Haemodynamic assessment and management of hypotension in the preterm

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ABSTRACT

The management of low blood flow states in premature neonates is fraught with many challenges. We remain over-reliant on regimented stepwise protocols that use mean blood pressure as a threshold for intervention to guide treatment, without giving due consideration to the underlying pathophysiology. The current available evidence does not reflect the need to concentrate on the unique pathophysiology of the preterm infant and thus leads to widespread misuse of vasoactive agents that often do not provide the desired clinical effect. Therefore, understanding the underlying pathophysiological underpinnings of haemodynamic compromise may better guide choice of agent and assess physiological response to the selected intervention.

INTRODUCTION

The management of low blood flow states in premature infants is complex. However, in the neonatal field, there remains a drive to oversimplify both the diagnosis of the condition and its treatment. We remain over-reliant on the mean blood pressure (BP) as a threshold for intervention, and we use regimented stepwise protocols to guide this intervention without giving due consideration to the underlying pathophysiology. This current approach is driven by the dearth of data and the lack of robust, well-conducted randomised controlled trials to guide management. The clinical trials on vasoactive agents to date are marred by small numbers, significant heterogeneity in the infants recruited, the agents used, the outcomes measured and the thresholds for intervention. If we are to ever provide an accurate, evidence-based approach to the management of low blood flow states, we need to reconsider how we design and run clinical trials, with more emphasis put on prerandomisation elucidation of the primary pathophysiological basis for hypotension, homogenisation of groups, careful consideration of which thresholds to initiate treatment at, and which agents to study.[1 2] In the interim, adopting a pathophysiology-based approach to identify the underlying aetiology of the low blood flow state, guide choice of agent and assess physiological response to the selected intervention should be undertaken.[3]

HAEMODYNAMICS IS MORE THAN A MEAN BP

Lack of evidence for using mean BP

The thresholds for consideration of a stable or compromised circulation are an ongoing challenge for neonatologists.[4] In preterm infants, there is a consistent association made between lower BP and short-term complications such as intraventricular haemorrhage (IVH) and necrotising enterocolitis (NEC), which are probably associated with poorer long-term outcomes (such as developmental delay). For example, the German Neonatal Network examined the lowest mean BP on day 1 following birth in almost 5000 preterm neonates <32 weeks' gestation and concluded that lower BP was associated with a higher risk of IVH. Furthermore, the neonates with the lowest BPs had a greater risk of severe IVH. On multivariate regression analysis, the group found that a mean BP less than the gestational age in the first 24 hours of life was a predictor for IVH, bronchopulmonary dysplasia and death.[5] However, it remains unproven whether low BP in neonates is causative of or merely correlative with these adverse outcomes.[6] In addition, there has never been any evidence supporting the premise that raising BP improves short-term or long-term outcomes. On the contrary, the use of antihypotensive therapy in premature infants in a regimented fashion is associated with an increased risk of death and neurodevelopmental impairment at 2 years of age, independent of early BP changes.[7]

Complexity of the cardiovascular system

The aim of treating hypotension and low blood flow states is to maintain cellular metabolism. This requires adequate cardiac output (CO) and a normal blood oxygen concentration to sustain end-organ perfusion and tissue oxygenation. Several studies have highlighted the importance of CO in predicting adverse outcomes. Superior vena cava (SVC) flow is suggested as a surrogate marker for CO in preterm infants,[8] with low SVC flow being associated with IVH and adverse neurodevelopmental outcomes.[9] Similarly, a low left ventricular (LV) output can be a precursor to the evolution of IVH in this population.[10] CO is determined by preload, afterload, myocardial contractility and heart rate.[6] Furthermore, preload, afterload and heart rate influence cardiac contractility, as described by the length–tension, force–velocity and force–frequency relationships, respectively. The length–tension relationship (also known as the Frank-Starling curve) describes the increased sarcomere length and tension resulting from an increase in preload. This, in turn, results in augmentation of the force of contraction. The force–velocity relationship describes the increase in contractility in the face of increasing afterload. However, there is a threshold beyond which contractility actually decreases with further increasing afterload (referred to as decoupling).[11] The force–frequency relationship describes

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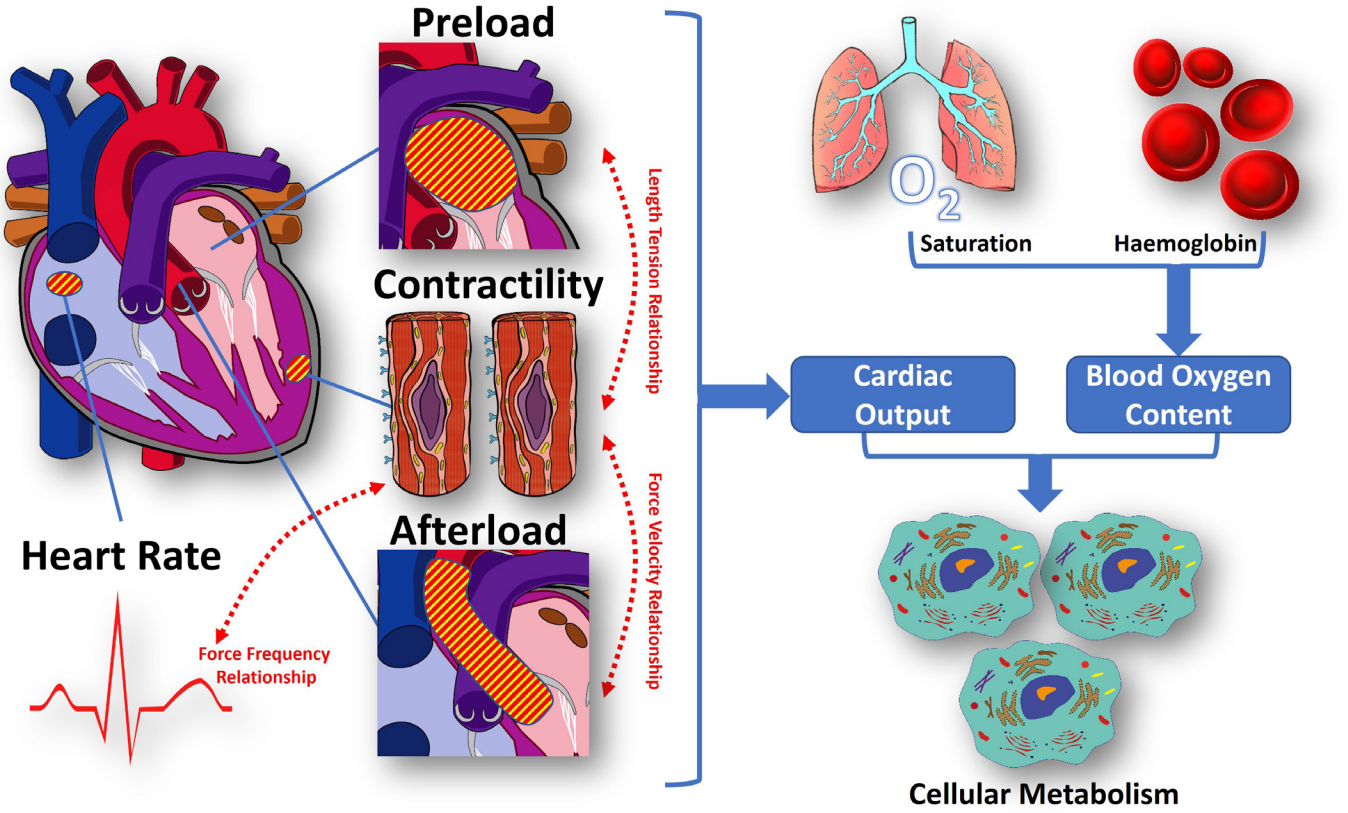


Figure 1 Cellular metabolism is the goal. CO is determined by preload, afterload, contractility and heart rate. CO and adequate blood oxygen concentration determine cellular metabolism. CO, cardiac output.

the increase in contractile force with increasing chronotropy (heart rate) in the presence of adequate preload[12] (figure 1).

PRETERM MYOCARDIUM IS UNIQUE

Adopting a physiology-based approach in managing low blood flow states in preterm infants dictates a thorough understanding of the unique properties of the cardiovascular system of premature infants. The premature myocardium has distinct developmental differences characterised by an immature and inefficient contractile apparatus, in addition to a lack of elastic compliant tissue and a preponderance of stiff fibres.[13 14] This results in a compromised length–tension relationship, where increased preload can result in a flattened response to increased volume and pulmonary venous congestion. An aberrant force–velocity relationship results in early decoupling and a fall in contractility in the face of high afterload accompanied by increased dilation of the ventricular cavity. A lack of adequate adrenergic innervation and paucity of receptors can also potentially compromise the force–frequency relationship. This can culminate in an absence of the expected inotropic effect of medications. There is reduced diastolic filling time in preterm neonates since more time is spent in systole than diastole; this is also coupled with a relatively longer isovolumic relation time compared with term infants despite a faster heart rate, reflecting the increased stiffness of the myocardium and further compromising filling time.[15 16] This can further contribute to pulmonary venous congestion.[15] Vasoactive agents have a predominant vasopressor effect in extremely low gestational age neonates (ELGANs). This is because of the greater proportion of α-1 receptors in peripheral vasculature and the concomitant paucity of β-1 receptors in the myocardium.[17] There is often little or no cardiac reserve in times of stress in ELGANs (eg, sepsis and NEC). This is due to an immature hypothalamic–pituitary axis,[18] which does not lead to the expected adrenergic stress response and upregulation of adrenergic receptors that are found in term neonates (figure 2).

BETTER APPROACH TO CHARACTERISING LOW BLOOD FLOW STATES

Utility of systolic and diastolic BPs

It is evident from the complexity described previously that relying on mean BP in isolation is fraught with challenges and should be abandoned as it can be misleading.[19] For example, a preterm infant at 30 weeks' gestation with a mean BP of 30 mm Hg may on the surface appear to have a stable cardiovascular assessment; however, a systolic BP of 32 mm Hg and a diastolic BP of 25 mm Hg reveals poor transition and acute pulmonary hypertension where the therapeutic approach would be afterload reduction and support of myocardial contractility. Another preterm infant of a similar gestation and mean BP might have a systolic BP of 40 mm Hg and a diastolic BP of 10 mm Hg, suggesting vasoactive shock, where the therapeutic approach would be increasing SVR and maintaining intravascular volume. Therefore, more attention should be paid to the systolic and diastolic readings when characterising circulatory stability or selecting a cardiovascular intervention. Normative population-based data for systolic arterial pressures are available[20 21] and should be referenced when attempting to diagnose low blood flow states. It is important to recognise that BP in the premature population is dynamic and generally increases over the first 24 hours and beyond until hospital discharge.[22 23] Therefore, using centile like reference charts for each gestational age bracket may be necessary in order

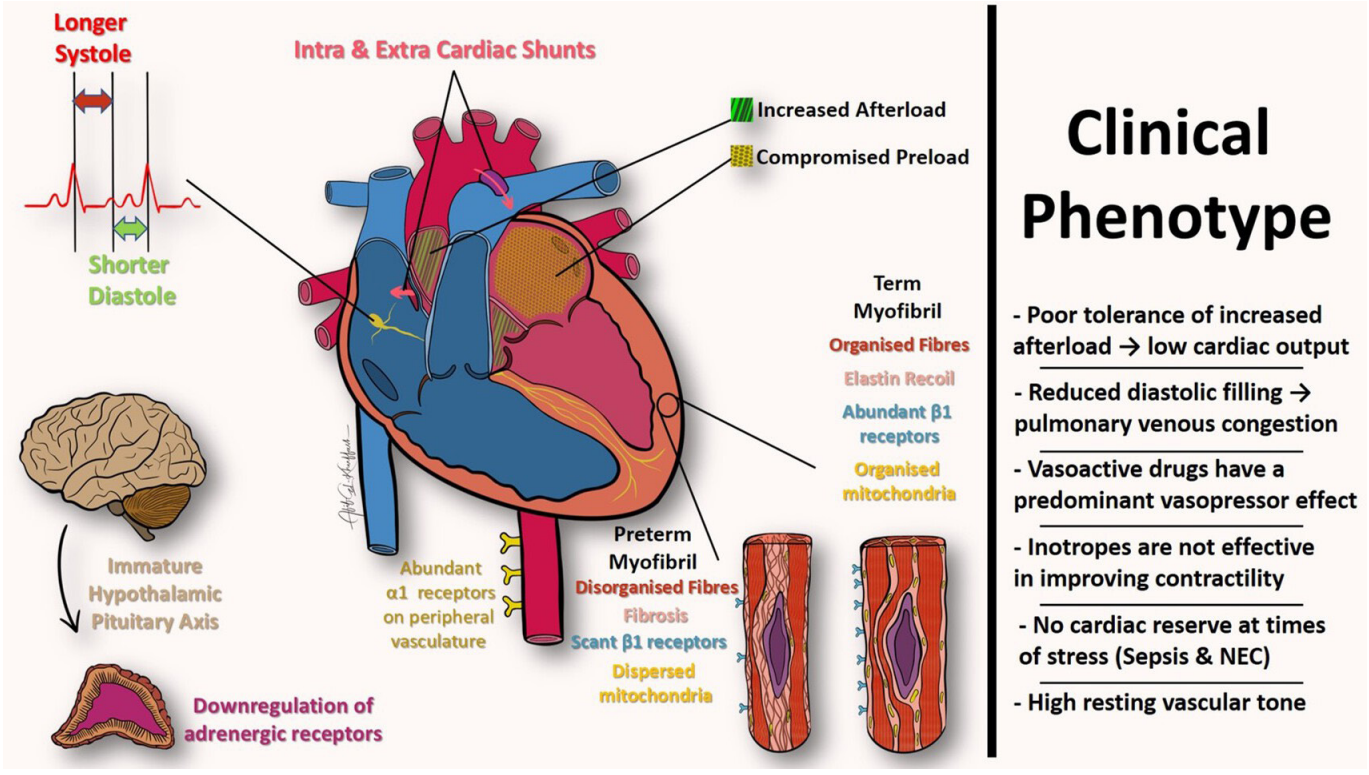


Figure 2 Premature pathophysiology is unique. Differences in the preterm and term myocardia and underlying pathophysiological processes lead to a unique clinical phenotype in the preterm neonate when the cardiovascular system becomes compromised. NEC, necrotising enterocolitis.

to more accurately diagnose hypotension. Systolic arterial pressure is a useful surrogate marker of myocardial contractile force and CO. A low value can indicate a diminishing stroke volume. Systolic BP is mainly determined by preload and contractility. Diastolic arterial pressure can be used as a surrogate marker for systemic vascular resistance (SVR) and represents the capacitance of the vessels in terms of their resistance and the force exerted by the blood inside the vessel walls. It is compromised in fluid loss, left-to-right shunts and capillary leakage due to vasodilatory shock. Combined systolic and diastolic hypotension is usually an end-stage phenomenon of a rapidly progressive condition.[1] Combining this rationale with the clinical scenario can often aid in the determination of the primary pathophysiological component (or a combination thereof) responsible for the low blood flow state. This may be due to compromised preload (requiring fluid resuscitation or restoration of adequate pulmonary blood flow), a raised afterload (requiring vasodilator and inotropic therapy), low afterload (requiring vasopressor support) or poor contractility (requiring inotropic support).

Use of echocardiography to support the assessment of low blood flow states

Echocardiography may further aid in deciphering the underlying reason for myocardial dysfunction and a low blood flow state. There are several excellent and thorough discussions available in the literature detailing the clinical utility of echocardiography in determining the underlying pathophysiology in low blood flow states. The reader is directed to these sources for a more in-depth appraisal.[24–28] Most echocardiography measurements of myocardial function are load dependent and, as such, are not direct measures of intrinsic contractility. Therefore, low values can be hard to interpret in isolation without clinical context. However, newer measurements, such as deformation (particularly strain rate measurements), are less influenced by loading conditions, and thus, low values of these markers may directly indicate poor contractility[12 29 30] (figure 3).

NOT ALL INOTROPES ARE INOTROPES

Vasoactive agents used in the neonatal field are often misunderstood and incorrectly collectively referred to as 'inotropes'. This misnomer, via the lack of accurate description of the effects of various inotropes, unfortunately supports a 'one-size-fits-all' approach to the management of low blood flow states in this population. Using the correct nomenclature and acknowledging that some vasoactive substances have multiple effects is the first step in understanding their mode of action. Primary inotropes (such as epinephrine, milrinone and dobutamine) are drugs that increase cardiac contractility and potentially CO. Primary vasopressors (such as norepinephrine, dopamine and vasopressin) induce vasoconstriction and raise diastolic and mean BPs. Lusitropic drugs (such as milrinone) promote myocardial relaxation, and chronotropic drugs (such as epinephrine and dobutamine) increase heart rate. The mechanism of action and clinical consideration of commonly used vasoactive agents are summarised in table 1.

WHEN SHOULD WE USE CORTICOSTEROIDS?

Preterm infants may have a relative cortisol deficiency secondary to the immature hypothalamic–pituitary axis and subsequent suboptimal response to stress.[31] They may be useful agents in refractive hypotension or when significant blood loss/asphyxia is likely to affect the perfusion of the adrenal glands.[32 33] Corticosteroids may act by increasing the sensitivity of adrenergic receptors to catecholamines, increasing catecholamine receptor expression, increasing the availability of cytosolic calcium in vascular smooth muscle and reducing the production of local

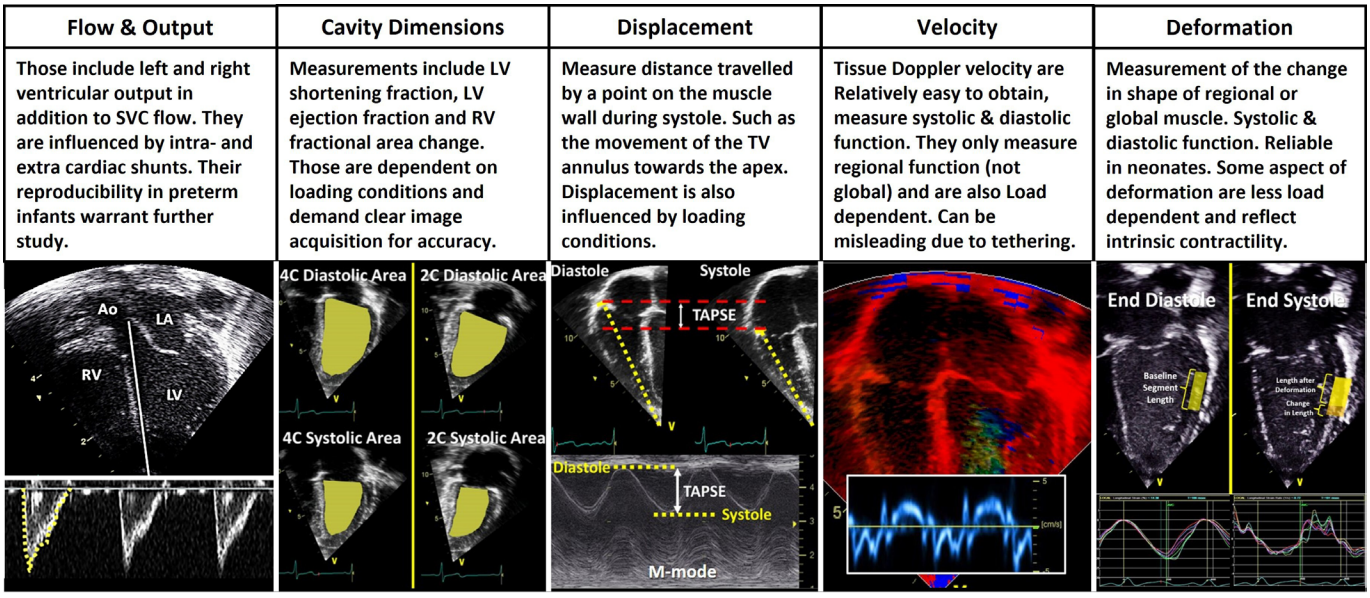


Figure 3 Echocardiography assessment of myocardial function. LV, left ventricular; RV, right ventricular; SVC, superior venacava; TV, tricuspid valve.

vasodilators such as nitric oxide and prostaglandins. Corticosteroids can also promote the release of vasoactive catecholamines (such as norepinephrine) from the adrenal glands. Despite their association with NEC and intestinal perforation, they can be considered following failure to respond to two inotropes or if there is evidence of adrenal insufficiency.

ROLE VOLUME EXPANSION IN LOW BLOOD FLOW STATES

The benefit of using crystalloids or colloids to treat hypotension has not been established. In hypotensive normovolumic neonates, volume expanders generally do not improve arterial pressure. They do, however, increase LV output in the short term.[34] Liberal administration of fluid is not recommended as there are no data to suggest benefit. Indeed, some data suggest a detrimental effect in preterm neonates with a higher incidence of patent ductus arteriosus (PDA), NEC and death.[35] The subpopulation of neonates that benefit from fluid resuscitation includes infants with vasoactive shock (sepsis and NEC) and infants with a history suggestive of blood loss, such as a large antepartum haemorrhage, placental abruption or a large IVH; packed red blood cells may be more appropriate in this group. In addition, volume support is recommended when considering an inodilator such as milrinone. There are inconsistent data regarding the use of colloids in the neonatal population; albumen is associated with risk of fluid retention and may impair gas exchange. However, it may be of benefit in cases of significant third spacing such as advanced NEC or sepsis.

CLINICAL SCENARIOS LEADING TO LOW BLOOD FLOW STATES

Clinical assessment and a recognition of the usual underlying pathophysiology associated with common clinical presentation can aid in devising a more tailored approach to management. There are many causes of neonatal hypotension and shock. Therapy must be specifically directed to the underlying cause. It is worth noting that more than one cause may be present at any one time (eg, placental blood loss *and* asphyxia) (figure 4).

A. *Transitional circulation and hypovolaemia*. The fall in preload following umbilical cord clamping (especially with immediate cord clamping) and the sudden increase in afterload create an unfavourable milieu for the preterm myocardium. CO is usually low in the early neonatal period. Diastolic BP is not usually low initially due to the high SVR. Hypovolaemia will result in depleted intravascular volume which usually manifests as a fall in diastolic BP. Causes include placental blood loss, fetomaternal haemorrhage, twin-to-twin transfusion syndrome, birth trauma, massive pulmonary haemorrhage and disseminated intravascular coagulation.

B. *PDA*. A haemodynamically significant PDA results in pulmonary overcirculation and systemic hypoperfusion. Flow across the PDA following the initial transitional period becomes left to right (systemic to pulmonary) as a result of falling pulmonary vascular resistance (PVR). There is increased pulmonary blood flow, increased pulmonary venous return, increased LV preload and increased LV output. This does not translate into improved systemic blood flow and classically presents as a low diastolic BP and a high/normal preductal systolic BP (resulting in a wide pulse pressure).[36] However, invasive measurements of BP using umbilical arterial catheters may reveal lower systolic and diastolic pressures as postductal systemic blood flow may be compromised.[37] Management strategies include elimination of the shunt (medical/surgical treatment) or a limitation in the velocity of the shunt by increasing PVR (permissive hypercapnia, increasing positive end-expiratory pressure). With chronic PDA exposure, LV dilatation may be accompanied by a reduction in systolic function; an inotropic agent with little or no effect on SVR, such as dobutamine, may be required.

C. *Postligation cardiac syndrome*. Following prolonged PDA exposure, the left ventricle is chronically exposed to left-to-right shunting and becomes dilated and reconditioned due to the chronically low afterload and increased preload. PDA ligation results in a sudden reversal of this physiological state to that of a high afterload and significantly reduced preload environment (due to the falling PVR). This can lead to progressive LV systolic dysfunction over the subsequent few hours following the procedure and is clinically manifested as oxygenation failure and systolic hypotension (with normal diastolic pressure). Pulmonary venous hypertension can also occur. This could be coupled with adrenal insufficiency,

Table 1 Vasoactive agents used in the neonatal intensive care unit

Agent	Mechanism of action	Clinical considerations
Predominant vasopressors		
Dopamine	It has mixed β-1 and α-adrenergic effects, in addition to its dopaminergic effects. Up to 25% of dopamine is converted to norepinephrine. It can have an unpredictable effect in premature infants. Due to the relative abundance of α-1 receptors in preterm infants, vasoconstrictive effects can occur at low levels, leading to increased SVR and PVR and potentially reducing CO and end-organ perfusion.[45]	Dopamine exhibits many extracardiac effects including impaired cerebral autoregulation[46] and pituitary suppression resulting in reduced levels of thyroid stimulation hormone and thyroxine in addition to prolactin.[47] Higher doses of dopamine may be associated with arrhythmias.[48] The use of dopamine should be reconsidered. Recent data suggest that dopamine is associated with increased mortality, neurological injury and morbidity including NEC.[49 50] This finding of increased mortality and morbidity is also observed in older children.[51]
Norepinephrine	A potent vasopressor as it has predominant α-1 effects and weaker β-1 effects. Norepinephrine will raise BP without and effective increase in CO. Norepinephrine may decrease PVR through α-2 stimulation and nitric oxide release. In term infants with acute pulmonary hypertension, norepinephrine can increase PVR but to a lesser ratio than SVR, with an associated improvement in pulmonary blood flow.[52]	It may be a useful agent to use in severe cases of vasodilatory shock associated with NEC and/or sepsis. Norepinephrine demonstrates favourable survival and postuse morbidity compared with dopamine in preterm infants with sepsis, and therefore, it may be the preferred first-line agent clinical scenarios of septic shock.[49]
Vasopressin	It exerts its effects through V1 receptors, resulting in an increase in SVR through phospholipid-mediated calcium release and a theoretical fall in PVR secondary to nitric oxide release.[53] Its antidiuretic properties are mediated through V2 receptors, found in the collecting ducts of the kidneys.	It has a potential role in the treatment of severe diastolic hypotension in infants with septic shock who do not respond to more traditional vasopressors and/or corticosteroids. Given its potential PVR-lowering properties, it may have a role in the treatment of pulmonary hypertension. The lack of chronotropic effects makes it an ideal choice in situations where maintaining vascular tone without an increase in heart rate is required. Clinical examples include severe septal hypertrophy secondary to gestational diabetes and hypertrophic obstructive cardiomyopathy.[27] It must be used with caution, as evidence of safety is currently lacking and there are reports that it may lead to oliguric renal failure or liver necrosis secondary to compromised splanchnic perfusion in some patients.[54]
Predominant inotropes		
Epinephrine	An endogenous catecholamine with β-1 effects at lower doses and α-adrenergic effects at higher doses, resulting in a combined inotropic and vasopressor effect Low-dose epinephrine may increase CO in neonates more effectively than dopamine. This is achieved through β-1 stimulation, which results in an increase in SV and heart rate.	Prolonged use may be associated with myocardial ischaemia and dysfunction as it increases myocardial oxygen demand. At higher doses, it is an effective vasopressor, raising both SVR and PVR through α-adrenergic stimulation. Epinephrine use in preterm infants is associated with a rise in lactate and blood glucose levels; this effect may be independent of dosing and duration and can be reversed with discontinuation of therapy.[55]
Dobutamine	A synthetic inotrope with predominant β-1-mediated increase in myocardial SV, heart rate and β-2 vascular vasodilatory action; it increases CO and reduces SVR. This could result in a marginal increase in BP.[56 57]	Due to the relative lack of expression of β-2 receptors in preterm vasculature, its vasodilatory effect is not generally seen in this population, although caution is still advised with higher doses. Dobutamine is considered in clinical situations of increased afterload and impaired myocardial contractility such as cold shock, asphyxia and pulmonary hypertension.
Inodilator		
Milrinone	Acts via phosphodiesterase III inhibition, thereby increasing the bioavailability of cyclic AMP; this leads to vasodilation in systemic and pulmonary vasculature in addition to inotropic and lusitropic myocardial effects.	In the literature, evidence of its use in neonates is limited to case series demonstrating an improvement in oxygenation when used in combination with inhaled nitric oxide in the setting of acute pulmonary hypertension.[58 59] Its lusitropic and potential inotropic properties make it an effective agent in the presence of right ventricular and left ventricular dysfunction in the setting of pulmonary hypertension. In addition, it has been used in preterm infants following patent ductus arteriosus ligation to prevent low CO states and subsequent respiratory deterioration.[60]

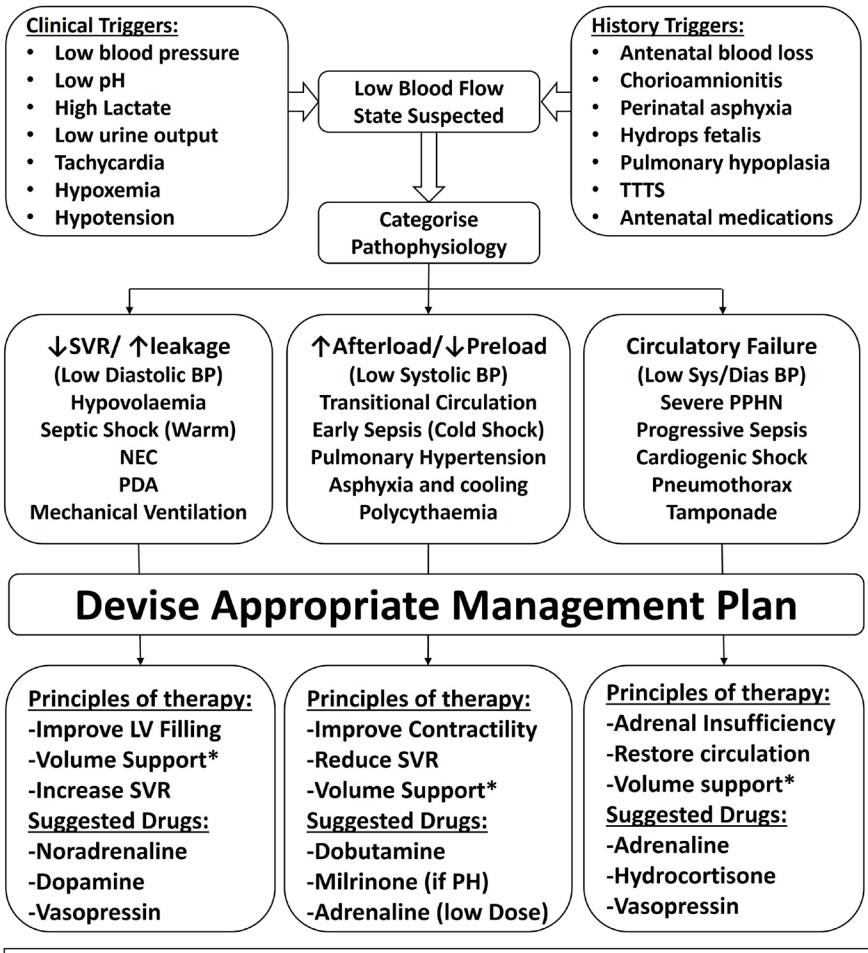
BP, blood pressure; CO, cardiac output; NEC, necrotising enterocolitis; PVR, pulmonary vascular resistance; SV, stroke volume; SVR, systemic vascular resistance.

which can compound the problem. Treatment strategies include afterload-reducing agents such as milrinone, inotropes such as dobutamine or low-dose epinephrine and the judicious use of corticosteroids.[38]

D. *Sepsis and NEC*. Sepsis and NEC result in an inflammatory response syndrome, causing peripheral vasodilation and capillary vessel bed leakage. This is mediated via excessive proinflammatory cytokine release and altered endothelial function. There is an initial compensatory increase in heart rate and a preponderance for the left ventricle to become hyperdynamic in an attempt to increase CO. This gives a clinical picture termed 'warm shock', which is characterised by a normal systolic BP and a low diastolic BP. This phase can be managed by cardiovascular agents with predominant vasopressor properties, such as norepinephrine. However, myocardial contractility can quickly deteriorate in the setting of sepsis that is coupled with an increase in SVR in an effort to divert blood to essential organs, termed 'cold shock'. This results in a fall in systolic BP. Cardiovascular agents that increase myocardial contractility and maintain vascular tone (such as epinephrine) are appropriate in this scenario. The use of corticosteroids for presumed adrenal insufficiency should also be considered here.

E. *Pulmonary hypertension*. Acute pulmonary hypertension in premature infants is an increasingly diagnosed condition with an estimated incidence of up to 10% in infants <34 weeks. It is associated with high mortality (up to 70%) and high degree of neurodisability (up to 80%) in survivors.[39] It is defined as the failure of the decline in PVR to a level sufficient to promote adequate pulmonary blood flow to ensure adequate oxygenation. Trials of prophylactic or early rescue (within the first two postnatal days) use of inhaled

Suggested Approach to Hypotension in Preterm Infants



Blood Pressure Reference Ranges

Gestation	Sys 3rd	Dias 3rd	Mean 3rd
24	32	15	26
25	34	16	26
26	36	17	27
27	38	17	27
28	40	18	28
29	42	19	28
30	43	20	29
31	45	20	30
32	46	21	30
33	47	22	30
34	48	23	31
35	49	24	32
36	50	25	32

Vasoactive Drugs Mode of Action

	SV	SVR	PVR
Adrenaline	↑↑↑	↑↑↑	↑↑
Noradrenaline	↑/≈	↑↑↑	↓/≈
Vasopressin	≈	↑↑↑	↓/≈
Dobutamine	↑↑	↓/≈	≈
Milrinone	↑↑	↓↓	↓↓
Dopamine	↑	↑↑	↑↑↑

SV = stroke volume; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance
↑ = increase; ↓ = decrease; ≈ = no effect

Practical Considerations:

- * Volume support should be considered in the presence of a history of blood loss and or the use of an inodilator agent
- Do not treat a single indicator of low blood flow state in isolation unless strong clinical evidence of an antenatal event
- Central intravenous access should ideally be obtained - some of the vasoactive medications can have cutaneous effects
- If central access is not achievable then a low lying UVC or a peripheral cannula can be used to restore circulatory integrity
- Ideally, invasive arterial access should be used to monitor blood pressure especially if there is no response to one agent
- Cuff BP should be interpreted with caution especially in very small infants
- Consider hydrocortisone if hypotension unresponsive to 2 therapeutic agents
- Early echo consult is advisable for severe hypotension / hypotension unresponsive to treatment / significant hypoxaemia
- Therapeutic algorithm may vary depending on pathophysiology as determined by echo consult (if available)

Figure 4 Suggested approach to hypotension in preterm infants. When a low blood flow state is suspected in the preterm infant, the underlying pathophysiology should be categorised. This can be divided into three broad categories: decreased preload, increased afterload or circulatory failure. An appropriate management plan should be devised in response to the categorised pathophysiological process. BP third centile reference ranges should be used to determine whether intervention or a pretreatment echocardiogram (if available) should be considered. Vasoactive agents should be chosen based on their modes of action in order to achieve the desired effect on the underlying categorised pathophysiological process. BP, blood pressure; Dias, diastolic; LV, left ventricular; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; Sys, systolic; TTTS, twin-to-twin transfusion syndrome; UVC, umbilical vascular catheter.

nitric oxide (iNO) to prevent chronic lung disease, mortality and improve long-term neurodevelopmental outcomes have yielded conflicting results. It must be remembered that these trials did not evaluate infants for presence of echocardiography confirmed pulmonary hypertension prior to trial inclusion. It is possible that many patients included in these trials had exclusive parenchymal lung disease, which for obvious reasons failed to respond to iNO. Hypoxaemic respiratory failure in preterm infants is multifactorial, and the use of echocardiography in this scenario could be beneficial in distinguishing arterial lung disease from parenchymal disease. The principles of management include treatment of the underlying condition, optimisation of lung aeration, addressing the underlying V:Q mismatch, and inducing pulmonary vasodilatation and preventing or reversing pulmonary vascular remodelling.[40 41]

F. *Other important considerations*. Cardiogenic shock can result in compromised contractility and a fall in systolic BP. If

left untreated, this will also lead to a fall in diastolic BP. Causes include asphyxia, arrhythmia, cardiomyopathy, myocarditis, pneumothorax and high mechanical ventilatory pressure. There may be associated hydrops fetalis antenatally. Drug-induced myocardial compromise should also be considered; for example, the use of opiates, vasodilator drugs prescribed for other indications (such as milrinone and prostaglandins) should be closely monitored. Recent evidence suggests that the maternal use of labetalol for pregnancy-induced hypertension may reduce LV performance at birth. The clinical implications of this phenomenon remain unstudied.[42] Endocrine disorders such as adrenal haemorrhage and adrenogenital syndromes result in BP instability and can lead to a fall in both systolic and diastolic BPs. Finally, congenital heart disease should always be considered, especially in clinical scenarios when conventional therapy does not result in the desired response.

FUTURE CONSIDERATIONS AND CONCLUSION

In this review, we offered an alternative pathophysiology-based approach to the management of low blood flow states in preterm infants while recognising the relative lack of evidence to support such approach. Going forward, we need to radically change how we assess the impact of various treatment strategies of low blood flow states in order to optimise outcomes in this vulnerable group of infants by considering alternative methods of investigation: cluster randomisation by centre, for example, facilitates comparing outcomes of centres using regimented protocols with centres adopting a pathophysiology-based approach; and the use of large registries, or the implementation of Standardised Clinical Assessment and Management Plans can also facilitate the gathering of large quantities of data to help in assessing various treatment approaches. This undertaking will require a huge deal of co-ordination, investment in echocardiography training (and all it entails[43 44]) and co-operation between centres. However, it would be a worthwhile undertaking if it means improving the management of the most vulnerable cohort in our society.

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