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Circulatory support of the sick preterm infant

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In the majority of preterm infants, especially during the immediate postnatal period, hypotension is primarily caused by abnormal peripheral vasoregulation and/or myocardial dysfunction and not by absolute hypovolemia. Therefore, aggressive volume resuscitation is not warranted and is potentially harmful. Volume support should be limited to 10–20 ml/kg of isotonic saline administration and, if sustained normalization of the blood pressure cannot be achieved, early initiation of cardiovascular pharmacological support is recommended. However, in preterm infants who present with an identifiable volume loss, the kind of fluid lost should first be replaced. Due to its beneficial cardiovascular and renal actions, dopamine is the drug of choice in the treatment of neonatal hypotension. Dobutamine may be added if myocardial dysfunction persists or develops during dopamine treatment. In some critically ill preterm infants, escalation of dopamine therapy or addition of epinephrine is necessary yet not always effective indicating the development of pressor resistant hypotension. Downregulation of cardiovascular adrenergic receptors and some degree of adrenal insufficiency may explain this phenomenon. In these patients, a brief course of steroid treatment may be successful in stabilizing the cardiovascular status and decreasing the requirement for pressor/inotrope support. However, well-designed randomized and controlled clinical trials are needed in the future to determine the effectiveness and potential short- and long-term side effects of steroid administration in preterm infants with pressor-resistant hypotension. In summary, management of the critically ill hypotensive preterm infant remains challenging and requires a better understanding of the pathophysiology of neonatal shock and improvements in our ability to evaluate cardiac output, organ blood flow, and tissue perfusion at the bedside.

Key words: hypotension, preterm infant, hypovolemia, myocardial dysfunction, peripheral vasoregulation, dopamine, dobutamine, epinephrine, hydrocortisone, dexamethasone

This chapter reviews the pathophysiology of neonatal shock and the definition, etiology, short- and long-term sequelae, and management of hypotension in the preterm infant in the immediate postnatal period defined as the first week of life. An in-depth discussion is provided on the mechanisms of action, pharmacodynamics, and side effects of sympathomimetic agents, volume support and steroid administration. Recent data on the contribution of adrenergic receptor downregulation and adrenal insufficiency to the development of pressor-resistant hypotension are also reviewed.

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Definition and phases of neonatal shock

Shock develops when oxygen delivery becomes inadequate to satisfy tissue oxygen demand. Shock presents in distinct phases of advancing severity characterized by specific pathological alterations in cardiovascular and renal function [1]. In the initial *compensated phase of shock*, vital organ function and blood pressure are maintained by neurohormonal compensatory mechanisms. However, especially in the immediate postnatal period in the preterm infant, the associated changes in cardiovascular and renal function are difficult to assess and the compensated phase of shock frequently goes

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undetected. With progression of the condition, shock enters its *uncompensated phase*. In this phase, failure of the neurohormonal compensatory mechanisms results in the clinically recognizable symptoms of systemic hypotension and, with further progression of the process, the development of metabolic acidosis. Thus, in the preterm infant, shock is most frequently recognized in its uncompensated phase. If cardiovascular support and treatment of the primary initiating event are delayed or prove to be ineffective, shock enters its final irreversible phase with irreparable cellular damage resulting in death.

Definition of systemic hypotension in the preterm infant

The normal physiologic range for blood pressure is best defined by the presence of intact organ blood flow autoregulation. However, the lower and upper limits of this developmentally regulated physiologic blood pressure range have not been determined in the preterm or term infant [2,3]. Instead, the 'normal' blood pressure limits have been defined as the gestational- and postnatal-age-dependent blood pressure values between the 10th and 90th percentiles [3–5]. Thus, the decision to treat hypotensive non-acidotic preterm infants is based on arbitrary blood pressure limits *without proven physiologic relevance*. In the absence of information on the physiologic blood pressure range, however, this chapter will continue to use the gestational- and postnatal age-dependent arbitrary 'normal' blood pressure limits ([3], Fig. 1) recognizing the potentially fundamental shortcomings of our present clinical practice.

Etiology of systemic hypotension in the preterm infant

In the vast majority of pediatric patients, *absolute hypovolemia* is the primary cause of hypotension [1]. However, especially during the immediate postnatal period, *abnormal peripheral vasoregulation and myocardial dysfunction* are the most frequently encountered primary etiological factors of hypotension in the preterm infant [2,6,7]. Indeed, the lack of a relationship between blood volume and blood pressure [8,9], and the finding that dopamine is at least twice as effective in normalizing blood

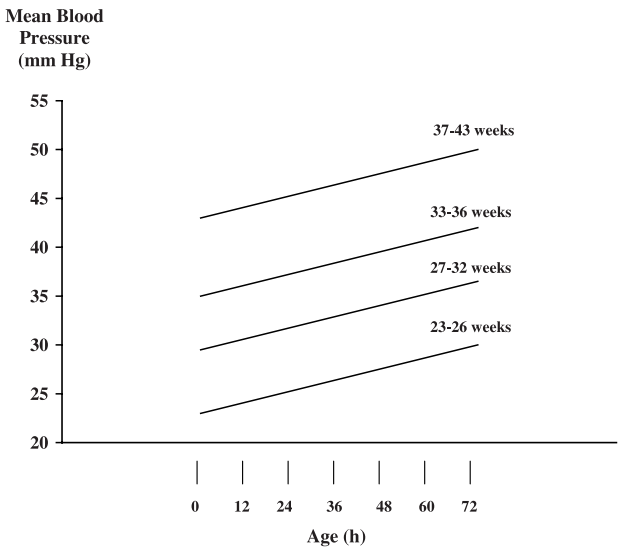

Figure 1. Gestational- and postnatal-age-dependent normogram for mean blood pressure values in preterm neonates during the first weeks of life. The normogram is derived from continuous arterial blood pressure measurements obtained from 103 neonates with gestational ages between 23 and 43 weeks. Each line represents the lower limit of 80% confidence interval of mean blood pressure for each gestational age group. Thus, 90% of infants for each gestational age group is expected to have a mean blood pressure equal or greater than the value indicated by the corresponding line (the lower limit of confidence interval). From Nuntnarumit P, Yang W, Bada-Ellzey HS. Blood pressure measurements in the newborn. *Clin Perinatol* 1999; **26:** 981–996, with permission [3].

pressure than is volume administration [10] strongly support that absolute hypovolemia is a less frequent primary cause of neonatal hypotension. However, in preterm infants with evidence of acute blood loss, excessive transepidermal water loss or excessive urine output, absolute hypovolemia should be considered as the primary cause of hypotension and the treatment adjusted accordingly.

Abnormal regulation of peripheral vascular resistance resulting in peripheral vasodilation plays a major role in the development of hypotension in preterm infants. Since routine assessment of peripheral vascular resistance is confounded by technical difficulties, there are mostly indirect lines of evidence supporting this notion. These include the recognition of the non-specific inflammatory response syndrome [11], evidence for dysregulated endothelial nitric oxide production (Ronald I. Clyman, personal communication, 1999) and the superiority of dopamine over dobutamine in the treatment of hypotension (see below).

The role of *myocardial dysfunction* as a primary etiological factor of hypotension in the severely

asphyxiated preterm infant has been well documented [12]. In addition, a prospective study has now found evidence for its etiological role in hypotension in preterm infants without severe perinatal asphyxia [7].

Finally, there are cases such as asphyxiated preterm infants where absolute hypovolemia, myocardial dysfunction and abnormal peripheral vascular tone all play a role in the etiology of hypotension. The management of these critically ill asphyxiated hypotensive preterm infants presents an extremely difficult challenge and requires sound understanding of the pathophysiology of shock and appreciation of the impact of prematurity on cardiovascular and other organ functions.

Short- and long-term effects of systemic hypotension in the preterm infant

Because of the resultant decrease in brain blood flow and oxygen supply [13], severe hypotension in the preterm infant is associated with a higher incidence and increased severity of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and long-term neurodevelopmental sequelae [4,13–15] compared to normotensive preterm infants. Severe hypotension may also have detrimental gastrointestinal, renal and hepatic effects contributing to the development of necrotizing enterocolitis, and renal and hepatic injury [1,6]. Therefore, it is widely accepted that early and effective treatment of hypotension leading to sustained stabilization of the cardiovascular status increases the chance of improved neurological outcome and survival in the preterm infant. However, since systemic blood pressure is the function of blood flow and systemic vascular resistance, blood pressure may not always appropriately reflect the status of organ blood flow in the non-acidotic preterm infant. Indeed, low cerebral blood flow has recently been suggested to be a risk factor for the development of IVH in the absence of hypotension [16].

Management of systemic hypotension in the preterm infant

In order to utilize the most appropriate initial treatment strategy of hypotension, one must first attempt to identify the primary etiological factor or combination of factors resulting in the clinical presentation of hypotension. However, it should be kept in mind that the treatment must also address all the ensuing major components of the disturbed circulation and not only the primary initiating event.

Volume administration

Since absolute hypovolemia is a less frequent primary factor in the development of neonatal hypotension, especially in the immediate postnatal period [8–10], indiscriminate volume administration is not warranted and is potentially harmful. Yet, it is common practice for hypotensive preterm infants to routinely receive repeated boluses of 10–20 ml/kg of volume. This is being done despite the findings that increased volume administration is associated with augmented pulmonary, cardiovascular, gastrointestinal and central nervous system morbidity and mortality in this patient population [17,18]. However, since objective assessment of the intravascular volume status at the bedside is not possible, cautious volume administration of 10–20 ml/kg is a reasonable clinical approach in the initial treatment of hypotensive preterm infants without evidence of absolute volume loss. In these patients, if sustained normalization of the blood pressure cannot be achieved with the *single* volume bolus, early initiation of dopamine administration is warranted [6,10,19–21].

The type of the initial fluid treatment (colloid versus crystalloid) in hypotensive preterm infants *without evidence of absolute volume loss* has also been the topic of considerable controversy. However, it has been demonstrated that the volume infused and not the albumin load is important in producing a sustained blood pressure increase [22]. Furthermore, a recent randomized controlled study comparing the effects of 10 ml/kg of isotonic saline to 5% albumin in the immediate postnatal period has found that isotonic saline is as effective as 5% albumin in increasing the blood pressure [23]. This trial has also demonstrated that isotonic saline caused less fluid retention following its administration and, similar to the results of an earlier study [8], the findings suggest an impairment of gas exchange in infants receiving 5% albumin. The increased capillary permeability of the sick preterm infant may, at least in part, explain these findings.

If there is an *identifiable volume loss*, the kind of fluid lost should be replaced. In cases of blood loss,

transfusion with packed red blood cells following the initial crystalloid bolus, or packed red blood cells suspended in fresh frozen plasma with a hematocrit around 55%, may be used. In cases of increased transepidermal water losses, higher free water administration without an increase in sodium supplementation is indicated [18]. When polyuria is present, the composition and volume of the replacement fluid may be adjusted to the urinary sodium and free water losses. However, replacement of half of the excessive urinary losses with 0.45% saline will usually suffice.

In adults, intravascular volume increases only by 25–40% of the volume bolus when isotonic saline is used, while albumin is preferentially retained in the intravascular compartment [24]. In contrast, in sick preterm infants [23] and adults with impaired capillary integrity [25], crystalloids and colloids appear to be equally effective in the initial treatment of hypotension. However, unlike isotonic saline, albumin may induce a fluid shift from the intracellular compartment [24], which could be potentially harmful especially in the immature brain. Finally, there is a renewed debate over the possible association of the use of albumin with increased mortality in hypotensive patients [26]. Thus, based on the available information, it is reasonable to suggest that, unless evidence of intravascular volume loss or hypoalbuminemia is present, volume support in hypotensive preterm infants should be provided in the form of 10–20 ml/kg of isotonic saline administered over 15–30 min. If ineffective, this single volume bolus should be followed by the early initiation of pharmacological cardiovascular support with dopamine [6,10,19–21].

Pressors and inotropes

Pressor (dopamine, epinephrine, norepinephrine) and inotrope (dobutamine) treatment was introduced decades ago in the management of neonatal hypotension mostly without appropriately designed randomized and blinded clinical trials. In addition, the majority of the studies investigating the effects of these medications simply monitored only the changes in heart rate, blood pressure and urinary output in response to the treatment. Not until recently have a few studies focused on the changes induced by these cardiovascular agents in other physiologically relevant aspects of cardiovascular function such as myocardial contractility and organ blood flow [2,20,27]. However, there is still virtually no information available on the effects of these agents on tissue oxygen delivery and consumption in the neonate [28].

Dopamine

Dopamine, an endogenous catecholamine, is the sympathomimetic amine most frequently used in the treatment of hypotension in preterm infants [6]. It exerts its cardiovascular actions via the dose-dependent stimulation of the cardiovascular dopaminergic, α and β-adrenergic receptors ([6], Tables 1 and 2). In addition, by stimulating the epithelial and peripheral neuronal dopaminergic and adrenergic receptors, the drug exerts significant renal and endocrine effects independent of its cardiovascular actions [6,21].

Dopamine affects all three major determinants of *cardiovascular function* (preload, myocardial contractility, and afterload). By decreasing venous capacitance, dopamine augments preload [6]. However, the majority of its actions on raising blood pressure are due to the drug-induced increases in both myocardial contractility [6,20,27] and peripheral vascular resistance (afterload) [6,20,27] with some of the α- and β-adrenergic cardiovascular effects resulting from its partial conversion to norepinephrine [6,21]. It is important to note that, while the effect on afterload raises blood pressure, if dopamine administration results in excessive increases in afterload, it may compromise cardiac function [27]. Via its selective renal vascular dopaminergic effects, dopamine increases total renal blood flow [2] and glomerular filtration rate [6,19,21] in preterm infants as early as 23 weeks' gestation. However, dopamine does not appear to selectively increase the mesenteric blood flow in the immature infant [2], suggesting the absence of a functionally mature mesenteric dopaminergic vasodilatory response in this patient population. Based on these findings, administration of low-dose dopamine to augment mesenteric blood flow is not recommended in normotensive preterm infants with necrotizing enterocolitis. However, in preterm infants with necrotizing enterocolitis and non-hypovolemic shock, blood pressure should be normalized with appropriate pressor support, because the hypotension-induced decrease in mesenteric blood flow is likely to further compromise tissue perfusion in the affected intestine [2,6,29]. It is unclear whether dopamine administration results in direct changes in the pulmonary circulation [6].

Table 1. Adrenergic and dopaminergic receptor-dependent cardiovascular actions of the most frequently used sympathomimetic agents

Agent	Cardiovascular adrenergic and dopaminergic receptors*					
	Cardiac receptors			Peripheral vascular receptors		
	α_1†	β_1 (β_2)†	Dopamine	α_1/α_2	β_2	Dopamine
	↑contractility	↑rate ↑conduction ↑contractility	↑contractility	Peripheral vaso-constriction	Peripheral vasodilation	Vasodilation in renal, mesenteric, and coronary circulation
Dopamine**	++#	++++#	+	++++	+	++++
Epinephrine	++	++++	∅	++++	+++	∅
Norepinephrine	++	++++	∅	++++	∅/+	∅
Dobutamine‡	++	++++	∅	+	++	∅

Estimated relative contribution of adrenergic and dopaminergic receptor stimulation to the cardiovascular actions of sympathomimetic amines.
∅: no effect; +: minimum effect; ++++: maximum effect. *: receptors other than the adrenergic and dopaminergic receptors also mediate some of the cardiovascular actions of the sympathomimetic agents (for example, the dopamine-induced stimulation of the serotonin receptors contributes to the peripheral vasoconstriction caused by higher doses of the drug); **: dopamine stimulates the α- and β-adrenergic and dopaminergic receptors in a dose-dependent manner; #: only approximately 50% of the positive inotropic effect of dopamine result from the direct stimulation of the myocardial adrenergic receptors [6]; †: the relative contribution of the α_1 and β_1 adrenergic receptors and the myocardial dopamine receptors to the increase in myocardial contractility in the neonate is unknown; ‡: 3-0-methyldobutamine, the major dobutamine metabolite, is a relatively potent and highly selective α_1-adrenoreceptor antagonist [38]. The α_1-adrenoreceptor inhibitory effects of this metabolite may contribute to the tendency of dobutamine to cause peripheral vasodilation. See text for details.

However, there is no evidence of a significant increase in extrapulmonary right-to-left shunting during dopamine treatment since the drug-induced increase in systemic blood pressure is not associated with impaired oxygenation in preterm infants [28]. This finding suggests that, even if dopamine causes some degree of pulmonary vasoconstriction, its pulmonary effects are only of limited clinical significance in this patient population [6]. Finally, dopamine or the drug-induced increase in blood pressure was not found to affect cerebral blood flow in non-asphyxiated normotensive preterm infants [2], suggesting the presence of autoregulation of cerebral blood flow in this patient population [2].

Independent to the above-described cardiovascular effects, dopamine exerts direct *beneficial renal* [2,6,21] *and endocrine* [6] actions in the preterm infant. Via its epithelial effects in the renal tubules, dopamine increases sodium, phosphorous, and free water excretion [6,21]. Dopamine administration may also be associated with increased bicarbonate losses [6]. Finally, by reversibly inhibiting renal Na^+, K^+-ATPase activity [30], dopamine may increase the hypoxic threshold of renal tubular cells during episodes of hypoperfusion and hypoxemia [6]. Among its endocrine actions, the drug-induced decreases in plasma prolactin and thyrotropin levels [6] are thought to be of clinical importance. The decrease in plasma prolactin may attenuate the preterm infant's propensity to edema formation [6]. The inhibition of thyrotropin release, on the other hand, necessitates the postponement of routine neonatal thyroid screening until after dopamine administration has been discontinued [6].

There is significant inter- and intra-individual variability in the dose of dopamine required to elicit cardiovascular responses of similar magnitude in preterm infants. Possible explanations for this phenomenon include the differences in the metabolism of dopamine [20,21,31], the production of local vasoregulatory hormones, the state of expression [32] and downregulation [33] of cardiovascular adrenergic receptors, and the differences in adrenal function [34,35]. If the cardiovascular compromise is recognized early, lower doses of dopamine (2–10 μg/kg/min) may be effective [6,19–21], most likely because of the developmentally-regulated enhanced expression of α-adrenoreceptors during early development [32] and the decreased metabolism of dopamine in the immediate postnatal period [6,21]. However, with the progression of the disease process, escalation of the dose of dopamine [6,36,37] or the addition of dobutamine [6,31] or epinephrine [37] may become necessary to maintain blood pressure in the desired range. Although most neonatologists do not advance the dose of dopamine beyond 20 μg/kg/min, there is no evidence that, when required to normalize blood pressure, high-dose dopamine treatment has detrimental vasoconstrictive effects [6,36,37]. The

Table 2. Cardiovascular actions of dopamine in the preterm infant[#]

Dose	Receptors	Vascular effects	Cardiac effects
Low dose (0.5–2 μg/kg/min)	Dopamine	↑↑↑Renal blood flow	↑Myocardial contractility*
	α (serotonin)	↑TPVR	
		Net effect on BP = ∅ or ↑	
Medium dose (2–10 μg/kg/min)	Dopamine	↑↑↑Renal blood flow	↑Myocardial contractility*
	β	↑Peripheral vasodilation	↑↑Myocardial contractility ↑Heart rate ↑Conduction velocity
	α (serotonin)	↑↑TPVR	↑↑Myocardial contractility ↑Venous return
		Net effect on BP = ↑↑	
High dose (>10 μg/kg/min)	Dopamine	↑↑↑Renal blood flow	↑Myocardial contractility*
	β	↑Peripheral vasodilation	↑↑↑Myocardial contractility ↑↑Heart rate ↑↑Conduction velocity
	α (serotonin)	↑↑↑TPVR	↑↑Myocardial contractility ↑Venous return
		Net effect on BP = ↑↑↑	

BP: blood pressure; TPVR: total peripheral vascular resistance; ∅: no effect; ↑: increase; #: there is a significant inter-individual variability in the dose of dopamine required to elicit cardiovascular responses of similar magnitude in different patients (see text for details); *: it is unclear whether myocardial contractility is increased by the selective stimulation of myocardial dopamine receptors in preterm infants (see text for details).
From Seri I: Cardiovascular, renal, and endocrine actions of dopamine in neonates and children. *J Pediatr* 1995; **126:** 333–344, with permission [6].

downregulation of the cardiovascular adrenergic receptors [33] and the occasional relative or absolute adrenal insufficiency [34,35] explain the decrease in the sensitivity of the cardiovascular system to the sympathomimetic agents in these critically ill preterm infants. Thus, with the advancement of the disease process, increased doses of pressors are needed to exert the same magnitude of cardiovascular response. The increased pressor requirement may be accomplished either by using higher doses of a single agent (dopamine) or a combination of two pressors (dopamine and epinephrine). However, the decision to add dobutamine (an inotrope) should be based on the status of myocardial function rather than the need for escalation of dopamine therapy.

Side effects of dopamine therapy include local tissue necrosis with extravasation of the infusate, tachycardia, arrhythmia and hyponatremia [6]. Hypertension and vasoconstriction may also occur, especially when the dose of dopamine is not weaned with the improvement in the clinical condition following spontaneous recovery, effective antimicrobial treatment and/or the initiation of steroid administration (see below). Close monitoring of the critically ill preterm infant receiving dopamine ensures early detection of side effects allowing for their immediate and effective treatment [6,21].

In summary, the beneficial and complex mechanisms of actions of dopamine and the pathophysiology of neonatal hypotension explain why dopamine has become the drug of choice in the treatment of the hypotensive preterm infant [6]. The drug should be started early at low to medium doses, and the dose escalated in a step-wise manner to achieve sustained normalization of the blood pressure [6,20,21]. There is no evidence that

dopamine treatment should not be increased beyond 20 μg/kg/min, if necessary. The factors affecting the decision to add dobutamine or epinephrine/norepinephrine or to initiate a brief course of steroid administration are discussed in the appropriate sections below.

Dobutamine

Dobutamine is a relatively cardioselective sympathomimetic amine with significant α- and β-adrenoreceptor-mediated direct inotropic effects and limited chronotropic actions [31,38]. The drug does not stimulate the cardiovascular dopaminergic receptors (Table 1). In the most effective dose-range of 2–15 μg/kg/min, dobutamine increases cardiac output mainly through the augmentation of stroke volume [27,31,38]. Dobutamine administration is usually also associated with a variable decrease in the total peripheral vascular resistance [27,31,38] and, at least in adults, with an improved coronary blood flow and myocardial oxygen delivery [38]. The clinically most important side effects of dobutamine include tachycardia, arrhythmia, and systemic hypotension or hypertension.

As with the other sympathomimetic amines, the cardiovascular actions of dobutamine are affected by the state of expression of the cardiovascular adrenergic receptors and by the adrenergic activity of some of the dobutamine metabolites ([38], Table 1). While approximately 50% of the positive inotropic effects of dopamine are indirect resulting from the drug-induced release of stored norepinephrine [6], dobutamine increases myocardial contractility exclusively through the direct stimulation of the myocardial adrenergic receptors [38]. Since myocardial norepinephrine stores are immature and rapidly depleted in the neonate [31], and since dobutamine may decrease afterload [31,38], preterm infants with primary myocardial dysfunction and elevated peripheral vascular resistance should be treated with dobutamine alone. These hemodynamic characteristics may be encountered in some patients with severe perinatal asphyxia [1].

However, in the majority of preterm infants, hypotension results from a decrease in the afterload with or without myocardial dysfunction. Therefore, as mentioned above, dopamine is the initial drug of choice in the treatment of the hypotensive preterm infant. Indeed, several randomized, blinded, controlled clinical trials have documented the superiority of dopamine over dobutamine in this patient population [27,39–41]. However, if signs of myocardial dysfunction persist or develop during dopamine treatment, the addition of dobutamine is recommended. In these patients, serial echocardiographic studies may aid in adjusting the afterload by the titration of the dose of dopamine to further improve cardiac output.

In summary, dobutamine is the drug of choice in asphyxiated hypotensive preterm infants with myocardial dysfunction who present with elevated peripheral vascular resistance. However, in most preterm infants, dobutamine should not be used as the initial sympathomimetic agent, but rather as an adjunct therapy when hypotension with myocardial dysfunction persists or develops during dopamine administration.

Epinephrine and norepinephrine

Despite the paucity of controlled studies in the neonatal patient population, both epinephrine [37,42] and norepinephrine [43] have been used in the treatment of hypotension in preterm infants not responding to dopamine at or beyond 20 μg/kg/min with or without additional dobutamine administration. It is not known whether there is a difference in the cardiovascular response and/or side effects between the combined use of epinephrine and dopamine compared to the use of increasing doses of dopamine beyond 20 μg/kg/min with or without dobutamine. However, when epinephrine is added to dopamine *and* dobutamine, dobutamine may be discontinued and the dose of dopamine decreased if possible. There have been no detrimental vasoconstrictive effects reported using either high doses of dopamine [36,37] or additional epinephrine [37,42] or norepinephrine [43], a finding best explained by the decreased cardiovascular sensitivity of these preterm infants which necessitated the high sympathomimetic support in the first place.

Epinephrine and norepinephrine induce similar increases in myocardial contractility and heart rate, and epinephrine may cause greater increases in left ventricular output in preterm infants compared to dopamine [42]. On the other hand, norepinephrine, due to the lack of its ability to effectively stimulate the vascular β-adrenergic receptors (Table 1), produces more prominent increases in peripheral vascular resistance than either epinephrine or dopamine. The combined administration of epinephrine or norepinephrine with dopamine may have the advantages of improved renal perfusion and increased renal fraction of cardiac output [44].

Side effect of epinephrine and norepinephrine include unpredictable inappropriate increases in total peripheral vascular resistance resulting in decreased cardiac output and tissue perfusion despite normal or elevated blood pressure values, and hypertension, tachycardia, decreased myocardial oxygen delivery, and severe tissue necrosis with extravasation of the infusate. An important practical limitation of the administration of epinephrine and norepinephrine is that accidental priming of the infusate results in sudden and excessive increases in blood pressure which may contribute to the development of central nervous system complications in this extremely vulnerable population. This side effect is much less prominent with the use of dopamine.

Steroid administration

There is accumulating evidence provided by randomized blinded prospective studies [45,46] and supported by retrospective observations [47–51] that brief dexamethasone or hydrocortisone treatment stabilizes the cardiovascular status and decreases the need for pressor support in critically ill preterm infants with 'pressor-resistant' hypotension. As mentioned above, during the course of critical illness, downregulation of the adrenergic receptors [33] leads to a gradual desensitization of the cardiovascular system to the effects of catecholamines, resulting in the need for escalating pressor support. In addition, relative or absolute adrenal insufficiency [34,35] may contribute to the development of pressor resistance. The ability of glucocorticoids to induce the expression of cardiovascular adrenergic receptors and some components of the second messenger systems [52,53] explains, at least in part, why steroid administration improves blood pressure and decreases the need for pressor support. In addition to this genomic effect, steroids exert certain non-genomic actions [53] including the inhibition of catecholamine metabolism and the release of vasoactive factors. Moreover, via a primarily mineralocorticoid-mediated effect [53], steroids instantly increase intracellular calcium availability, resulting in enhanced myocardial and vascular smooth muscle cell responsiveness to catecholamines. Indeed, recent data suggest that hydrocortisone treatment of the preterm infant presenting with pressor-resistant hypotension is associated with significant increases in blood pressure within 2 hr of its administration while

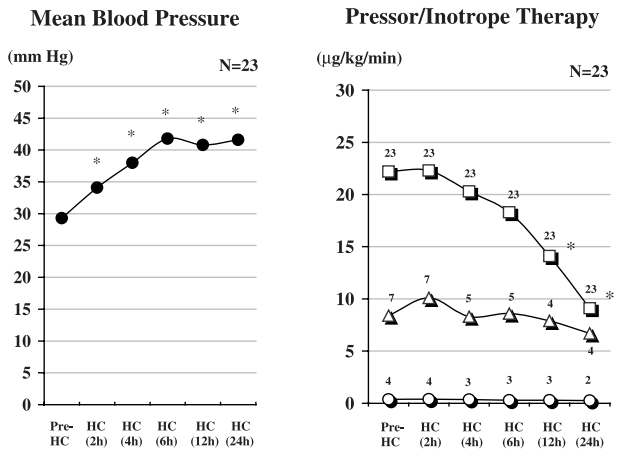

Figure 2. Changes in blood pressure and pressor and inotrope requirement in response to 2 mg/kg/day of hydrocortisone divided Q12 hours in 23 preterm infants with pressor-resistant hypotension. □: dopamine; △: dobutamine; ○: epinephrine; Numbers over the symbols: number of patients on the given sympathomimetic amine; *: $P<0{\cdot}05$ vs Pre-HC; HC: hydrocortisone. Mean blood pressure increased within the first 2 hr of HC administration from 29.9 ± 5.0 to 34.8 ± 5.2 mm Hg, and remained elevated at 6, 12 and 24 hr. The dose of dopamine was significantly decreased by 12 h of HC treatment. Although the dose of dobutamine and epinephrine remained unchanged, the number of patients receiving these two sympathomimetic amines decreased significantly. Fifteen of the 18 patients survived [51].

decreases in pressor requirement occur only after 8–12 hr of the first dose of the drug ([51], Fig. 2). It is tempting to speculate that the rapid increase in blood pressure results from the non-genomic steroidal actions, while the decreases in pressor requirement occurring after a longer period of time are mostly due to the genomic effects of steroids, which require new protein synthesis and receptor expression. However, no study has compared the onset of action and efficacy of hydrocortisone (both gluco- and mineralocorticoid actions) to those of dexamethasone (mainly glucocorticoid actions).

None of the studies investigating the cardiovascular effects of single-dose dexamethasone [45,47,49,50] or a mostly 1- to 3-day hydrocortisone administration [46,48,51,54] reported the occurrence of side effects. However, studies using higher cumulative doses and/or longer courses of steroids in an attempt to treat chronic lung disease have found evidence for potentially significant side effects. The most alarming findings are the increase in the incidence of intestinal perforations [55] and fungal infections [56], as well as the potential deleterious long-term effects of steroids on central nervous system development [57]. Although these

side effects have mainly been associated with longer steroid treatment and/or higher cumulative doses, extreme caution should be exercised when initiating a short course of steroid treatment to enhance cardiovascular stability in critically ill preterm infants with pressor resistant hypotension. Future randomized blinded clinical trials studying the effectiveness and potential side effects of brief and low dose dexamethasone and hydrocortisone administration are necessary to determine the role and type of steroid treatment in critically ill preterm infants with pressor resistant hypotension.

In summary, steroid administration in a carefully selected patient population with pressor-resistant hypotension may be employed using low cumulative steroid doses and thorough monitoring for the potential side effects. Perinatal sepsis does not appear to be a contraindication, at least as long as a single dose of dexamethasone is used [51]. Finally, it is important to emphasize that pressor-resistant hypotension should be defined by the instability of the cardiovascular status and severity of the associated capillary leak syndrome in the critically ill preterm infant and not by establishing arbitrary dose limits for the pressor treatment required to maintain the blood pressure in the desired range.

Supportive measures

Maintenance of a normal arterial pH and serum ionized calcium concentrations is necessary for the optimum cardiovascular response to catecholamines. Since an arterial pH of <7.25 compromises myocardial function in the preterm infant [58], it is recommended that the arterial pH be maintained above this range. Administration of sodium bicarbonate [18,58] or, in cases with severe combined respiratory and metabolic acidosis, that of tromethamine [18] rapidly improves arterial pH and thus myocardial performance.

In summary, sustained stabilization of the cardiovascular status with provision of appropriate blood pressure, cardiac output, tissue perfusion and oxygenation remains a difficult task in most of the critically ill hypotensive preterm infants. Treatment of these patients requires a thorough understanding of the etiology and pathophysiology of neonatal shock and that of the mechanisms of actions, pharmacodynamics and potential side effects of the sympathomimetic amines and the other medications used in their management.

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