

REVIEW ARTICLE

Inotropes in preterm infants – evidence for and against

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ABSTRACT

There is significant uncertainty regarding the optimal circulatory management of preterm infants, with research in the field limited by the paucity of safe, reproducible biomarkers of circulatory function. This review discusses the physiology and pathophysiology of circulatory function in preterm infants, describes the mode of action and evidence for and against commonly used and recently trialled inotropic therapies and provides recommendations for managing circulatory dysfunction in the transitional period and in the context of sepsis/necrotizing enterocolitis. We recommend a pragmatic approach of assessing multiple aspects of circulatory function (blood pressure alone correlates weakly with volume of flow) in each infant, tailoring therapy on the basis of the change in function desired and frequently reassessing response to intervention.

INTRODUCTION

Recent decades have seen dramatic improvements in the survival of preterm infants (1). These improvements are likely to be due to a combination of factors, including improved obstetric care and antenatal steroid and postnatal surfactant use. However, clinical thinking as to optimal postnatal circulatory management remains at a stand still (2).

Arterial blood pressure remains the most commonly monitored circulatory marker, despite its variable association with volume of blood flow (3,4). Whilst additional clinical markers (4) and laboratory measures (notably serum lactate) do serve to guide care, variability in clinical circulatory management is extreme (5). A recent study of North American neonatal units demonstrated a ten-fold variability in inotrope use in extremely preterm infants, and this variability was more closely associated with local clinician preference rather than patient demographics or clinical condition (6). Similar variation is seen in doses of inotropes

used (5), and in rates of intervention to close a patent ductus arteriosus (7).

Does variability in inotropic intervention matter? Well possibly not, given that no trial of inotropic intervention has ever shown benefit on clinically significant outcomes (8–10). However, circulatory failure appears to be particularly damaging during two critical periods in the preterm infant:

During the circulatory transition to extra-uterine life

In the first 24–48 h after birth, dramatic changes occur in preload conditions, myocardial contractility and systemic and pulmonary vascular resistance (11). There is evidence that episodes of low systemic flow occur in this time period (12) and are associated with intracranial haemorrhage (12), white matter injury (13) and adverse neurodevelopmental outcome (14).

During episodes of sepsis or necrotising enterocolitis (NEC)

In these circumstances, infants have clear evidence of circulatory failure and microvascular dysfunction, often presenting with low blood pressure and high cardiac output; though, low preload and decreased contractility may also lead to subsequent low output failure (15). Both sepsis and NEC are independently associated with adverse neurodevelopmental outcome (16), and whilst these also have an inflammatory causation, circulatory failure is the final cause of death in these infants.

The shortcomings of current circulatory support have been highlighted, and increased research has been called for (2). Whilst awaiting definitive evidence from clinical trials, it is our view that effective treatment of individual patients requires an understanding of the pathophysiology of circulatory failure when it is present, and tailoring of therapy to

Key Notes

The pathophysiology of preterm circulatory dysfunction in the transitional period is different from that encountered in sepsis/NEC. Further research is required to guide optimal circulatory management in different scenarios.

We recommend a pragmatic approach of assessing multiple aspects of circulatory function (blood pressure alone correlates weakly with volume of flow) in each infant, tailoring therapy on the basis of the change in function desired and frequently reassessing response to intervention.

achieve specific results, with frequent reassessments to see whether the chosen intervention has delivered the expected response.

CIRCULATORY PHYSIOLOGY

Circulatory function is governed by three principal factors: preload, contractility and afterload.

Preload

Represents the ventricular volume at end-diastole and is dependent upon the circulating volume and venous return. The relationship between cardiac preload and stroke volume is depicted by the Frank–Starling curve (Fig. 1). Until the top of this curve is reached, increased myocardial distension as a result of increased ventricular filling creates increased stroke volume. This effect is likely produced both by increased overlap between myosin and actin filaments and by increased stretch of sarcomeric titin molecules. Inotropes exert their influence on preload primarily by inducing constriction in peripheral venous capacitance vessels.

Contractility

(Inotropy) is what is most often thought of as cardiac function – the inherent strength of contraction of the cardiac musculature. Changes in myocardial inotropy are mediated through changes in intracellular calcium concentration. The sympathetic nervous system is the primary controller of calcium flux within the myocyte, though parasympathetic inhibition, heart rate, afterload and circulating catecholamines also play a role. Inotropic therapies aim to increase myocardial contractility by acting as agonists for the myocardial $\alpha 1$ and $\beta 1$ receptors – shifting the Frank–Starling curve up and to the left, producing a greater stroke volume for a constant end-diastolic volume (Fig. 1).

Afterload

Is the resistance that the heart must pump against and is dependent primarily on vascular tone in peripheral arterioles. Vascular tone is controlled through innate

mechanisms such as adrenergic receptors and levels of circulating prostaglandins and is again mediated through changes in intracellular calcium concentration. Agonists act upon $\alpha 1$ and $\alpha 2$ receptors in the peripheral vasculature causing increased peripheral vasoconstriction leading to a raised systemic vascular resistance. The increased afterload shifts the Frank–Starling curve down and to the right, reducing the stroke volume for any given end-diastolic pressure; the detrimental effects of an increased afterload may be partially offset by the conferred change in preload (17,18).

The role of sympathetic innervation and receptors is central to control of these key physiological parameters. A simplified summary of receptor types, locations and effects is given in Table 1.

The fact that adrenergic stimulation is responsible for increasing both cardiac inotropy and peripheral resistance may produce conflicting effects on flow volume. Increasing inotropy shifts the Frank–Starling curve up and to the left, increasing vascular resistance shifts the Frank–Starling curve down and to the right. Which factor wins this circulatory ‘tug-of-war’ will depend on each individual’s balance of cardiac and peripheral vascular receptors, the relative impact of an intervention on the different adrenergic receptor subtypes and potentially on the dose of inotrope used. A simplified summary of the mechanism of action of commonly used inotropes on adrenergic receptor subtypes is given in Table 2 (19).

The unique nature of the newborn preterm circulation

Numerous developmental factors mean that the circulatory physiology in the preterm infant is distinct from that seen at any other time (Table 3); though, it should be acknowledged that most data in this area are derived from animal rather than human studies and that there is considerable inter-species variation in circulatory development (20).

In addition to preload, contractility and afterload, the preterm circulation shows distinct heart rate patterns (high resting heart rate that may have a limited ability to increase cardiac output) and foetal shunt patterns (shunting through both the patent foramen ovale and patent ductus arteriosus) can be of high volume, even in the transitional period (21,22).

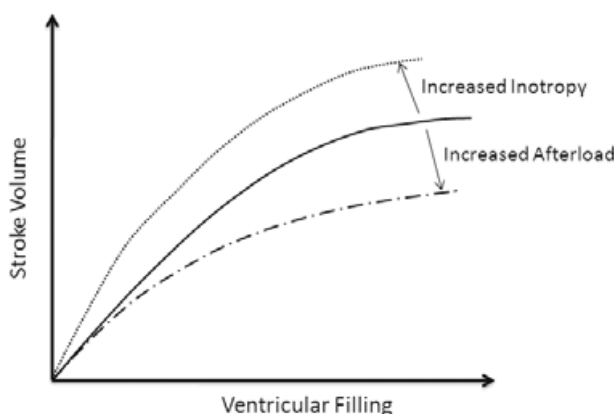


Figure 1 Frank–Starling curve showing effect of Increased Inotropy versus Increased Afterload on Stroke Volume.

Table 1 Table showing an overview of catecholamine receptor location and principal function

Receptor	Location	Action	Effect
$\alpha 1$	Myocardium	\uparrow Inotropy	\uparrow Contractility
$\alpha 1$	Peripheral vasculature	\uparrow Vasoconstriction	\uparrow Afterload (\uparrow Preload)
$\alpha 2$	Peripheral vasculature	\uparrow Vasoconstriction	\uparrow Afterload (\uparrow Preload)
$\beta 1$	Myocardium	\uparrow Inotropy	\uparrow Contractility
$\beta 2$	Peripheral vasculature	\downarrow Vasoconstriction	\downarrow Afterload (\downarrow Preload)

Table 2 The circulatory effects of commonly used inotropes adapted from Seri et al. *Semin Neonatal* 2001; 6, 85–95¹⁹

Agent	Cardiovascular adrenergic and dopaminergic receptors					
	Cardiac receptors			Peripheral vascular receptors		
	$\alpha 1$	B1 ($\beta 2$)	Dopamine	$\alpha 1/\alpha 2$	B2	Dopamine
	↑Contractility	↑Rate ↑Conduction ↑Contractility	↑Contractility	Peripheral vasoconstriction	Peripheral vasodilation	Vasodilation (?renal and mesenteric specific)
Dopamine	++	++++	+	++++	+	++++
Dobutamine	++	++++		+	++	
Adrenaline	++	++++		++++	+++	
Noradrenaline	++	++++		++++	+	

Table 3 Physiological effects of specific features of the preterm neonatal circulation

Preload	Contractility	Afterload
Risk of low circulating volume (early cord clamping, blood sampling)	Fewer myofibrils	Loss of low resistance placental circulation
Altered myocardial collagen balance	Altered sarcoplasmic reticulum/mitochondrial function	Increased peripheral alpha receptors
Altered titin subtypes	Risk of hypocalcaemia	Decreased peripheral beta receptors
High heart rate	Decreased adrenergic receptors	Increased pulmonary vascular resistance, mechanical ventilation
Low % of cardiac cycle spent in diastole	Decreased adrenergic innervation	

As in all other age groups inotropic therapies aim to increase myocardial contractility by acting as agonists for myocardial $\alpha 1$ and $\beta 1$ receptors. However, as shown in Table 2, preterm infants may have decreased cardiac adrenergic receptors and innervation, meaning that these infants may have an impaired response to inotropic intervention (11). In addition, preterm infants may have fewer mitochondria, decreased energy stores, immature sarcoplasmic reticular function and relatively increased myocardial connective tissue. All these aspects may impair inherent contractility in preterm infants (23) and response to inotropic intervention (24).

Resting peripheral vascular tone may also be high in the newborn preterm infant (11). Premature infants are likely to have increased peripheral alpha (constrictive) receptors and decreased peripheral beta (dilatory) receptors (20). There is also evidence that the premature myocardium has increased sensitivity to afterload such that contractility falls rapidly in the face of high resistance (23) – potentially because the premature left ventricle is conditioned to pump primarily to the low resistance placental circulation, a circulation which is removed at the instant of cord clamping.

The balance between inotropy and vasopression may be skewed in newborn premature infants, and interventions have the scope to increase resistance more than inotropy, potentially impairing volume of blood flow.

MARKERS OF CIRCULATORY FUNCTION

Producing definite evidence of the impact of inotropic interventions in individual infants or in clinical trials is

hampered by the lack of robust, repeatable non-invasive circulatory biomarkers in the newborn.

Systemic arterial blood pressure, the most commonly used surrogate of circulatory health is, in fact, a product of systemic blood flow and systemic vascular resistance. Particularly, during the transitional circulation, arterial blood pressure has repeatedly been shown to have minimal predictive value for low systemic perfusion (4) or low cerebral blood flow (25). Some studies have even suggested an inverse correlation between blood pressure and systemic blood flow during the transitional circulation (3), perhaps suggesting that vascular resistance is a greater determinant of blood pressure than volume of flow in this time period. In addition, changes in blood pressure in response to an intervention cannot determine whether the changes are because of changes in flow or resistance. Other clinical markers such as color, activity, capillary refill time, urine output and serum lactate level should clearly be used as part of a comprehensive clinical circulatory assessment, but all have significant limitations.

Outside the transitional circulation detecting circulatory failure is more straightforward. The most common pattern seen is of an ex-preterm infant becoming unwell with sepsis or NEC. These infants will develop lethargy, tachycardia, slow capillary refill time, decreased urine output and increasing lactate, all of which suggest significant circulatory compromise. In contrast to its limited predictive value in the transitional period, in these infants, a new drop in blood pressure is a very worrying sign.

A number of research tools have been employed to enhance understanding of circulatory function in the pre-term newborn. Echocardiography can provide indicators of cardiac filling, contractility and output (26). Because cardiac output does not equate to volume of systemic perfusion when the fetal shunt pathways are open, alternative measures such as volume of superior vena caval flow have been developed (27). These echo measures have clearly advanced understanding in the newborn, though all show limited repeatability (28). Near infra-red spectroscopy (NIRS) has also demonstrated changes in cerebral blood flow in pre-term infants, though again repeatability of the technique is limited (29).

EVIDENCE FOR AND AGAINST THE COMMONLY USED INTERVENTIONS

Fluid resuscitation

Fluid resuscitation remains the first step in management of hypotension or circulatory failure in many centres (19). Neonates are believed to rarely reach the top of the Frank-Starling curve, such that a bolus of intravenous fluid should produce an increase in cardiac output (irrespective of whether low preload was the initial cause of hypotension/circulatory failure). An infusion of 10 mL/kg of normal saline appears effective at raising cardiac output and blood pressure (30), though the duration of effect is not known. In determining how much and how often to use fluid boluses, the clinician should seek evidence of fluid loss (history of placental abruption) or maldistribution (sepsis/NEC). A systematic review of routine early volume expansion in the preterm infant showed no improvements in long-term outcome, morbidity or mortality (31).

The scenario of sepsis/NEC is worthy of particular focus. Functional circulating volume is often critically low in these infants because of peripheral vasodilatation and third spacing of fluid within the abdomen. Decreased preload should always be suspected in infants with sepsis/NEC, and further evidence for this may come from echocardiography (decreased filling in the inferior vena cava and cardiac chambers) or rapid response to fluid resuscitation. Studies in septic adults and children, especially those incorporating goal-directed therapy, suggest that aggressive fluid resuscitation improves survival (32). In our view, infants with sepsis/NEC outside the transitional period are generally undertreated in terms of volume resuscitation, though this opinion is not evidence based.

There is no evidence to support the use of either crystalloid or colloid above the other, and several studies have suggested that whichever fluid is used for volume expansion rapidly redistributes out of the vascular compartment (19). The exception to this would be with a history of blood loss, where a like-for-like replacement with packed red cell transfusion seems rational (19).

Dopamine

Dopamine is the most commonly used neonatal inotrope (33); it is the precursor of adrenaline and noradrenaline and

occurs naturally in the body. It consistently increases systemic arterial blood pressure (27). It is thought to exert its effect in neonates via dopaminergic, α_1 and α_2 , β_1 and β_2 receptors occurring in the myocardium and peripheral vasculature (Table 2). Stimulating all these receptors leads to an increase in preload, contractility and afterload, but in the premature infant peripheral α_1/α_2 effects may dominate resulting in marked peripheral vasoconstriction and a dominant increase in afterload. The balance between inotropy and vasopression is difficult to judge, however, both Roze et al. (34) and Osborn et al. (30) looked at the effects of different concentrations of dopamine infusion on measures of flow. Using dopamine infusions varying from 10 to 20 mcg/kg per min a significant rise in systemic arterial blood pressure was noted but without any significant change in cardiac output or superior vena cava (SVC) flow. The study by Roze et al. (34) included a crossover arm for infants who failed to increase blood pressure in response to dobutamine – infants switched to dopamine had significant increases in blood pressure and systemic vascular resistance but no change (and indeed a trend to a decrease) in left ventricular output.

With this evidence in mind, it is perhaps best to consider dopamine primarily as a vasopressor rather than an inotrope. However, one critical uncertainty persists – whether dopamine has a differential effect on the cerebral circulation. Aiming to establish a relationship between dopamine and cerebral blood flow Seri (35), Zhang (36) and Osborn (30) noted no significant responses in middle cerebral artery pulsatility index, anterior cerebral artery velocity or SVC flow, respectively, to dopamine infusions of 2.5–10 mcg/kg per min. However, Munro et al. (37) have used NIRS to demonstrate a rise in cerebral blood flow paired with a rise in systemic arterial pressure in infants commencing dopamine infusion. The debate over the impact of dopamine on cerebral perfusion is likely to go unresolved for some time as reliable markers of neonatal cerebral blood flow are lacking.

Some experts are currently advocating 'permissive hypotension' in preterm infants in the transitional period (38) – tolerating low blood pressure levels if there are no other signs of poor perfusion; others suggest maintaining mean arterial blood pressure above the gestational age in weeks, or even higher to support a potentially pressure-passive cerebral circulation (39).

Our current view is that the association between arterial blood pressure and cerebral perfusion is weak, that no clinical study has shown an improvement in long-term outcome with dopamine and that dopamine clearance in preterm infants is impaired giving significantly higher plasma levels even at infusion rates of 2–4 mcg/kg per min (35). Therefore, we do not automatically treat borderline low blood pressure in a stable preterm infant in the transitional period and always look for other markers of circulatory failure. If intervening to raise blood pressure, we regard dopamine primarily as a vasopressor, and start with a low dose titrating up depending on response. Further studies to assess the impact of dopamine on

cerebral blood flow should be a research priority in preterm infants.

Dobutamine

Dobutamine is a synthetic isoprenaline analogue which acts upon cardiac and peripheral α_1 , α_2 , β_1 and β_2 receptors but not dopaminergic receptors. In the peripheral vasculature, the vasodilatory β_2 effects are thought to outweigh vasoconstrictive α receptor stimulation, meaning that dobutamine may be both inotropic and vasodilatory. Roze (34) and Osborn (30) looked at changes in flow volumes pre- and post-dobutamine infusions ranging from 10 to 20 mcg/kg per min; they noted that although there were minimal changes in right ventricular output and modest changes in blood pressure, both the left ventricular output and SVC flow volumes increased significantly. An observational study using a dopamine infusion of 10 mcg/kg per min in 20 infants with evidence of circulatory failure also suggested a rise in left ventricular output (40).

Acknowledging that only a limited number of studies have been carried out, dobutamine appears primarily to be an inotropic agent, with little or no vasopressive effect in the preterm newborn.

Adrenaline and noradrenaline

Adrenaline and noradrenaline have not been extensively studied in the neonatal population. Adrenaline is fairly non-selective for all adrenergic receptor subtypes, but as preterm neonates are believed to have fewer peripheral β receptors than α receptors, adrenaline may have a predominant vasopressive effect, as seen with dopamine. Indeed, in preterm infants, adrenaline has very similar effects on blood pressure and cerebral perfusion to dopamine (41), though more study is required. Given that adrenaline increases neonatal lactate concentrations, it will be important to study its impact on both gluconeogenesis and tissue perfusion. Noradrenaline is noted to affect peripheral vascular β receptors less than α receptors and thus is likely to have an even more potent vasopressive effect. It has not been studied in the preterm population.

Given the lack of current evidence for their use in the preterm neonate, most centres only consider their use as 3rd or 4th line agents in resistant neonatal hypotension, but both are ripe for further study.

Milrinone

Milrinone is a selective phosphodiesterase III inhibitor that raises intracellular cAMP levels. Its predominant use in paediatric practice is in the maintenance of cardiac output post-cardiac surgery, where it shows inotropic and vasodilatory effects (42). However, in preterm infants, a randomized placebo-controlled trial of prophylactic milrinone did not improve cardiac output or SVC flow (43). Milrinone appeared to slow the constriction of the ductus arteriosus and this may have counterbalanced any potential positive effects on the systemic circulation. Whilst the dose used may have been lower than ideal, this study does not

currently support the use of milrinone as a prophylactic vasodilating inotrope in the preterm population.

Hydrocortisone

There is considerable evidence that some preterm infants experience vasopressor resistant shock because of a combination of transient adrenocortical insufficiency and down-regulation of cardiovascular adrenergic receptors (19). Hydrocortisone has been conclusively shown to have a vasopressive and inotrope-sparing effect in preterm infants, both in prophylactic and rescue modes (44), and it can produce an effect within 2–4 h of administration, but despite this its use remains particularly varied across neonatal units.

Residual concerns exist that it may raise blood pressure primarily through vasopression rather than inotropy; though, it has not been shown to decrease cardiac output. In addition, the side effect profile is worthy of note. There is some association between hydrocortisone use and spontaneous ileal perforation when co-administered with indomethacin (45).

In addition, there is appropriate concern over the potential for corticosteroids to cause neurodevelopmental handicap, although these concerns apply more to dexamethasone than hydrocortisone, and recent data examining the impact of hydrocortisone on brain growth (46) and neurodevelopmental outcome (47) appear reassuring.

Our current view is that hydrocortisone should remain as a treatment for refractory circulatory failure (inadequate cardiac output and systemic perfusion despite attempts at expanding circulating volume and the use of high infusion rates of first and second line inotropes) in critically ill preterm infants.

A PRAGMATIC APPROACH

Further research is clearly required to examine the basis of circulatory failure in preterm infants, improve cotside identification of circulatory failure and demonstrate the short-term effects of interventions including dose-dependency and cerebral-specific effects. Following this, studies powered to detect an improvement in neuro developmental outcome are required. Whilst this data are awaited, we would suggest a pragmatic approach to circulatory support in the preterm infant, bearing in mind the knowledge gaps that remain.

In all cases, a comprehensive circulatory assessment should include accurate history taking, clinical examination and cotside identification of circulatory failure. The components of the circulation, which are deemed to be failing, should be identified, and interventions should be targeted towards these.

In the transitional circulation, fluid resuscitation should be used judiciously, unless there is a history of fluid/blood loss. We would suggest being wary of the limited association between blood pressure and flow, whilst bearing in mind that improving blood pressure may specifically improve cerebral blood flow. If instituting dopamine to increase

blood pressure, we would suggest starting with a low dose and titrating cautiously to the response.

In broad terms, we consider dopamine to be primarily vasopressive, dobutamine to be primarily inotropic.

In circulatory failure secondary to sepsis/NEC, occurring after the transitional period, our opinion would be to mimic the adult and paediatric septic models, with early aggressive fluid resuscitation with 0.9% saline, combined with adequate ventilatory support. We would suggest considering use a vasopressor such as dopamine as first line therapy, but with early consideration of adding dobutamine to augment cardiac inotropy.

Use of adrenaline, noradrenaline and hydrocortisone should probably be reserved to infants who do not respond to these initial measures.

In all cases, we suggest frequent review of circulatory status to assess response to intervention and allow further tailoring of therapy.

CONCLUSIONS

Whilst inotrope infusions are widely used in the preterm population, their benefit in reducing long-term morbidity and mortality is unproven. Current clinical trials are limited by the use of suboptimal biomarker end-points. Whilst a more robust evidence base is awaited, we would suggest that circulatory intervention be considered in each individual infant on their own merits, that no one definite cut-off of blood pressure or other measure should dictate intervention and that therapy should be tailored to produce specific goals depending on the pathophysiology of the underlying circulatory failure.

CONFLICTS OF INTEREST

The author has declared no potential conflicts.

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