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Cardiovascular support of the sick neonate

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Summary
From fetal through to adult life the cardiovascular system undergoes striking developmental changes that determine cardiovascular function in health and disease. An appreciation of these changes aids our understanding of the therapeutic approaches to supporting the cardiovascular system in sick newborns. Cardiovascular assessments should include not only the blood pressure, but fluid balance, acid–base balance, electrolytes, cardiopulmonary interactions, and the potential haemodynamic contributions of a patent ductus arteriosus. As prolonged systemic hypotension may be detrimental it should be effectively managed. The major contributor to neonatal hypotension is not hypovolaemia but impaired myocardial function and regulation of peripheral vascular tone. Routine volume expansion should therefore be restricted to 10–20 ml/kg and greater attention given to the pharmacological regulation of peripheral vascular tone and treating myocardial dysfunction. There is also increasing recognition of the role of glucocorticoids in modulating the cardiovascular responsiveness to catecholamines and the beneficial effects of steroid administration to infants with refractory hypotension.

Practice points

General considerations

- Assess heart rate, urine output, acid–base balance, serum electrolytes and ionised calcium
- Replace fluid/blood losses and treat acidosis
- Optimise mechanical ventilation and reduce excessive intra-thoracic pressure (where applicable)
- Treat a haemodynamically significant patent ductus arteriosus

Specific therapies

- *Step* 1: Volume expansion limited to 10–20 ml normal saline/kg
- *Step* 2: Commence dopamine at 5–20 μg/kg/min (maximal dose may exceed 20 μg/kg/min)
- **Step* 3: Add dobutamine at 5–20 μg/kg/min
- **Step* 4: Add steroids as either dexamethasone 250 μg/kg (single dose) or as hydrocortisone 2.5 mg/kg IV 6 h for 48 h, then 1.25 mg/kg 6 h for 48 h and finally 0.625 mg/kg 6 h for 48 h
- **Step* 5: Add epinephrine at 0.05–2.5 μg/kg/min or norepinephrine at 0.1–1 μg/kg/min

*Ideally echocardiographic assessments of myocardial function should be made from step 3 and whenever escalation of therapy is contemplated.

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Basic cardiovascular physiology

The primary function of the cardiovascular system is the efficient transfer of substrates and oxygen from the environment to the body tissues. However, assessing the adequacy of organ blood flow and tissue oxygenation is difficult in practice, and blood pressure is often used as a surrogate measure of the adequacy of the systemic circulation. At birth, the neonatal cardiovascular physiology is determined by the preload (the amount of blood distending the ventricles just before contraction); afterload (the total resistance of the blood offered by the peripheral and central blood vessels and the ventricular mass); contractility (the intrinsic ability of the myocardium to contract), and the heart rate. Both foetal and newborn hearts demonstrate an intricate relationship between preload, afterload and cardiac contractility with marked deterioration in cardiac output being evident when preload and contractility are not matched to the afterload. Cardiac output may also be significantly affected by the rate of contraction. The dramatic increase in left ventricular output at birth largely uses up the neonatal heart's functional reserve and that there is little scope for further increases in cardiac output. Indeed soon after birth the cardiac output and heart rate slowly fall, inotropy increases and thus with increasing postnatal age the heart regains greater functional reserve enabling it to respond more efficiently to the stresses encountered during neonatal and post-neonatal life. The cardiac output and systemic vascular resistance determine the blood pressure. Cardiac output is determined by the circulating blood volume and myocardial contractility, whilst the systemic vascular resistance (afterload) is determined by factors that influence peripheral vascular resistance (such as a patent ductus arteriosus). Thus an appreciation of the regulation of neonatal cardiovascular physiology enables one to adopt the most appropriate clinical interventions to assist the infant with a compromised circulation.

Clinical relevance of hypotension in newborns

Although it may be more instructive to make detailed cardiovascular studies on instrumented laboratory animals, such invasive studies are impractical in newborn human infants and the assessment of cardiovascular function in such infants is often reduced to determination of blood pressure. Although blood pressure gives no information on preload or ventricular function, it is nonetheless an important physiological parameter and failure to maintain an adequate blood pressure is a common feature of circulatory compromise and has important clinical correlates. 'Normal' blood pressures have been described for newborn infants at various gestations and chronological ages from the first few hours of life through the neonatal period and beyond.[1] These studies demonstrate a dependency of blood pressure on gestational age and post-natal age. One such report, which has a wide appeal because of its simplicity, is the summative description of the normal numeric mean blood pressure as the infant's gestational age in weeks.[2] Clinicians commonly assume that bringing the systemic blood pressure to such 'normal values' restores organ or tissue perfusion back to normal and reduces both short and long-term adverse effects. However, as the normal physiological blood pressure range, which ensures adequate organ perfusion in neonates is unknown, there is uncertainty as to whether treatment of hypotension is as beneficial as clinicians generally presume. Although systemic hypotension has been shown to be associated with an increased risk of cerebral white matter damage, the majority of studies do not confirm these findings.[3] Despite the evidence from animal models suggesting that white matter injury may result from cerebral ischaemia and hypotension, there is currently no indisputable evidence that hypotension in newborn preterm infants contributes to cerebral white matter damage, and the subsequent development of cerebral palsy.[3] Epidemiological studies have also failed to provide irrefutable evidence of an association between systemic hypotension and periventricular leucomalacia. Nevertheless, systemic hypotension may be detrimental as hypotension is independently associated with impaired neurodevelopmental outcome. Of interest is the recent observation that among hypotensive low birthweight infants, cardiovascular support with low-dose dopamine or epinephrine improved both the blood pressure and cerebral perfusion.[4] Additionally, severe hypotension may also contribute to the onset of renal and hepatic injury as well as necrotising enterocolitis.

What causes hypotension in newborns?

The aetiology of neonatal hypotension is diverse and at times several potential causes may co-exist at the same time. Consequently the appropriate management of such infants may present a considerable challenge, and this requires the clinician to have an understanding of the pathophysiology of neonatal hypotension. Contrary to common belief, absolute hypovolaemia is not the primary cause of hypotension in newborns but rather myocardial dysfunction and impaired regulation of peripheral vascular tone. Corroborative evidence for this comes in the observation that volume replacement is only half as effective as dopamine administration in treating hypotension and that no relationship has been demonstrated between blood volume and hypotension in hypotensive preterm infants. Peripheral vascular tone appears to play a greater role in the regulation of blood pressure in newborns. Vascular smooth muscle tone is now known to be influenced by a variety of endothelium-derived substances with the overall tone being determined by the balance between mediators of vascular relaxation and contraction. Thus, there is evidence that nitric oxide overproduction (by inducible nitric oxide synthase) in sepsis may contribute to hypotension by inducing pathological vasodilation.[5] Similar roles have been suggested for other biological mediators, including eicosanoids, endothelin and catecholamines.

Impaired myocardial function has also emerged as a significant factor in the causation of neonatal hypotension particularly in asphyxiated newborns. The syndrome of transient myocardial ischaemia secondary to global myocardial ischaemia is characterised by, among other

things, congestive cardiac failure, hypotension, and a low systemic perfusion state. Some studies have suggested that a similar state may exist in the non-asphyxiated hypotensive preterm infant, though this is disputed by other workers.

Yet more recent studies have demonstrated the previously unrecognised role played by glucocorticoids in the postnatal cardiopulmonary adaptation. A recent study by Ng et al.[6] showed a correlation of serum cortisol with blood pressure in preterm infants, and in a randomised,controlled trial Efird et al.[7] recently demonstrated that the prophylactic administration of hydrocortisone significantly reduced the incidence of hypotension in extremely low birthweight infants during the first 2 days of life. Another study suggests that the impaired systemic response to vasopressors and inotropes may be the results of the downregulation of cardiovascular adrenergic receptors and their second messenger systems, and that this phenomenon may be countered by steroid administration.[8] Significantly low serum cortisol (adrenal insufficiency) may also contribute to the development of resistance to vasopressor and inotrope therapy.[8]

Clinical management

Assessment of the cardiovascular status

The adequacy of the systemic circulation may be judged by the adequacy of organ blood flow and tissue oxygenation, parameters that are difficult to assess in clinical practice, as already pointed out. It is possible to non-invasively ascertain the peripheral venous oxygenation using near infra-red spectroscopy but current methodology makes this impractical. Surrogate markers of circulatory compromise such as capillary refill times (peripheral perfusion), central–peripheral temperature difference, and measurement of central venous pressure are unreliable measures of the adequacy of the systemic circulation. Despite its limitations, blood pressure can both be readily and accurately measured, even if there may be disagreements on when to treat 'hypotension'. Assessment of circulatory adequacy should routinely include the heart rate, urine output, serum ionised calcium, and acid–base balance. As acidosis (arterial pH <7.25) impairs cardiac function in preterm infants, it should be rectified. Finally, echocardiography offers a practical tool to assess myocardial contractility, cardiac output, and the potential haemodynamic contributions of ductal shunting or pulmonary hypertension to the overall cardiovascular status and aids clinical decision making in assessing and treating circulatory compromise.

It should be remembered that cardiac and pulmonary function are intricately linked and interventions to improve pulmonary function (particularly mechanical ventilation) can produce deleterious effects on the cardiovascular system. Thus, lung over-distension during mechanical ventilation increases pulmonary vascular resistance and impairs right ventricular output and at extremes of lung hyperinflation biventricular cardiac output is seriously compromised.[9]

Treating hypotension

Volume administration

Despite the near universal practise of administering fluid boluses to hypotensive infants, hypovolaemia is a relatively uncommon cause of hypotension and excessive volume administration is associated with increased morbidity and mortality particularly from pulmonary haemorrhage in the extremely low birthweight infants. The volume administered is more important than the protein content of the fluid and isotonic saline is as effective in raising blood pressure as 5% albumin.[10] Additionally, saline caused less fluid retention than albumin during the first 48 h of life.[10] The routine use of albumin in critical care has been further discouraged due to its association with increased mortality and the observation that albumin use in treating hypotensive preterm infants is associated with impaired gas exchange. Therefore unless there is evidence of blood loss, or excessive fluid or protein losses (when it would be necessary to replace the fluid lost with an equivalent volume of the same fluid), only 10–20 ml of 0.9% saline/kg should be administered over 15–30 min. Thereafter should blood pressure remain suboptimal, vasopressors (e.g. dopamine, epinephrine or norepinephrine) and inotropes (e.g. dobutamine) should be commenced.

Vasopressors and inotropes

These agents were introduced into neonatal intensive care on the basis of the experience gained on adults. The relatively few recent studies in neonates have largely focussed on the effects of these agents on neonatal cardiovascular physiology with scant details on the impact of these treatments on organ blood flow, tissue perfusion, neonatal morbidity and mortality.

Dopamine

Dopamine is an endogenous catecholamine, which is partly converted to norepinephrine in sympathetic nerve endings. It exerts cardiovascular effects via the stimulation of cardiac dopaminergic, α- and β-adrenergic receptors. Furthermore, independently of the above effects, dopamine stimulates peripheral α- and β-adrenergic receptors, serotonin receptors and peripheral neuronal dopaminergic receptors. Its actions are dose-dependent. The three determinants of cardiovascular function (namely preload, afterload and contractility) are all affected by dopamine (Table 1). Dopamine also has additional α- and β-adrenergic cardiovascular effects resulting from its conversion to norepinephrine.[11] Dopamine selectively and directly increases renal blood flow and glomerular filtration rate[11] in preterm infants by stimulating renal dopaminergic receptors. This selective vasodilatory effect of dopamine has not been demonstrated on the mesenteric blood supply in preterm infants. However, in preterm infants with protracted arterial hypotension refractory to volume therapy, dopamine (at 10 μg/kg/min) effectively raised the mean arterial blood pressure and increased intestinal perfusion.[12] Dopamine may also decrease plasma prolactin, which may

Table 1 Physiological actions of commonly used drugs.

Drug	Cardiac effects	Peripheral vascular effects
Dobutamine	Augments myocardial contractility and cardiac output via α_1- and β_1-adrenergic receptor stimulation	Peripheral vasodilation via β_2-adrenergic receptor stimulation with minor peripheral vasoconstriction via α_1/α_2-adrenergic receptor stimulation
Dopamine	Augments myocardial contractility and cardiac output via α_1- and β_1-adrenergic and dopaminergic receptor stimulation	Peripheral vasoconstriction via α_1/α_2-adrenergic receptor stimulation with minor peripheral vasodilation via β_2-adrenergic stimulation and significant renal, mesenteric and coronary vasodilation via dopaminergic receptor stimulation
Epinephrine	Augments myocardial contractility and cardiac output via α_1- and β_1-adrenergic receptor stimulation	Peripheral vasoconstriction in the skin (α_1/α_2-adrenergic receptors) but vasodilation in muscles (β_2-adrenergic receptors)
Steroids	Augments myocardial contractility by upregulating expression of adrenergic receptors and increasing cytosolic calcium availability in myocardial cells	Prolongs catecholamine activity by decreasing catecholamine metabolism, inhibits pathological vasodilation, and increases the effective circulating blood volume by diminishing the capillary leak syndrome
Norepinephrine	Augments myocardial contractility and increases heart rate	Peripheral vasoconstriction via α_1/α_2- and β_1-adrenergic receptor stimulation

reduce the tendency to oedema formation in preterm infants.

It is commonly presumed that the pharmacodynamic effects of dopamine vary depending on the administered dose with dopaminergic effects being predominant at low doses, and with increasing doses, β- then α-effects becoming more prominent. However, this dose–response profile was derived from healthy adult volunteers. It is now recognised that during severe illness the response of the cardiovascular system to dopamine may be diminished due to adrenergic receptor downregulation,[13] adrenal insufficiency[14] and the effects of locally produced vasodilators. These processes lead to the development of refractory hypotension unresponsive to standard doses of dopamine or other sympathomimetics. Consequently, higher doses of sympathomimetic drugs may be required to produce the same response in sicker patients. Prematurity further attenuates the cardiovascular responsiveness to drug therapy. Partly as a result of the variable metabolism of dopamine, substantial intra- and inter-individual variation in dopamine pharmacokinetics exists which results in marked variation in the doses of dopamine required to produce equivalent pharmacological actions. Consequently, dopamine therapy should be adjusted to the individual needs of each patient and not just protocol driven. For this reason there is considerable debate as to what the optimal dose of dopamine should be. When dopamine therapy has to be escalated in order to optimise blood pressure some recommend step-wise increments in the dopamine dose to 20 μg/kg/min and thereafter adding dobutamine (5–20 μg/kg/min) followed by steroids or epinephrine/norepinephrine. This scheme is not evidence-based and there is currently no evidence to support that dopamine doses >20 μg/kg/min are necessarily deleterious. Indeed dopamine doses of >20 μg/kg/min did not reduce the urine output of sick newborn infants.[15] The studies on the effects of dopamine on pulmonary haemodynamics are contradictory. However, given the possibility of excessive peripheral vasoconstriction (from α_1/α_2 effects), which could impair cardiac output, it would be prudent to exercise caution when contemplating high-dose dopamine therapy. The side-effects of dopamine include hypertension, tachycardia, arrhythmia, hyponatraemia and extensive tissue necrosis following extravasation.

Dobutamine

Dobutamine is a synthetic analogue of isoprenaline, which is fairly cardioselective with predominant β_1-adrenergic activity (direct inotropic effects), some chronotropic effects and a reduced propensity for peripheral α_1- and β_2-adrenergic receptors. It has no dopaminergic activity. It increases cardiac output by increasing myocardial contractility and the stroke volume and causes peripheral vasodilation (via β_2 peripheral vascular receptors) making it the preferred agent for treating hypotensive infants with poor cardiac output and myocardial dysfunction as seen in severe asphyxia. Some reports have suggested that at doses of 10–20 μg/kg/min dobutamine predominantly raises blood pressure but below this dose it primarily improves left ventricular function. Generally, however, dopamine is superior to dobutamine in treating preterm infants with hypotension, a fact borne out by several randomised, controlled trials.[16] However, when there is echocardiographic evidence of impaired myocardial contractility dobutamine should be commenced either alone or as additional therapy. Side-effects include systemic hypotension (or hypertension), tachycardia and arrhythmias.

Epinephrine and norepinephrine

Epinephrine is an endogenous catecholamine synthesised and secreted by the adrenal medulla, whereas norepinephrine is a catecholamine neurotransmitter synthesised in neurones and released from peripheral adrenergic nerve endings. Epinephrine and norepinephrine produce very similar cardiac effects (augmentation of heart rate and contractility) whereas peripherally norepinephrine has more profound vasoconstrictive effects (epinephrine has β_2-effects that are absent in norepinephrine). Although these agents are widely use in neonates, there are few reported studies on their efficacy. Epinephrine in doses of up to 2.6 μg/kg/min produced a rapid improvement in blood pressure without decreasing urine output (or other adverse cardiovascular effects) in hypotensive preterm infants who failed to respond to dopamine.[17] The addition of epinephrine to dopamine therapy in hypotensive neonates has been reported to increase the blood pressure without decreasing urine output, while another report suggested that norepinephrine infusions were safe in critically ill neonates. Nonetheless, epinephrine and norepinephrine have unpredictable pharmacodynamics and may impair cardiac output and tissue perfusion at doses that cause marked peripheral vasoconstriction. Other adverse effects include marked tissue damage at extravasation sites, hypertension and tachycardia.

Steroids

Several recent studies have demonstrated that sick newborn infants have low serum cortisol levels and a relative adrenal insufficiency,[14] which is associated with hypotension refractory to volume expansion, vasopressors and inotropes. Administration of glucocorticoids to such infants leads to a restoration of blood pressure and decreased the need for sympathomimetic agents.[8] These observations may partly be explained by the role played by glucocorticoids in regulating the expression of cardiovascular adrenergic receptors and their signal transduction mechanisms.[18] Sick preterm infants in particular are unable to produce adequate amounts of endogenous glucocorticoids to maintain cardiovascular functional integrity. As a consequence of this endogenous steroid deficiency there is adrenergic receptor downregulation, cardiovascular desensitisation to sympathomimetics and vasopressor resistance develops. Glucocorticoids promote gene transcription, the synthesis of new adrenergic receptor proteins and their expression a process that takes several hours. In addition steroids rapidly exert other beneficial systemic effects (which do not require gene transcription).[8] These include improved myocardial and vascular smooth muscle cell responsiveness to catecholamines through increasing intracellular calcium availability, inhibiting catecholamine metabolism and decreasing norepinephrine reuptake by sympathetic nerve endings thereby increasing circulating levels of catecholamines. Furthermore, steroids improve capillary integrity by reducing the capillary leak syndrome and they also limit the pathological vasodilation, which occurs in sepsis, by inhibiting inducible nitric oxide and prostacyclin production.[5] These direct effects of steroids are thought to account for the improvements in blood pressure noted within 2 h of starting hydrocortisone treatment.[8] Studies to date have reported the use of single-dose dexamethasone (250 μg/kg)[19] or hydrocortisone using various dose regimens over 1–3 days[20] with no adverse effects. However, early use of high-dose hydrocortisone in extremely low birthweight infants has been associated with disseminated fungal infection. More recently, there has been heightened concern on the adverse effects of long courses or cumulative doses of steroids used for treating chronic lung disease on long-term neurodevelopmental outcome. Although, the cumulative doses or duration of steroid therapy in the above studies have been short, the potential for long-term adverse neurological outcomes exists, and until this has been carefully evaluated, caution should be exercised when using steroids for circulatory support in preterm infants.

Conclusions

The regulation of the cardiovascular system in newborns is a complex developmentally regulated process that is affected by co-existent disease processes and the medical interventions instituted to support the sick infants (e.g. mechanical ventilation). Supporting the circulation in sick newborns therefore requires an understanding of the pathophysiology of circulatory failure in newborns. In addition to addressing hypotension (however defined), one needs to assess the infant's fluid and electrolyte balance, acid–base status, ventilatory adequacy, and treat sepsis and/or a significant ductal shunt. A stepwise and logical approach is advocated. Overt or hidden blood or fluid losses should be replaced with appropriate volumes of the same type of fluid. Routine volume expansion should be restricted to 10–20 ml isotonic saline/kg. Thereafter dopamine should be instituted early, followed by dobutamine preferably after echocardiographic assessment of myocardial function. The next step would be to use steroids (hydrocortisone or dexamethasone) as this may restore the cardiovascular system responsiveness to sympathomimetics. Finally epinephrine or norepinephrine may also be used, while carefully monitoring the heart rate and the degree of peripheral vasoconstriction, as marked tachycardia and intense peripheral vasoconstriction (especially with norepinephrine), may impair cardiac output. Serial echocardiographic assessments should be made in infants requiring escalating drug therapy. Dobutamine may be the drug of choice in asphyxiated and hypotensive infants with echocardiographic evidence of myocardial dysfunction (in whom peripheral vascular resistance is often increased).

In conclusion, there is still much work to be done in elucidating the mechanisms underlying the regulation of the newborn circulation in health and disease. Studies examining the impact of the above treatments on neonatal morbidity and mortality are much needed.

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