may be affected by a number of practices in the active management of labor.

The traditional management of labor has been to clamp and then cut the umbilical cord upon delivery of the child and prior to delivery of the placenta. This practice has been aimed at reducing the risks of blood loss from both mother and newborn and, at the same time, allowing for access to the neonate, should resuscitation be required.

The effect of delays in cord clamping and other practices to enhance placental transfusion on preterm infants outcomes has been the subject of two Cochrane reviews [45,46].

A delay in clamping of the umbilical cord has been the most commonly adopted strategy. There is, however, no consensus as to what constitutes a significant delay. Definitions in published literature range from 30–90 s following delivery of a preterm infant. The position of the neonate in relation to the uterus (and therefore the placenta) during the time period prior to cord clamping has also been studied.

Milking of the umbilical cord is another alternative. The practice involves milking a section of umbilical cord approximately 20 cm long towards the umbilicus prior to clamping of the cord. This practice has been thought to hasten placental transfusion and may be more convenient in scenarios requiring immediate access to the newborn for resuscitation.

A meta-analysis of studies showed that neonates receiving improved placental transfusion through delayed cord clamping showed no difference in mortality, but a lesser requirement for transfusions for anemia and hypotension. Data also suggest protection against P/IVH, NEC and sepsis. There was no difference in Apgar scores when compared with untreated groups, suggesting that resuscitation was not significantly hindered by these practices. A small randomized controlled trial showed decreased transfusion requirements, increased hemodynamic stability and a decreased incidence of chronic lung disease in very preterm babies having undergone milking of the umbilical cord [47,48].

Neonatal life support guidelines are now advocating a delay in cord clamping of at least 1 min [49].

**Inotropes & vasopressors**

Inotropes are drugs that act on the myocardium to increase the force of cardiac contraction and, hence, the cardiac output. None of the inotropes presently in use have an exclusively inotropic effect. Most inotropes also affect heart rate and vascular tone. Their effect on the cardiovascular system is therefore the net result of all of these influences. This usually translates to an increase in blood pressure, but not necessarily to an increase in end-organ perfusion.

Pulmonary vascular resistance is an important consideration in the neonatal population. This would be expected to fall dramatically at birth as the lungs inflate and oxygenate, but may fail to do so under certain conditions, resulting in persistent pulmonary hypertension of the newborn. Systemic hypotension is commonly encountered in pulmonary hypertension of the newborn. The use of a vasoconstricting agent such as dopamine in such a circumstance may result in increased pulmonary vascular resistance, resulting in a reduction in cardiac output, an increase in right to left shunting or both [50].

Variations in the effects and metabolism of inotropes resulting from gestational age and organ dysfunction are not completely understood. It follows that there has been and still is significant debate as to which inotropes should be utilized and when in neonates. It is pertinent to note that evidence for the use of inotropes is based almost exclusively on known pharmacological action, rather than on assessment of meaningful clinical outcomes (Table 1) [51].

Resuscitation guidelines advocate considering the use of inotropes in cases of hypotension that persist, despite adequate volume resuscitation [37,42]. However, defining the adequacy of volume resuscitation has proven to be challenging,
particularly in the neonatal population, in whom the presence of a transitional circulation may mimic hypovolemic states. In the majority of preterm infants, especially in the immediate postnatal period, hypotension is caused by abnormal vasoregulation as opposed to hypovolemia [14].

Table 1. Inotropes and their effects on neonates.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Pharmacology</th>
<th>Physiological effects†</th>
<th>Dosage‡</th>
<th>Practical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>D1, D2, β1, β2</td>
<td>Increases contractility and vascular resistance At lower doses, dopamine is claimed to be a vasodilator (acting on dopaminergic and then β-receptors), but at higher doses, it has a greater effect on vasoconstriction</td>
<td>Neonates: 5–20µg/kg/min PICU starting dose: 3–5 µg/kg/min May have an effect at 1 µg/kg/min in healthy children</td>
<td>Associated with vasoconstriction, so requires a long or central line</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Predominant β1</td>
<td>Affects contractility without increasing vascular resistance Dobutamine has a greater action on β-receptors, producing vasodilation, tachycardia and chronotropy</td>
<td>Neonates: 5–20 µg/kg/min PICU starting dose: 3–5 µg/kg/min Maximum dose 20 µg/kg/min</td>
<td>Can be infused via peripheral line</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>α1, α2, β1, β2</td>
<td>Increases contractility (with increased vascular resistance at higher doses) Theoretically, epinephrine acts more on the β- than α-receptors and so should increase BP by increasing cardiac rate and contractility. Dopamine and dobutamine are less potent and have less peak effect than epinephrine or norepinephrine. All may produce tachycardia. Higher doses lead to receptor desensitization, but can be used sometimes</td>
<td>Neonates: 100–300 ng/kg/min Others: 0.1 titrated up to 1.5 µg/kg</td>
<td>Associated with vasoconstriction, so requires a long or central line</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α1, α2, β1</td>
<td>Norepinephrine has a proportionally greater action on the α-receptors and so increases BP by vasoconstriction</td>
<td>Neonates: 20–100 ng/kg/min initially, up to 1.0 µg/kg/min as base. Others: 20–100 ng/kg/min initially, up to 1.0 µg/kg/min as base. Higher doses lead to receptor desensitization</td>
<td>Associated with vasoconstriction, so requires a long or central line</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>ADH agonist in arterioles</td>
<td>May replace basal vasopressin levels in cases of severe hypotension</td>
<td>0.018–0.12 units/kg/h May be used as rescue treatment</td>
<td>–</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>–</td>
<td>–</td>
<td>In neonates: 2.5 mg/kg 6-hourly Others: 1 mg/kg 6-hourly</td>
<td>Uncertainty about role as rescue or primary treatment</td>
</tr>
<tr>
<td>Milrinone</td>
<td>PDE III inhibitor</td>
<td>–</td>
<td>0.5–0.75 µg/kg/min</td>
<td>–</td>
</tr>
</tbody>
</table>

Usual concentrations in use at Adler Hey PICU: epinephrine and norepinephrine: 0.1 µg/kg/min as a starting dose increased up to 1.5 µg/kg/min. 0.3 mg per kg body weight (i.e., 3 mg for a 10 kg child) made up to 50 ml and then run at 1 ml/h will give 0.1 µg/kg/min. Dopamine and dobutamine: 3–5 µg/kg/min increasing to 15–20 µg/kg/min. 15 mg/kg body weight made up to 50 ml and run at 1 ml/h will give 5 µg/kg/min. Vasopressin 1 unit/kg made up to 50 ml run at 1–3 ml/h will get 0.02–0.06 units/kg/h.

†Not all these effects have been validated in neonates or some older age groups.
‡Short half-lives due to breakdown.
§Norepinephrine doses are expressed here as a base. 1 mg norepinephrine acid tartrate = 500 µg base.
ADH: Antidiuretic hormone; BP: Blood pressure; PDE III: Prostaglandin III; PICU: Pediatric intensive care unit.
Reproduced with permission from [50].

Dopamine is the time-honored first-line catecholamine inotrope. It acts on the myocardium to increase cardiac contractility and on the vascular smooth muscle, increasing peripheral vascular resistance. It is thought to be more effective than dobutamine in restoring blood pressure as the latter drug acts mostly on the
myocardium. Given its vasoconstrictive effects, dopamine requires central access for administration, which may be time consuming, especially in critical scenarios. Dopamine is usually better tolerated than adrenaline and noradrenaline, as it causes less tachycardia. There is some evidence that dopamine affects renal arterial blood flow and low-dose dopamine of <5 µg/kg/min may actually cause vasodilatation of the renal arteries, improving urine output and serum creatinine levels. There are no data suggesting any effect on survival with the use of low-dose dopamine in neonates.

The optimal doses for dopamine and dobutamine in preterm neonates are not known. Pharmacokinetic studies have shown wide variations in plasma concentrations between preterms given the same dose. This probably reflects differences in metabolism and clearance, which is independent of weight and gestational age. There is a poor correlation between plasma concentrations of dopamine and dobutamine, and SBP response [52–55].

There are few studies on the effect of dopamine on neonates. A positive effect on left ventricular output has been demonstrated with doses of between 5 and 10 µg/kg/min in term and preterm infants [55,56,57]. Dopamine has been shown to have immunomodulatory effects in sick children and to reduce plasma levels of T4, TSH and prolactin [58]. Further study is needed on the significance of these findings.

A Cochrane review by Osborn published in 2009 compared the outcomes from two trials in neonates treated with dopamine, as opposed to volume expansion with albumin [59]. A meta-analysis of published evidence showed no difference in mortality. Dopamine did produce a greater response in blood pressure and lower failure rate (persistent hypotension) when compared with albumin [60,61].

Treatment with dopamine has been shown to have a significantly greater effect than dobutamine in increasing SBP, but there is no significant difference in SVC flow or right ventricular output between the two drugs. There is little change in blood pressure in the higher dose ranges of dobutamine (10–20 µg/kg/min); however, a significant rise in SVC flow has been noted as doses were increased to the upper reaches. No significant differences in long-term morbidity and overall mortality have been noted between the two drugs. Treatment failure has been shown to be substantial with either inotrope [30,62].

The use of adrenaline and noradrenaline is usually reserved for neonates with refractory hypotension who have not responded to volume resuscitation. Both increase cardiac contractility and heart rate. Both are potent vasoconstrictors, but adrenaline may cause vasodilatation at low doses.

Phosphodiesterase type 3 inhibitors such as milrinone disrupt the breakdown of cGMP and cAMP, which in turn modulate vasodilatation. They possess positive inotropic effects, but their use in shock is limited by their vasodilatory effect, which in turn makes them suitable for use in infants with pulmonary hypertension or with a poor cardiac output following cardiac surgery.

The hormone vasopressin and its analog terlipressin are potent vasoconstrictors utilized in adult intensive care units for fluid and catecholamine refractory hypotension and shock. Their use in neonatology is not well established. A recent Cochrane review concluded that there is a paucity of data with regard to the safety and efficacy of the use of vasopressin, and its analogs in refractory neonatal hypotension [63].

**Steroids**

Critical illness in newborn babies may result in the downregulation of adrenergic receptors, leading to a desensitization of the cardiovascular system to the effects of circulating catecholamines [64]. Glucocorticoids have been shown to induce the expression of adrenergic receptors [65] and to inhibit catecholamine metabolism. The mineralocorticoid effects of steroids enhance intracellular calcium levels, resulting in improved myocardial contractility and increased myocardial and vascular smooth muscle response to catecholamine.

The safety and efficacy of using hydrocortisone in the treatment of hypotension in preterm babies is as yet unproven. Steroids have traditionally been used in the treatment of persistent hypotension that has not responded to fluid therapy and inotropic support.

A Cochrane review by Ibrahim _et al._ published in 2011 analyzed four studies totaling 1,23 babies [66]. Corticosteroid therapy for preterm infants with hypotension refractory to volume expansion and dopamine treatment was shown to be associated with a statistically significant reduction in persisting hypotension [67]. No statistically significant effects on long- or short-term mortality outcomes were found. No significant short-term adverse consequences have been reported with the use of short, low-dose regimes. However, studies using higher, cumulative doses of steroids in the treatment of chronic lung disease have reported an increased incidence of intestinal perforation,
fungal infections and potential long-term adverse effects on neurodevelopment (68).

Conclusion
Hypotension is a commonly encountered problem in neonatal critical care. It is being increasingly acknowledged that blood pressure is a poor marker of organ perfusion in newborns and that organ perfusion is a much more important determinant of morbidity and mortality than blood pressure, particularly with respect to neurological outcome.

Several techniques exist and several more are in development for the assessment of tissue perfusion, vascular filling and cardiac function. These can help form a picture of the pathology causing decreased tissue perfusion. The decision as to whether or not to treat hypotension, and whether to use volume expansion, inotropes or other therapies rests on the judgment of the clinician based on the information available. There is scope for more research and development into noninvasive means of assessing hemodynamics. Echocardiography carries

Executive summary

Background
- Hypotension is a common problem in sick newborns, especially in preterm babies.
- Definition of hypotension has so far proved to be difficult, especially in the preterm population.
- Blood pressure is a marker for organ circulation.
- Systemic blood pressure (SBP) correlates poorly with systemic blood flow as measured by superior vena cava (SVC) flow.
- Poor SVC flow is strongly correlated with adverse outcomes.

Neonatal physiology & the etiology of circulatory failure: a practical approach to assessment of organ perfusion
- SVC flow is the gold standard in assessing organ perfusion, but is technically demanding and cannot provide continuous real-time monitoring.
- Capillary refill time correlates poorly with skin perfusion and hypovolemia.
- Echocardiography is gaining increasing importance in the assessment of cardiac output and contractility, vascular filling and SVC flow.
- Serial lactic acid measurements can be useful in the detection of anaerobic metabolism in underperfused tissues.
- Urine output is an insensitive marker of tissue hypoperfusion.
- New techniques such as near infrared spectroscopy, white light spectroscopy and laser Doppler are showing promise as noninvasive means of providing real-time monitoring of tissue and cerebral perfusion.

Treatment strategies
- Volume expansion
  - No evidence for routine administration of volume expansion in very preterm and extremely low-birth weight infants.
  - There is significant debate as to which fluid to use in hypotensive babies: crystalloids, albumin, plasma or gelatine-based substitutes. No significant differences in benefits have been found.
  - No studies comparing packed cell transfusions to other fluids exist.
  - Feto–placental transfusion techniques have been studied and found to decrease the incidence of hypotension and the need for transfusion, but not to affect mortality.
- Vasopressors
  - Vasopressor drugs may also have chronotropic and inotropic effects, which will have a complex effect on the newborn’s circulatory system and not necessarily result in preserved organ perfusion, despite responses in SBP.
  - Dopamine is frequently utilized as a first-line vasopressor.
  - Newborns treated with dopamine have been shown to have the same mortality as those treated with albumin, but have better SBP responses.
  - Newborns treated with dopamine and dobutamine have been shown to have similar morbidity and mortality rates. However, the use of dopamine elicits a stronger SBP response.
- Steroids
  - Steroids are usually reserved for refractory hypotension. No significant differences in morbidity and mortality have been shown in newborns treated with hydrocortisone compared with those treated with volume expansion or dopamine.
  - There are concerns that steroids may affect long-term neurological outcome.

Conclusion
- Development of new techniques for noninvasive real-time assessment of tissue perfusion is important to allow targeted therapies that would minimize the chances of adverse effects and optimize response.
- Echocardiography is playing an increasingly important role in the management of the sick newborn and is rapidly becoming a core skill in neonatology.
- A consensus needs to be reached on the definition of neonatal circulatory failure.
great promise in this respect, but requires training of operators and a significant investment in equipment.

All therapies available have potential deleterious effects on the newborn. More research is required into the pharmacokinetics and effects of drugs and fluids on the newborn population, and how these are affected by gestational age, birth weight and comorbidities.

Future perspective
Two large collaborative projects funded by the EU-FP7 framework are addressing the research question about a new definition of neonatal circulatory failure. In addition, the HIP trial will study an age-appropriate formulation of dopamine [103]. The Neocirculation consortium will do the same for dobutamine [104]. The consortia will pool their results together with the Safe-BoosC study group in order to develop a new definition of neonatal shock, as well as guidelines for diagnosis and treatment.

Acknowledgements
The authors would like to thank P Nuntnarumit and M Turner for permission to reprint their figure and table, respectively.

Financial & competing interests disclosure
H Rabe and H Rojas are members of the Neocirculation consortium. H Rabe conducted industry-sponsored studies on white light spectroscopy and acted as a paid advisor for MBR Optical systems (Wuppertal, Germany). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References
Papers of special note have been highlighted as:
• of interest
** of considerable interest

Establishes blood pressure norms for term and preterm newborns.

Establishes that hypotension is not a reliable marker of low blood volume in preterm infants.

Gives a comprehensive review of the pathophysiology of hypotension in preterm infants and identifies current treatment strategies and dilemmas.

**Review of noninvasive techniques available or under study for cardiovascular assessments in newborn infants.**


**Establishes a link between poor superior vena cava flow in the neonatal period and poor long-term neurodevelopmental outcomes.**


**Comprehensive review of inotropic support in newborns and pediatric patients, complete with pharmacological properties and doses.**


68. O’Shea TM, Kothadia JM, Klimepeter KL et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low-birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics 104(1 Pt 1), 15–21 (1999).


Websites

101. SafeBoosC. www.safeboosc.eu


103. Management of hypotension in the preterm extremely low gestational age newborn. HIP trial. www.hip-trial.com

104. Neocirculation. www.neocirculation.eu