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The Use of Cardiotonic Drugs in Neonates

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Key Points:

1. There is a distinct lack of age appropriate cardiotonic drugs and adult formulations are administered without evidence based knowledge on their dosing, safety, efficacy and long term effects.
2. Dopamine remains the most commonly studied and prescribed cardiotonic drug in the neonatal intensive care unit (NICU), but evidence of its effect on end organ perfusion is still lacking.
3. Unlike adult and paediatric critical care, there are significant gaps in knowledge on the use of various cardiotonic drugs in various forms of circulatory failure in the NICU.
4. Performing clinical trials in this area has been challenging and highlights the need for international collaborations, the importance of synergy between the Food and Drug Administration (FDA) and European Medicines Agency (EMA), and the inclusion of industry in the conduct of such trials.

The Use of Cardiotonic Drugs in Neonates

1. Introduction

Inotrope/vasopressors are commonly used in the NICU but with wide variations in practice regarding indications, duration and dosing[1,2]. Following delivery neonates need to adapt their cardiorespiratory system from intrauterine to extrauterine life. During this transition phase, many additional factors can impact this process including timing of umbilical cord clamping, chorioamnionitis, inadequate oxygenation, relative adrenal insufficiency and infection, especially in the most extreme preterm neonates. These interrelated factors often result in a clinical picture characterized by low blood pressure which often is treated with agents such as dopamine, dobutamine, noradrenaline, or corticosteroids[3].

None of these drugs are currently licensed for the use in preterm or term neonates in spite of the introduction of the Medicines in Children's Acts in several countries [4]. Due to lack of age appropriate formulations, many adult formulations are administered without evidence based knowledge on their safety, efficacy, long term effects of excipients and age appropriate dosing [5,6]. Recently efforts have been initiated to address these deficiencies through funding large randomized trials of inotropes in newborns [7,8].

Neonatal circulatory failure may occur in many settings. Hypovolemic shock, an infrequent cause of hypotension in the immediate transition period, may be minimised by providing enhanced placental transfusion[9-12]. A recent meta-analysis in preterm neonates receiving placental transfusion found an increased death rate (30%) if the cord was clamped immediately [13]. Long term follow up studies in preterm and term neonates have shown a good safety profile with improved neurodevelopmental outcomes up to 4 years of age [14-17]. In term neonates, circulatory failure may occur in the setting of early onset sepsis, persistent pulmonary hypertension of the newborn, perinatal asphyxia, or as a result of complex congenital cardiac defects. Preterm neonates more often have difficulty in adapting their circulation to extra-uterine life during the first 72 hours of birth. Additional causes for circulatory failure later during their hospital stay include sepsis, necrotizing enterocolitis, and patent ductus arteriosus.

Defining circulatory failure in the newborn poses many challenges for clinicians. Traditionally blood pressure has been the main criteria utilized to define the adequacy of circulatory wellbeing. Numerous blood pressure reference ranges exist, based on gestational age, birth weight and postnatal age. Defining mean blood pressure values below a particular centile , or less than absolute values, less than gestational age equivalent in mmHg has been the most popular definition [3,18] used, but this is too simplistic an approach. More recently other surrogate markers of circulatory failure have been considered, such as base excess and blood lactate as markers of poor tissue perfusion [19,20]. Cardiac function and organ perfusion are now assessed by functional echocardiography, tissue Doppler, pulse plethysmography or near infrared spectroscopy (NIRS) [21]. Treatment algorithms and guidelines often

rely on preferences of local clinicians and their ability to use these additional assessment methods [5]. While a number of groups continue to evaluate the role of additional monitoring tools in haemodynamic assessment[22-25], further evaluation and clinical trials are necessary before they are routinely incorporated into clinical practice[26] (see Figure 1). In the following sections we review some of the most commonly prescribed drugs and the conditions in which they are used.

2. Inotropic/ Vasopressors/ Inodilators

Dopamine

Dopamine is the most commonly used inotrope in the treatment of neonatal hypotension [27,28] and is certainly the most studied of all the cardiotonic drugs used in newborn care. There are numerous observational studies of its use in neonates and there are now over 20 randomised controlled trials comparing dopamine to other agents, including placebo. Dopamine works through stimulation of α and β adrenergic receptors and dopaminergic receptors. The results of these numerous observational studies is a number of postulated effects, suggesting a dose dependent effect on different organs systems [29,30]. The standard administration is by continuous infusion at doses of 2-20 mcg/kg/min with the assumption being that the lower doses of 2-5 mcg/kg/min mainly affect the dopaminergic receptors[31,32],. Further increasing the dose stimulates α adrenergic receptors causing vasoconstriction and increases in systemic vascular resistance[33]. Although this leads to an increase in cardiac contractility and output [28,34], evidence from randomised controlled trials suggests that dopamine may have a negative impact on cardiac output through an inotrope/vasopressor imbalance[35-37]. It would be too simple to state that above a certain level one effect is greater than the other, but certainly with increasing doses one is likely to see more vasopressor than inotrope effects and thus the potential to impair end organ perfusion becomes a reality. There is a great deal of overlap in these effects, particularly in critically ill neonates. The choice of an appropriate drug for a specific clinical condition depends on a number of complex interrelated factors including determinants of cardiovascular function and the underlying disease process. There are a number of studies that have assessed the pharmacokinetic (PK) and pharmacodynamic (PD) properties of dopamine in the paediatric population, some of these in neonates[38-46]. The methods of analysis have differed which may account for some of the variability across the studies. The effects on systemic, pulmonary, and cerebral haemodynamics can be monitored at the bedside. Echocardiographic assessment, in particular in the presence of a patent ductus arteriosus[47,48] , has provided some insights into the systemic and pulmonary effects. NIRS has permitted a better understanding of the potential effects on cerebral oxygenation, blood flow, and autoregulation. It has been suggested that dopamine may have negative effects on the cerebrovascular autoregulatory capacity in very preterm neonates[49] which has not been seen by others[50]. In a follow up study, neurodevelopmental outcome at three years may be worse in neonates treated with dopamine versus dobutamine[51]. In a meta-analysis of observational studies, dopamine not only increased BP but also cerebral blood flow[52]. There are no studies comparing dopamine versus placebo in neonates with low blood pressure including evaluating the effects on measures of cerebral perfusion/ cerebral oxygenation. Such studies are warranted.

Dobutamine

Dobutamine is often used as a second line inotropic agent if a maximum dose of dopamine has been reached[27]. It is a synthetic inotrope which directly stimulates α and β1 receptors in the myocardium. Dobutamine increases cardiac output by increasing contractility and heart rate. In addition, it can have a vasodilatory effect through stimulation of peripheral β2 receptors [53,54]. Dobutamine is administered by continuous infusion with recommended doses of 5-20 mcg/kg/min. Several studies have compared dopamine with dobutamine for circulatory failure and most have demonstrated a greater increase in mean blood pressure with dopamine administration[34,36,55]. However, dobutamine has been observed to increase right and left ventricular output in comparison to dopamine. Comparative studies reported a 21% increase in left ventricular outflow with dobutamine and observed a 14% decrease with dopamine [35,36]. Dobutamine has been shown to increase superior vena cava blood flow in comparison to both dopamine and placebo in neonates with low blood pressure. As with all studies of cardiotonic drugs, very little long term neurodevelopmental outcome data are available.

Epinephrine

Epinephrine (Adrenaline) is secreted by the adrenal medulla as an endogenous catecholamine. It stimulates α and β receptors. It is typically used in protracted neonatal hypotension if dopamine and dobutamine do not achieve the desired effects[6]. However, it is used as a first line agent by some as determined from surveys of practice [2,56]. The effects on the circulation are generally dose dependent. At lower doses the stimulated β receptors cause vasodilation in the systemic and pulmonary circulations. It also increases heart rate and cardiac stroke volume. At increasing doses α receptors mediated effects are seen resulting in vasoconstriction [28]. The infusion should be administered through a central venous line with a dosing range of 0.05-1.0 mcg/kg/min. Higher doses of have been used but are not recommended[57,58].

There are very few randomised controlled studies of epinephrine in preterm neonates[59] . Pellicer and colleagues compared dopamine to epinephrine in preterm neonates with low blood pressure. The clinical effects and the side effect profile included a significant increase in heart rate, serum glucose concentration, and rise in lactate after 24-36 hours of continuous infusion compared to dopamine[60].

Norepinephrine

Norepinephrine is an endogenous catecholamine which is released from adrenergic nerve endings. It has strong stimulating effects on α and β1 receptors and weaker effects on β2 receptors. Noradrenaline has more potent α mediated effects compared to adrenaline which results in vascular constriction with a subsequent increase in SVR and BP. It may be useful in septic shock, in order to correct the low SVR [61]. Although a number of cohort studies have reported the effects of norepinephrine in preterm neonates[62,63], randomized controlled trials to confirm these findings are lacking. Norepinephrine might have a role in treating circulatory failure in severe Persistent Pulmonary Hypertension of the Newborn due to a reported pulmonary vasodilator effect[62]. Administration should be via central venous access at doses of 0.02-1 mcg/kg/min.

Milrinone

Milrinone is a Type III phosphodiesterase inhibitor which acts directly on the myocardium through its inotrope and lusitrope effects. In addition, it can cause vasodilation in the systemic and pulmonary circulation which makes it a drug of choice for treatment of Persistent Pulmonary Hypertension[64]. In a comparative study of levosimendan versus milrinone in neonates undergoing cardiac surgery, cerebral tissue oxygenation measurements were similar for both groups during the immediate 24 hour postoperative phase[65]. In contrast, peripheral oxygenation showed an increase in the levosimendan group and a decrease in the milrinone group together with an increase in lactate. Serial assessments of cardiac function by echocardiography did not demonstrate any differences between both groups.

There is limited evidence for use of milrinone in preterm neonates. It did not prevent the development of a low flow state in high risk preterm neonates when compared to placebo[66,67]. While Halliday and colleagues found no benefit for prophylactic milrinone administration following PDA ligation in preterm neonates, others have found a possible benefit[68-70]. Dosing regimens vary, but milrinone is often started with a loading dose of 50 mcg/kg followed by a continuous infusion. There is one PK study which recommends a bolus infusion of 0.73 mcg/kg/min over 3 hours followed by a continuous infusion of 0.16 mcg/kg/min in preterm neonates[71]. Side effects of tachycardia and hypotension have been described, so it should be used cautiously in the setting of low blood pressure.

Vasopressin

Vasopressin is an endogenous peptide which is expressed in the hypothalamus. The initial prohormone preprovasopressin is converted to provasopressin and vasopressin in the pituitary gland.[72]It causes vasoconstriction through stimulation of vasopressin V1 receptors in smooth muscle. In addition, it has a vasodilatory effect on cerebral and renal arterioles by stimulation of vasopressin V2 receptors. Overall data on the use in preterm and term neonates is limited and mostly reported as case series [73-78]. Dosing is by continuous infusion of 0.00001-0.003 unit/kg/min. There is quite a variation in the literature regarding the appropriate dosing and bolus administration of 2-20 mcg/kg every 4-6 hours has been reported. Due to the short half-life of 5-15 minutes, the effects last only for about 30-60 minutes. A recent pilot study in 20 very preterm neonates compared vasopressin to dopamine during the first 24 hours of life. Both agents resulted in similar increases in BP but with less tachycardia in the vasopressin group [79]. However, more studies are needed before any recommendations can be made for its routine use in the preterm neonate.

Levosimendan

Levosimendan is used in adults with acute decompensated congestive heart failure. In neonates it has mainly been used in during cardiac surgery as an inodilator. Levosimendan acts as a calcium sensitizer. It binds to C cardiac troponin and enhances the sensitivity of contractile myofilaments to intracellular calcium in the cardiac muscle cells, thus improving myocardial contractility[80,81] . It activates sarcolemnal K-sensitive adenosine triphosphate channels of vascular smooth muscle cells which has vasodilatory effects. It is thought to have protective effects on ischemia of brain and kidney tissue in neonates. Improved tissue oxygenation measured by NIRS has been reported in a cohort of

neonates undergoing cardiac surgery.[82,83] Infusion doses for neonates range from 0.1-0.2 mcg/kg/min. The potential benefits include increased cardiac output and cardiac index as well as a decrease in heart rate and lactate levels [83]. The side effects include hypotension which needs careful and continuous monitoring. There is no reliable data on the use of levosimendan in preterm neoantes and its use as such cannot be recommended at present.

Despite their ongoing use there is surprisingly very little PK and PD data available on the drugs highlighted above. Table 2 provides a summary of the PK/PD studies on dopamine in the neonate. What is evident from this table is the lack of more recent PK/PD data, especially in the very preterm neonate. Smits and colleagues propose an outline on how to use haemodynamic and cerebral monitoring to study pharmacodynamics in neonates[84]. This sort of monitoring will aid in better understanding the effects of inotropes, especially on brain perfusion in very preterm neonates. Figure 1 provides an overview of these potential processes and mechanisms and the monitoring tools available.

3. Treatment Scenarios

There are a number of treatment categories in which cardiotonic drugs are administered to the neonate. These include, but are not limited to, the clinical situations outlined below and listed in Table 2. These categories were chosen since these are common situations in which the agents are prescribed in the NICU.

3.1 Transitional Low Blood pressure in the Preterm Neonate

The most common situation in which cardiotonic drugs are administered to neonates is in the first day of life, primarily in preterm neonates with evidence of low blood pressure[85,86]. Uncertainty remains over criteria used to define low blood pressure, criteria upon which to intervene, and what treatment strategy should be employed[87]. Currently, the majority interventions occur when the blood pressure is below a defined value for a certain period of time, with the most common cardiotonic drug administered being dopamine[27]. This approach is primarily based on familiarity; dopamine has been used as the primary inotrope since the 1970's and when administered will generally result in an increase in blood pressure, which has been the main focus of cardiovascular stability. This approach is now being questioned by many groups, with the focus shifting towards assessment of flow rather than blood pressure[88,89].However, defining cardiovascular stability during transition remains a key challenge. In a recent observational study by Batton and colleagues which included over 360 preterm neonates born at less than 27 weeks gestation across 16 sites, almost 55% were treated for cardiovascular instability, with over 30% of neonates receiving a cardiotonic drug (mostly dopamine)[85].

Although dopamine has been the subject of a number of systematic reviews[52,90] and over 20 randomised controlled trials in neonates, significant uncertainty remains[91]. Most studies have been characterized by small numbers, heterogenous inclusion criteria, and limited short and long-term follow up. While data obtained from these studies is very informative, the limitations need to be acknowledged. A recent observational study by the Epipage

group have highlighted the potential benefits of an interventional approach to low blood pressure during the transitional phase of adaptation, suggesting that neonates who receive an intervention are less likely to sustain brain injury compared to neonates who have an observational approach to care only[92]. It is fair to say that this complex problem remains unresolved, but a number of ongoing or planned studies in this area may shed further light on the problem in the future.

3.2 Pulmonary Hypertension (PH)

While the incidence of PH seems to have decreased, and improved management strategies have resulted in fewer neonates requiring more extensive interventions, PH remains a significant problem in newborn care. Supporting the cardiorespiratory system in the setting of PPHN is primarily based on the use of nitric oxide, and the evidence suggests that the number needed to treat to prevent one neonate requiring ECMO is low (five)[93]. However, there is limited data on the use of various cardiotonic agents in the setting of PPHN[94]. The effect of each agent on systemic and pulmonary vascular resistance as well as ductal and atrial shunting needs to be considered. Finally the effects on he the peripheral vasculature, in particular cerebral vasculature, also needs to be considered. There is currently no obvious first line agent and the appropriate choice of first line inotropes/inodilators/lusitrope remains unclear.

The role of echocardiography in the setting of PPHN is crucial, both to determine the extent of the problem and also to determine the effect of various intervention strategies[95]. Animal data suggest that epinephrine may be a more suitable agent than dopamine as it has a relatively lower increase in pulmonary vascular resistance compared to dopamine[96]. However, norepinephrine may be a better alternative. The use of milrinone has increased significantly in the NICU[97], primarily in the setting of PPHN. Although there are a number of case reports and case series, there are no randomized controlled trials addressing the use of milrinone in the setting of PPHN [98-100]. There is currently one small pilot trial enrolling and a larger planned study of milrinone in the setting of congenital diaphragmatic hernia. However, it should be noted that enrollment into such studies may prove difficult. A recent multisite randomized trial of bosentan in the setting of PPHN failed to enroll sufficient numbers of neonates[101]. The reasons included the changing clinical spectrum and difficulties in obtaining timely informed consent. These challenges have afflicted a number of other studies in the area of cardiovascular support and will be discussed in a later section.

3.3 Cardiovascular Instability in the Setting of Sepsis

Sepsis remains a common problem in newborn care, predominantly in low resource settings. Septic shock is a condition of inadequate tissue perfusion secondary to cardiovascular dysfunction occurring with suspected or certain systemic infection. It is interesting to note the recent guidance provided by the Surviving Sepsis Campaign. The algorithm addresses a goal directed approach to therapy and the initial inotrope suggested is dopamine I If resistant to therapy, epinephrine should be administered. However, there is very limited evidence to support such an approach, and we would suggest than an alternative approach be given consideration. There have been a number of

trials in the paediatric population, from one month of age upwards comparing dopamine to epinephrine in the setting of sepsis. The consistent finding in this age group is that epinephrine is associated with improved survival in fluid refractory hypotensive shock[102]. Another consideration is the effect of sepsis on drug PK/PD. This is not well understood in the neonate and undoubtedly an individualized approach with particular dosing regimens needs to be carefully considered. One recent trial compared epinephrine and dopamine as a first-line vasoactive drug in 40 neonates with fluid-refractory septic shock in a low resource setting[103]. The initial starting dose of epinephrine was 0.2 µg/kg/min and dopamine 10 µg/kg/min, with subsequent increases of each agent depending on the response. All-cause mortality by 28 days was very high (70%) in the epinephrine vs dopamine group (80%) . The authors concluded that epinephrine (0.2–0.4 µg/kg/min) and dopamine (10–20 µg/kg/min) had comparable efficacy and safety in neonatal septic shock. However mortality was extremely high and generalizability of these findings needs to be interpreted cautiously.

3.4 Cardiovascular Instability in the Setting of Perinatal Asphyxia and Therapeutic Hypothermia

The definition of perinatal asphyxia is broad but typically characterized by evidence of metabolic acidosis, low Apgar scores, and the need for initial respiratory support. The primary insult can have implications for cardiovascular function, often in the setting of multiorgan dysfunction. Echocardiography findings after asphyxia include decreased contractility and cardiac output, impaired end diastolic filling, and increased pulmonary artery pressure. The presence of some cardiac biomarkers is associated with altered echocardiographic findings. For neonates with evidence of clinical encephalopathy in the setting of perinatal asphyxia, the primary therapy is therapeutic hypothermia. This has been associated with a reduction in heart rate, stroke volume, and cardiac output and an increase in PH[104-107]. However, these changes do not seem to be associated with an increase in mortality or adverse neurodevelopmental outcome in a meta-analysis of various trials of cooling strategies compared to controls. Therapeutic strategies include use of various agents such as dopamine, dobutamine and epinephrine. There is no consensus as to which agent may be the most appropriate and the majority of the current evidence available is derived from animal studies[108,109].

4. Administration of Agents

There are no neonatal specific cardiotonic formulations and this presents significant challenges, particularly in very preterm neonates where effective and timely delivery of an inotrope infusion may be crucial. There are many problems with the current use of adult preparations. A ready to use neonatal formulation means avoidance of unnecessary delays in formulation preparation. It would also avoid unnecessary dilutions which are both time consuming and also increase the likelihood of contamination or a drug error. Stability testing would be needed with neonatal specific formulations to ensure that the solution has an equal distribution of the drug as opposed to the current method which involves dilutions where there may be unequal distribution resulting in a risk of boluses of

drug being administered. These problems can only be overcome with the use of specific ready to use neonatal formulations.

Even with the use of neonatal specific formulations, other administration challenges include very low infusion rates and relatively large dead space considerations which will result in long lag times before the drug gets to the desired location. The syringe size, the diameter and length of the tubing are other important factors that need to be considered. Upward displacement of the syringe pump results in a potential increase in the flow rate. With lower the infusion rates, the greater the relative bolus delivery of the drug. [110-113] Physicians need to be aware of these potential side effects and minimise their occurrence.

Inotropes as molecules can be quite unstable if exposed to oxygen and diluted in infusion mixtures. A study on the stability of typical Dopamine and Dobutamine infusions made from adult formulations used in the NICU demonstrated two time points of significant changes in the concentration of Dopamine. Time point one was within the first 30 minutes of preparing the infusion and the second time point was after approximately 12 hours after the Dopamine infusion[114]. Drug concentrations fell by more than 7% which is outside the standard tolerance rate. It is therefore suggested to wait for 30 minutes before connecting a new infusion mixture to the neonate for infusion and to change dopamine infusions after 12 hours rather than every 24 hours. However, more frequent changing of inotrope infusions carries their own unwanted side effects and perhaps of more importance is the development of stable neonatal formulations.

5. Future Directions

The study of cardiotonic drugs in the neonate appears to be particularly challenging, especially in comparison to other areas of newborn care. There are no large randomized controlled trials evaluating the efficacy of various agents in the conditions outlined above. This is in stark contrast to the pediatric and adult population where large randomized controlled trials have been performed and have helped to inform practice. There are many potential reasons to explain this dearth of studies. Since there are no neonatal specific formulations available, it is more challenging to perform studies in time sensitive situations. The incidence of the various conditions outlined seems to have decreased somewhat over time, which again makes it more challenging to enroll. Obtaining valid informed consent also remains a major hurdle to recruitment. A number of trials have met challenges in enrollment. These include a study on neonatal hypotension in extreme preterm neoantes[115], a study of corticosteroid in cardiovascular instability in late preterm neoantes[116] and a study of bosentan use in PPHN[101]. These serve as a stark reminder of the challenges in conducting studies in this area and highlight the need for international collaborations, the importance of synergy between the FDA and EMA and the inclusion of industry in the conduct of such trials. The role of the International Neonatal Consortium is crucial to facilitating this engagement and ensuring the foundations are established to finally try and answer some of these age old questions with clear and concise evidence.

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Figure 1

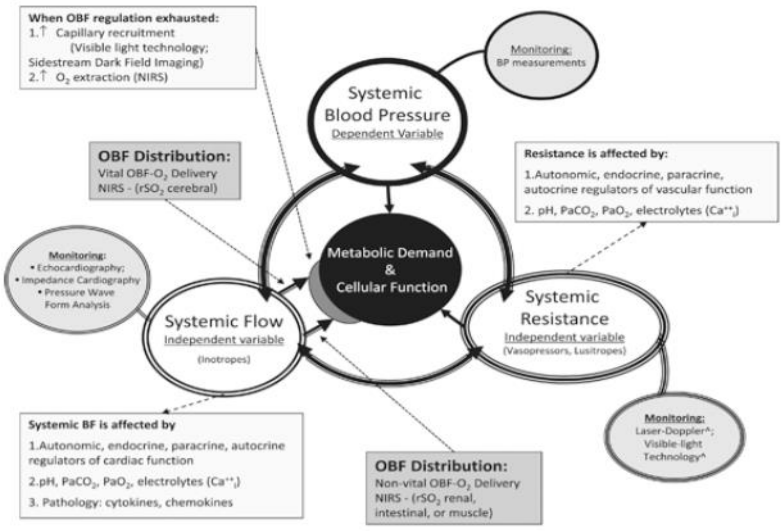

Figure 2

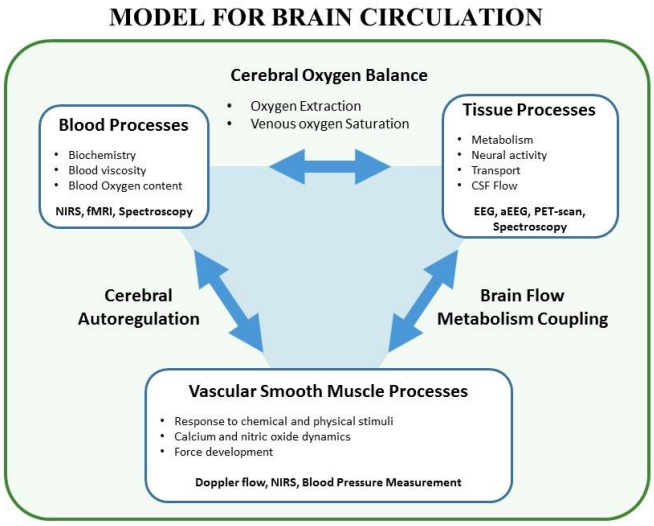

Table 1. Overview of inotropes used for treatment of cardiovascular failure in neonates

Drug name	**Receptors**	**Proposed Physiological effects related to cardiovascular failure**	**Dosing in newborns**	**Administration**
Dopamine	β1,β2 agonist, dopaminergic receptors	Increases in HR, blood pressure, myocardial contractility and variable effects on SVR	2-20 mcgg/kg/min	Continuous infusion through central venous line
Dobutamine	α and β1 agonist, weak effect on β2	Increases heart rate, myocardial contractility and stroke volume.	5-20 mcg/kg/min	Continuous infusion via peripheral or central venous line
Epinephrine	α1, α2, β1, β2 agonist	Increases heart rate and stroke volume, variable effect on systemic vascular resistance	0.05-1.0 mcg/kg/min	Continuous infusion through central venous line
Norepinephrine	α1, α2, β1 agonist	Increases heart rate, myocardial contractility and vascular resistance causing vasoconstriction and increase in blood pressure.	0.02-1 mcg/kg/ min	Continuous infusion through central venous line
Levosimendon	Calcium sensitizer activating sarcolemnal K-sensitive adenosine triphosphate channel at cellular smooth muscle level	Increases cardiac output and cardiac index. Vasodilatory effects, may cause decrease in heart rate and decrease in blood pressure	0.1-0.2 mcg/kg/min	Limited evidence after cardiac surgery.
Milrinone	Type III phosphodiesterase inhibitor	Decrease of pulmonary and systemic vascular resistance, may cause increase in heart rate and decrease in blood pressure.	0.2-1 mcg/kg/min A bolus of 50 mcg/kg may be considered	Continuous infusion through central venous line
Vasopressin	Vasopressin 1 receptors for vasoconstriction in systemic arteries Vasopressin 2 receptors for vasodilation in cerebral, renal and pulmonary circulation	Increase in blood pressure, cardiac output. May decrease pulmonary vascular resistance.	0.00001-0.003 units/kg/min	Continuous infusion through central venous line. Used as rescue treatment in persistent cardiovascular failure during sepsis.

Table 2. Some unanswered questions in the treatment of cardiovascular failure and how echocardiography may influence the choice of agent used. Evidence supporting these interventions is limited and future clinical studies are essential.

Conditions	Typical Echo findings	Possible agents
Preterm transitional low blood pressure	Normal	Observation, low dose epinephrine or dopamine
	Decreased myocardial contractility	Low dose epinephrine or dobutamine
	Presence of Large PDA	Consider NSAID
Persistent Pulmonary Hypertension	Low systemic blood pressure	Consider epinephrine
	Decresed RV function	Consider doutmaine or Milrinone
		Monitor Blood pressure continuously
Cardiac dysfunction in the setting of sepsis	Decreased contractility	Consider epinephrine
	Increased pulmonary artery	Consider doutmaine or Milrinone
	Low systemic blood pressure	Consider epinephrine, norepinephrine
Cardiac dysfunction in the setting of therapeutic hypothermia	Decreased contractility	Consider epinephrine
	Increased pulmonary artery	Consider doutmaine or Milrinone
	Low systemic blood pressure	Consider epinephrine, norepinehrine

Legends for Figure

Figure 1: Monitoring of blood pressure (BP), blood flow, blood flow distribution, and vascular resistance. NIRS, Near-infrared spectroscopy; OBF,organ blood flow; rSO2, regional tissue oxygen saturation. (From Soleymani S, Borzage M, Seri I: Hemodynamic monitoring in neonates: advances and challenges. J Perinatol 30:S38–S45, 2010. Used with permission from NaturePublishing Group.)

Figure No. 2 The adapted brain circulation model: Overview of the hemodynamic effects on the brain. Interaction between the 3 processes (blood processes, vascular smooth muscle processes and tissue processes) and 3 mechanisms (cerebral autoregulation, blood flow metabolism coupling and cerebral oxygen balance) as well as value of the appropriate monitoring tools. Reproduced with permission from Bentham