# What Inotrope and Why?

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**KEYWORDS**

• Hypotension • Cardiovascular compromise • Inotrope • Newborn

**KEY POINTS**

- There are significant gaps in the knowledge about diagnostic thresholds and choices of therapeutic interventions that can improve morbidity and mortality in neonates with cardiovascular compromise.
- Current use of inotropes in neonates is largely based on the pathophysiology of cardiovascular impairment and anticipated actions of inotropes because of limited outcome data from randomized controlled trials.
- Research studies of alternative study design unraveling the linkage of cardiovascular impairment and use of inotropes with important clinical outcomes are needed for future progress.

## INTRODUCTION

The primary function of the cardiovascular system is to meet oxygen and nutritional demands of organs under various physiologic and pathologic conditions.[1] To achieve this, the heart contracts against vascular resistance and drives blood to the lungs for oxygenation and into the systemic circulation for organ perfusion. The force of cardiac contraction, ventricular end-diastolic blood volume, and perfusion pressure are the main determinants of cardiovascular performance through an interplay between cardiac output (CO), vascular resistance, and neuroendocrine mechanisms.[2] In neonates, the physiology of blood circulation can get disrupted in many clinical conditions, resulting in impaired organ perfusion and hypoxia. Persistent circulatory compromise can lead to derangement of metabolism, acidosis, organ dysfunction, and eventually adverse outcomes.[3,4] Several clinical and biochemical parameters are used to determine cardiovascular stability and recognize circulatory compromise.[5,6] Functional echocardiography and near-infrared spectroscopy (NIRS)–derived data have significantly improved the understanding of central and regional circulation as well as the need and choice of cardiovascular therapy.[7–9] The primary objective of cardiovascular therapy is to optimize clinical outcomes by improving organ perfusion. With the current

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therapeutic options and knowledge of cardiovascular physiology, neonatal hemodynamic disturbances can be effectively addressed in most instances. However, the lack of significant improvement in clinical outcomes highlights major gaps in the understanding of an accurate and reliable assessment of adequacy of organ perfusion, precise thresholds, and choices of therapeutic interventions for cardiovascular compromise.

This article presents an overview of common neonatal hemodynamic disturbances, merits and shortcomings of the circulatory parameters that guide cardiovascular therapy, and medications commonly used to support the cardiovascular system and achieve the desired therapeutic end points. Although not accurate, in this article the term inotrope is used for medications that alter myocardial contractility, relaxation, heart rate, and/or vascular tone.

## HEMODYNAMIC ASSESSMENT

### *Blood Pressure*

Even though an evidence-based definition of threshold for intervention is lacking, blood pressure (BP) remains one of the most common triggers for cardiovascular therapy in neonates.[6,10] BP acts as a driving force for blood flow. Just as an increase in vascular resistance can also increase BP, the utility of low BP as an indicator of reduced blood flow becomes limited. Research shows poor correlation of BP with CO, systemic blood flow, and organ perfusion in neonates.[11,12] Similarly, cerebral oxygenation does not correlate consistently with BP when the cerebral circulation is in the autoregulatory zone.[13–15]

### *Skin Perfusion and Urine Output*

When there is a gap between oxygen demand and supply, the body prioritizes perfusion of vital organs, which results in reduction of distal capillary flow in less vital organs.[16] Poor skin perfusion and urine output are, therefore, hypothesized to be early indicators of circulatory compromise. However, skin capillary refill time is unreliable for recognizing low systemic blood flow in preterm neonates.[17] The utility of urine output is also limited in neonates because of physiologic oliguria in first 24 to 48 hours, restricted ability of renal tubules to concentrate urine in response to intravascular volume changes, and technical difficulties in accurate measurement of urine output.[18]

### *Perfusion Index*

The perfusion index (PI) is the ratio of pulsatile signal from arterial blood flow and nonpulsatile signal from venous blood flow, skin, and other local tissues. The PI depends on the infant's gestation and postnatal age and it correlates with central blood flow, severity of clinical disease, and outcomes in neonates.[19–21] However, there is no consensus about how to use PI for therapeutic decision making in neonates.

### *Cardiac Ultrasonography*

CO is an important determinant of oxygen delivery and the authors therefore think that it should be monitored regularly in sick neonates. In preterm neonates, the use of left or right ventricular output as an indicator of systemic blood flow may not be accurate because of left-to-right shunts across the patent ductus arteriosus (PDA) and foramen ovale. Therefore, measurement of superior vena cava (SVC) flow, which reflects cerebral blood flow, is used as a surrogate for systemic blood flow.[22] One of the main limitations of blood flow measurements is that it does not represent myocardial or vascular function independently but the result of interaction between the two. Myocardial performance assessed with cardiac ultrasonography using conventional, tissue

Doppler, and speckle tracking parameters that represent ventricular base-to-apex movements can help in the understanding of cardiovascular compromise in sick neonates.[23,24]

### *Near-Infrared Spectroscopy*

NIRS enables noninvasive, real-time, and continuous measurement of regional oxygenation and perfusion.[25] Studies show that low cerebral oxygenation is associated with adverse long-term outcomes, and the burden of hypoxia can be reduced if infants are monitored by NIRS.[26,27]

### *Blood Lactate Levels*

Lactic acid is a terminal product of the anaerobic metabolism of glucose and is commonly increased in the setting of tissue hypoxia and ischemia. High serum lactate level correlates with severity of illness and adverse outcomes in neonates.[28,29]

## CIRCULATORY COMPROMISE: THERAPEUTIC APPROACHES AND END POINTS

No single circulatory parameter can be consistently and reliably used to diagnose, quantify, and guide management of clinically important hemodynamic compromise in neonates. Data on the association between low BP and outcomes of preterm infants are conflicting. Earlier studies reported a higher incidence of major intraventricular hemorrhage and ischemic brain lesions in preterm neonates with low BP during the transitional period.[30,31] However, more recent studies do not support this association and caution against use of inotropes during transitional period to increase BP in otherwise well preterm neonates.[26,32,33] Capillary refill time and semiquantitatively measured skin mottling correlate with outcomes in children and adults, but data in neonates are limited.[34,35] Low SVC flow in the early transitional period is associated with significantly increased mortality, major intraventricular hemorrhage, and developmental impairments in preterm neonates.[4,36] However, therapy to prevent and improve low SVC flow resulted in limited clinical benefits.[37–39] Similarly, NIRS-guided cardiovascular interventions did not improve long-term outcomes in preterm infants.[27,40] Early and effective clearance of lactate can improve survival in neonates with sepsis, perinatal asphyxia, and congenital heart disease.[41]

Neonatologists generally consider a range of hemodynamic parameters to make decisions about inotrope use (**Table 1**). The choice of an inotrope is usually based on the understanding of the pathophysiology of the disease process, physiologic effects and side effect profile of inotropes, evidence of efficacy of the inotrope on the relevant hemodynamic parameters, and the desired therapeutic end points.

**Table 1**
**Circulatory parameters used for assessment of neonatal hemodynamics**

| Hemodynamic Component | Suitable Circulatory Parameters |
|---|---|
| Intravascular volume | Urine output, BP, cardiac chamber volumes, vena cava collapsibility |
| Cardiac function | BP, urine output, CO, ejection fraction, myocardial performance index, tissue Doppler and deformation parameters |
| Vasomotor regulation | Skin perfusion, pulse volume, BP, CO |
| Systemic blood flow | Skin perfusion, SVC flow, CO, urine output, NIRS |
| Cellular metabolism | Blood lactate, base excess |

Hemodynamic goals and therapeutic end points for term neonates with septic shock have been described, and include maintaining heart rate, BP, and oxygen saturation within the normal range for age; warm extremities; good volume peripheral pulses; capillary refill time equal to or less than 2 seconds; urine output greater than 1 mL/kg/h; less than 5% difference between the preductal and postductal oxygen saturations; SVC flow greater than 40 mL/kg/min; CO greater than 3.3 L/min/$m^2$; and absence of echocardiographic evidence of pulmonary hypertension.[42,43] In addition, maintaining NIRS-derived cerebral oxygen saturation and cerebral fractional tissue oxygen extraction within the reference range might be useful to ensure adequacy of cerebral perfusion.[44] However, these end points may not be applicable to very preterm infants, especially in the first 72 hours of life.

## CARDIOVASCULAR EFFECTS OF COMMON INOTROPES

### *Target Cardiovascular Receptors*

Most inotropes alter the force of muscle contraction by changing the intracellular calcium concentration. The cardiovascular actions of commonly used inotropes are mediated predominantly through adrenergic, dopaminergic (DA), and vasopressin receptors (**Table 2**).[45–47] Variation in the maturity of receptors and the pharmacokinetics of medications may produce different hemodynamic responses in preterm and term infants.[48] A summary of the predominant cardiovascular effects of inotropes is presented in **Table 3**.

### *Dopamine*

Dopamine is an endogenous catecholamine precursor of norepinephrine with sympathetic and neuroendocrine actions. It is the most commonly used and studied inotrope

**Table 2**
**Common target cardiovascular receptors for inotropes**

| Receptor | | Location | Action | Clinical Effect |
|---|---|---|---|---|
| Alpha-adrenergic | $\alpha_1$ | Cardiomyocytes, vascular smooth muscle | Smooth muscle cell contraction | Increased cardiac contractility and vascular resistance |
| | $\alpha_2$ | Presynaptic neurons, vascular smooth muscle | Reduced sympathetic activity | Reduced vascular resistance |
| Beta-adrenergic | $\beta_1$ | Cardiomyocytes | Smooth muscle cell contraction | Increased cardiac contractility and heart rate |
| | $\beta_2$ | Vascular, bronchial muscle cells | Smooth muscle cell relaxation | Reduced vascular resistance, bronchodilation |
| Dopaminergic | $DA_1$ | Splanchnic blood vessels | Smooth muscle cell relaxation | Splanchnic vasodilatation and increased blood flow |
| | $DA_2$ | Central nervous system | Noradrenaline inhibition | Movements and neurobehavioral effects |
| Vasopressin | $V_1$ | Vascular smooth muscle | Smooth muscle cell contraction | Increased vascular resistance |
| | $V_2$ | Vascular smooth muscle | Smooth muscle cell relaxation | Reduced vascular resistance |

**Table 3**
**Predominant cardiovascular effects in neonates of common inotropes**

| | | Dopamine | Dobutamine | Adrenaline | Norad-renaline | Milrinone | Vasopressin |
|---|---|---|---|---|---|---|---|
| Heart rate ($\beta_1$) | | ++ | ++ | +++ | +++ | + | 0/+ |
| Contractility ($\alpha_1$, $\beta_1$) | | ++ | +++ | +++ | ++ | +++ | 0/+ |
| CO ($\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$) | | ++ | +++ | ++ | +/0 | ++ | 0/+ |
| SVR ($\alpha_1$, $\alpha_2$, $\beta_2$, $DA_1$) | | +++[a] | –/+ | +++[a] | ++++ | – | +++ |
| PVR ($\alpha$1, $\alpha$2, $\beta$2, $DA_1$) | | ++/– | –/+ | –/+ | –/+ | – | – |
| BP ($\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$) | | +++ | +/– | +++ | ++++ | – | +++ |
| SVC flow | | + | ++ | No | No | 0 | No |
| Tissue perfusion | | + | + | + | + | + | +/– |
| NIRS ($\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$) | $rCSO_2$ | + | + | ++ | + | No | No |
| | FTOE | – | – | – | – | No | No |

*Abbreviations:* FTOE, cerebral fractional tissue oxygen extraction; No, not reported; PVR, pulmonary vascular resistance; $rCSO_2$, regional cerebral oxygen saturation; SVR, systemic vascular resistance.

[a] Vasodilatation and reduction in vascular resistance at low doses.

in neonates.[48] At low dosages (0.5–2 μg/kg/min), it produces vasodilatation in the renal, mesenteric, and coronary vascular beds through the dopaminergic receptors.[47,49] Dopamine possesses $\alpha_1$ vasopressive and $\beta_1$ inotropic effects at usual dosages (2–10 μg/kg/min). It effectively increases systemic BP and cerebral blood flow in hypotensive neonates.[50] Dopamine has an unpredictable effect on the pulmonary vascular resistance and can potentially aggravate hypoxia through right-to-left shunting across the PDA in infants with pulmonary hypertension.[51] Most studies using dopamine were performed in preterm infants during the transitional period, so there may be limitations to extrapolating its clinical response in other hemodynamic conditions (**Table 4**). Adverse effects of dopamine include transient reduction of thyroid-stimulating hormone, prolactin, and growth hormone levels, and excessive peripheral vasoconstriction with subsequent decrease in the CO at higher doses.[52]

### *Dobutamine*

Dobutamine is a synthetic catecholamine that increases cardiac contractility, heart rate, and CO, and produces moderate vasodilatation.[53] Tachycardia and increased contractility can potentially increase myocardial oxygen consumption.

### *Adrenaline*

Adrenaline is an endogenous catecholamine. At lower dosages (0.02–0.1 μg/kg/min), it increases contractility and heart rate with modest vasodilatation.[49] Adrenaline also increases cerebral blood flow by increasing systemic BP.[54] At high dosages (>0.5 μg/kg/min) it causes excessive vasoconstriction, disorganized energy use, hyperglycemia, and increased lactate levels.[55] Preterm infants who receive very high dosages of adrenaline (>1 μg/kg/min) have a high risk of mortality.[56]

**Table 4**
**A summary of randomized control trials evaluating inotropes in neonates**

| Study, Year | n | GA/BW | PNA | Clinical Pathophysiology | Intervention | Hypotension or Low Blood Flow Before Intervention | Result |
|---|---|---|---|---|---|---|---|
| Baske et al,[96] 2018 | 40 | All | 4–10 d | Late-onset sepsis | Dopamine, adrenaline | Yes | Comparable reversal of shock, resolution of metabolic acidosis, morbidity and all-cause mortality at 28 d |
| Rios & Kaiser,[84] 2015 | 20 | <30 | <24 h | Transitional | Dopamine, vasopressin | Yes | Equally efficacious. Less tachycardia with vasopressin |
| Bravo et al,[83] 2015 | 28 | <31 | <24 h | Transitional | Dobutamine, placebo | Yes | Dobutamine increased SVC flow with higher heart rate and faster correction of metabolic acidosis |
| Batton et al,[116] 2012 | 10 | <27 | <24 h | Transitional | Dopamine, hydrocortisone, placebo | Yes | Poor recruitment to the study |
| Paradisis et al,[39] 2009 | 90 | <30 | <6 h | Transitional | Milrinone, placebo | Some | Milrinone did not prevent low SVC flow |
| Filippi et al,[118] 2007 | 35 | <1500g | <24h | Transitional, EOS | Dopamine, dobutamine | Most | Dopamine more effective for increasing MAP. Dopamine caused a reduction in thyroid-stimulating hormone |
| Pellicer et al,[54] 2005 and Valverde et al,[55] 2006 | 60 | <32 | <24 h | Transitional | Dopamine, adrenaline | Yes | Equally efficacious for hypotension, urine output and CBF. High heart rate, lactate, and glucose levels with adrenaline |
| Osborn et al,[37] 2002 | 42 | <30 | <24 h | Transitional | Dopamine, dobutamine | Yes | Dopamine more effective for increasing MAP. Dobutamine more effective for increasing SVC flow. Similar mortality and morbidity |
| Ruelas-Orozco & Vargas-Origel,[119] 2000 | 60 | | <24 h | Unclear | Dopamine, dobutamine | Yes | Equally efficacious for increasing MAP |
| Lundstrom et al,[120] 2000 | 36 | <33 | 0–9 d | Most transitional | Dopamine, volume | No | Dopamine more effective for increasing MAP, but not LVO and CBF |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bourchier & Weston,[121] 1997 | 45 | <1500 g | <24 h | Transitional | Dopamine, hydrocortisone | Yes | Dopamine and hydrocortisone equally effective in increasing MAP |
| Phillipos et al,[122] 1996 | 20 | All | <24 h | Transitional hypotension in very preterm, EOS | Dopamine, adrenaline | Yes | Comparable increase in MAP and tachycardia. Dopamine reduces and adrenaline increases LVO |
| Hentschel et al,[123] 1995 | 20 | <37 | 0–17 d | Most transitional, late-onset sepsis | Dopamine, dobutamine | Yes | Equally efficacious in increasing MAP and intestinal perfusion |
| Klarr et al,[124] 1994 | 63 | <35 | <24 h | Transitional | Dopamine, dobutamine | No | Dopamine more effective for increasing MAP |
| Greenough & Emery,[125] 1993 | 40 | <35 | 1–6 d | Most transitional | Dopamine, dobutamine | No | Dopamine more effective for increasing MAP |
| Rozé et al,[126] 1993 | 20 | <32 | — | Unclear | Dopamine, dobutamine | Yes | Dopamine more effective for increasing MAP. Dobutamine increases and dopamine reduces LVO |
| Gill & Weindling,[127] 1993 | 39 | <32 | <24 h | Transitional | Dopamine, volume | Yes | Dopamine more effective for increasing MAP. No difference in mortality, IVH, BPD, and ROP |
| Cuevas et al,[128] 1991 | 49 | <37 | <24 h | Transitional | Dopamine, placebo | No | Dopamine more effective for increasing MAP and urine output. No difference in resolution of acidosis and clinical outcomes |
| DiSessa et al,[105] 1981 | 14 | Term | <24 h | Asphyxia | Dopamine, placebo | Yes | Dopamine increased MAP and shortening fraction |

Hypotension or low blood flow defined in this table as MAP less than gestational age or SVC flow less than 41 mL/kg/min.

*Abbreviations:* BPD, bronchopulmonary dysplasia; BW, birthweight; CBF, cerebral blood flow; EOS, early-onset sepsis; GA, gestation at birth (weeks); IVH, Intraventricular haemorrhage; LVO, left ventricle output; MAP, mean arterial pressure (mm Hg); n, number of participants; PNA, postnatal age; ROP, retinopathy of prematurity.

### *Noradrenaline*

Noradrenaline is an endogenous catecholamine with predominant vascular and myocardial $\alpha_1$, mild to moderate myocardial $\beta_1$, and minimal $\beta_2$ actions. Its principal cardiovascular effect is peripheral vasoconstriction combined with moderate positive inotropy.[57] In addition, noradrenaline has a vasodilatory effect in the pulmonary vascular bed in neonates with high basal pulmonary vascular tone.[58,59] Higher doses of noradrenaline should be used cautiously in infants with impaired cardiac function because excessive tachycardia can potentially increase myocardial oxygen demand and worsen ventricular function. Metabolism and clearance of noradrenaline depend on the gestational age, body weight, and severity of illness in infants.[60]

### *Milrinone*

Milrinone is a phosphodiesterase type III inhibitor and acts by increasing intracellular cyclic AMP and calcium concentrations in the cardiac and vascular smooth muscle cells. It improves systolic and diastolic ventricular function through positive inotropic and lusitropic effects on the myocardium independent of adrenoreceptors. It also has a vasodilatory effect in the systemic and pulmonary vascular bed.[61] Milrinone has a half-life of approximately 4 hours and its clearance depends on renal function, gestational age, and postnatal age of neonates.[62,63]

### *Vasopressin*

Arginine-vasopressin is a potent endogenous vasoconstrictor. The vascular effects of vasopressin are mediated through the $V_1$ and $V_2$ receptors in the blood vessels.[64] At low doses, vasopressin causes selective vasodilatation ($V_2$) in pulmonary, coronary, and cerebral vasculature and vasoconstriction ($V_1$) in other vascular beds, resulting in increased mean arterial pressure and decreased pulmonary to systemic pressure ratio in infants with pulmonary hypertension.[65,66] In neonates, vasopressin has been predominantly used for fluid and catecholamine resistant shock. Adverse effects of vasopressin include hyponatremia, transient thrombocytopenia, and hepatic necrosis.[67,68]

## COMMON HEMODYNAMIC DISTURBANCES

### *Transitional Circulatory Compromise*

Normal cardiovascular transition after birth involves an initial dramatic and later gradual decrease in pulmonary vascular resistance resulting in a several-fold increase in pulmonary blood flow and left ventricular preload.[69,70] A series of neuroendocrine changes augment left ventricular contractility and help establish a new balance between systemic blood flow and BP following loss of the low-resistance placental circulation.[71] As the cardiovascular system adapts over the first 2 to 3 days after birth, the ductus arteriosus undergoes functional closure with stabilization of CO, systemic blood flow, and vascular resistance. The transitional cardiovascular challenges may become overwhelming for the adaptive responses of immature myocardium and neuroendocrine mechanisms in preterm infants.[72,73] Transitional maladaptation can lead to myocardial dysfunction, vasomotor instability, and hypoperfusion-reperfusion–mediated brain injury.[74,75] In addition to prematurity, antenatal complications, timing of cord clamping, loss of blood volume, perinatal infections, asphyxia, and high mean airway pressure also influence the normal cardiovascular transition after birth.[76–80]

Establishing a link between the use of inotropes during transition and long-term outcomes is challenging because of wide variation in the use of inotropes, illness severity

between the treated and nontreated infants, independent influence of the causes of circulatory compromise on outcomes, and factors beyond the transitional period.[32,81] Because both transitional hypotension and inotrope use have been identified as risk factors for adverse outcome in preterm infants, caution should be exercised while deciding for or against inotropes.

Dopamine is more effective than dobutamine in increasing the BP.[82] Dobutamine produces a significantly greater increase in CO and SVC flow compared with dopamine, with a rapid resolution of metabolic acidosis.[37,83] Adrenaline is as efficacious as dopamine in normalizing systemic BP and improving cerebral perfusion in preterm infants, albeit with more tachycardia and higher blood lactate levels.[54] In a small randomized control trial, vasopressin produced a comparable increase in BP in extremely low birth weight infants without producing tachycardia.[84] Despite the differential cardiovascular effects of inotropes, the risk of major intraventricular hemorrhage, periventricular leukomalacia, and death or neurodevelopmental impairment remains comparable in preterm infants with transitional hemodynamic disturbances treated with inotropes.[37,50,82,85]

### *Patent Ductus Arteriosus*

In about 65% of extremely low birth weight infants, the ductus arteriosus remains patent beyond the first week of life.[86] The direction and magnitude of shunt depends on the size of the duct and the pressure gradient between systemic and pulmonary circulations. A large duct is associated with reduced left ventricular afterload, increased preload, and high stroke volume.[87] Although this may be beneficial in the early phase, shunting of a large amount of systemic blood into the pulmonary circulation and reversal of diastolic blood flow in the aorta can potentially reduce perfusion pressure and organ blood flow.[88,89] In addition, over a period of time the heart remodels and left ventricular diastolic dysfunction can develop.[90] Significantly increased pulmonary blood flow and left ventricular diastolic dysfunction can lead to pulmonary congestion and hemorrhagic pulmonary edema.[89,90]

Effective management of cardiovascular compromise secondary to a large duct unresponsive to pharmacologic closure is challenging. Because left ventricular systolic function is not compromised until late, administration of inotropes without significant vasopressor effect, such as dobutamine and milrinone, does not increase BP. However, the increase in systemic BP produced by pressor-inotropes such as noradrenaline can lead to a decreased systemic blood flow by further increasing the left-to right shunting. Because of its nonselective vasopressor effect on both systemic and pulmonary vasculature, dopamine may be preferable for management of hypotension associated with a large duct.[51]

### *Inflammatory Conditions*

The imbalance between the proinflammatory and antiinflammatory mediators generated during neonatal sepsis or necrotizing enterocolitis leads to a widespread inflammation, endothelial injury, and intravascular coagulation, which result in a variety of hemodynamic disturbances with impaired microcirculation, tissue oxygen delivery, and use.[43,91] Along with upregulated local vasodilators such as nitric oxide and prostaglandins, cytokines produce generalized vasodilatation and capillary leak with intravascular volume depletion and hypotension. Most commonly, neonates with sepsis present with increased heart rate, stroke volume, and systemic blood flow (warm shock). In the late phase myocardial dysfunction, reduced stroke volume and excessive vasoconstriction (cold shock) may develop.[92–95] In many neonates, endothelial

dysfunction disrupts the equilibrium between endogenous vasodilators and vasoconstrictors, leading to pulmonary hypertension.[43]

In general, predominant vasopressors are preferred for management of warm shock and inotropes with additional vasodilator action for cold shock.[92,94,95] Dopamine is the most commonly used first-line inotrope in septic shock. Depletion of endogenous catecholamine stores is considered a potential limitation for use of dopamine in sick neonates with septic shock. However, in a randomized controlled trial, dopamine and adrenaline had comparable efficacy in increasing BP, maintaining hemodynamic stability, and improving metabolic acidosis in septic neonates with warm shock.[96] The risk of intraventricular hemorrhage, necrotizing enterocolitis, chronic neonatal lung disease, and retinopathy of prematurity, and the chances of survival, were also similar. There is a paucity of data on choice of inotropes in septic neonates with cold shock. In a cohort of septic neonates with fluid and dopamine resistant circulatory shock, noradrenaline effectively improved cardiac function, BP, and tissue perfusion.[58,59,97] In the absence of data from randomized controlled trials, noradrenaline may be preferable in neonates with septic shock who have pulmonary hypertension because of its favorable effect on the ratio of pulmonary to systemic vascular resistance. Limited evidence suggests that vasopressin and its analogues can also be useful in septic neonates with refractory shock and high pulmonary vascular resistance.[98]

### *Perinatal Asphyxia*

Hypoxic ischemia in the perinatal period can have a negative impact on the cardiovascular transition. Common hemodynamic disturbances include ventricular dysfunction, peripheral vasoconstriction, and pulmonary hypertension.[99,100] An initial period with reduced systemic blood flow, lactic acidosis, and oliguria is followed by a reperfusion phase with high systemic blood flow.[91,101,102] Less frequently, asphyxiated neonates present with excessive peripheral vasodilation and capillary leak syndrome with relative/absolute intravascular hypovolemia.[103] Both dopamine and dobutamine improve cardiac performance and systolic BP in asphyxiated neonates but do not reduce mortality or neurodevelopmental impairment.[104,105] In asphyxiated neonates who have persistent pulmonary hypertension, milrinone improves global cardiac function and reduces pulmonary vascular resistance and oxygen requirement.[62,63]

Therapeutic cooling may cause sinus bradycardia, increase in vascular resistance and reduction in CO.[106] However, because of concurrent reduction in oxygen consumption, hypothermia-induced cardiovascular changes do not seem to have adverse impact on organ perfusion. Infants with severe encephalopathy and autonomic dysfunction may continue to have higher heart rates and cerebral blood flow despite hypothermia compared with less encephalopathic infants with intact autonomic function.[102] Hypothermia can potentially reduce the activity of temperature-dependent enzyme systems, slow down metabolism, prolong half-life of drugs, and alter receptor response. However, if renal and hepatic dysfunction caused by asphyxia is accounted for, there is limited evidence at present to recommend change in the choice and dose of medications during therapeutic cooling.[107]

### *Pulmonary Hypertension*

Persistent pulmonary hypertension of the newborn (PPHN) may develop in a neonate because of inappropriately high pulmonary vascular resistance or because of underdevelopment, maldevelopment, structural remodeling, or obstruction of the pulmonary vasculature.[100] Although persistence of high pulmonary vascular resistance is most commonly seen in the setting of transitional circulatory maladaptation, neonatal sepsis, congenital heart disease, and pulmonary parenchymal diseases also often

present with PPHN. High pulmonary pressure leads to reduced pulmonary blood flow, systemic venous return, ventilation-perfusion mismatch, hypoxia, and right ventricular dysfunction over time. Low left ventricular preload, compensatory tachycardia, and leftward septal deviation can reduce the left ventricular filling, compliance, and systolic performance.

In neonates, when PPHN with right ventricle dysfunction is the primary cause of circulatory compromise, milrinone improves cardiac function and reduces pulmonary vascular resistance and oxygen requirement.[62,63] Noradrenaline can be helpful when pulmonary hypertension is associated with low systemic vascular resistance and CO as a primary or add-on inotrope.[108] In a case series of neonates with refractory pulmonary hypertension, vasopressin improved oxygenation, BP, and renal perfusion, and reduced nitric oxide requirement.[109]

## CONSIDERATIONS FOR THE FUTURE

The overall use of inotropes in neonatology has reduced in the last decades because of preventive measures and acceptance of alternative thresholds for treatment.[110] Maternal transport to a regional neonatal center, antenatal glucocorticoids, delayed cord clamping, early surfactant administration, and reducing mechanical ventilation were all effective in reducing cardiovascular compromise during transition. However, if cardiovascular compromise does occur, there are very few new studies to guide treatments.[46]

Currently available data suggest that neonates present with a wide variety of hemodynamic patterns. It is likely that the threshold for hemodynamic parameters that causes irreversible damage is variable based on individual differences. This individual variation makes it difficult to design pragmatic eligibility criteria for future trials. Therefore, it is unlikely that targeting 1 hemodynamic parameter using a 1-size-fits-all approach of the large-scale randomized trial will lead to major advances in neonatal hemodynamic management, and that alternative trial designs need to be considered. A large database with individual patient data and hemodynamic parameters could help capture clinical variation and help design a model to predict risk of morbidity and clinical decision limits.[111] Some neonatal networks collect data on inotrope use but, for most, this has not become standard.[112,113] To our knowledge, no neonatal network is routinely collecting and reporting data on the occurrence of low BP, low blood flow, or abnormal cerebral saturation levels (irrespective of definition) in high-risk infants.

A large multicenter N-of-1 trial design using longitudinal multimodal monitoring could also be proposed. N-of-1 clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy of different interventions, and thus an approach toward individualized medicine.[114,115] The typical crossover design of the N-of-1 trial cannot eliminate all confounding factors, and blinding might be more costly. However, combining multiple N-of-1 trials and analyses is possible to create a sufficient sample size. The results of N-of-1 trials would be of immediate benefit to the patients and the treating physicians, and, if enough of them are pursued, could lead to identification of patient characteristics that ultimately differentiate those that benefit from a particular intervention from those that do not. The ultimate goal of an N-of-1 trial is to determine the optimal or best intervention for an individual patient using objective data-driven criteria. Preferred hemodynamic targets, treatment criteria, and first-line treatment can be according to the unit preference, thus overcoming another major issue of individual preferences in lack of progress in hemodynamic management in newborns. There is an unwillingness among clinicians to join a trial that addresses hemodynamic problems in neonatal intensive care, even though

there is emerging physiologic and clinical evidence that alternative approaches are safe and possibly more effective. Two recent trials exploring the treatment of hypotension and the PDA could only enroll 17% and 24% of the eligible infants respectively.[116,117] Barriers to enrollment included lack of physician equipoise leading to fewer parents being approached and infants in the trial given open label treatments. John Dryden, a seventeenth-century English poet, quoted that "first we make our habits, and then our habits make us." Neonatologist have been using dopamine as first-line treatment in almost any clinical situation with hemodynamic compromise, even though it has been abandoned by most pediatric and adult intensivists. It seems old habits are hard to break.

## DISCLOSURE

The authors have nothing to disclose.

**Best Practices**

*What is the current practice for prescribing inotropes in neonates?*

- Understanding pathophysiology of disease processes and cardiovascular compromise
- Guidelines on inotrope use based on anticipated physiologic actions and side effect profile

*What changes in current practice are likely to improve outcomes?*

- Therapeutic decision making based on multimodal hemodynamic assessment
- Cautiously balancing short-term and long-term benefits against risks of inotrope

*Is there a clinical algorithm? If so, please include: No*

Major recommendations
- Evidence-based perinatal care that prevents cardiovascular compromise
- Exploring the role of inotropes in improving neonatal morbidity and mortality using alternative study designs

Strength of the evidence: small randomized control trials and cohort studies.

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