The use of inotropes, lusitropes, and vasopressors is common in neonates with cardiovascular compromise. Although the understanding of cellular mechanisms of action of these medications is well founded, there is little information on their clinically relevant long-term benefits in the neonatal patient population. In addition, if not appropriately titrated, these medications may induce abrupt, excessive, and potentially harmful increases in blood pressure and systemic and organ blood flow. Thus, in addition to the cardiovascular compromise, treatment by suboptimal administration of inotropes, lusitropes, and vasopressors may contribute to short- and long-term morbidities in critically ill preterm and term neonates. Prompt diagnosis of neonatal cardiovascular compromise by state-of-the-art hemodynamic monitoring of blood pressure and systemic and organ blood flow and careful titration of the vasoactive agents to the optimal hemodynamic response are thought to be of importance in decreasing mortality and morbidity associated with shock and its treatment in preterm and term neonates.

Unfortunately, there is little evidence on what vasoactive medications to use in what patient and when, at what dose to start, how to titrate the drug, and what parameters to monitor. Because addressing these issues is only possible by opinion- and experience-based reasoning without much evidence at present, this article focuses on describing the documented, developmentally regulated hemodynamic actions of inotropes, lusitropes, and vasopressors, and their short-term hemodynamic benefits and risks. Although there are several reasons to stay away from advocating...
experience-based reasoning on the use, benefits, and potential harm of these medications, the notion that experience in medicine might be best defined as “an ability to make a mistake repeatedly with increasing confidence” is one of the reasons with which few would argue.

**MECHANISMS OF ACTION OF INOTROPES, LUSITROPES, AND VASOPRESSORS**

An inotrope is a manufactured or naturally occurring substance with a primary pharmacologic effect of increasing myocardial contractility. For the classical inotropes (eg, dobutamine) or vasopressor-inotropes (eg, epinephrine and dopamine), the mechanisms of increasing myocardial contractility are primarily based on stimulating α- or β-adrenergic and dopaminergic receptors located on the cell membrane of myocardial cells. Stimulation of these receptors leads to activation of a chain of intracellular events hinging on receptor-specific cyclic adenosine monophosphate (cAMP)–dependent or independent increases in intracellular calcium availability resulting in increased actin–myosin bridge formation and thus contractility (Fig. 1).17
Another class of inotropes, the phosphodiesterase (PDE) inhibitors (e.g., amrinone or milrinone), rather selectively decrease the activity of PDE-III, the enzyme responsible for degradation of cAMP. The resulting increase in intracellular cAMP concentration leads to the chain of events described for the classical inotropes with the end-result of increased myocardial contractility.

A lusitrope is a manufactured or naturally occurring substance that increases the rate of myocardial relaxation. The lusitropic property depends on the compound’s ability to reduce intracellular calcium concentration by cAMP-dependent activation of the inward-pumping calcium channels on the sarcoplasmic reticulum, or to promote calcium dissociation from troponin C primarily during diastole.

A vasopressor is a manufactured or naturally occurring substance that increases vascular tone. Vascular smooth muscle tone is regulated by complex cellular mechanisms involving a delicate balance between vasodilator and vasoconstrictor factors, and the availability of cytosolic calcium plays a central role in this process (Fig. 2). Vasopressors exert their peripheral vasoconstrictive effects primarily through binding to α1-adrenergic and vasopressin1A (V1a) receptors activating the enzyme phospholipase C in the vascular smooth muscle. Phospholipase C in

![Fig. 2. Regulation of vascular tone in vascular smooth muscle cells.]( Modified from Klabunde RE. Available at: [http://www.cvphysiology.com/Blood%20Pressure/BP011b.htm](http://www.cvphysiology.com/Blood%20Pressure/BP011b.htm); with permission.)
turn increases inositol triphosphate leading to release of calcium from the sarcoplasmic reticulum.

Most of the medications used for cardiovascular support in the neonatal intensive care unit have dose-dependent inotropic, lusitropic, and vasopressor effects albeit to a varying degree and, for the compounds exerting their cardiovascular actions by receptor stimulation, with various sensitivity to the cardiovascular adrenergic, dopaminergic, and vascular vasopressin receptors (Tables 1 and 2). Discussed next are the developmentally regulated mechanisms of action of these medications, their cardiovascular effects, and the specific cardiovascular pathophysiology and clinical scenarios where each medication might be beneficial.

**DOPAMINE**

Dopamine is the most commonly used cardiovascular medication in the neonatal intensive care unit. Dopamine exerts its cardiovascular effects by dose-dependent stimulation of the α- and β-adrenergic and dopaminergic receptors and by its serotoninergic actions. In adults and older children, low doses of dopamine (2–4 μg/kg/min) primarily simulate the vascular dopaminergic receptors. Vascular dopaminergic receptors are selectively expressed in the renal, mesenteric, and coronary circulations and to a lesser extent in the pulmonary circulation and the extracranial vessels of the neck and head. At moderate doses (5–10 μg/kg/min), dopamine increases contractility and heart rate by stimulating the cardiac β₁, β₂, and α₁-adrenergic and the dopaminergic receptors; at high doses (≥10–20 μg/kg/min) dopamine also increases systemic and probably pulmonary vascular resistance (PVR) by stimulating vascular α₁ receptors. Approximately 50% of the positive inotropic effects of dopamine are caused by the dopamine₂-receptor stimulation induced release of norepinephrine stored in the peripheral sympathetic nerve endings in the myocardium. Because myocardial norepinephrine stores get depleted within 8 to 12 hours, dopamine, especially in the preterm neonate with decreased myocardial norepinephrine stores, is a less effective positive inotrope in the long run compared with epinephrine.

Because of maturational differences in the expression of the α- and β-adrenergic receptors, in neonates without adrenoreceptor downregulation, clinical

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cardiovascular actions mediated by adrenergic, dopaminergic, and vascular vasopressin receptors</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Adrenergic, Dopaminergic, and Vasopressin Receptors</td>
</tr>
<tr>
<td></td>
<td>α₁/α₂ᵇ</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>++++</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>0</td>
</tr>
<tr>
<td>+Inotropy</td>
<td>0</td>
</tr>
<tr>
<td>+Chronotropy</td>
<td>0</td>
</tr>
<tr>
<td>Cond. velocity</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abbreviations: Cond. velocity, conduction velocity; +Chronotropy, positive chronotropy; +Inotropy, positive inotropy.*

Estimated relative vascular (vasoconstriction and vasodilation) and cardiac (inotropy, chronotropy, and conduction velocity) effects mediated by the cardiovascular adrenergic (α₁/α₂ and β₁/β₂), dopaminergic (DA₁/DA₂), and vasopressin (V₁a) receptor subtypes.

α₂-receptors cause arterial vasodilation and venous vasoconstriction.

Renal, mesenteric, coronary circulation > pulmonary circulation > extracranial vessels of the neck.
manifestations of vascular \(\alpha\)-adrenoreceptor simulation (eg, increased systemic vascular resistance [SVR]) become apparent even at low-to-medium doses.\(^3,4,28\) Therefore, in neonates with escalating dopamine infusion, the pattern of receptor stimulation is first dopaminergic, then \(\alpha\)-adrenergic, and finally \(\beta\)-adrenergic (Fig. 3).\(^3,4,28\)

**Table 2**
Estimated relative cardiovascular receptor stimulatory effects of inotropes, lusitropes, and vasopressors

<table>
<thead>
<tr>
<th></th>
<th>Adrenergic, Dopaminergic, and Vasopressin Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\alpha_1/\alpha_2)</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>++++</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++++</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++++</td>
</tr>
<tr>
<td>Dopamine(^a)</td>
<td>++++</td>
</tr>
<tr>
<td>Dobutamine(^b)</td>
<td>+/-0</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>0</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0</td>
</tr>
<tr>
<td>PDE-III inhibitors</td>
<td>0</td>
</tr>
<tr>
<td>PDE-V inhibitors</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviations:** \(\alpha_1/\alpha_2/\beta_1/\beta_2\), subtypes of \(\alpha\)- and \(\beta\)-adrenoreceptors; DA, dopamine; DOB, dobutamine; PDE, phosphodiesterase enzyme; PDE-III inhibitors used in neonates, amrinone, milrinone; PDE-V inhibitors used in neonates, sildenafil; \(V_{1a}\), vasopressin receptor expressed in the vasculature.

\(^a\) Dopamine also has serotoninergic actions.

\(^b\) Efficacy of dobutamine is independent of its affinity for adrenoreceptors.

Fig. 3. Dose-dependent cardiovascular, renal, and endocrine effects of dopamine in neonates. Receptor-specific hemodynamic, renal, pulmonary, and endocrine actions of dopamine are shown in the absence of adrenoreceptor downregulation (\(^*\)denotes the effects demonstrated in preterm neonates). (Modified from Seri I. Management of hypotension and low systemic blood flow in the very low birth weight neonate during the first postnatal week. J Perinatol 2006;26:S8–13; with permission.)
Of note is that the hemodynamic effects and the clinical response to dopamine (and other vasopressors and inotropes) is altered by downregulation of adrenergic receptors caused by the critical illness–associated prolonged endogenous and the treatment-associated exogenous receptor stimulation. Furthermore, because cardiovascular adrenergic receptor expression is regulated by corticosteroids, the documented higher incidence of relative adrenal insufficiency also contributes to the observed attenuated hemodynamic response and the development of vasopressor-dependence in preterm and term neonates. These effects are especially seen in patients with prolonged exposure to dopamine and other vasopressors and inotropes. Therefore, pharmacodynamics is more important than established pharmacokinetic data when vasopressors and inotropes are used and their effectiveness considered. In addition, the cardiovascular response to these medications also depends on the developmentally regulated expression and function of the cardiovascular adrenergic and dopaminergic receptors and second messenger systems, and on the dysregulated local production of vasodilators, such as prostaglandins and nitric oxide in patients with a critical illness.

**Effect on Systemic Blood Pressure**

The efficacy of dopamine in raising blood pressure in hypotensive neonates has been consistently demonstrated. In a randomized controlled trial of dopamine versus hydrocortisone for treatment of hypotension in very-low-birth-weight infants, dopamine was effective in increasing blood pressure 100% of the time. Similarly, randomized controlled trials of dopamine versus dobutamine have demonstrated that dopamine is more effective in increasing blood pressure.

**Effect on Cardiac Output**

Dopamine, when appropriately titrated, has been shown to either increase or have no significant effect on cardiac output. Padbury and colleagues reported an increase in cardiac output and blood pressure in preterm and term infants after titration of dopamine up to 8 μg/kg/min. The increase in cardiac output is caused by the drug-induced increases in myocardial contractility demonstrated by increased ventricular ejection fraction, even in the 1-day-old very preterm neonate. However, Roze and colleagues reported an increase in SVR without a significant change in cardiac output in hypotensive preterm infants treated with a dopamine infusion of 12 to 20 μg/kg/min. It is tempting to speculate that, in neonates without significant adrenoreceptor downregulation, the drug-induced increase in SVR at higher doses may attenuate the drug’s effect of increased myocardial contractility on cardiac output. Along these lines, in a small subset of preterm infants, higher doses of dopamine resulted in excessive increases in SVR, potentially decreasing cardiac output. These findings point to the importance of establishing an optimum hemodynamic target (pressure and flow); titrating the drug in a step-wise fashion; and the need to monitor systemic blood pressure and blood flow. Overall, the increase in blood pressure observed with dopamine infusion (especially at higher doses) is mainly caused by increases in the SVR, although increases in cardiac output (mainly at moderate doses) also contribute to the rise in blood pressure. It must be remembered, however, that receptor downregulation, relative adrenal insufficiency, and dysregulated vasodilator release modify the “effective dose-range” of dopamine in the given patient and explain the lack of response to conventional doses in several critically ill neonates. Indeed, findings of a small case series in neonates not responding to conventional doses of dopamine suggest that dopamine at doses of 30 to 50 μg/kg/min increased blood pressure and urine output. However, because the drug might
induce significant vasoconstriction at higher doses, administration of high-dose dopamine might result in decreased cardiac output and organ (including brain) blood flow, and therefore blood pressure and systemic and organ blood flow need to be monitored in these critically ill neonates.\textsuperscript{12}

**Effect on Pulmonary Vascular Bed**

Because hypotension commonly occurs during the first few postnatal days when the ductus arteriosus is open, understanding the impact of dopamine on the pulmonary vascular bed is important. For example, if dopamine increased SVR out of proportion to the drug-induced increase in PVR in neonates with a patent ductus arteriosus (PDA), blood pressure would increase but a decrease in systemic blood flow might occur, because the left-to-right shunting through the ductus may also increase. Yet, there are only limited data on the effect of dopamine on the pulmonary vasculature. In hypotensive preterm infants, Liet and colleagues\textsuperscript{40} estimated mean pulmonary and systemic blood pressure by assessing the flow velocity through the PDA. Dopamine infusion had variable effects on the ratio of pulmonary-to-systemic blood pressure with half of patients showing an increase and the other half a decrease in the ratio. Relative to SVR, PVR increased in one-half and decreased or did not change in the other half of the studied population. The finding that patients with a low pretreatment pulmonary/systemic blood pressure ratio responded to dopamine primarily with a more pronounced increase in their PVR suggested that hypotensive infants with a significant left-to-right shunt might benefit from dopamine infusion. Indeed, Bouissou and colleagues\textsuperscript{41} subsequently found indirect evidence that dopamine decreases left-to-right ductal shunting in hypotensive preterm infants with a hemodynamically significant PDA and thereby improves systemic perfusion. These authors suggested that the increase in superior vena cava (SVC) flow (used as a surrogate of systemic blood flow) and the decrease in cerebral artery resistance index without any change in left ventricular output provided evidence for a decrease in left-to-right ductal shunting. Although this might well be the case, it is also possible that the observed increase in cerebral blood flow (CBF) might have been related to the increase in blood pressure in these critically ill neonates with impaired CBF autoregulation rather than to the decrease in ductal shunting. The limited available data suggest that dopamine has variable effects on the pulmonary vascular bed and in a subset of patients with abnormally increased baseline pulmonary blood flow (ie, neonates with significant left-to-right ductal shunting) dopamine may increase PVR out of proportion to the increase in SVR and thus lead to improved systemic blood flow while raising blood pressure. Along these lines, it is tempting to speculate that the increased pulmonary blood flow in patients with a PDA induces upregulation of pulmonary vasoconstrictive mechanisms, such as $\alpha_1$ and endothelin receptor expression, as a physiologic response to attenuate pulmonary overcirculation. Dopamine (or other vasopressors) then increases PVR more readily than in patients without preexisting pulmonary overcirculation.

**Effect of Dopamine on CBF**

Dopamine is thought to be devoid of any direct effect on the cerebral vascular bed.\textsuperscript{42} Recent studies in lambs even suggest a possible role for dopamine in the regulation of cerebral flow–metabolism coupling.\textsuperscript{43} However, confirmation of these findings is needed before the potential clinical relevance of the drug-associated cerebral flow–metabolism coupling can be further investigated. In hypotensive preterm infants without intact CBF autoregulation, titration of dopamine (or other vasopressors or inotropes) in a stepwise fashion to achieve the “optimal” mean blood pressure resulted in...
an increase in CBF. Munro and colleagues also demonstrated similar findings and showed that, although blood pressure and CBF increase, CBF autoregulation is not immediately reestablished. Therefore, abrupt and significant elevation in blood pressure induced by the inappropriate use of excessive doses of these vasoactive medications can result in sudden and potentially harmful increases in CBF. In the vulnerable extremely premature neonate, especially after an episode of hypoperfusion, excessive increases in CBF may then lead to reperfusion injury or hemorrhage. Finally, the available very limited information suggests that at least 50 to 90 minutes of relative hemodynamic stability may be required for CBF autoregulation to be reestablished in preterm neonates after a hypotensive episode.

**Effect of Dopamine on Mesenteric and Renal Blood Flow**

In the human preterm neonate, the selective vasodilatory effects of dopamine on the mesenteric blood flow have not been consistently demonstrated. Furthermore, higher doses of dopamine in patients with no significant adrenoreceptor downregulation may result in vasoconstriction of the mesenteric vascular bed. The administration of even low doses of dopamine does not seem to be indicated to selectively increase intestinal blood flow in preterm neonates.

Dopamine has more consistently been shown to increase renal blood flow in preterm neonates. However, this hemodynamic finding only partially explains the improvement in urine output after starting dopamine infusion in hypotensive neonates. Interestingly, intrarenally produced dopamine, by directly affecting renal microhemodynamics (eg, glomerular filtration rate), tubular epithelial and paracrine, and renal endocrine functions, plays an important regulatory and modulatory role in overall renal function. Although discussion of the renal epithelial, paracrine, and endocrine effects of dopamine is beyond the scope of this article, it is important to remember that dopamine causes significant and clinically relevant increases in renal sodium, phosphorous, ammonia, and free-water excretion and decreases in urinary concentrating capacity. The complex renal actions of dopamine may, at least in part, explain the finding that in indomethacin-treated preterm infants with impaired renal perfusion, dopamine increases renal blood flow and urine output. However, because these findings have not been consistently demonstrated, routine use of dopamine to prevent the indomethacin-associated renal dysfunction is not warranted.

Overall, the unique hemodynamic profile of dopamine makes this drug suitable as a first-line medication for the treatment of most forms of neonatal cardiovascular compromise. In addition, the need to carefully titrate the drug and monitor pressure, and directly or indirectly systemic blood flow, and endocrine actions of dopamine need to be kept in mind and further investigated to fully establish the safety and efficacy of this medication in neonates. In clinical practice, the drug-induced inhibition of thyroid-stimulating hormone must be kept in mind especially when using dopamine during the first postnatal days. Accordingly, the neonatal screen should be repeated once the patient has been off dopamine for at least 12 hours.

**DOBUTAMINE**

Because dobutamine has an asymmetric carbon atom, there are two enantiomers of the medication with different affinity for adrenergic receptors. The negative isomer is primarily an $\alpha_1$-receptor agonist and increases myocardial contractility and SVR. The positive isomer is a $\beta_1$- and $\beta_2$-receptor agonist causing increases in the myocardial contractility, heart rate, and conduction velocity, and decreases in SVR. In addition,
the main metabolite of dobutamine, (+)-3-O-methyl-dobutamine, exerts $\alpha_1$-receptor inhibitory effects and in itself it decreases myocardial contractility and SVR. Because dobutamine consists of 50% of the positive and negative isomer, the net effects of dobutamine administration are increases in myocardial contractility and, to a lesser extent, heart rate, and either no effect or a decrease in SVR (Table 3).\textsuperscript{52} As with dopamine, the developmentally regulated differences in vascular $\alpha$- and $\beta$-adrenoreceptor expression affect the cardiac and peripheral vascular response to dobutamine. Because during early development cardiovascular $\alpha$-adrenergic receptor expression is upregulated while maturation of $\beta$-adrenergic receptors lags behind,\textsuperscript{24,25} very preterm neonates are likely to respond to dobutamine with attenuated decreases in SVR and thus with more pronounced increase in blood pressure compared with term neonates. However, systematic dose–response studies comparing the cardiovascular effects of dobutamine in preterm neonates with those in term neonates are not available.

The cardiovascular effects of dobutamine are also dose-dependent (Fig. 4). At very low doses (2.5 $\mu$g/kg/min) no significant hemodynamic effects have been observed in neonates with cardiovascular compromise.\textsuperscript{53} However, moderate doses (5–7.5 $\mu$g/kg/min) of dobutamine lead to increases in cardiac output, whereas at higher doses (5–20 $\mu$g/kg/min) dobutamine increases cardiac output and blood pressure even in hypotensive preterm infants.\textsuperscript{53} An additional effect of dobutamine on increasing cardiac output has been demonstrated in hypotensive preterm infants receiving dopamine.\textsuperscript{54} In general, dobutamine is more effective than dopamine in increasing cardiac output in neonates with myocardial dysfunction. Although dobutamine at doses of 10 or 20 $\mu$g/kg/min was also found to be more effective than dopamine used at the same two doses at increasing low SVC flow in preterm infants during the first postnatal day, even dobutamine had limited efficacy\textsuperscript{34} and the clinical relevance of these findings remains unclear. Neonates with myocardial dysfunction respond favorably to dobutamine, as evidenced by increases in cardiac output, minutes after the initiation of the drug infusion followed by increases in organ blood flow hours later.\textsuperscript{55} Of note is that higher doses of dobutamine may lead to decreased myocardial compliance potentially affecting ventricular filling especially in patients with myocardial hypertrophy.

Dobutamine is the drug of choice to increase cardiac output in neonates with myocardial dysfunction, and its use likely results in increases in organ blood flow and blood pressure in these patients. However, its effect on organ blood flow may be variable and seems to depend on the underlying pathophysiology. Thus, the hemodynamic response to dobutamine makes the drug’s use suitable for clinical situations TABLE 3
Mechanisms of action of dobutamine enantiomers and metabolites

<table>
<thead>
<tr>
<th>Enantiomers, Metabolites</th>
<th>Pharmacologic Activity</th>
<th>Heart</th>
<th>Vasculature</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) dobutamine</td>
<td>$\alpha_1$</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>(+) dobutamine</td>
<td>$\beta_1/\beta_2$</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>(+)-3-O-methyl-dobutamine</td>
<td>$\alpha_1$</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>(±) dobutamine</td>
<td>$\alpha_1/\beta_1/\beta_2$</td>
<td>↑↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Adrenergic receptor stimulatory and inhibitory effects of the left (-) and right (+) rotating enantiomers of dobutamine and its major metabolite ((+)-3-O-methyl-dobutamine) are shown. The form of dobutamine used in clinical practice is depicted as (±) dobutamine. $\alpha_1/\beta_1/\beta_2$ = subtypes of $\alpha$- and $\beta$-adrenoreceptors; ↑, 0, ↓ = increase, no effect, or decrease on myocardial function or vascular tone. The relative effect is indicated by the number of symbols.
where poor myocardial contractility with unchanged or increased SVR is the primary underlying cause of the cardiovascular compromise, such as perinatal asphyxia or the very preterm neonate with poor systemic blood flow and vasoconstriction during the transitional period. In contrast, in conditions with low SVR (eg, vasodilation) as the dominant underlying cause of the hemodynamic disturbance, such as seen in the early stages of septic shock or the very preterm neonate with vasodilatory shock during the transitional period, dobutamine is not the appropriate first drug of choice. However, addition of dobutamine to dopamine in patients with cardiovascular compromise caused by impaired myocardial function and vasodilation is a reasonable approach and may be effective.

**EPINEPHRINE**

Epinephrine exerts its cardiovascular effects by stimulating the $\alpha$- and $\beta$-adrenergic receptors in a dose-dependent manner (Fig. 5). At low doses (0.01–0.1 $\mu$g/kg/min) epinephrine primarily stimulates the cardiac and vascular $\beta_1$- and $\beta_2$-adrenoreceptors receptors leading to increased inotropy, chronotropy, and conduction velocity and peripheral vasodilation (primarily in the muscles), respectively. At doses greater than 0.1 $\mu$g/kg/min, epinephrine also stimulates the vascular and cardiac $\alpha_1$-receptors causing vasoconstriction and increased inotropy, respectively. The hemodynamic effects of vascular $\alpha_2$-receptor stimulation are less prominent. The net hemodynamic effects of epinephrine administration are significant increases in blood pressure and systemic blood flow caused by the drug-induced increases in SVR and cardiac output. The increase in blood pressure (and possibly cardiac output) increases CBF in hypotensive preterm neonates.

There are limited data on the cardiovascular effects of epinephrine in neonates. The previously cited randomized controlled clinical trial of dopamine versus epinephrine demonstrated that the two medications have similar efficacy in improving blood pressure and increasing CBF in hypotensive preterm infants. However, patients randomized to epinephrine more frequently developed increased serum lactate levels independent of the improvement in their hemodynamic status and hyperglycemia.
requiring insulin treatment. These metabolic effects are most likely explained by the drug-induced stimulation of \( \beta_2 \)-adrenoreceptors in the liver and skeletal muscle resulting in decreased insulin release and increases in glycogenolysis leading to increases in lactate production, respectively.

In clinical practice, some neonatologists use epinephrine as the first choice of drug in the treatment of hypotensive neonates with vasodilatory shock with or without myocardial dysfunction. However, most neonatologists use the drug if the patient is unresponsive to higher doses of dopamine (with or without dobutamine). Overall, epinephrine is as effective as dopamine in treating hypotension. However, its metabolic effects need to be kept in mind because the increases in serum lactate limit the use of sequential serum lactate measurements to indirectly follow the changes in the cardiovascular status. The associated hyperglycemia might require initiation of insulin administration. Also, because epinephrine is a potent vasoconstrictor, extreme caution is warranted when titrating and weaning the drug and on syringe changes dictated by pharmacy or nursing protocols. However, the significant effects of epinephrine on the vascular tone and myocardial contractility make it an effective choice for the treatment of conditions where low vascular resistance with or without impaired myocardial contractility is the primary underlying cause of the cardiovascular compromise, such as in septic shock or certain cases with asphyxia-associated hemodynamic compromise.

**VASOPRESSIN**

Vasopressin has widespread physiologic effects, although its primary physiologic role is regulation of extracellular osmolality. The vascular effects of vasopressin occur by stimulation of the G protein–coupled \( V_1a \) and \( V_2 \) receptors expressed in the cardiovascular system. The \( V_1a \) and \( V_2 \) receptors induce vasoconstriction and vasodilation by activation of the IP3 and cAMP pathways, respectively. The potent vasoconstrictive effects of vasopressin dominate the cardiovascular response when it is used as an infusion.

Vasopressin administration has been suggested to be beneficial in vasodilatory shock and deficiency of endogenous vasopressin production in adults and children.
with septic shock\cite{59} and infants and children after cardiac surgery for congenital heart disease (CHD).\cite{60} In these studies on patients unresponsive to conventional vasopressors, a relative hypersensitivity to vasopressin administration has been found. Several case reports in a small number of hypotensive preterm and term neonates unresponsive to conventional vasopressors have reported mostly beneficial effects of vasopressin or terlipressin, a long-acting vasopressin agonist. For a thorough review of the literature on this subject, the reader is referred to the relatively recent review by Meyer and colleagues.\cite{61} Because terlipressin has also been reported to decrease pulmonary artery pressure in animal models of hypoxic pulmonary constriction,\cite{62} a recent case report describes its use and systemic and pulmonary effects in a neonate with congenital diaphragmatic hernia and pulmonary hypertension.\cite{63} It is clear that more information from prospective observational and randomized controlled trials is needed before vasopressin use in neonates with vasopressor-resistant shock can be recommended. At present, low-dose hydrocortisone is the drug of choice in clinical practice in neonates with vasopressor-resistant shock, although hydrocortisone administration is not without potential side effects especially in the very preterm neonate in the immediate postnatal period.\cite{30,64}

**MILRINONE**

Milrinone is a selective PDE-III inhibitor and thus it exerts its cardiovascular effects through the inhibition of cAMP degradation. By increasing the concentration of cAMP, milrinone enhances myocardial contractility, promotes myocardial relaxation, and decreases vascular tone in the systemic and pulmonary vascular beds. Given this intriguing profile of cardiovascular actions, milrinone has been most commonly used in the postoperative care of patients with CHD to treat low cardiac output state\cite{65} and in near-term and term neonates with persistent pulmonary hypertension of the neonate (PPHN) as an adjunct to inhaled nitric oxide (iNO).\cite{66,67}

There are very limited data on the cardiovascular effects of milrinone in preterm and term neonates. The only randomized controlled clinical trial of milrinone performed in neonates evaluated the effects of the medication on preventing low SVC flow in extremely preterm infants.\cite{68} This well-designed study did not provide evidence for beneficial effects of milrinone administration, because the incidence of low SVC flow was similar in the treatment and placebo groups. Furthermore, milrinone-treated subjects had an increased incidence of tachycardia, low blood pressure, and hemodynamically significant PDA. Comparing with a historical control group, findings of a recent study suggest that milrinone administration immediately after ligation of the ductus arteriosus in preterm infants with relatively low cardiac output might reduce hemodynamic instability during the first 24 hours after the procedure.\cite{69} Given that myocardial dysfunction is common after PDA ligation,\cite{70} the inotropic and lusitropic properties of milrinone are likely responsible for the observed beneficial effects.

It remains unclear whether milrinone exerts significant myocardial effects immediately after delivery in the human neonate. According to studies in developing animals, PDE-IV rather than PDE-III is the most active enzyme responsible for cAMP metabolism in the fetal heart.\cite{71} The findings that milrinone has a poor inhibitory effect on PDE-IV and upregulation of PDE-III and downregulation of PDE-IV expression only start at birth\cite{71} explain why it takes 3 to 7 days after delivery until the inotropic effects of milrinone can convincingly be demonstrated in the immature animal model.\cite{71,72}

Other than the potential benefits of milrinone in improving cardiac output, the medication may also have beneficial effects in the treatment of PPHN especially in cases unresponsive to iNO. In a small case series of nine term infants with PPHN
unresponsive to iNO, oxygenation index significantly improved within a few hours after starting milrinone.\textsuperscript{73} Recent findings explain, at least in part, the cellular basis of the enhanced responsiveness to milrinone in neonates with PPHN unresponsive to iNO.\textsuperscript{74} Contrary to endogenous nitric oxide, exogenous (inhaled) nitric oxide upregulates PDE-III in the smooth muscle cells of the pulmonary vasculature resulting in a decrease or loss of the cAMP-dependent vasodilatory mechanisms.\textsuperscript{74} Addition of milrinone to iNO has been proposed to restore pulmonary vasodilatory mechanisms dependent on cAMP; both the cyclic guanosine monophosphate (nitric oxide–dependent) and cAMP vasodilatory systems become operational, potentially resulting in increased pulmonary vasodilation and improvement in oxygenation in these patients.

Because none of the cardiovascular effects of milrinone (inotropy, lusitropy, and pulmonary vasodilation) has been convincingly demonstrated in neonates without CHD, further well-designed studies on milrinone in neonates with primary myocardial dysfunction and PPHN are urgently needed.

**LEVOSIMENDAN**

Levosimendan exerts its positive inotropic effects by enhancing binding of calcium to troponin C. Calcium binding to troponin C induces a conformation change in the troponin complex, which results in the uncovering of the myosin binding-site on actin and thereby making it accessible to myosin.\textsuperscript{75} The calcium-sensitizer effect of this medication is unique because the other more commonly used inotropes exert their effects either through increases in intracellular cAMP concentration or by the inositol triphosphate-induced increases in intracellular calcium availability (see Fig. 1). In addition, by activating the ATP-sensitive potassium channels, levosimendan also has vasodilatory properties. Similar to that of milrinone, the drug’s hemodynamic profile of positive inotropy and peripheral vasodilation is especially beneficial in patients with myocardial dysfunction, because the reduction in the afterload contributes to improvements in cardiac output.

Levosimendan is a relatively new cardiovascular medication used primarily in adults with congestive heart failure.\textsuperscript{76} Recently, its use in postoperative care of infants with CHD has been reported.\textsuperscript{77,78} However, the experience with this medication in preterm or term neonates is limited and appropriately designed clinical trials are needed to establish the benefits and describe the risks of levosimendan use in neonates without CHD.

**SUMMARY**

A solid understanding of the mechanisms of action of cardiovascular medications used in clinical practice along with efforts to develop comprehensive hemodynamic monitoring systems to improve the ability to accurately identify the underlying pathophysiology of cardiovascular compromise are essential in the management of neonates with shock. This article reviews the mechanisms of action of the most frequently used cardiovascular medications in neonates. Because of paucity of data from controlled clinical trials, evidence-based recommendations cannot be made for the clinical use of these medications. That said, it is suggested that careful titration of the given medication with close monitoring of the cardiovascular response using echocardiography and a combination of the recently developed technologies\textsuperscript{12} if available might improve the effectiveness and decrease the risks associated with administration of these medications. Although there is evidence for short-term hemodynamic benefits of cardiovascular supportive care in neonates when inotropes, lusitropes, and vasopressors or a combination of these medications is used tailored to the
underlying pathophysiology of the cardiovascular compromise, the impact of these medications on the clinically most relevant long-term outcome measures is not well understood.6,10,79,80

REFERENCES