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Inotropes in term neonates

Systemic hypotension is common in infants requiring intensive care. This article covers the pathophysiology of this condition and the importance of treating it. The article outlines management plans for the rational use of inotropes in these hypotensive newborns and suggests which further options are available in refractory cases.

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Key points

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1. Systemic hypotension is a common complication in infants on the paediatric intensive care unit and requires an individualised approach.
2. Treatment is unnecessary for those who have adequate perfusion and no signs of shock.
3. Although most term newborns will respond to standard treatment, several other options are available to treat the refractory cases.
4. Clinical assessment and supportive measures are equally important.

Between one third to a half of all babies admitted for neonatal intensive care become hypotensive within 24 hours of admission. This systemic hypotension is a relatively common complication of preterm birth but also affect full term sick neonates with a range of medical and surgical conditions. Increasingly, more neonates are admitted to the paediatric intensive care unit peri-operatively needing circulatory support. This article is written from the perspective of a paediatric intensivist, who often faces the challenge of treating low blood pressure in the face of poor evidence to support any treatment options. It will review the use of vasoactive drugs in hypotensive newborn infants and suggest what further options may be available in refractory cases.

Circulatory adaptation at birth

The time immediately after birth is a critical period for the newborn, as transition is made from fetal to neonatal life. This transition is a complex multi-organ system process[1]. The ability to make these adjustments may be more difficult for a premature infant. Fetal circulation is characterised by a low systemic vascular resistance due to the presence of a low resistance placental vascular bed. In contrast, the pulmonary vascular resistance is high, allowing only 6-12% of the cardiac output to travel to the lungs. After birth, with contraction of the umbilical arteries and separation from the placenta, systemic vascular resistance rises rapidly. Pulmonary vascular resistance falls progressively as lungs expand. The ductus arteriosus shunts blood predominantly from right to left *in utero*, but changes to shunt predominantly from left to right after birth, as a result of the changes in systemic and pulmonary vascular resistance. Pulmonary blood flow increases resulting in increased pulmonary venous return. This increases the preloading of the left ventricle thereby increasing left ventricular output. If complications occur during this transition, blood pressure may be affected.

Blood pressure measurement

Direct, invasive measurement obtained from a well-positioned, unobstructed intra-arterial catheter is the gold standard. Mean blood pressure is minimally affected by the mechanical properties of the intra-arterial catheter and the transducer system, micro air bubbles and site (central versus peripheral)[2]. If direct measurements are not available, a Doppler probe with an appropriate sized cuff gives a similar degree of accuracy, although it tends to overestimate the blood pressure in the hypotensive ranges. It would appear that oscillometric systems are inaccurate when the systolic blood pressure is less than 40mmHg.

Definition of hypotension

A number of studies have looked at the blood pressure ranges in the newborns.[2-5] Perhaps the best data on normal values can be found in a study done in the northern region in the UK. After four hours and before 24 hours of age, the systolic blood pressure should not be lower than the gestational age in weeks. The commonly cited 'rule of thumb' defines hypotension as mean blood pressure below an infants' gestational age in weeks[6]. However it must be stressed that blood pressure alone remains an unreliable measure of either cardiac output or of systemic oxygen delivery (see below) and should not be treated in isolation.

Physiology of blood pressure regulation

Blood pressure is the product of cardiac output and systemic vascular resistance. Cardiac output is the product of heart rate

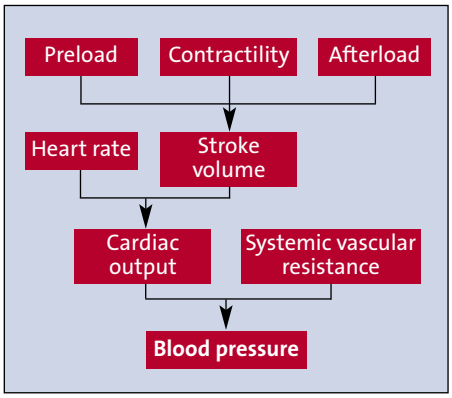

TABLE 1 Physiology of blood pressure[7].

and stroke volume. Stroke volume is dependent on the amount of blood returning to the heart (preload), strength of myocardial contractility (the pump) and the resistance against which the heart must pump (after load). Newborns have a limited ability to increase the stroke volume. Hence, neonatal cardiac output is more dependent on heart rate.

The strength of myocardial contractility depends on the filling volume and pressure, as well as on the maturity and integrity of the myocardium. Thus hypovolaemia, arrhythmias, extreme prematurity, hypoxia, acidosis, electrolyte imbalances (especially hypocalcaemia) and infections will affect the myocardial contractility, which may lead to a fall in cardiac output. If systemic vascular resistance (after load) is too high, the ability of the myocardium to pump against the increased resistance may become compromised and the cardiac output will fall.

Significance of hypotension in sick neonates

Systemic hypotension may reduce the blood flow to the vital organs and make them vulnerable to ischaemic injury. Hypotension is independently associated with adverse neurodevelopmental outcome[9]. In addition, the duration and severity of hypotension may be important[10,11]. In a recent article, Barrington[12] has emphasised the concept of 'permissive hypotension'. Treatment of systemic hypotension in infants with good perfusion and no signs of shock is probably unnecessary and could be potentially harmful. Assessment of adequate perfusion can be very difficult and the intensivist must use clinical judgement to decide when to treat. However, in sick neonates with systemic hypotension and signs of shock, it is important to treat the low blood pressure.

I. HYPOVOLAEMIA
- Massive pulmonary haemorrhage
- Acute surgical emergencies
- Intracranial/subgaleal haemorrhage
- Disseminated intravascular coagulation
- Dehydration: insensible water losses/polyuria
- Third space losses, e.g. sepsis due to necrotising enterocolitis
- Decreased venous return
  - Air leak syndromes
  - High positive end expiratory pressure (PEEP)/high frequency oscillation

II. CARDIOGENIC SHOCK
- Birth asphyxia
- Congenital heart disease
  - Duct dependant lesions with closure of the duct
  - Total anomalous pulmonary venous connection
- Postoperative cardiac surgery
- Cardiomyopathy
- Myocarditis
- Arrhythmias

III. SEPTIC SHOCK

IV. ENDOCRINE
- Adrenal haemorrhage
- Congenital adrenal hyperplasia

V. DRUGS: Sedation on the ICU

TABLE 2 Causes of neonatal hypotension[8].

In the clinical settings, it is difficult to assess the adequacy of blood flow to the organs as it depends (among other things) on cardiac output and end organ vascular resistance. Therefore, blood pressure is used as an indirect measure of perfusion. When the oxygen delivery to the tissues is compromised, shock ensues. Shock remains a major cause of neonatal morbidity and mortality.

Treatment of hypotension

The most common pathological factors for neonatal hypotension are:

1. Inappropriate peripheral vasoregulation resulting in vasoconstriction (usually first 24 hours after birth) or vasodilatation (usually day 2 onwards).
2. Dysfunction of the immature myocardium.

Volume replacement

Absolute hypovolaemia may be the primary cause of neonatal hypotension in a full term neonate with a medical or surgical problem[13]. If there is an identifiable volume loss, ideally the same kind of fluid should be replaced. For example, in cases of blood loss, blood transfusion should be given. If bleeding occurs secondary to disseminated intravascular coagulation, fresh frozen plasma, cryoprecipitate or platelet rich plasma should be used. This serves a dual purpose of treatment of the underlying problem and as volume replacement. In cases of greater transepidermal water losses or polyuria, administration of saline with more free water is indicated.

If the cause of hypovolaemia or of hypotension is unclear, isotonic saline should be used. A bolus of 10mL/kg (5mL/kg in case of perioperative cardiac newborn) over 20-30 minutes may bring about a sustained increase in blood pressure. In such a case a further bolus can be repeated, if necessary. However, if the central venous pressure (CVP) increases without appreciable increase in blood pressure, hypovolaemia is unlikely. In such a situation treatment with an inotrope is indicated. The rationale for administration of an inotrope to a hypotensive newborn unresponsive to volume therapy is to increase systemic perfusion pressure, and thereby systemic blood flow and oxygen delivery.

Inotropes

Drugs that improve myocardial contractility are called inotropes. They increase the peak force of contraction under isometric conditions. Drugs that increase the heart rate are called chronotropes. Generally, they accelerate the heart and may also have inotropic properties. The action of these drugs on the myocardium can be due to an effect on the calcium transit (up-stream regulation)[14] or on the sensitivity of the contractile proteins to calcium (down-stream regulation). No inotrope currently used in clinical practice increases the force of contraction by a direct effect on the myofibrils. A group of drugs known as calcium sensitizers is currently under investigation. Certain drugs (calcium antagonists) have the property of inhibiting calcium transit and thus cause a fall in contractility, relaxation of muscles and reduced conduction in sinoatrial and atrioventricular nodes. These are negative inotropes. This article will concentrate on positive inotropes.

Classification of inotropes[15]

Inotropes can be classified into three major groups depending on their mode of action. Class I drugs increase intracellular calcium; class II drugs increase sensitivity of actomyosin to calcium ions, whereas class III drugs act through metabolic or endocrine pathways. Some drugs will have multiple modes of action and belong to more than one class. Characteristics of an ideal inotrope (**TABLE 3**), commonly used inotropes in neonates (**TABLE 4**) and general rules and precautions during inotropes administration are listed (**TABLE 5**).

Inotropes

Adrenergic receptors fall into three categories: α-adrenergic, β-adrenergic and dopaminergic (DA) receptors (**TABLE 6**). Nearly all inotropes in clinical use are cleared by first order kinetics. Therefore, changes in infusion rate linearly correlate to plasma concentrations, making them practical to titrate to clinical effect. Due to their rapid metabolism (liver), these inotropes have short half lives (in minutes). Hence, these agents should be administered as continuous infusions. However, the phosphodiesterase inhibitors are cleared by the kidney and have longer half-lives.

- Does not increase myocardial oxygen demand
- Does not change heart rate
- Does not cause vasoconstriction
- Redistributes blood flow to vital organs
- Direct acting (does not rely on release of endogenous amines)
- Demonstrates lusitropy (see text)
- Predictable and easily titrable
- Lacks tolerance
- Compatible with other vasoactive substances
- Energy neutral, energy sparing or inoprotective

TABLE 3 Characteristics of an ideal inotrope.

Dopamine

Dopamine is a naturally occurring catecholamine precursor of noradrenaline. It was first synthesised in 1910 and shown to be a neuro hormone in 1959. As it possesses inotropic and vasopressor properties, it is often referred to as an inovasopressor[16]. Its actions are dose-dependent (see **TABLE 4**) on dopaminergic, α and β adrenergic receptors. It also exerts independent renal and endocrine effects[17]. Dopamine affects all three major determinants of cardiovascular function (preload, myocardial contractility and after load). By decreasing venous capacitance, it augments preload. It increases myocardial contractility and systemic vascular resistance by direct stimulation of

- Ensure adequacy of ventricular filling
- Administer inotropes through accurate infusion devices
- Use a dedicated lumen of a central line or PICC line. Single strength dobutamine can be infused peripherally.
- Never flush the infusion line.
- Infusions should be written as per the unit protocols and should be changed regularly (at least every 24 hours). Changeover of the new syringe should be according to the unit policy.
- Check compatibilities with other drugs being given simultaneously.
- Use inotropes for short term circulatory support, but weaning should be a slow process.
- Extravasations may produce extensive tissue necrosis. Follow unit policy for management.
- When infusion rates of stronger agents fall below 0.5mL/hr, tiny boluses can cause massive pressure changes. Consider half strength solutions.
- If the inotrope appears to be ineffective, check delivery apparatus. Make up new infusion.

TABLE 5 Administration of inotropes.

Drug	Site of action (predominant receptors)	Dose range (micrograms/kg/min)	Haemodynamic effects
Dopamine	Dopaminergic (1 & 2) α adrenergic β adrenergic	1-4 4-10 11-20	Renal and mesenteric vasodilatation Inotrope Vasopressor, ↑SVR, ↑PVR
Dobutamine	β_1 & β_2 adrenergic minor α adrenergic effect	5-20	Inotrope, ↓SVR, ↑CO
Adrenaline (Epinephrine)	α_1 adrenergic β_1 & β_2 adrenergic	0.03-0.1 0.1-1.0	Inotrope, some ↓SVR Vasopressor, ↑SVR
Noradrenaline (Norepinephrine)	α_1 & α_2 adrenergic	0.1-1.0	Vasopressor, ↑↑SVR
Dopexamine	β adrenergic	1-6	Inotrope ↓SVR ↑splanchnic blood flow?
Vasopressin	V_1	0.0003-0.002 units/kg/min or 0.018-0.12 units/kg/hr	↑↑SVR (No inotropic effect)
Milrinone	Phosphodiesterase Inhibitor Produces effects at β_1 & β_2 receptors	Bolus 50-75 µg/kg Infusion 0.35-0.75	Inodilator, lusitropy ↑contractility and ↓SVR
Methylene blue	Inhibition of cGMP/nitric oxide pathway	IV infusion of 1mg/kg over one hour	Vasopressor, ↑SVR
Hydrocortisone	Enhanced sensitivity to circulating catecholamines	Surgical stress 10mg/kg/day Acute profound shock 50mg/kg/day	Uncertain – effects of circulating catecholamines

KEY: SVR – Systemic Vascular Resistance; PVR – Pulmonary Vascular Resistance; CO – cardiac output

TABLE 4 Drugs used in the management of neonatal hypotension.

α and β receptors. Approximately 50% of these effects are secondary to peripheral conversion to noradrenaline.

In dopaminergic doses, it increases renal blood flow and glomerular filtration rate, increases sodium, phosphorous and free water excretion. It may increase bicarbonate losses. By reversibly inhibiting renal Na^+, K^+ -ATPase activity, dopamine may increase the hypoxic threshold of renal tubular cells during episodes of hypoperfusion and hypoxaemia. Its endocrine actions include decrease in plasma prolactin and thyrotropin levels. There can be a significant inter-and intra-individual variability in the dose of dopamine required to elicit the above effects. Lack of response may suggest vasopressin exhaustion[18]. In severe illness, the response to dopamine may be diminished due to adrenergic receptor down regulation, adrenal insufficiency and effects of locally produced vasodilators.

Receptor	Action on circulation
α_1	Vasoconstriction (increase in contractility)
α_2	Vasoconstriction (presynaptic sympathetic inhibition)
β_1	Increase in heart rate (sinus node)
	Increase in contractility (atrium and ventricle)
	Increase in conduction (atrioventricular node)
β_2	Vasodilatation (bronchodilatation)
Dopaminergic 1	Renal and mesenteric vasodilatation
Dopaminergic 2	Vasodilatation

TABLE 6 Adrenergic receptor subtypes [14].

Dobutamine

Dobutamine hydrochloride is a cardio selective synthetic analogue of isoprenaline, developed in 1973. It possesses both inotropic (β_1 adrenergic stimulation) and chronotropic (β_2 adrenergic stimulation) properties. It has no dopaminergic activity. It increases cardiac output by increasing myocardial contractility and the stroke volume and causes peripheral vasodilatation. Thus, it is a preferred agent for infants with poor cardiac output, myocardial dysfunction and increased systemic vascular resistance as seen in perinatal asphyxia.

Adrenaline and noradrenaline

Adrenaline is an endogenous catecholamine with direct α and β adrenergic actions, and is released from the adrenal medulla in response to stress. At low doses, it increases myocardial contractility and peripheral vasodilatation (β_1 and β_2 effects). At higher doses, stimulation of α receptors causes peripheral vasoconstriction and increased systemic vascular resistance.

Noradrenaline is a catecholamine neurotransmitter released from peripheral adrenergic nerve endings. It is a potent vasopressor increasing heart rate, myocardial contractility and systemic vascular resistance. Lack of β_2 effects distinguishes it from adrenaline.

Dopamine and adrenaline have similar α and β agonist activities, adrenaline being more potent. Hence contrary to popular belief, if dopamine is being ineffective in maintaining blood pressure at higher doses (≥15μg/kg/min), adrenaline should be added and dopamine slowly withdrawn. A 'rule of thumb' is if systolic pressure is low, use adrenaline; if diastolic pressure is low, use noradrenaline.

Side effects

Clinically important side effects include tachycardia, arrhythmias, worsening of V/Q mismatch, increased systemic and pulmonary vascular resistance (except dobutamine) and hyperglycaemia (adrenaline).

Dopexamine

Dopexamine is a synthetic catecholamine with strong β_2 activity and less pronounced β_1, α and dopaminergic activity. It is a positive inotrope increasing cardiac output by decreasing systemic and pulmonary vascular resistance. There may be some gut protective effect either by increased splanchnic blood flow or redistribution of gut flow to the mucosa (the main site of oxygen use in the gut). It may have a role in acute surgical conditions in the neonate[19, 20].

Phosphodiesterase inhibitors/milrinone

The phosphodiesterase (PDE) inhibitors are a class of drugs called bibyridines that mediate both inotropy and vasodilatation and hence are often referred to as inodilators. These agents mediate their effect by preventing hydrolysis of cAMP (type III PDE inhibitors e.g. milrinone, enoximone, amrinone) or cGMP (type V PDE inhibitors, e.g. sildenafil, dipyridamole).

Milrinone was first developed in 1981. It increases the cAMP concentrations that improve myocardial contractility and also decreases systemic and pulmonary vascular resistance resulting in decreased ventricular afterload. Unique to this class of agents, milrinone also aids in diastolic relaxation of the ventricles ('lusitropy'). It increases pulmonary artery blood flow. Milrinone has an inotropy:vasodilatation ratio of 1:20. When used in combination with β agonists, milrinone has an additive effect. Thus it is often administered as part of combination therapy with adrenaline and noradrenaline.

Milrinone is primarily bound to plasma proteins (~75%) and excreted through the kidneys. It has a long half-life. Due to the large volume of distribution, a loading dose should be used. In a recent randomised controlled trial, milrinone did not prevent low systemic blood flow during the first 24 hours in very preterm infants[21].

Steroids

The sick neonate may suffer from relative or absolute adrenocortical insufficiency[22]. Glucocorticoids are involved in regulating the expression of cardiovascular adrenergic receptors. Sick neonates may be unable to produce adequate amounts of endogenous glucocorticoids to maintain cardiovascular functional integrity. As a consequence there is a down regulation of adrenergic receptors and cardiovascular desensitisation to sympathomimetics. This results in vasopressor resistance. Steroids help maintain cardiovascular homeostasis by several other mechanisms[23].

Interestingly, adrenal insufficiency can present with low cardiac output and high systemic vascular resistance or high cardiac output and low systemic vascular resistance. As hydrocortisone has both glucocorticoid and mineralocorticoid effects, it is recommended to treat adrenal insufficiency.

Calcium

The pathophysiology of myocardial dysfunction includes decreased intracellular calcium. Ionised hypocalcaemia occurs due to parathyroid

ischaemia. Calcium is a vasoconstrictor and increases systemic vascular resistance and ventricular contraction even when the ionised calcium level is normal. Calcium does not increase myocardial oxygen demand. However, calcium is the final pathway to cell death and is important in reperfusion injury. Therefore in PICU calcium is only used as an inotrope if hypocalcaemia is present, to counteract the effects of raised potassium (following cardio-pulmonary bypass) or in emergency as a temporary measure.

The disadvantages of using calcium are that the effect is short lived (20-30 minutes) and continuous infusion cannot be used.

Vasopressin

Vasopressin is a naturally occurring hormone produced by the posterior pituitary. There are three types of vasopressin receptors: the V_1 receptors are expressed in vascular smooth muscles, with V_{1a} being present in all vessels, while V_{1b} are confined to the pituitary gland. The V_2 receptors mediate renal effects.

The proposed mechanism(s) of action are:

- release of calcium from sarcoplasmic reticulum
- potentiation of vasoconstrictive effects of noradrenaline
- inactivation of ATP-gated potassium channels
- inhibition of nitric oxide and atrial natriuretic peptide-induced cGMP production.

In shock, after initial elevation, serum vasopressin levels drop due to depletion of stores[24]. In this situation, a modest dose of vasopressin can usually resensitise the vessels to catecholamine (noradrenaline) raising blood pressure[25].

Terlipressin

Terlipressin is a synthetic analogue of vasopressin with a long half-life. It has a higher V_{1a}/V_2 receptor ratio and hence is more efficient than vasopressin for vasoconstriction[26].

Other agents

Several other agents have been used as rescue therapy. These are not inotropes, but by their actions, have an effect on myocardial contractility and systemic vascular resistance. Controlled trials are needed to evaluate their usefulness.

Methylene blue

In septic shock, excess synthesis of nitric oxide occurs through the activation of soluble guanylate cyclase and production of cyclic guanosine monophosphate. Methylene blue inhibits this activation[27]. A dose of 1mg/kg over an hour has been used.

Tri-iodothyronine

Tri-iodothyronine is an effective inotrope, which has been used to preserve cardiac function. A recent randomised controlled trial in neonates showed that use of tri-iodothyronine, as a post cardiac surgery inotrope, improved outcomes[28,29].

Naloxone

Naloxone has been reported anecdotally to lead to haemodynamic recovery in neonates[30]. Naloxone is a potent pure opioid antagonist. In severe septic shock there is release of the body's own endogenous opioids (β endorphins), which can reduce blood pressure and cardiac output. Naloxone counteracts this effect. A bolus dose at 0.1 to 0.3mg/kg has been tried[31]. However; the effect on concurrent opiod administration (e.g. morphine/fentanyl for analgesia) and precipitation of 'withdrawal symptoms' should be borne in mind.

Levosimendan

This class II drug has multiple actions. It increases myofilament calcium sensitivity, improves diastolic relaxation, causes vasodilatation, and does not increase myocardial oxygen consumption. At higher doses, it has a phosphodiesterase inhibitor effect. It is unaffected by the down regulation of β adrenergic receptors. It has a short half life (approximately one hour) and is completely metabolised. Infusions of 0.1-0.4 μg/kg/minute with a preceding bolus (6-24 μg/kg) have been used. Clearly this drug has a huge potential but there are no studies in neonates to confirm this.

Supporting measures

Despite the availability of sophisticated cardiovascular monitoring an intensivist obtains much information helpful for the assessment of cardiovascular status from careful and frequent observation and examination of the patient. Therefore, the most important principle should be *reassess, reassess, reassess.* This is especially true if escalation of treatment is required. This should, ideally be, supported by 2D echocardiography. A number of clinical, haematological, biochemical and monitoring parameters are available to help achieve this.

Respiratory support

Optimise the respiratory support to reduce the work of breathing. Avoid hypoxia and hypocarbia. High mean airway pressure and PEEP will increase intra-thoracic and intra-alveolar pressure and so hinder cardiac filling, resist pulmonary and capillary blood flow and reduce cardiac output. Treat air leaks (e.g. pneumothorax) promptly. Optimise the use of analgesics and sedatives (e.g. fentanyl and midazolam), which improve patient synchrony but can drop blood pressure. Procedures like suctioning of the airway, installation of surfactant and routine nursing care can affect blood pressure. Inadvertent movement of head/neck over the body can increase systemic vascular resistance and drop cardiac output[32]. Therefore the policy 'minimum handling' should be adopted.

Cardiac shunts

Intra-cardiac (persistent foramina ovale) and extra cardiac (patent ductus arteriosus [PDA]) shunts can significantly affect ventricular output. A significant PDA should be treated after consultation with a paediatric cardiologist.

Intensive care monitoring parameters

When looking at the monitoring parameters, it is vital to look at the trends.

Heart rate

Tachycardia may have a number of causes but can be a sign of hypovolaemia. Tachycardia may give insufficient time for effective diastolic ventricular filling. Similarly, sinus bradycardia will reduce cardiac output, as the immature heart has only a limited ability to increase stroke volume. Non-sinus arrhythmias may impair ventricular filling reducing cardiac output. A 12-lead ECG will help determine the rhythm.

CVP

A reliable CVP <3 indicates hypovolaemia and is likely to respond to fluid bolus[33]. Serial measurements of mixed venous saturations (normally >70%) can give an idea of tissue oxygen delivery, severity of shock and response to treatment[34]. Measurements of the arterial to venous oxygen content difference ($AVDO_2$) can

further help in assessing the adequacy of cardiac output. Normal values are less than 5mL O_2/100mL blood; values more than 25 suggest reduced cardiac output.

Urine output

Normally more than 20% of cardiac output goes to the kidneys. Hence oliguria (urine output <1mL/kg/hour) is an early sign of low cardiac output, reflecting impaired renal perfusion.

Perfusion

A prolonged capillary refill time (>3-5 seconds) or a widened central-peripheral temperature gap suggests hypoperfusion. However, ultrasound and near infrared spectroscopy data have shown that many of these parameters are relatively poor indicators of acute changes in organ blood flow in the sick neonate[35].

Haematology

Anaemia commonly compounds the problem of hypotension. Transfusion with adult haemoglobin shifts the oxygen dissociation curve to the right, makes more oxygen available to the tissue mitochondria due to higher haemoglobin content and also acts as a fluid bolus.

Biochemical markers

Persistent metabolic acidosis and a rising lactate (>2.5 mmol/L) on an arterial blood gas suggest hypoperfusion and anaerobic metabolism. Unfortunately, again, the correlation is poor[36]. Arterial pH less than 7.25 compromises myocardial function and causes catecholamine unresponsiveness. Administration of small doses of sodium bicarbonate to raise arterial pH above 7.25 and anion gap less than 16 should be carried out. Among others, an important side effect is hypercarbia which will need adjustment in minute ventilation. Hypocalcaemia (see above) and hypophosphataemia (shifts oxygen dissociation curve to left) must be corrected. Hyperglycaemia can occur secondary to stress, sepsis, TPN, steroids and inotropes (especially adrenaline therapy). It may induce osmotic diuresis and deplete intravascular volume. This should be treated with insulin. A combination of glucose and insulin has a further advantage of acting like an inotrope[37]. Addressing these small issues helps to further stabilise the blood pressure. However, the most important principle still remains to reassess at every step.

Conclusion

In summary, sustained stabilisation of the neonatal blood pressure is a difficult task that requires an individualised approach. In a normovolaemic newborn resistant to catecholamine, several other options are available to treat hypotension. Prospective, randomised controlled trials are urgently required to assess whether any of these interventions improve clinical outcomes.

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