

Systemic and Pulmonary Effects of Vasopressors and Inotropes in the Neonate

Istvan Seri

USC Division of Neonatal Medicine, Department of Pediatrics, Children's Hospital Los Angeles, and Women's and Children's Hospital, LAC/USC Medical Center, Keck School of Medicine, University of Southern California, Los Angeles, Calif., USA

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Key Words

Neonatal hypotension · Organ blood flow · Dopamine · Dobutamine · Epinephrine

Abstract

This paper briefly reviews the systemic and pulmonary hemodynamic actions of the most frequently used vasopressor-inotropes and inotropes in the preterm and term neonate. It is important to note that very little is known about the medium- and long-term cardiovascular and neurodevelopmental benefits of the use of these medications in the neonate.

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Pathogenesis and Phases of Neonatal Shock

For the definition and pathogenesis of neonatal hypotension and low systemic perfusion, the reader is referred to recently published articles [1–3]. As treatment of neonatal shock should be directed to address the primary pathogenesis of the cardiovascular compromise (hypovolemia, myocardial dysfunction, abnormal peripheral vasoregulation or a combination of these factors), the prompt recognition of the primary pathogenetic factor(s) is of utmost importance.

In addition, as neonatal shock presents in phases of advancing severity, an understanding of the characteristics of the three phases of shock is essential for the practising neonatologist [4]. In the initial *compensated phase*, vital organ (brain, heart and adrenal glands) perfusion and blood pressure are maintained by neuroendocrine compensatory mechanisms via redistribution of blood flow from non-vital organs. This phase can be best recognized by a decrease in urine output and changes in peripheral perfusion. However, our ability to accurately evaluate tissue perfusion in the neonate, especially in the immediate postnatal period, remains limited as the indirect clinical signs of tissue hypoperfusion, such as capillary refilling time and urine output, poorly correlate with systemic perfusion in this patient population [1, 5]. Furthermore, lactic acidosis does not always accurately represent the state of tissue perfusion as, for instance, it may worsen as organ perfusion improves [1–3]. If not recognized and/or treated, shock then enters its *uncompensated phase*. In this phase, as neuroendocrine compensation fails, systemic hypotension and generalized tissue ischemia develop affecting every organ. In the neonate, shock is most frequently recognized in its uncompensated phase by the presence of hypotension, oliguria and evolving lactic acidosis. Even then, because of the lack of a universally accepted gestational- and postnatal age-dependent definition of neonatal hypotension, the recognition of

shock may be further delayed until signs of significant organ hypoperfusion develop. Finally, if treatment is delayed or is ineffective, shock enters its irreversible phase resulting in multiorgan failure and death.

In neonates, especially in the very low birth weight (VLBW, <1,500 g) neonate during the first postnatal day, the use of functional echocardiography may be of value in detecting low systemic perfusion [6]. However, functional echocardiography is not routinely available. Moreover, its routine use has not yet been documented to result in improved outcome. So, what should the practising neonatologist rely upon at the bedside when facing the hemodynamically unstable neonate?

To answer this question, it is important to note that the primary etiology/pathogenesis of neonatal hypotension can be suspected by the clinical presentation of cardiovascular compromise and its timing. Thus, on the first postnatal day hypotension and/or decreased systemic blood flow usually occurs because of delayed adaptation of the immature myocardium to the sudden postnatal increase in systemic vascular resistance in the extremely low birth weight (ELBW, <1,000 g) neonate or peripheral vasodilation and hyperdynamic myocardial function in VLBW neonates born to mothers with chorioamnionitis. Furthermore, in any neonate during the first postnatal day, hypotension may be caused by peripheral vasodilation or, less frequently, vasoconstriction due to sepsis, or by perinatal depression with secondary myocardial dysfunction and/or abnormal peripheral vasoregulation. From the second postnatal day on, hypotension occurs most frequently because of a hemodynamically significant patent ductus arteriosus, relative adrenal insufficiency presenting with vasopressor resistance, sepsis or necrotizing enterocolitis. Understanding the pathogenesis of the circulatory compromise is the cornerstone of initiating the appropriate first line of management such as volume replacement in hypovolemia, inotrope administration in myocardial compromise without vasodilation, and vasopressor/inotrope administration in vasoregulatory shock.

Mechanisms of Action of Vasopressors

Dopamine, among the vasopressor-inotropes, is the most frequently used vasoactive amine for the treatment of neonatal hypotension and low systemic perfusion [1, 3, 7]. Dopamine exerts its cardiovascular actions via the dose-dependent stimulation of the cardiovascular dopaminergic, α - and β -adrenergic and serotonin receptors

[7]. The drug-induced increases in peripheral vascular resistance and myocardial contractility [1, 7, 8] are the clinically most relevant hemodynamic actions of dopamine [1, 3]. Dopamine administration should be tailored to the drug's pharmacodynamic effects rather than driven by the conventional dose recommendations [1, 7]. Dopamine also causes selective vasodilation and increased blood flow to the kidneys and, probably, the intestine in the preterm neonate [1, 9]. In addition, it has complex and often clinically relevant endocrine effects [7]. Although, in animal models, dopamine receptors are present in the pulmonary circulation and thus one would expect pulmonary vasodilation to occur at least at lower dopamine doses, the drug's effect on the pulmonary circulation has not been well documented in the human neonate. Although at higher doses dopamine may cause a variable degree of pulmonary vasoconstriction, especially in a subpopulation of preterm neonates [10, 11], clinical findings indicate that the drug-induced increase of the systemic vascular resistance is almost always greater than that of the pulmonary vascular resistance even during high-dose dopamine administration [7, 10].

Epinephrine is the other vasopressor-inotrope used with increasing frequency for the treatment of neonatal shock. Epinephrine exerts its cardiovascular actions primarily via the stimulation of the cardiovascular α - and β -adrenergic receptors. Epinephrine has more potent inotropic effects than dopamine and also exerts its vasoconstrictive effects at relatively lower doses. Epinephrine has recently been shown to be as effective as dopamine at increasing blood pressure and normalizing cerebral blood flow in VLBW neonates during the first postnatal day [12]. There are differences, however, between dopamine and epinephrine in the metabolic response of the patient to these medications. For instance, epinephrine causes an augmentation of lactic acidosis in the VLBW neonate [12]. This observation should be kept in mind when monitoring the changes in acid-base balance, as the expected improvement in lactic acidosis may not occur in the epinephrine-treated neonate. However, this finding is unlikely to be related to ongoing tissue hypoperfusion and is caused instead by the epinephrine-induced increase in gluconeogenesis [12]. However, this observation may make the use of epinephrine less practical as it is not possible to differentiate at the bedside between tissue ischemia-induced and gluconeogenesis-associated lactic acidosis.

Mechanisms of Action of Inotropes

Dobutamine is a cardioselective sympathomimetic amine with significant α - and β -adrenoreceptor-mediated direct inotropic effects and moderate chronotropic actions [13]. Dobutamine administration is usually also associated with a variable decrease in total peripheral vascular resistance in the pediatric and adult patient population [13]. However, since peripheral β -adrenergic receptor maturation lags behind that of the α -adrenoreceptors and since cardiovascular α -adrenoreceptor expression is inversely related to gestational age [7], dobutamine administration, in the preterm neonate, usually increases blood pressure by increasing cardiac output without exerting a significant effect on systemic vascular resistance [14]. However, in the term infant, a decrease in the systemic vascular resistance should be expected and taken into consideration when selecting the most appropriate initial vasoactive amine for the treatment of neonatal cardiovascular compromise. Finally, unlike dopamine [7], dobutamine increases myocardial contractility exclusively through the direct stimulation of the myocardial adrenergic receptors. In addition, although not consistently documented, dobutamine may decrease pulmonary vascular resistance. In summary, dobutamine is the drug of choice in the initial treatment of the hypotensive neonate

with myocardial dysfunction and without evidence of significant peripheral vasodilation [13]. The clinician should be careful though when using dobutamine at higher doses, as it may decrease myocardial compliance especially in diastole leading to a decrease in diastolic filling and thus stroke volume.

Milrinone, a phosphodiesterase-III inhibitor, exerts its cardiovascular effects primarily by enhancing intracellular cAMP content. A major theoretical advantage of milrinone over dobutamine is that milrinone improves diastolic myocardial function and decreases pulmonary vascular resistance more readily [15]. However, there are no data on its effects in neonates aside from the term neonate with congenital heart disease presenting with low cardiac output syndrome following cardiopulmonary bypass and cardiac surgery [15].

In summary, dopamine, epinephrine and dobutamine remain the most frequently used sympathomimetic amines in the treatment neonatal cardiovascular compromise. As their pharmacodynamic profile is different, a thorough understanding of the pathophysiology of neonatal shock and of the mechanisms of action of these medications is necessary for the neonatologist to choose the most appropriate vasoactive amine or a combination of these medications for the treatment of neonatal shock.

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