## Chapter 9: Vasoactive Medications

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# INTRODUCTION

**FOCUS POINTS**

1. The increased metabolic rate of children comparing to adults requires a different selection of vasoactive drugs to restore and maintain the oxygen delivery to the tissues and support the circulation during periods of stress or sepsis.
2. Phenylephrine has a very narrow therapeutic spectrum in the pediatric population, mostly limited for patients with tetralogy of Fallot (TOF) and hypertrophic obstructive cardiomyopathy (HOCM)
3. Milrinone is used in pediatric patients with congenital heart disease, cardiomyopathy, and heart failure and in patients with increased pulmonary vascular resistance (PVR).
4. Dopamine is still used to improve tissue perfusion and urine output in neonates and premature infants.
5. Newborn myocardium contractility depends significantly on serum calcium levels. Hypocalcemia needs to be promptly identified and corrected.

# SYMPATHOMIMETIC DRUGS, INOTROPES, AND VASOACTIVE DRUGS

## Epinephrine

Epinephrine is an endogenous catecholamine that is being produced and secreted in the blood stream by the adrenal medulla after direct stimulation from sympathetic efferent fibers. It combines with pre- and postsynaptic adrenergic receptors in the periphery to generate a stress response. Epinephrine has more pronounced β1 and β2 receptor effect and less α1 and α2 effect. It produces a positive inotropic and chronotropic effect on the heart and causes splanchnic vasoconstriction and vasodilation of the skeletal muscle vascular bed in order to facilitate the flight or fight response. Additionally, it increases gluconeogenesis and glycogenolysis, supplying the body with the nutrients to meet the high metabolic demands associated with the stress state. As a β1-agonist, it is a very effective bronchodilator.

In clinical practice, epinephrine is used as an infusion for patients with left ventricular systolic dysfunction or right heart failure in order to increase the oxygen delivery to the body. It increases the oxygen consumption of the myocardium, which can be a limitation on its use for older adult patients with coronary artery disease. The absence of coronary artery disease in the pediatric population makes epinephrine the choice of preference.

The infants and children have high metabolic demands with an oxygen consumption of 10 to 14 mL/kg for infants dropping to 5 to 7 mL/kg after the first year. The oxygen demand increases even more in critically ill or septic patients, and a pharmacologic support that increases the cardiac output helps the cardiovascular system meet this demand.[1,2]

Most common uses of epinephrine in pediatric patients are as follows:

**Sepsis and hypotension in the ICU**: Epinephrine is the first drug of choice for critically ill patients with a wide range of doses. The effects of the treatment on the oxygen delivery can be indirectly assessed by measuring the blood pressure or directly measured by the mixed venous saturation ($SvO_2$) or using NIRS (near-infrared spectroscopy). When the pharmacological treatment fails, patients may require extracorporeal

membrane oxygenation (ECMO) support. Most of these patients have been on high doses of epinephrine for at least 48 hours resulting in downregulation of their adrenergic receptors. The abrupt discontinuation of the adrenergic drugs may result in severe hypoglycemia. It may be beneficial to continue a low-dose 0.01 to 0.03 mcg/kg/min epinephrine infusion and slowly wean to prevent such hypoglycemic events. Steroid administration may also be required for pediatric patients to augment the response to the catecholamines and maintain better hemodynamic stability.[3]

**Anaphylaxis:** Epinephrine is used as an intramuscular (IM) or intravenous (IV) (10 mcg/kg for pediatric patients) bolus injection for severe anaphylactic reactions or shock. The initial bolus has to be followed by an infusion with rates of up to and even higher than 1 mcg/kg/min. Epinephrine not only counteracts the effects of histamine but also stabilizes the mast cells in order to prevent further histamine release.[4] The infusion should be titrated to the effects (blood pressure, bronchospasm) and be accompanied with the administration of H1/H2 blockers, steroids, and cessation of the allergenic triggering factor.

**Pediatric Advanced Life Support (PALS):** Epinephrine is part of the PALS protocol for patients with a nonperfusing rhythm. The dose is 10 mcg/kg IV or intraosseous (IO) repeated every 3 to 5 minutes. For administration of the epinephrine through the endotracheal tube the dose is not known with recommendations varying from 3 to 10 times higher than the IV dose followed by a flush of 2 to 5 mL of saline (depending on the size of the patient) followed by a couple of breaths so that the medication can reach the alveoli.

**Anesthesia:** All the anesthetic agents have direct or indirect negative inotropic and/or vasoplegic effects. A low dose of 0.02 to 0.05 mcg/kg/min of epinephrine can counteract these effects especially for congenital cardiac patients undergoing noncardiac procedures. This can also minimize the necessary fluid administration. This infusion can be weaned at emergence from anesthesia with no hemodynamic instability especially if the patient did not need it preoperatively.

## Norepinephrine

Norepinephrine is an endogenous catecholamine being secreted by all the postganglionic sympathetic neurons. In clinical practice it is being used as an infusion for patients with profound hypotension. It directly binds mainly to the α1 and less to the β1 receptors (Table 9-1).

Table 9-1

**Vasoactive Drugs**

| Medication | Receptors Affected | Bolus | Infusion |
|---|---|---|---|
| Calcium chloride | | 30 mg/kg | |
| Calcium gluconate | | 10 mg/kg | |
| Epinephrine | Mainly $\beta_1$ and $\beta_2$ | 1–10 mcg/kg | 0.01–0.5 mcg/kg/min |
| Dopamine | Dopamine | | 0.5–5 mcg/kg/min |
| | $\beta_1$ | | 5–15 mcg/kg/min |
| | α | | >15 mcg/kg/min |
| Labetalol | Nonselective β, $\alpha_1$ | 0.25–1 mg/kg | 0.2–1 mg/kg/h |
| Milrinone | cAMP phosphodiesterase inhibition | 25–50 mcg/kg | 0.125–0.5 mcg/kg/min |
| Norepinephrine | $\alpha_1$ and $\beta_1$ | | 0.02–0.3 mcg/kg/min |
| Nicardipine | Calcium | | 0.5–10 mcg/kg/min |
| Phenylephrine | α1 | 10 mcg/kg | 0.1–1 mcg/kg/min |
| Vasopressin | $V_1$ and $V_2$ | | 0.2–0.5 mU/kg/min |

It has strong vasopressor effects (increases the systolic, diastolic, and mean arterial pressure) and intermediate inotropic effects. It may cause a reflex decrease of the heart rate or maintain it at the same levels.

It is being used in the pediatric population in combination with epinephrine when the mean arterial blood pressure is not sufficient for the perfusion of critical organs such as the brain and kidneys, or the diastolic pressure is not sufficient for myocardial perfusion.

The dose of administration varies from low doses of 0.02 to 0.05 mcg/kg/min up to 0.3 mcg/kg/min. At these high doses, clinicians choose to add another agent such as vasopressin in the treatment plan to maintain hemodynamic stability.

## Vasopressin

Vasopressin is a hormone secreted by the posterior pituitary grand. The osmoreceptors of the hypothalamus sense an increase of serum osmolality causing secretion of vasopressin in the bloodstream. Vasopressin subsequently acts on the collecting ducts of the kidneys, mostly via the V2 receptors, increasing free water retention, resulting in increased intravascular volume and decreased serum osmolality. Other mechanisms that stimulate the secretion of vasopressin are the decreased vascular volume/pressure, pain, and stress.

Vasopressin action on the V1 receptors offers a different mechanism than the adrenergic one, augmenting vascular tone but lacking any inotropic effects. Its action is based on the IP3/DAG pathway (inositol triphosphate/diacylglycerol), which causes an increase in the ionized calcium.

Vasopressin and its analogue DDAVP also stimulate the endothelium to secret von Willebrand factor through the cAMP pathway.

The pulmonary vasculature lacks vasopressin receptors. Patients with increased pulmonary vascular resistance (PVR) and reduced systemic vascular resistance benefit the most by the administration of vasopressin. The infusion rate is 0.2 to 0.5 mU/kg/min up to 0.04 U/min.

Vasopressin is part of the Advanced Cardiac Life Support (ACLS) protocol for a nonperfusing rhythm and a 40-U bolus can replace the epinephrine in one of the first two boluses. In the Pediatric Advanced Life Support (PALS) cardiac arrest, it is not routinely recommended because there is no clear evidence of improving the ROSC (Return of Spontaneous Circulation).[5–12]

## Phenylephrine

Phenylephrine is a pure α1 agonist. It increases systemic vascular resistance and may cause a profound reflex bradycardia. Although it has no inotropic effects and for that reason is a poor choice for the pediatric population who respond to stress with a high cardiac output state, phenylephrine has still a very important role in the management of some pediatric diseases such as tetralogy of Fallot (ToF). This congenital heart disease is characterized by an overriding aorta, perimembranous ventricular septal defect, right ventricular hypertrophy, and pulmonary stenosis. ToF patients may require much higher doses per kilogram (up to 10 mcg/kg bolus) of phenylephrine than adults especially during their intraoperative management. Increase of the heart rate in the preoperative area from anxiety and decrease of the systemic vascular resistance (SVR) on induction can cause right to left shunt and cyanosis refractory to oxygen administration. The drug of choice is phenylephrine because it lacks any inotropic effect, increases SVR, and causes reflex bradycardia.

Another pediatric population that may require phenylephrine administration is children with dynamic or fixed left ventricular outflow tract (LVOT) obstruction. In the presence of subaortic membrane, hypertrophic obstructive cardiomyopathy, congenital aortic valve stenosis, or supravalvular aortic stenosis (William's syndrome), the preservation of the afterload maintains the perfusion of the coronary arteries making phenylephrine an ideal medication for emergencies and intraoperative management. Additionally, in the presence of dynamic obstruction the preservation of the afterload prevents the almost complete emptying of the left ventricle (LV) which worsens that LVOT obstruction and the gradient across it.

### Milrinone

Milrinone is a drug with intracellular action. It inhibits the cAMP phosphodiesterase (PDE) isoenzyme peak III in the myocyte and increases the ionized calcium levels as a result of increased cAMP. Milrinone has a positive inotropic and lusitropic effect on the myocardium. In the peripheral vascular system, the intracellular increase of the cAMP causes a decrease in the vascular tone. In the pulmonary vasculature, milrinone directly reduces pulmonary vascular resistance. Although not as effective as inhaled nitric oxide (iNO) or the cGMP PDE inhibitors, the combined pulmonary vasodilatory and inotropic effect on the right ventricle can improve the cardiac output and systemic perfusion for patients with pulmonary hypertension and/or right heart failure.

It has no direct diuretic effects but the increase in the cardiac output may cause an increase in the urine output.

Milrinone has a half-life of 2.3 hours and it is 70% bound on plasma proteins. The dose used in clinical practice is 25 to 50 mcg/kg bolus over 10 minutes followed by infusion of 0.125 to 0.5 mcg/kg/min up to 0.75 mcg/kg/min in rare clinical conditions.

High doses of 0.5 to 0.75 mcg/kg/min may cause profound vasoplegia (reduced SVR in the setting of normal or elevated cardiac output) in adults. Other side effects with such high-dose administration include flushing and headaches.

In the pediatric population milrinone is a commonly used drug in high doses without any side effects seen in adults. Pediatric patients with cardiomyopathy and heart failure (eg, enterovirus cardiomyopathy), patients with increased PVR [hypoplastic lung due to congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn (PPHN)], and congenital heart patients are the main populations that benefit from the use of milrinone.

### Dopamine

Dopamine is an adrenoreceptor with a dose-dependent action and affinity to receptors. At low dose (0.5–5 mcg/kg/min) dopamine activates the dopamine-specific receptors located in the renal vascular bed causing vasodilation and diuresis. At intermediate dose (5–15 mcg/kg/min) dopamine has a $\beta_1$ agonist action increasing contractility and heart rate, whereas in high doses (>15 mcg/kg/min) it activates α-adrenoceptors increasing systemic vascular resistance.

The use of dopamine has been limited to the last decade as it has not been proven to reduce the incidence of renal failure. Some studies support its use in the NICU because of increase in urine production for low birth weight and premature neonates.[13]

## Digoxin

Digoxin is a glucoside with positive inotropic and negative chronotropic effects on the heart. It is frequently used for patients with congenital heart disease with circulation in parallel (eg, Norwood physiology) or series (eg, Fontan physiology) and patients with dilated cardiomyopathy.

Digoxin inhibits the $Na^+/K^+$ adenosine triphosphatase ($Na^+/K^+$ pump) competing with potassium for the same binding area. This is the reason that the levels of serum potassium affect the action of the digoxin. Potassium levels and digoxin levels should be measured frequently especially at the beginning of the treatment and periodically after initiation of treatment.

Digoxin has a very low therapeutic index meaning that the safety window between therapeutic and toxic doses is very narrow. The signs of toxicity can be gastrointestinal in nature, cardiac dysrhythmias, or mental status changes. Digoxin can be given IV but most frequently is given PO postoperatively or through a nasogastric tube. The most common clinical dose is 3 to 6 mcg/kg/day divided in 2 doses/day.

## Ionized Calcium

Newborns are prone to hypocalcemia during their first days of life. Risk factors include prematurity, small for gestational age (SGA), maternal diabetes, and perinatal asphyxia/hypoxia. The latter causes reduction in circulating calcium by an increase in calcitonin levels which inhibit calcium release from the bones.

Immature sarcoplasmic reticulum unable to regulate calcium levels makes the also immature myocardium dependent on influx of calcium through the sarcolemma and serum ionized calcium.

Hypocalcemia can be a bigger concern during surgical procedures that require administration of albumin or citrated blood products. Citrate is primarily metabolized in the liver to bicarbonate. In infancy the hepatic enzymes are immature, and the liver is unable to remove the citrate from the blood stream resulting frequently in citrate intoxication during transfusion. Citrate intoxication can also occur during massive transfusion in pediatric trauma patients with rapid administration of blood products. The first clinical signs that will alert the anesthesiologist are QT prolongation, hypotension, increased central venous pressure (CVP), and coagulopathy.[14]

Calcium comes in two preparations: calcium chloride and gluconate. To date there has been no difference in outcome between administration of calcium chloride versus calcium gluconate. Studies in the 1980s and 1990s during anhepatic phase of liver transplant patients have shown that calcium gluconate does not depend on hepatic metabolism to release calcium. The main difference providers should be aware of is that calcium chloride carries three times more calcium ions per milligram. They can both be given as a bolus or infusion. Bolus should not exceed 10 mg/kg for calcium chloride or 30 mg/kg for calcium gluconate due to the risk of cardiac dysrhythmias. In awake patients, an intravenous calcium bolus may cause dysphoria and flushing, both transient effects. Calcium gluconate can also be given as a PO supplement.

## Levosimendan

Levosimendan is a newer drug that has been used in Europe and Asia for more than a decade but has not yet been Food and Drug Administration (FDA) approved in the United States (as of August 2019). It is a calcium sensitizer that acts at a molecular level on the cardiac myofilament and exhibits positive inotropic effects. It also causes vasodilation in the periphery, the coronary arteries, and the pulmonary arteries. PO administration has been studied but there is only IV formulation available.

Initially, levosimendan was developed for use in adults with acute or decompensated chronic heart failure. In the last decade this has been used in younger patients, even infants, exhibiting a safe profile. Currently, it is frequently used in pediatric patients with either congenital heart disease or cardiomyopathy. There have also been case reports for its use in sepsis-related heart failure in infants, but the vasodilatory effects have to be carefully considered.[15]

The dose is 6 to 12 mcg/kg bolus followed by an infusion of 0.1 mcg/kg/min. The elimination half-life of the drug is 1 hour but the active metabolite has a half-life of 80 hours.

# PARASYMPATHOMIMETIC DRUGS AND VASODILATORS

## Phenoxybenzamine

Phenoxybenzamine is an oral α-adrenergic antagonist that has been traditionally used in the preoperative preparation of patients with pheochromocytoma.

After the initiation of the α blockade process a β-blocker may need to be added in the regimen to ameliorate tachycardia. β-Blockers should not be added unless α blockade has been established because their initiation may potentiate hypertension ($\beta_2$ blockade of skeletal muscle vasodilation).

Patients are expected to respond with a decrease in arterial pressure and increased weight due to the replenishment of the intravascular volume. Common side effects include orthostatic hypotension, nasal congestion, and flushing.

Phenoxybenzamine has a half-life of 24 hours. The dose for pediatric patients is 0.25 to 1 mg/kg/day divided into 2 to 3 doses.

## Phentolamine

Phentolamine is a pure α-adrenergic blocking agent. It has a half-life of 19 minutes. The dose range is 0.2 to 2 mcg/kg/min. In pediatrics it is used for the following cases:

**Pheochromocytoma:** preoperative preparation or intraoperative management of hypertension.

**Extravasation of norepinephrine** (or other vasoactive drugs) followed by skin necrosis: The dose is 0.1 to 0.2 mg/kg up to 10 mg, diluted in normal saline and infiltrated locally.

**Single ventricle patients:** It has been shown that α blockade in the intraoperative and postoperative period of the first stage of Norwood palliation helps in balancing the Qp:Qs and improves systemic perfusion.

**Cardiopulmonary bypass (CPB):** Phentolamine can be used to facilitate homogeneous and fast cooling during CPB.

## Captopril

Angiotensin-converting enzyme (ACE) inhibitors block the transformation of angiotensin I to angiotensin II and prevent the production of aldosterone. The primary effect is afterload reduction, but it is also proven that ACE inhibitors improve outcome by inhibiting the remodeling process and prevent the left ventricular enlargement for patients with cardiomyopathy, heart failure, and congenital heart disease.

It is often being administered with a selective aldosterone antagonist (spironolactone) to prevent hypokalemia and its dysrhythmia side effects.

Captopril is being used orally with a starting dose of 0.3 mcg/kg/day up to 4 to 6 mcg/kg/day divided in 3 to 4 doses.[16,17]

## Labetalol

Labetalol is a nonselective β-blocker with combined $\alpha_1$ blocking activity. It can be administered PO or IV as a bolus or drip. The half-life is approximately 6 hours. The pediatric dose is 0.25 to 1 mg/kg IV or 0.2 to 1 mg/kg/h. The peak effect of a single dose is 15 minutes, so redosing to effect should take that into consideration.

Because of its dual adrenoreceptor effects, special attention should be paid in children with history of reactive airway disease and pediatric patients with increase in QT interval and AV blocks.

## Nitroglycerin

Nitroglycerin acts by releasing nitric oxide (NO) and by increasing the cGMP in the smooth muscles of vessels, causing primarily venous and coronary dilation.

The dose is 0.2 to 1 mcg/kg/min. The use of nitroglycerin in the pediatric population is very limited.

### Sodium Nitroprusside

Sodium nitroprusside is an intravenous agent with very potent vasodilatory effects. It mainly acts on arterioles and less on the venous system with no direct cardiac effect.

It acts through the NO pathway with a half-life of only 2 minutes. The duration of the treatment is limited especially in patients with decreased renal function because cyanide ions can be accumulated to toxic levels. The regular dose is 0.2 to 4 mcg/kg/min (maximum 10 mcg/kg/min). The use of nitroprusside is not very common for pediatric patients.

Some providers use it immediately postoperatively after the second-stage palliation for single ventricle patients (Glenn procedure) or during aortic coarctation repair for afterload reduction.

It can also be used in low doses for patients undergoing deep hypothermic cardiac arrest to achieve more even and quicker cooling or rewarming.[18,19]

### Nicardipine

Nicardipine is a calcium channel blocker with a selective action mainly in the systemic arterial bed and coronary arteries and minimal effect on the myocardium.

It can be administered PO or IV, is 95% bound on proteins, is metabolized by the liver, and has a half-life of 8.6 hours. The initial dose for an infusion is 0.5 mcg/kg/min increased up to 5 to 10 mcg/kg/min. For teenagers or young adults, the dose can be given starting at 1 mg/h and going up to 15 mg/h.

It can be used for patients that undergo procedures with vascular anastomosis or manipulation and need tight blood pressure control. It is also the drug of choice for blood pressure control of neurosurgical patients or patients with traumatic brain injury.

Frequently, patients on immunosuppression after a transplant or chemotherapy may exhibit increased systemic vascular resistance and require blood pressure control, which can be achieved effectively by nicardipine while they are nothing per Os (NPO) or still need titration of their medications.

### Nimodipine

Nimodipine is an orally administered lipophilic calcium channel blocker with high selectivity for the cerebral arteries. It is used to prevent cerebral vasospasm following subarachnoid hemorrhage that has potentially devastating outcomes. Its mechanism of action is not quite clear in humans. Although the neurologic outcomes are significantly better, the angiographic evidence is not always in agreement. It is highly possible that the neuroprotective effects of nimodipine are related to the prevention of calcium influx in the damaged cells that promotes apoptosis.[20]

In children, the dose is not clear and careful titration is required to avoid hypotension. Nimodipine is also being studied for migraine prevention in the pediatric population.

### Clevidipine

Clevidipine is a newer ultrashort acting calcium channel blocker that is being used perioperatively for blood pressure control or controlled hypotension. The half-life is 1 minute. It is rapidly hydrolyzed by esterases in the blood and extravascular tissue. Its use in the pediatric population has been studied with infusion rates reported to be in the 0.5 to 5 mcg/kg/min range.[21,22]

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