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Hemodynamic instability in the critically ill neonate: An approach to cardiovascular support based on disease pathophysiology

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ABSTRACT

Hemodynamic disturbance in the sick neonate is common, highly diverse in underlying pathophysiology and dynamic. Dysregulated systemic and cerebral blood flow is hypothesized to have a negative impact on neurodevelopmental outcome and survival. An understanding of the physiology of the normal neonate, disease pathophysiology, and the properties of vasoactive medications may improve the quality of care and lead to an improvement in survival free from disability. In this review we present a modern approach to cardiovascular therapy in the sick neonate based on a more thoughtful approach to clinical assessment and actual pathophysiology. Targeted neonatal echocardiography offers a more detailed insight into disease processes and offers longitudinal assessment, particularly response to therapeutic intervention. The pathophysiology of common neonatal conditions and the properties of cardiovascular agents are described. In addition, we outline separate treatment algorithms for various hemodynamic disturbances that are tailored to clinical features, disease characteristics and echocardiographic findings.

Introduction

At no other time in development does a human undergo such dramatic change as in the evolution from a fetus at the limits of viability to the term neonate. Superimposed on this changing physiology is the impact of disease states, changes in condition due to environmental exposure and medically indicated therapy. With improvements in knowledge and technology have come an increase in survival of the most fragile neonates; throughout the field there has been increasing need to understand the pathophysiology of disease and the specific actions of therapies. In this review, we will provide an overview of hemodynamic implications of common disease conditions and highlight the clinically relevant properties of cardiovascular medications. We will outline an approach to management that is guided by assessment of clinical parameters and echocardiography if available and is tailored to disease pathophysiology.

Relevance of arterial pressure to contemporary hemodynamic care

Historically, the approach to neonatal cardiovascular support has been based largely on crude measures of the adequacy of the pulmonary or systemic circulation (e.g., blood pressure).

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A singular approach based on mean arterial pressure (MAP) alone represents a physiologic oversimplification and is highly questionable; the majority of normative references have been generated by consensus and expert opinion. Traditional teaching focuses on maintaining mean blood pressure over a set value, most commonly the gestational age (GA) in weeks, using boluses of fluid and the catecholamine receptor agonists dopamine and dobutamine. However, as interest in neonatal hemodynamics has continued to evolve it has been increasingly demonstrated that neonatal cardiovascular physiology is more complex, dynamic and diverse than has previously been appreciated.

The association between blood pressure and impaired neurodevelopmental outcome has been investigated extensively; yet, there has been no consistent link identified which further questions the validity of arbitrary treatment thresholds based on MAP alone. The lack of clarity regarding causality may relate to heterogeneity in methodology and lack of untreated controls; however, failure to consider the heterogeneity of the underlying disease and the impact of treatment is likely a significant contributor. During the transitional period, when neonates are at the greatest risk of intracranial complications, blood pressure is a poor surrogate of blood flow. Cerebral blood flow is governed by a complex interplay between systemic and pulmonary vascular resistance, cardiac output, end-organ resistance of the brain and the effects of therapy on the circulation. Additionally, though there is emerging evidence that the preterm brain is governed by the same rules of autoregulation as adults; it has been suggested that dopamine administration destroys this gentle balance.[1] It is biologically plausible that dysregulation of cerebral blood flow is a significant contributor to the risk of intracranial hemorrhage and white matter injury; hence, it is important to understand and optimize brain perfusion.

Physiological considerations in preterm infants

Extensive research has been done in adults on understanding the regulation of myocardial performance and control of vascular tone. However, the immature fetal cardiovascular system is fundamentally different and relatively less well understood. In contrast to the adult heart, in which 60% of the myocardium is muscular, at early preterm gestations the myocardium contains only 30% contractile tissue, which is relatively disorganized in its alignment.[2] Additionally, the mechanisms of control of myocyte activity such as the sarcoplasmic reticulum and t-tubule system are underdeveloped[2] and there is an overrepresentation of mitochondria which are relatively disorganized.[3] This is tolerated in fetal life due to low placental resistance. However, studies on neonatal lambs have shown that at baseline, markers of myocardial performance are high.[4] This implies that the neonatal myocardium is less contractile and is functioning near its physiological capacity. Therefore, the ability to respond to additional stress placed by metabolic demands (e.g., infection, changing loading conditions) or inotropes may be limited.

The adrenergic system also differs in the immature neonate. There is limited sympathetic innervation to the preterm myocardium and, in animal models it has been shown that as increasing innervation occurs throughout gestation, so too does the proliferation of adrenoreceptors.[5] This suggests that preterm adrenoreceptors demonstrate a unique pattern of upregulation in the face of increasing stimulation. This may explain the finding that myocardial adrenoreceptors show a pattern of "denervation hypersensitivity" in which small concentrations of catecholamine achieve maximal stimulation.[6] Similarly, adrenoreceptors in the peripheral vasculature demonstrate ontogeny. At early gestations, there are few $\beta 1$ receptors but many active $\alpha 1$ receptors.[7] Thus the balance of response to catecholamine stimulating agents is skewed towards peripheral vasoconstriction and afterload augmentation at the expense of cardiac output, which may not be desirable in some patients. That these effects are most pronounced at the earliest gestation and diminish with maturation may underlie some of the variability in response to exogenous catecholamines that is demonstrated in the literature. This underscores the need to be thoughtful when extrapolating from adult data.

Assessment of cardiovascular stability

The traditional approach to defining hemodynamic stability, based almost entirely on arterial pressure, is limited. A healthy cardiovascular system is defined by its ability to adequately deliver sufficient oxygen to the tissues to meet metabolic demands; hence, treatment decisions must include assessment of end-organ function. Evaluation begins with a comprehensive history with particular attention to relevant maternal, perinatal and postnatal factors that may predispose to cardiovascular compromise and should include a physical examination focused on the function of each end-organ. A single parameter is insufficient to inform decision-making; there is considerable variability in normal and multiple confounding factors that affect end-organ function (Table 1).

Blood pressure (BP) is the most commonly used surrogate of end-organ perfusion; however, there are multiple physiologic confounders that make BP an unreliable marker of systemic blood flow (SBF), particularly in preterm infants. The most common definition of low BP is a consensus opinion generated based on the observation that preterm infants typically have MAP greater than their GA in weeks.[8] Several observational studies in small populations have attempted to define "normal" BP and limited data has been published[9] (Table 2). Doppler echocardiography studies of blood flow in the superior vena cava (SVC) have shown that there is a weak relationship between BP and blood flow, particularly in the first 24 h of life when the brain is most vulnerable. In a group of 126 preterms studied at 5 h of age, BP and SVC flow were discordant 42% of the time.[10] Other work has shown that using MAP < GA correctly categorized only 71% of neonates with low SVC flow while 12% were falsely labeled as hypotensive.[11] Low SBF in preterm infants is common. It has been documented to occur in 35% of neonates born before 30 weeks and 61% of neonates born before 27 weeks.[12] In practice, it should be considered in all extremely preterm infants regardless of blood pressure; on the converse, treating low BP in the absence of other markers of end-organ underperfusion might lead to unnecessary

Table 1 – Clinical indicators of cardiovascular health.[16]

Clinical indicator	Pathophysiology	Confounding factors
Tachycardia	Increasing HR may increase CO if stroke volume unchanged	Medications, pain, temperature, agitation
Systolic hypotension	Marker of decreased CO	Transitional circulation, left-to-right shunts
Diastolic hypotension	Marker of systemic vascular resistance and preload	Transitional circulation, left-to-right shunts
Increased capillary refill time	Vasoconstriction of skin	Wide range of normal
Pallor/acrocyanosis	Vasoconstriction of skin	Lighting, temperature, skin tone, anemia
Decreased level of consciousness	Decreased cerebral perfusion pressure	Sedative medications, meningitis, seizures
Decreased urinary output	Decreased renal perfusion pressure	Renal pathology, transitional changes
Elevated lactate	Anaerobic metabolism	Some IEM, haemolysed labs, gluconeogenesis
Metabolic acidosis	Anaerobic metabolism	Bicarbonate loss
Low central venous saturation	Increased oxygen consumption	Catheter placement, peripheral shunts, necrotic tissue

HR = heart rate, CO = cardiac output, SV = stroke volume, IEM = inborn error of metabolism.

intervention. Echocardiography may be an invaluable addition to clinical assessment and identification of these patients; in adult intensive care it has been shown to change management in 30% of patients.[13]

Characterizing the etiology of hemodynamic instability

Identifying the etiology of low SBF may be difficult and is often multifactorial. In the setting of acute hemodynamic collapse, it is essential to consider congenital cardiac lesions that result in duct-dependent SBF (e.g., hypoplastic left heart syndrome, coarctation of the aorta, critical aortic stenosis). In these cases, consultation with a paediatric cardiologist should be sought early. MAP is the most common parameter used to define hemodynamic instability clinically. However, the individual components of systolic (SAP) and diastolic (DAP) arterial pressure may provide valuable insight into underlying pathophysiology, but are rarely considered in routine clinical practice. SAP is reflective of the contractile force and output of the left ventricle and a low value reflects diminished stroke volume (SV). It is determined by 3 factors: left ventricular (LV) preload, contractility and afterload. DAP, in contrast, is reflective of the resting pressure of blood against the vessel walls and is predominantly related to systemic vascular resistance and volume status. Common conditions leading to systolic hypotension include those that lead to low LV preload, poor myocardial contractility or high LV afterload (Fig. 1). In euvolemic patients the most common causes of diastolic hypotension are those that lead to a larger than normal vascular bed. This may be because of vasodilation as in the case of warm septic shock or because of diastolic run off into the pulmonary vascular system in the setting of left-to-right shunt via a patent ductus arteriosus[14] (Fig. 2). Combined systolic and diastolic hypotension reflects a common end-point, which occurs because the circulatory system fails to adapt to ongoing hemodynamic stress. It may be difficult to identify the etiology in rapidly progressive conditions such as severe septic shock; however, the events leading up to the decompensation may provide clues. In some neonates, there is a history and/or clinical symptoms consistent with a clear primary cause of hypotension and understanding the pathophysiology of hemodynamic instability in these common conditions may guide management decisions (Table 3).

Table 2 – Blood pressure thresholds at third percentile according to gestational age (GA).[16]

GA (weeks)	SYSTOLIC (mmHg)	MEAN (mmHg)	DIASTOLIC (mmHg)
24	32	26	15
25	34	26	16
26	36	27	17
27	38	27	17
28	40	28	18
29	42	28	19
30	43	29	20
31	45	30	20
32	46	30	21
33	47	30	22
34	48	31	23
35	49	32	24
36	50	32	25

Hemodynamic instability in the preterm infant

(i) *Patent ductus arteriosus* (PDA) when hemodynamically significant results in a progressive volume of left ventricular output are being diverted from systemic to pulmonary circulation. Though ductal size is a contributing factor, a primary determinant of flow between systems is the difference in pressure between the chambers on either side. Therefore, transductal shunt volume increases as pulmonary vascular resistance (PVR) declines and systemic vascular resistance (SVR) rises after birth; this may result in low SBF and progressive systemic steal particularly to post-ductal organs such as the bowel and kidney.[15] This classically presents as low diastolic BP with normal or slightly elevated systolic BP (hence, wide pulse pressure). In some patients, the high volume of pulmonary blood flow (PBF) returning to the

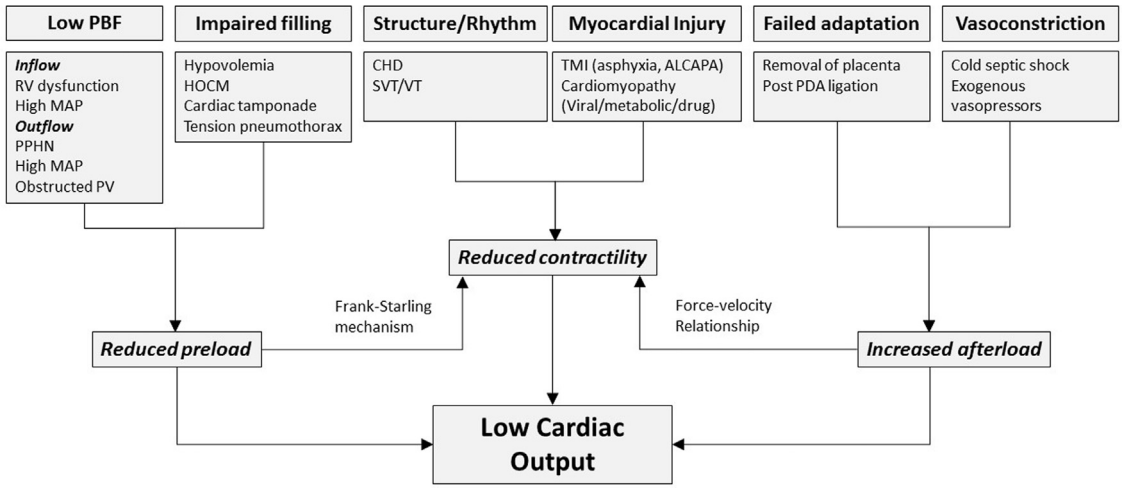

Fig. 1 – Factors contributing to low cardiac output with clinically relevant examples. Multiple factors may lead to low cardiac output and these factors may be additive. Low pulmonary ventricular preload reduces LV filling and further exacerbates impaired contractility by the Frank–Starling mechanism. Increased ventricular afterload causes systolic wall stress and negatively affects contractility via the force–velocity relationship. RV = right ventricle, MAP = mean airway pressure, PPHN = persistent pulmonary hypertension, PV = pulmonary veins, HOCM = hypertrophic obstructive cardiomyopathy, SVT = supraventricular tachycardia, VT = ventricular tachycardia, TMI = transient myocardial ischemia, ALCAPA = anomalous left coronary arising from pulmonary artery, PDA = patent ductus arteriosus.

left side of the heart may not be well tolerated, particularly in the most immature patients. Inability of the LV to augment systolic performance to compensate for a rapid increase in preload may lead to suboptimal cardiac output and both systolic and diastolic hypotension. Simultaneously, high left atrial backpressure contributes to pulmonary venous hypertension, which may result in pulmonary hemorrhage. Principles of management include pharmacologic or surgical closure and limitation of left-to-right shunt by strategies to increase PVR (e.g., permissive hypercapnia, positive end-expiratory pressure).[16] Support for LV systolic performance may be indicated in patients with systolic hypotension; the selection of inotropic agents which augment LV systolic performance without systemic vasoconstriction is desirable, hence dobutamine rather than dopamine may be preferable although a direct head to head comparison in this population has not been performed.

(ii) After *ligation of a hemodynamically significant PDA*, a rapid change in loading conditions may again occur. In neonates with a high volume shunt the left heart is hypervolemic and exposed to the low afterload of the combined systemic and pulmonary circulation. Ligation of the DA results in an immediate reduction in left atrial filling pressure and, in accordance with the Frank–Starling law, early hemodynamic instability may occur due to low-preload associated reduction in contractility.[17] However, provided mean airway pressure is not excessive, there is no obstruction to blood return to the heart (e.g., pneumothorax, pericardial effusion) and intravascular volume status is adequate, this rarely occurs; removal of left-to-right shunt represents a return to normovolemia and not a pathologically low volume state. Exposure to increased afterload upon sudden PDA closure, in contrast, increases LV systolic wall stress and leads to progressive LV systolic dysfunction over a period of 6–12 h after surgery.[18] This leads to a clinical phenotype characterized by systolic hypotension with normal or high diastolic BP; untreated, this may progress to severe hemodynamic instability and oxygenation failure due to pulmonary venous hypertension. Cardiovascular treatments which augment LV systolic performance and

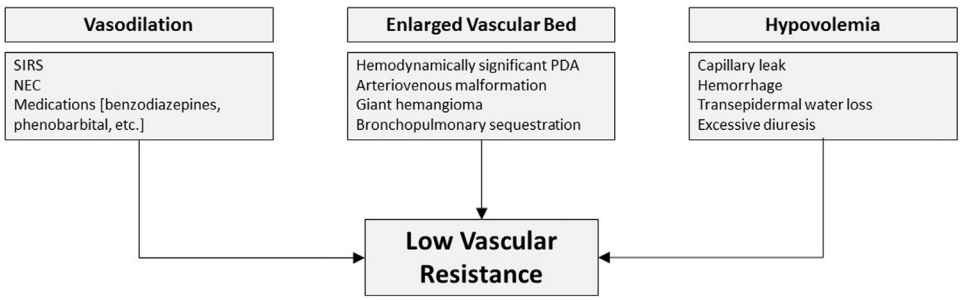

Fig. 2 – Factors contributing to low systemic vascular resistance with clinically relevant examples. Low resting pressure in diastole may occur when vascular bed is larger than usual or volume status is low. SIRS = systemic inflammatory response syndrome, NEC = necrotizing enterocolitis.

lower afterload (e.g., milrinone, dobutamine) are preferable. Adrenal insufficiency in preterm infants undergoing PDA ligation may occur in some patients and may result in early hemodynamic instability and inotrope resistant shock.[19]

(iii) *Sepsis and necrotizing enterocolitis* (NEC) cause systemic inflammatory response syndrome (SIRS) which results in a release of cytokines and alteration of endothelial function associated with vasodilation and capillary leak.[20] This results in lower SVR and third space volume losses. The cardiovascular system adapts by increasing heart rate and the LV becomes hyperdynamic in an attempt to augment cardiac output to meet the high tissue demands (warm shock). This increases myocardial oxygen demand and may cause systolic dysfunction (cold shock).[20] Cardiovascular support using agents with vasoconstricting effects (e.g., vasopressin, norepinephrine, dopamine) is the appropriate initial goal of therapy for neonates with warm shock. However, neonates may progress to or initially present with cold shock, which occurs in severe infection when the circulatory system is vasoconstricted in an effort to redistribute blood to the essential central circulation due to impending circulatory failure. These neonates have high SVR and impaired LV myocardial performance.[21] Cardiovascular agents with predominant inotropic effects (e.g., dobutamine, epinephrine) are recommended. In some patients, particularly those with refractory hemodynamic instability early use of corticosteroid agents (e.g., hydrocortisone) for presumed adrenal insufficiency may be indicated.

Hemodynamic instability in the term infant

(i) *Perinatal hypoxic-ischemic injury* results in transient myocardial ischemia in approximately one-third of patients.[22] This may result in impaired systolic performance and low left ventricular output (LVO). Simultaneously, therapeutic hypothermia results in peripheral vasoconstriction which increases diastolic pressure and may mask hypotension. Cardiovascular agents which augment myocardial performance without systemic vasoconstriction (e.g., dobutamine) may be required. Additionally, hypoxia ischemia is associated with comorbid conditions including pulmonary hypertension and adrenal injury,[23] which may also affect the cardiovascular system and influence treatment choices.

(ii) *Persistent pulmonary hypertension* (PPHN) is a failure of normal decline in PVR after birth. Low PBF leads to poor left heart filling and therefore, low LVO despite normal LV systolic performance. Simultaneously, the right ventricle (RV) is exposed to high afterload which contributes to systolic wall stress and is associated with increased myocardial oxygen demand which is not met by supply due to changes in right coronary artery (RCA) flow. Under normal conditions, the right coronary artery is perfused in systole and diastole; in the absence of pulmonary hypertension a significant pressure gradient exists throughout the cardiac cycle between the RCA ostium in the aortic root and the cavity pressure in the RV. High RV systolic pressure reduces RCA systolic flow and low systemic BP leads to a decline in RCA diastolic flow.[24] This leads to RV myocardial ischemia which causes progressive RV dilation and dysfunction and may further reduce PBF. Therapeutic goals in neonates with oxygenation failure and compromised systemic hemodynamics include reduction of PVR and augmentation of RV systolic function.

(iii) *Infants of diabetic mothers* have an increased risk of hypoxic-ischemic encephalopathy (HIE), PPHN and congenital heart disease, specifically hypertrophic obstructive cardiomyopathy[25] (HOCM); therefore, hemodynamic considerations in these neonates is particularly complex and requires broad consideration. Septal hypertrophy leads to LV diastolic dysfunction and may impair LV filling.[26] These neonates need high LA pressure and conditions that result in low PBF are poorly tolerated. Reduction in pulmonary venous return leads to decreased SV and, in an attempt to improve LVO, tachycardia. The latter is not desirable as a higher heart rate reduces time for diastolic filling and further impairs LVO. Exogenous administration of positive inotropes further complicate the situation by further reducing LV filling time. In these neonates, it is important to maintain high left heart filling pressure, avoid tachycardia and avoid positive inotropes. Cardiovascular agents that augment cardiac preload and induce systemic vasoconstriction (e.g., vasopressin) are desirable. There may a role for use of selective beta blockade (e.g., esmolol) in the chronic management of these patients.

Specific cardiovascular therapeutic agents

Though low arterial pressure is an imperfect surrogate for low SBF, it remains the most readily available bedside measurement of circulatory adequacy. With an understanding of its limitations and careful appraisal of pathophysiology, a combination of BP thresholds and the information gathered from ancillary investigations may guide management (Fig. 3). In general, as compared to adult literature, there is less emphasis on volume and more on appropriate selection of vasopressor or inotropic agents.

Volume

The traditional approach to systemic hypotension considered volume expansion as a pre-requisite first line therapy, irrespective of the etiology.[27] It is more appropriate to consider volume expansion with a crystalloid solution (e.g., 0.9% saline) in clinical situations consistent with hypovolemia, independent of GA. If there is a history of hemorrhage or significant anemia, packed red blood cell transfusion is indicated. However, without this history evidence suggests that crystalloid and colloid have equal efficacy. In fact, crystalloid is typically preferred over albumin as it is associated with a lower risk of fluid retention and albumin has been associated with impaired gas exchange.[28,29] In preterm infants without a history of acute blood loss or hypovolemia the role of fluid is less clear. Evidence from animal experimental models has shown that rapid administration of

Table 3 – Suggested approach to management based on clinical findings and disease physiology in common clinical conditions.

Disease	Presenting features	Pathophysiology	Suggested management approach
PDA	Low DAP, mild systemic end-organ dysfunction	Left-to-right shunt	***First line*** Shunt limitation strategies (PCO_2 50–60 mmHg, minimize FiO_2, optimize PEEP and Hb) Ductal closure: e.g., NSAID, acetaminophen, surgery
	Low SAP and DAP, severe end-organ dysfunction, pulmonary hemorrhage	Left-to-right shunt with poor LV systolic compensation	***First line*** Shunt limitation strategies, ductal closure ***Second line*** Positive inotropic agent: e.g., dobutamine
Post PDA ligation	Low SAP, respiratory deterioration, hypoxia	LV systolic dysfunction and high afterload	***First line*** Positive inotropic agent: e.g., dobutamine (if low DAP), or milrinone (if normal or high DAP) ***Second line*** Hydrocortisone if impaired adrenal response
Sepsis/NEC	Warm shock: Low DAP, tachycardia	Vasodilation, capillary leak, relative or absolute hypovolemia, high cardiac output	***First line*** Volume (crystalloid, blood products) Vasopressor agents: e.g., dopamine ***Second line*** Vasopressor agents: e.g., vasopressin, norepinephrine
	Cold shock: Low SAP or severe/combined hypotension	Vasoconstriction, low cardiac output	***First line*** Modest use of volume expansion (crystalloid or blood products) Positive inotropic agent: e.g., epinephrine ***Second line*** Hydrocortisone
Hypoxic-ischemic injury	Low SAP, normal oxygenation	LV or RV systolic dysfunction	***First line*** Positive inotropic agent: e.g., dobutamine ***Second line*** Positive inotropic agent: e.g., epinephrine Prostaglandin (if restrictive or no DA) Hydrocortisone if refractory
	Low SAP, oxygenation impairment	LV systolic dysfunction with PPHN	***First line*** Positive inotropic agent: e.g., dobutamine ***Second line*** Epinephrine (positive inotrope, may worsen oxygenation), may require selective pulmonary vasodilation: e.g., iNO Prostaglandin (if restrictive or no DA)
	Low SAP, oxygenation impairment	RV systolic dysfunction with PPHN	***First line*** Positive inotropic agent: e.g., dobutamine ***Second line*** Selective pulmonary vasodilator: e.g., iNO Prostaglandin (if restrictive or no DA) ***Third line*** Epinephrine (positive inotrope, may worsen oxygenation) Systemic vasoconstriction and pulmonary vasodilation: e.g., vasopressin, norepinephrine
PPHN	Hypoxemia, low SAP	Low LV preload, right-to-left ductal shunt, Normal LV and RV systolic function	***First line*** Sedation, muscle relaxation, optimum ventilation, pulmonary vasodilators e.g., iNO ***Second line*** Milrinone if normal MAP and DAP Vasopressin if low MAP and DAP Prostaglandin (if restrictive or no DA)
	Hypoxemia, low SAP	Low LV preload, right-to-left ductal shunt, LV and/or RV systolic dysfunction	***First line*** Optimize MAP for lung disease, reduce if possible, sedation & muscle relaxation Pulmonary vasodilator (iNO) Dobutamine (if low MAP/DAP) Milrinone (if normal or high MAP/DAP) ***Second line*** Vasopressin (if low MAP/DAP)

Table 3 (continued)

			Prostaglandin (if restrictive or no DA)
IDM	Tachycardia, low SAP, respiratory distress	LV diastolic dysfunction, impaired filling	*First line* Volume to optimize left atrial pressure, avoid inotropes and tachycardia *Second line* Increase afterload: e.g., vasopressin

SAP = systolic blood pressure, MAP = diastolic blood pressure, DAP = diastolic blood pressure, Hb = hemoglobin, LV = left ventricle, RV = right ventricle, PDA = patent ductus arteriosus, NEC = necrotizing enterocolitis, PPHN = persistent pulmonary hypertension, IDM = infant of diabetic mother, iNO = inhaled nitric oxide, NSAID = non-steroidal anti-inflammatory drug.

volume without hypovolemia results in no change in cardiac output or blood pressure.[30] The neonatal literature is limited to small studies. Modest increase in both SVC flow and LVO have been shown in some human infants with low SBF. This suggests that low LV preload was a component of low cardiac output in these infants. Though it is biologically plausible that modest volume expansion has a positive effect on hemodynamics in some neonates, caution should be exercised. Volume expansion has no effect on cerebral oxygen delivery, as compared to cardiotropic agents (e.g., dopamine) which may provide small increases in markers of cerebral oxygenation as measured by near infrared spectroscopy (NIRS).[31] Excess fluid administration is associated with increased morbidity and mortality.[32] A trial of 10–20 ml/kg of crystalloid is recommended as an important component of the initial management of hypotension if deemed clinically relevant and appropriate for the specific pathophysiology in question. In addition to the above reasons, concealed hemorrhage may be difficult to detect in clinical practice. If this is unsuccessful early initiation of pharmacologic support is recommended.

Pharmacologic therapy

The mainstay of pharmacologic therapy includes exogenous administration of various catecholamine agonists each of which have different mechanisms. The selection of a specific catecholamine should consider specific developmental and pathophysiological factors unique to the index case. These drugs interact with a population of myocardial and peripheral adrenoreceptors including 2 major types (α and β), each of which has multiple subtypes[33] (Fig. 4). In addition to the catecholamine agents, two other classes of medications are increasingly used in the management of hemodynamic instability in neonates. These are the hormone vasopressin and its analogs and phosphodiesterase inhibitors (e.g., milrinone). Cardiovascular therapeutic agents may be divided into drugs that have predominantly vasopressor activity (e.g., dopamine, vasopressin, norepinephrine) and those with predominantly inotropic activity (e.g., dobutamine, milrinone) based on their receptor profile and mechanism of action (Table 4). Epinephrine is an inotropic agent with variable dose dependent vasoactive effects. The effects of hydrocortisone are complex with multiple interacting mechanisms of action. Choice of therapeutic agent should depend on the pathophysiology of the underlying disease state and the intended effect.

Systemic effects of primary inotropic agents

Dobutamine is a synthetic catecholamine developed in the 1970s. It is supplied as a racemic mixture in which the (+) enantiomer has predominantly β1 and β2 adrenergic activity and (−) enantiomer has α1 adrenergic effects.[36] In animal studies, dobutamine has been shown to increase cardiac output via effects on both heart rate and stroke volume.[37–39] The chronotropic effect of dobutamine may occur early after initiation of infusion; however, tachycardia is less clinically significant as compared to selective β agonists (e.g., isoproterenol) and after the first 10–60 min of infusion, the positive inotropic properties of dobutamine dominate its therapeutic effect. Though dopamine has consistently been identified as superior at increasing blood pressure, echocardiography studies have identified that dopamine's predominant mechanism is via peripheral vasoconstriction with little increase in LVO[40] or SVC flow.[41] Dobutamine, in contrast, has been shown to increase cardiac output by increasing stroke volume in a dose dependent fashion. In the peripheral circulation the β2 mediated vasodilation and α1 mediated vasoconstriction have effects which negate each other; hence, there is minimal impact on systemic BP and afterload. Consequently, dobutamine may be more effective at improving SBF. In a randomized, blinded trial SVC flow increased by 35% in preterm neonates receiving dobutamine as compared to a 1% decrease in dopamine treated neonates.

Milrinone is a selective phosphodiesterase 3 (PDE-3) inhibitor that increases intracellular 3′5′ cyclic adenosine monophosphate (cAMP) by blocking the enzyme pathway for its degradation. PDE-3 is present in vascular smooth muscle and myocardium.[42] In both the pulmonary and systemic vasculature, the presence of increased cAMP results in an increase in NO signaling which decreases intracellular calcium and leads to vasodilation. Milrinone has been shown in adult[42,43] and neonatal subjects to lead to reduction in systemic blood pressure. Hence, extreme caution should be used with administration of milrinone to hypotensive patients, particularly as the half-life of milrinone in term neonates is approximately 4 h[44] and is likely to be prolonged in the presence of organ dysfunction, prematurity, and hypoxic-ischemic encephalopathy with/without therapeutic hypothermia. Despite this limitation, milrinone has been shown to improve hemodynamics by using indices of right and left ventricular function in a variety of cardiovascular conditions in the term neonate. These include post-cardiac surgery[43], congenital diaphragmatic hernia,[45] and PPHN.[46] In preterm

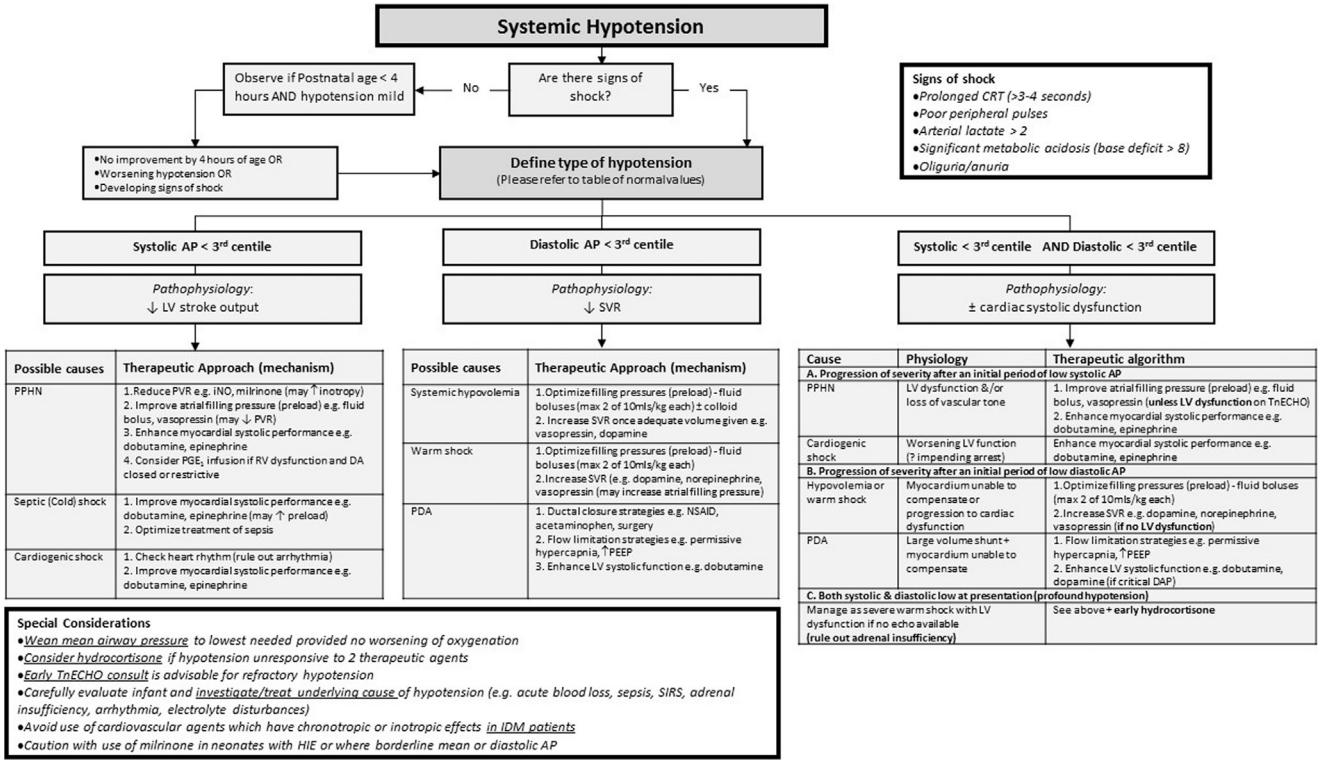

Fig. 3 – Algorithm for the assessment and treatment of hypotension according to systolic, diastolic and combined systolic and diastolic categories.[16] CRT = capillary refill time, AP = arterial pressure, LV = left ventricle, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, iNO = inhaled nitric oxide, PGE_1 = prostaglandin E_1, NSAID = non-steroidal anti-inflammatory drug, PEEP = positive end-expiratory pressure, PDA = patent ductus arteriosus, PPHN = persistent pulmonary hypertension, TnECHO = targeted neonatal echocardiography, SIRS = systemic inflammatory response syndrome.

infants, a randomized trial failed to demonstrate benefit in preventing early low SBF in a general population of newborn extremely low birth weight (ELBW) neonates.[47] However, this study failed to consider heterogeneity of causes of low SVC flow (e.g., hypovolemia, PPHN, PDA) in the study population, which is likely to have impacted the results. In specified populations of preterms, PDE-3 inhibition has a role. Milrinone prophylaxis is associated with a lower risk of post-operative instability after ligation of hemodynamically significant ductus arteriosus.[48] An improvement in oxygenation and RV function has been documented in ELBW infants with pulmonary hypertension.[49] Augmentation of intracellular cAMP leads to positive inotropy, lusitropy, reduction in PVR and reduction in systemic afterload which may all contribute to beneficial effects in these populations.

Systemic effects of primary vasopressor agents

Dopamine is an adrenergic agent with variable and unpredictable effects in the immature neonate. It is an agonist of multiple receptors including α, β, and dopaminergic receptors and approximately 25% of infused dopamine is converted into norepinephrine which may contribute to its cardiovascular effects; dopamine also has a variety of non-hemodynamic effects demonstrated in adult, neonatal and animal models. Animal models suggest renal effects at low doses, an increase in myocardial contractility via α adrenergic effects at moderate doses and a predominant vasoconstrictive effect via adrenergic receptors at higher doses. In the neonate, there is limited pharmacodynamic data and this progression is less clear. In fact, it has been shown that there is considerable variability in response to dopamine between individual neonates even at similar doses. When administered at doses of 6–8 μg/kg/min, some neonates demonstrate an increase in LVO, through augmented myocardial performance, with a modest increase in MAP; at equivalent doses other patients demonstrate a larger increase in MAP, due to exaggerated systemic vasoconstriction, but at the expense of a reduction in LVO and end-organ perfusion.[40] An increase in blood pressure without a change in heart rate, suggesting significant activation of α but not β receptors, has been demonstrated with doses as low as 2–4 μg/kg/min in some preterm neonates.[50] High doses of dopamine have been associated with arrhythmia in several models.[51] This variability is likely related to dose independent developmental variation in adrenergic receptors among neonates leading to differences in the balance of inotropic versus vasoconstrictive effects. The clinical implication of this degree of unpredictability is a concern; caution should be used in immature patients when dopamine is used, particularly at higher doses. Additionally, it has been suggested that the metabolism and clearance of dopamine are decreased in preterm neonates,[50] which may further underscore the need for cautious use. In specific disease states, such as vasodilator septic shock where vasoconstriction is the desired effect, however, this may be

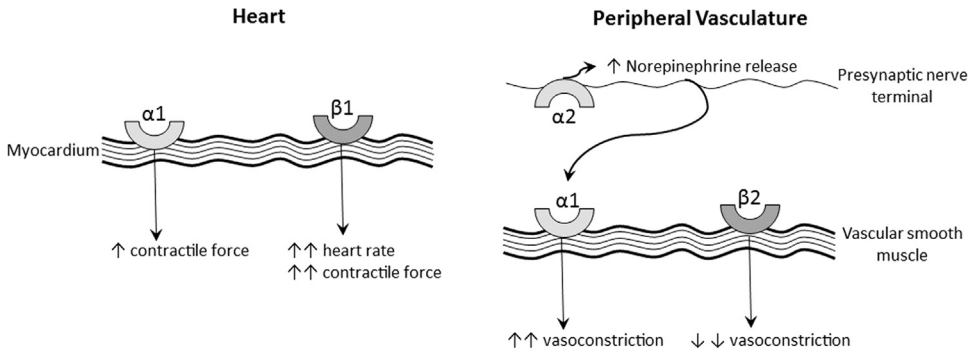

Fig. 4 – Dominant distribution of adrenoreceptors subtypes in the heart and peripheral vasculature. α1 receptors are present in both heart and vascular smooth muscle (VSM) and increase inotropy and vasoconstriction. α2 receptors increase release of norepinephrine from the presynaptic membrane thereby stimulating α1 mediated vasoconstriction. β1 receptors are present in the myocardium and increase inotropy and chronotropy. β2 receptors induce vasodilation in VSM.[33,35]

less relevant. In addition to its effects on systemic hemodynamics, dopamine has important actions in localized vascular beds such as coronary and renal vessels. In a piglet model dopamine increases coronary blood flow in proportion to myocardial oxygen demand suggesting no net change in myocardial oxygen delivery.[52] The renal vasculature has received particular attention. In healthy human adult and animal models low dose dopamine has been associated with diuresis and naturesis and is known to produce vasodilation of the renal vascular bed resulting in an increase in renal blood flow.[51] This is thought to be due to inhibition of norepinephrine release via activation of the DA-1 subclass of peripheral dopamine receptor in the renal vasculature.[53] However, in neonatal experimental models this action has not been shown. Dopamine has no effect on renal blood flow in newborn piglets, and in fact produces an increase in renal vascular resistance and reduction in urinary output even at low doses.[53] Similar results have been shown in other neonatal animal models. This may be related to immaturity of the dopaminergic receptor system in the neonate; the observed response occurs due to activation of the dominant peripheral α receptors resulting in renal vasoconstriction.

Norepinephrine, a potent non-selective α agonist with some effect at the β1 receptor, is a first line therapy in adult and pediatric vasodilator shock. It is an endogenous catecholamine which predominantly arises due to release from sympathetic nerve terminals with a minor component released from the adrenal medulla. In human adults and animal models, norepinephrine is associated with increase in SVR and SAP with little or no change in heart rate or CO.[54] Studies in human neonates are sparse; however, there is limited experience suggesting that norepinephrine may be effective in some term neonates with shock refractory to dopamine and dobutamine.[55]

Vasopressin is an endogenous neuropeptide which is secreted from the posterior pituitary gland. It has a variety of actions, chiefly, regulation of plasma osmolarity, circulating blood volume and vascular tone. The osmotic effects of vasopressin play a role in defending against hypovolemia and hemorrhage.[56] This is mediated by V2 receptors in the collecting duct of the kidney, where the primary action is water reabsorption via regulation of aquaporins. Though vasopressin increases renal blood flow,[57] its use in non-hypovolemic patients may be associated with hyponatremia due to fluid retention and naturesis which resolves with discontinuation of administration. In major organs in the systemic circulation (e.g., skin, liver, pancreas), vasopressin is a potent vasoconstrictor. This action is mediated via V1 receptors located in vascular smooth muscle which, when stimulated, because an overall increase in SVR and increase in BP. Additionally, in the presence of ACTH, vasopressin is associated with an increase in adrenal cortisol secretion; hence, it may act synergistically with catecholamine therapy.[58] Vasopressin has been shown to improve hemodynamics and short-term physiologic end-points in adult and paediatric patients with severe sepsis.[56] Although human neonatal data is limited, there have been reports of successful use of vasopressin in catecholamine resistant shock.[59–61] Cardiac output may decrease with vasopressin therapy; caution is advised in neonates known to have or who are at higher risk for impaired myocardial performance. In isolated heart preparations, vasopressin has been associated with negative inotropy without myocardial ischemia and with prolongation of diastolic indices.[62,63] The mechanism and clinical significance are not known. Finally, stimulation of central nervous system vasopressin receptors (V3) is associated with a reduction in heart rate. Though this effect remains to be proven in neonates, it has theoretical benefit

Table 4 – Comparison of net actions of predominant vasopressors (dopamine, norepinephrine, vasopressin) and predominant inotropes (dobutamine, epinephrine, milrinone) on SV, SVR, and PVR.[34]

Agent	SV	SVR	PVR
Dopamine	↑	↑↑	↑↑↑
Norepinephrine	↑/(no effect)	↑↑↑	↓/(no effect)
Vasopressin	↓	↑↑↑	↓
Dobutamine	↑↑	(no effect)	(no effect)
Milrinone	↑↑	↓↓	↓↓
Epinephrine	↑↑↑	↑↑↑	↑↑

SV = stroke volume, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance.

in some conditions, particularly for hypotensive infants with LV diastolic dysfunction associated with septal hypertrophy.

Systemic effects of agents with both inotrope and vasopressor activity

Epinephrine is an endogenous catecholamine that is released by the adrenal gland in response to stressful stimuli. It is a potent non-selective α agonist and also activates both β1 and β2 receptors.[33] It has been studied in normal animal models and models of neonatal disease physiology such as perinatal asphyxia and hypoxic respiratory failure. In a piglet model doses <1.6 μg/kg/min epinephrine increase CO and lower both PVR and SVR, while doses >1.6 μg/kg/min may lower CO and increase SVR and PVR.[64] In comparative studies, epinephrine has been shown to increase stroke volume, cardiac output, and systemic vascular resistance; hence, systemic blood pressure to a greater degree than dopamine.[65,66] In human neonates, the studies of the effects of epinephrine are limited; however, in small populations, low dose epinephrine has been suggested as having a superior effect on CO as compared to equivalent doses of dopamine due to a more significant increase in both heart rate and SV.[67,68] Epinephrine, however, is associated with metabolic derangement not seen with dopamine. This includes an increase in plasma lactate and serum glucose due to an increase in gluconeogenesis and to exacerbation of metabolic acidosis.[68] Similar to dopamine, the effects of epinephrine in other systemic vascular beds have been investigated. The effect of epinephrine on coronary hemodynamics is complex. In isolated coronary artery preparations, direct injection of epinephrine results in constriction of the coronary vascular bed.[69] Given the increase in myocardial oxygen demand that occurs with the inotropic and chronotropic effects of epinephrine, chronic use may lead to myocardial ischemia. In the piglet model, it has been shown that systemic infusion of epinephrine results in a reduction in coronary vascular resistance; hence, an increase in coronary blood flow, that greatly outstrips the increased demand.[64] There is also evidence that prolonged exposure to high-dose epinephrine infusion in the neonatal porcine model is associated with myocardial injury and impaired compliance via rupture of sarcolemma and deposition of calcium graduals in the mitochondria.[70]

Corticosteroids are frequently used in the management of hypotension in preterm and sick term neonates. In particular hydrocortisone has been shown to increase systemic blood pressure in preterms with refractory hypotension within 2–6 h[71] without compromising cardiac function, systemic or end-organ blood flow.[72] The mechanism is complex and multifactorial. At a cellular level both the mineralocorticoid and glucocorticoid effects of exogenous steroid administration are implicated in its hemodynamic effects (Fig. 5). Upregulation and potentiation of receptor pathways for both α agonists and angiotensin II have been documented.[73] Cytosolic calcium availability in vascular smooth muscle is increased instantly and steroids inhibit local production of vasodilators such as inducible nitric oxide synthase and prostacyclin.[75] In physiologic models it has been shown that repetitive stimulation of catecholamine receptors results in decoupling from intracellular signaling mechanisms and therefore, downregulation of the response to stimulus.[76] This may be countered by provision of exogenous corticosteroid which may increase cell surface adrenergic receptor expression.[77] In addition to direct cellular effects, glucocorticoids have endocrine effects that act to increase circulating catecholamines, which may be of particular benefit in preterm neonates. Relative adrenal insufficiency in the face of critical illness has been documented in all human populations.[78] Neonates are uniquely vulnerable due to immaturity and abrupt loss of placental secretion of high levels of corticotrophin releasing hormone at delivery. Unexpectedly low serum cortisol levels in the face of clinical instability have been documented in term neonates who subsequently have a normal response to exogenous ACTH.[78] This suggests a deficient pituitary signal with intact adrenal function. Preterm infants may have the compounding effect of immature adrenal enzyme systems. Glucocorticoids induce the final enzyme in the conversion of stored norepinephrine to epinephrine in the adrenal gland and hence, increase the release of epinephrine into circulation, bypassing these limitations. Finally, corticosteroids have been implicated in improving capillary leak[75] in sepsis and therefore may increase circulating volume in these patients. Hydrocortisone, a combined mineralocorticoid and glucocorticoid, is the most well studied corticosteroid and is typically given in a dose of 2–4 mg/kg/d. A common regime is to give a loading dose of 2 mg/kg followed by 2 mg/kg daily in divided doses Q12 h or Q6 h.

Pulmonary effects of cardiovascular therapies

In the neonate, the effects of cardiovascular agents on PVR are of particular importance for two reasons. Due to the dramatic physiological change required to transition from intrauterine to extrauterine circulation, disease processes associated with dysregulation of pulmonary blood flow and hypoxemia are common. Secondly, the frequent presence of shunts at the ductal and atrial level may significantly affect systemic hemodynamics, particularly when cardiovascular agents have differential effects in systemic versus pulmonary vascular beds (Table 4).

Exposure to significant hypoxia results in vasoconstriction in both pulmonary and systemic vasculature; however, there is a greater effect on PVR which results in an increase in the PVR:SVR ratio.[52] Drugs that have a favorable profile may include those that have a relatively greater vasoconstrictive effect on the systemic vasculature and, when pulmonary hypertension is associated with myocardial dysfunction, those with positive inotropic properties. In neonates with myocardial dysfunction and PH, dobutamine is a good first line agent as it has positive inotropic properties and little, if any, effect on the vasculature.[38] The net result is an increase in pulmonary and SBF in equal proportion and little change in PVR:SVR ratio. Both vasopressin and milrinone may have favorable effects in the pulmonary circulation and may be used in different circumstances. Milrinone is a potent vasodilator of the pulmonary vascular bed; its positive inotropic and lusitropic properties make it attractive in neonates with

pulmonary hypertension. Use is limited by systemic vasodilation, particularly when the neonate has low mean or diastolic BP; therefore, it is not recommended for neonates with pulmonary hypertension and systemic hypotension. Vasopressin has a weak vasoconstrictive or even vasodilatory effect in the pulmonary, coronary and cerebral circulation. The specific mechanisms of this are unclear; however, physiological studies suggest that vasodilation is endothelium dependent and related to release of nitric oxide.[56] Studies in humans and adult animals have demonstrated reduction in PVR with vasopressin therapy; it has been used successfully to increase SVR and reduce PVR in cardiac surgery patients.[79] Its properties make it a good choice as a single agent or adjunct for neonates with normal LV systolic function, high PVR and low SBF/systemic hypotension. There are case reports of successful use in neonates with pulmonary hypertension.[80] Norepinephrine has limited evidence in neonates; however, there is some suggestion of augmentation of systemic BP with reduction in PVR in term neonates with pulmonary hypertension.[81]

The effects of dopamine and epinephrine on PVR have been compared in both human and animal neonatal models. In comparative trials, epinephrine has been consistently shown to have a superior profile. Both drugs have combined α and β effects; however, while epinephrine is non-selective, dopamine predominantly stimulates the β1 subtype.[33] This may account for some of the difference in their effect on PVR, though the specific mechanism is unknown. While both drugs increase both SVR and PVR, epinephrine does so proportionally, thereby preserving the PVR:SVR ratio while dopamine produces a greater increase in PVR.[52] In neonates with refractory hypoxic respiratory failure, severely impaired oxygenation may prohibit the use of either drug. However, when small increases in PVR may be tolerated and positive inotropy is required, epinephrine is a superior agent.

Using physiology to guide management

An understanding of the pathophysiology and the properties of different therapies allows an individualized approach to management. It is prudent to first evaluate whether blood pressure readings are accurate and whether there is co-existing low SBF. If the clinical situation is consistent with compromised hemodynamics and treatment is indicated, an assessment of systolic versus diastolic hypotension may provide insights regarding the pathophysiologic nature of the disturbance and guide treatment (Fig. 3).

Approach to systolic hypotension

Initial steps should include management of non-cardiovascular factors contributing to low LV filling such as high mean airway pressure and pneumothorax. It is uncommon for hypovolemia to be a significant contributor to cardiogenic shock; after an initial 10–20 ml/kg of crystalloid to increase preload, further volume in the initial phase is unlikely to be of additional benefit and may lead to delay in instituting inotropic support, which has demonstrated to be more effective. Neonates with sepsis are at risk of hematologic derangement and blood products may be needed to correct these. Oxygen carrying capacity should be maintained by packed red blood cell (pRBC) transfusion. Agents used in the treatment of low systolic BP are primarily those that augment stroke volume; empiric therapy for neonates with cardiogenic shock (e.g., HIE) is an inotropic agent such as dobutamine. Epinephrine is more potent and should be considered in cases of severe myocardial depression or where systemic hypotension co-exists. Epinephrine is associated with an increased risk of metabolic complications and therefore should be weaned as soon as possible. Cold septic shock is often characterized by impaired systolic performance which should be treated similarly in an effort to augment cardiac output to overcome high SVR. In infants with associated hypoxemia, PPHN should be considered. The first goal of therapy in these patients is to improve left atrial filling and institute strategies to lower pulmonary vascular resistance, such as optimizing alveolar ventilation, sedation and/or muscle relaxation, and selective pulmonary vasodilators (e.g., inhaled nitric oxide) should be considered first line. Milrinone is a useful adjunct and has shown been shown to have synergistic pulmonary vasodilator effects when co-administered with nitric oxide.[82] Neonates with low or borderline mean/diastolic BP require careful consideration as milrinone may cause significant hypotension. Milrinone should be used with extreme caution in neonates with PPHN and HIE, as drug metabolism may be impaired leading to exaggerated drug level and consequential hypotension. Vasopressin increases SVR and may concurrently vasodilate the pulmonary vascular bed resulting in improved systemic BP, reduction in right-to-left ductal shunt, improved pulmonary blood flow and consequent improved left atrial preload. Caution is advised when cardiac function is unknown or impaired as there may be negative inotropic and chronotropic effects and increased LV afterload may not be tolerated without myocardial support.

Approach to diastolic hypotension

Liberal use of volume is recommended in conditions compatible with acute volume depletion (e.g., abdominal wall defects, acute blood loss) and acute hemorrhage should be treated with pRBC transfusion. The rate of administration depends on the underlying disease process; rapid administration (over 10–30 min) of 15–20 ml/kg of O^- blood may be indicated in hemodynamic collapse after an acute hemorrhage. Inotropic agents should be avoided in hypovolemia as these neonates are typically hypercontractile and tachycardia may impair filling and worsen SBF. If pharmacologic support is required agents with predominant vasopressor properties are recommended. In the setting of a *hemodynamically significant PDA*, diastolic hypotension is best managed by strategies to increase PVR and therefore, reduce left-to-right shunt [e.g., minimizing oxygen (e.g., target SpO_2 88–92%), permissive hypercapnia (e.g., CO_2 50–60 mmHg), optimizing positive end-expiratory pressure]. This alone may be sufficient to resolve low diastolic BP and improve SBF. Neonates with progressive hemodynamic instability despite careful attention to these factors should be considered to have inadequate LVO and dobutamine may be an appropriate therapy to augment SBF. Systemic vasoconstrictors should be avoided. Maintaining oxygen carrying capacity by pRBC transfusion for hemoglobin <100 is recommended to optimize tissue oxygen

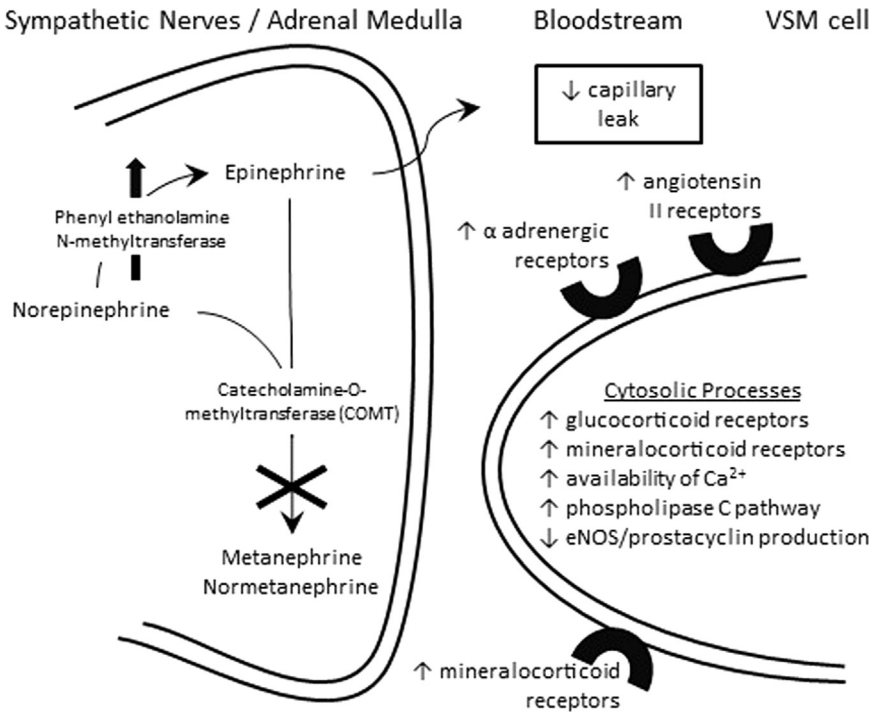

Fig. 5 – Major mechanisms of action of hydrocortisone. At the cellular level, hydrocortisone upregulates genomic production of cell surface receptors for vasoactive substrate and rapidly modifies intracellular second messaging systems associated with vasoconstriction. In sympathetic nervous tissue, conversion from NE to E is increased and the rate limiting enzyme in the breakdown of catecholamines (COMT) is inhibited resulting in an increase in vasoconstrictive mediators. Capillary leak is reduced.[73–75]

delivery. Closure of the PDA using medical or surgical management to limit the impact of chronic left-to-right shunt should be guided by echocardiography. Neonates with *NEC/SIRS* require a composite approach. Many patients may have significant third space losses, making assessment of intravascular volume status difficult. Volume up to a maximum of 60 ml/kg may be required in aliquots of 10–20 ml/kg. Vasodilation is a prominent feature[20] and many patients have a hypercontractile LV on echocardiography and normal or high cardiac output[21]; initial therapy is with crystalloid followed by early consideration of systemic vasoconstrictors such as dopamine. Targeted neonatal echocardiography (TnECHO) may be an invaluable aid to decision-making, particularly in infants who have failed to respond to a single agent.[21] Use of more potent vasoconstrictors (e.g., vasopressin, epinephrine, norepinephrine) should be guided by TnECHO wherever possible. Hydrocortisone should be considered in neonates that fail to respond to one inotrope, recognizing that it may take several hours to be effective.[71]

Approach to combined systolic and diastolic hypotension

Progression of severity results in either deterioration of LV function or loss of vascular tone and echocardiography may be useful. Neonates who present with profound hypotension should be managed as severe warm septic shock with presumed associated LV dysfunction. Modest volume expansion followed by agents that increase SVR should be considered. Dopamine remains first line and both norepinephrine and vasopressin may be considered. Neonates with compromised LV function may deteriorate if afterload is increased without supporting contractility and epinephrine may be more appropriate. Hydrocortisone should be considered early.

The role of targeted neonatal echocardiography (TnECHO)

In all neonates, it is important to consider that physiology changes rapidly over time with adjustments in management and progression of disease. Intra-arterial blood pressure monitoring, frequent investigation of biochemical markers (e.g., gas, lactate) and longitudinal reassessment is essential. Access to longitudinal TnECHO offers enhanced diagnostic accuracy, novel physiologic insights and enables ongoing monitoring of response to therapeutic intervention.[83] The interaction between disease pathophysiology and specific cardiovascular agents used may be complex; oftentimes, more than one agent is required to optimize therapy in critically sick neonates. The relative effects of disease and therapy may be impossible to distinguish without direct interrogation of actual physiology using TnECHO. The addition of multiple agents without interval reassessment may lead to unnecessary iatrogenicity and complications; for example, when used in combination, dopamine and dobutamine may lead to a hyperdynamic state with supranormal cardiac output without changes in blood pressure.[84] In neonates with IDM these effects are exaggerated as the specific cardiac phenotype (septal hypertrophy) tolerates hyperinotropy poorly leading to compromised cardiac output due to limited ventricular filling. When possible ineffective agents

should be discontinued and subtle changes in clinical condition could indicate emergence of side effects or competing effects of medications. In general, three or more simultaneous medications should be avoided. In at-risk populations, echocardiography may provide clarity by uncovering novel pathophysiologic insights that require a different approach to therapy and may only be identified with a very high index of suspicion on clinical grounds (e.g., infant of diabetic mother, twin-to-twin transfusion syndrome, suspected pericardial effusion). In other populations, such as a neonate with hypoxic-ischemic encephalopathy and concurrent pulmonary hypertension, the physiology may be complex with multiple competing factors; direct visualization is the only way to target therapy. Referral for TnECHO should be considered in the assessment of neonates with critical hypotension or low SBF refractory to first line therapy. Echocardiographic assessment of preterm infants is invaluable in distinguishing between aetiologies of diastolic hypotension and low SBF.[83] The specific findings of PDA, hypovolemia that occurs in association with intracranial hemorrhage, and sepsis may be difficult to distinguish on clinical exam. Bounding pulses, murmur and wide pulse pressure are evidence of hyperdynamic circulation that may be attributable to any single pathology or a combination thereof and treatment varies considerably.

Neonates with HIE also benefit from comprehensive assessment of myocardial function. It may be difficult to detect a true low cardiac output state if a neonate is undergoing therapeutic hypothermia. The ability of BP and heart rate to predict circulatory adequacy is confounded by changes in myocardial conduction velocities,[85] vascular tone[85] and redistribution of cardiac output[86] due to therapeutic hypothermia. Elevated lactate, metabolic acidosis and symptoms of end-organ dysfunction may be due to the initial insult or ongoing low SBF. Dobutamine is recommended for LV or RV dysfunction identified on TnECHO. Second line therapy may include epinephrine, particularly for hypotensive patients. Prostaglandin may be indicated in severe LV dysfunction to support post-ductal blood flow via right-to-left shunt and in severe RV dysfunction to reduce systolic wall stress by reducing RV afterload[87] (Table 3).

Assessment of myocardial function is also indicated in infants with PPHN, particularly with refractory hypoxemia or hemodynamic instability[88] (Table 3). If RV performance is compromised agents with inotropic properties are indicated. Epinephrine should be used cautiously in neonates with severe hypoxemia as the α-adrenergic effect may result in elevation of PVR and worsen oxygenation.[66] Milrinone is an ideal agent if systemic BP is normal.[88] Combination therapy using dobutamine and vasopressin may be effective in hypotensive neonates. If RV function is severely impaired and the ductus arteriosus is closed or restrictive, prostaglandin infusion should be considered to reduce RV afterload.[87,88] Right-to-left ductal shunt may also be advantageous for systemic circulation. Though the post-ductal oxygen content is lower, perfusion may improve. Caution should be used in neonates with both PPHN and myocardial impairment as dramatic changes in loading conditions may not be tolerated. Frequent reassessment is recommended.

Conclusions

The neonatal population is unique and varied. The pathophysiology of hemodynamic compromise is complex and a thoughtful approach to therapy is required. Many of the medications used in adult and paediatric intensive care settings may be used in the neonate; however, the unique characteristics of neonatal physiology including differences in myocardial architecture, cellular receptors, the presence of shunts and differences in disease pathology make direct extrapolation inaccurate. Further study is needed to delineate "normal" physiology and understand both the disease states and therapy with a goal of optimizing care and improving the intact survival of our fragile patients.

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