Management of Systemic Hypotension in Term Infants with Persistent Pulmonary Hypertension of the Newborn (PPHN) – An Illustrated Review

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Abstract

In persistent pulmonary hypertension of the newborn (PPHN) the ratio of pulmonary vascular (PVR) to systemic vascular resistance (SVR) is increased. Extrapulmonary shunts (patent ductus arteriosus and patent foramen value) allow for right-to-left shunting and hypoxemia. Systemic hypotension can occur in newborns with PPHN due to variety of reasons such as enhanced peripheral vasodilation, impaired left ventricular function and decreased preload. Systemic hypotension can lead to end organ injury from poor perfusion and hypoxemia in the newborn with PPHN. Thus, it must be managed swiftly. However, not all newborns with PPHN and systemic hypotension can be managed the same way. Individualized approach based on physiology and echocardiographic findings are necessary to improve perfusion to essential organs. Here we present a review of the physiology and mechanisms of systemic hypotension in PPHN, which can then guide treatment.

Introduction

The fetal circulatory system is characterized by high pulmonary vascular resistance (PVR) and low systemic vascular resistance (SVR). The high PVR is due to relative hypoxemia, lack of alveolar ventilation with fluid-filled lungs and circulating pulmonary vasoconstrictors.[1] The low SVR is secondary to low-resistance umbilical and placental circuit. High PVR and low SVR lead to right-to-left shunts at the level of the ductus arteriosus (PDA) and foramen ovale (PFO). At birth, alveolar ventilation and oxygenation reduces PVR with an eight-to-tenfold increase in pulmonary blood flow, and cord clamping increases SVR. The high SVR and low PVR with a systemic blood pressure significantly higher than pulmonary arterial pressure is a life-long feature of postnatal circulation unless altered by disease. Failure to achieve this transition leads to persistence of high PVR in the postnatal period leading to persistent pulmonary hypertension of the newborn (PPHN).[2] This review outlines the etiology and management of systemic hypotension in PPHN.

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Pathophysiology of PPHN[3]

Elevated PVR in PPHN can be idiopathic/primary, secondary to lung disease (either parenchymal, alveolar space disease or pulmonary hypoplasia) or cardiac dysfunction. Normal cardiac physiology verses that of PPHN is shown in figure 1A–1D. Increased PVR leads to bidirectional or right-to-left shunting at the PFO and PDA and increases right ventricular (RV) afterload.[4] The right-to-left shunting at the PFO reduces RV preload. The RV afterload can be transiently reduced by a right-to-left PDA shunt if the ductus remains open. Initial increases in afterload cause RV hypertrophy and increases contractility; however, persistent and excessive elevation of PVR is associated with myocardial stretching, ischemia, hypoxemia and acidosis leading to RV dysfunction (table 1).[5] Left ventricular (LV) dysfunction can lead to pulmonary venous hypertension and increase pulmonary arterial pressure and reduce systemic output. LV preload decreases secondary to low pulmonary venous return and/or bulging of the interventricular septum to the left. Additionally, hypoxemic respiratory failure can be a primary driver for left ventricular dysfunction. Abnormal interaction between the two ventricles, ischemia, hypoxemia and metabolic acidosis contribute to LV dysfunction.[4] Left ventricular dysfunction can also exacerbate and lead to inhaled nitric oxide (iNO)-resistant PPHN by increasing pulmonary venous hypertension.[6] Arteriovenous malformations – commonly either intracranial (vein of Galen malformation) or hepatic can present with PPHN and systemic hypotension and should be included in the differential diagnosis.[7–9] Rarely, the clinical characteristics (phenotype) of PPHN can be mimicked in situations with normal PVR and reduced SVR due to conditions such as sepsis.[10,11]

Normal blood pressure

The optimal systemic blood pressure during management of PPHN is not clear. There are several studies evaluating normal systemic systolic, diastolic and mean pressure during the first week after birth in term infants. Results from one such study are shown in table 2.[13] However, instead of exclusively focusing on blood pressure numbers, the clinician should look for signs of hypoperfusion (figure 2).

Hemodynamic assessment – flow, perfusion vs. pressure

Systemic blood pressure and heart rate are the most commonly used parameters for assessment of systemic perfusion. However, blood pressure does not correlate well with perfusion in neonates. Mean and diastolic pressures correlate poorly with LV output.[14] Pulse pressure and, to a less extent, systolic blood pressure correlate better with LV output.[14] Clinical signs such as mental status, capillary refill and urine output are compromised during late phases of systemic hypoperfusion. Non-invasive monitoring of perfusion index (PI), pleth variability index (PVI), pulse oximetry (SpO_2), and near-infrared spectroscopy (NIRS) can detect changes in systemic perfusion.[15] Blood gas analysis and serum lactate are invasive mechanisms to assess systemic perfusion. In the last decade, bedside targeted neonatal echocardiography has become a popular mode of hemodynamic assessment.[16]

Causes of systemic hypotension in PPHN

Low SVR and systemic hypotension requiring treatment are common in infants with PPHN. Two-thirds of infants with PPHN requiring ventilation and 87% infants requiring ECMO are on 3 or more inotropes.[17] The etiology of hypotension in PPHN is summarized in table 3 and figure 3.

Fluid management

Many infants with systemic hypotension and PPHN receive fluid boluses prior to initiation of vasoactive agents.[17] The relationship between intravascular blood volume and blood pressure is not clear in neonates.[18] Additionally, the mechanism of hypotension in PPHN is often not due to hypovolemia. In fact, routine administration of fluid boluses to an infant with PPHN without clinical evidence of hypovolemia, may potentially further exacerbate RV failure. Thus, fluid bolus administration should be targeted and only administered if there are other indications of hypovolemia, such as low central venous pressure (CVP), documented excessive losses or concerns for increased insensible losses.

Vasoactive infusions

If the hypotension or poor perfusion does not appear to be due to hypovolemia, vasoactive infusions are commonly initiated. The goal of vasoactive therapy is to improve oxygen delivery and perfusion (figure 4). The use of vasoactives to increase systemic blood pressure to supraphysiological levels (higher than the means shown in table 2) to minimize right-to-left shunt is not appropriate. Such practice increases RV afterload and hastens RV failure.[19] Also, in the setting of LV dysfunction, postductal systemic perfusion is supplemented by a transductal right-to-left shunt. Additionally, if an infant appears to have evidence of adequate oxygen delivery (i.e. normal lactate, normal urine output, no lethargy and without evidence of end-organ injury), despite having hypotension, then tolerating permissive hypotension may be appropriate. It is important to focus on evaluation and correction of hypoperfusion and not manage blood pressure numbers during management of PPHN.

Several vasoactive medications may be useful to treat hypotension associated with PPHN in neonates. All vary in mechanisms of action (figure 5) and may provide benefit or harm in different physiologic circumstances. For example, vasoactive infusions can have the following effects: inotropy (heart contractility), chronotropy (heart rate), lusitropy (heart relaxation), vasoconstriction (or vasopressors) and/or vasodilation. Some vasoactive medications have more than one effect and the effects can vary depending on dose. Understanding the physiology behind the neonate's hypotension and the medication's mechanism of action is necessary to choose the best treatment. A synopsis of each medication is provided in Boxes 1–8 and figure 6.

Dopamine

Dopamine has conventionally been the first line therapy for hypotension in neonates including management of septic shock.[20] However, its non-specific mechanism of action and effects on pulmonary versus systemic circulatory system has special implications in PPHN. Dopamine is a central neurotransmitter and is also a precursor to norepinephrine. It directly stimulates D_1 and D_2 receptors and directly (or through metabolism to norepinephrine)

stimulates α_1, β_1 and β_2 receptors. Therefore, dopamine can result in vasoconstriction, vasodilation, inotropy, and/or chronotropy depending on the dose.[21] Additionally, the effect dopamine has on systemic versus pulmonary circulation varies with dose.[22] For example, in a neonatal lamb model, dopamine selectively increased systemic arterial pressure at lower doses without significantly increasing pulmonary arterial pressure, thus increasing pulmonary blood flow in lambs without PPHN.[2] However, in lambs with PPHN, the pulmonary vasculature is remodeled and pulmonary arterial pressure is more sensitive to vasoconstrictor effects of dopamine, and therefore dopamine did not increase pulmonary blood flow.[2]

In human neonates, the varying effect of dopamine on pulmonary arterial pressure has also been shown.[22] In a study of 18 preterm newborns, the ratio of pulmonary/systemic arterial pressure increased (a preferential increase in pulmonary arterial pressure) in half of the newborns.[22] This same study demonstrated changes in direction of blood flow across the PDA. After dopamine initiation, 2 of 11 newborns had PDA flow change from initially left-to-right to bidirectional shunting suggesting further elevation of PVR.[22]. Thus, in a newborn with PPHN requiring dopamine infusion, monitoring of the directionality of PDA flow and pulmonary arterial pressure with serial echocardiograms is necessary.

Norepinephrine

Norepinephrine is more selective than dopamine with regards to receptor stimulation, acting primarily on α_1 receptors resulting in vasoconstriction and minimal inotropic effect on β_1 receptors. The vasoconstriction mechanism could affect both systemic and pulmonary arterial pressure. Interestingly, fetal lamb models have shown norepinephrine may decrease the basal pulmonary vascular tone through stimulation of α_2 receptors and nitric oxide release.[23] In newborns with PPHN, norepinephrine has been shown to increase pulmonary arterial pressure; however, unlike dopamine, the ratio of pulmonary/systemic arterial pressure decreased following norepinephrine infusion (0.98 to 0.87, $p < 0.001$).[24] This study also noted decreased oxygen requirement and increased post-ductal oxygen saturation supporting the notion of increased pulmonary blood flow following norepinephrine infusion.[24]

Epinephrine

Epinephrine is less selective than norepinephrine and its stimulation on α and β receptors vary by dose. At lower doses epinephrine has predominant β effect causing chronotropy and inotropy. Thus, for an infant with depressed myocardial function, epinephrine may be useful. In pediatric trials, epinephrine has been shown to be superior to dopamine with faster resolution of shock and lower mortality.[25,26] However, in neonatal trials, epinephrine and dopamine were comparable.[27,28] However, epinephrine was associated with more metabolic disturbances such as hyperglycemia and lactic acidosis.[27]

Dobutamine

Dobutamine is predominantly a β_1 agonist resulting in significant inotropic effect. Thus, it may be useful for neonates with decreased cardiac function. However, the potential chronotropic effect must be considered. In a review of dobutamine, neonatal studies noted

increased heart rate for all doses evaluated (5, 10, and 20 mcg/kg/min – studies of 2.5 and 7.5 mcg/kg/min did not report on heart rate).[29] Studies also noted both increase and decrease in PVR with dobutamine.[29] Specifically in neonates, a study among premature infants with depressed myocardial function noted decreased fraction of inspired oxygen (FiO_2) following dobutamine initiation, potentially reflecting increased pulmonary blood flow.[30] Additionally, studies have shown dobutamine improves and maintains systemic blood pressure better than dopamine and with less left ventricular stress.[31,32] While dobutamine is predominately a β_1 agonist, it is also a mild β_2 and α_1 agonist. The β_2 effects of dobutamine are thought to reduce SVR, however the reduction in SVR more likely due to sympathetic withdrawal once cardiac function has improved. The overall net effect is expected to be significant inotropy, such that the other effects of dobutamine are likely trivial in comparison. However, it most suitable for patient with LV dysfunction as the primary or major contributing factor leading to poor perfusion.

Milrinone

Milrinone is a phosphodiesterase 3 inhibitor which results in increased levels of cyclic adenosine monophosphate (cAMP). The increase in cAMP results in inotropic effect on myocardium and vasodilation, which may benefit neonates with PPHN and impaired myocardial function. In neonatal lambs, milrinone resulted in relaxation of pulmonary arteries in both controls and lambs with PPHN.[33] In a study of 11 newborns with PPHN, milrinone has been shown to improve PaO_2 and reduce FiO_2, iNO, and mean airway pressure needs – suggesting improved pulmonary blood flow.[34] Additionally, while the newborns experienced transient decrease in systemic arterial pressures, overall hemodynamics improved as noted by decreased lactic acid and a trend towards decreased inotropic score.[34] However, this study excluded infants with systemic hypotension.[34] The systemic vasodilator effects of milrinone need to be considered, particularly in the setting of PPHN. Additionally, studies have generally only evaluated outcomes during the first 72 hours of milrinone initiation. Thus, while it is likely safe for longer administration, the effects beyond this in patients with PPHN are unknown.[34,35] There are current two multicenter trials underway evaluating the use of milrinone in CDH[36] and PPHN.[37]

Levosimendan

See Web Appendix for levosimendan details.

Vasopressin

There are three subtypes of vasopressin receptors, V_{1-3}. V_1 receptors are located in the vasculature beds and commonly known for their potent vasoconstrictive properties on systemic vasculature with minimal increase/decrease in PVR leading to a decrease in the pulmonary/systemic arterial pressure ratio.[39] The mechanism of vasodilation in the pulmonary vasculature is thought to be from stimulation of oxytocin endothelial receptors and subsequent NO pathway activation.[40] Siehr et al. evaluated three vasoactive medications (phenylephrine, vasopressin and epinephrine) in 15 pediatric patients with pulmonary hypertension, and vasopressin was the only infusion that consistently decreased the pulmonary/systemic arterial pressure ratio.[39]

Specifically in newborns, Mohamed et al. reported a case series of newborns with PPHN in which vasopressin was used as a "rescue" therapy for refractory pulmonary hypertension and systemic hypotension despite iNO and vasoactive infusions.[41] In this series, vasopressin resulted in improved oxygenation index and reduced iNO.[41] Three of the 10 newborns were also receiving milrinone. However, the improvement in oxygenation index persisted when excluding the newborns that received milrinone from the analysis.[41] However, it is notable that 4 of the 10 newborns died, and two required extracorporeal life support (ECLS), which may reflect their severity of illness at the time vasopressin was initiated as a rescue therapy in this series.[41] Acker et al. reported a case of 13 newborns with CDH that received vasopressin for refractory hypotension. All 13 newborns in this series met ECLS criteria prior to vasopressin initiation. Eleven patients received vasopressin prior to initiation of ECLS (the other two received vasopressin concurrently with ECLS initiation). In 6 of those 11, ECLS was no longer indicated due to overall improved hemodynamics.[42] In both the Acker and Mohamed series, vasopressin was used essentially as a rescue therapy after other interventions failed. Thus, earlier initiation of vasopressin in newborns with pulmonary hypertension warrants additional research.

However, it is notable that prior studies did not elaborate on the mechanism of hypotension in the newborns that received vasopressin. Assumingly, when considering its mechanism of action, vasopressin could be beneficial for a patient with low SVR and good LV function and potentially harmful for a newborn with poor LV dysfunction by increasing SVR (or LV afterload). Contrary to this assumption, low dose vasopressin has been beneficial in the post-operative management of newborns following the Norwood procedure or arterial switch operation (less fluid resuscitation needs and lower inotropic scores in the first 24 hours in the vasopressin group).[43] The low cardiac output state of these newborns is multifactorial, but likely involves some degree of LV dysfunction. The lack of deleterious effects from vasopressin in these situations may be related to improved coronary perfusion.[44] None the less, more information on the pathophysiology of newborns with PPHN treated with vasopressin will be useful in future studies to help better determine situations in which it should be used.

The effect vasopressin has on sodium and water balance has to be considered prior to initiation. Vasopressin can alter sodium and water balance via two mechanisms – V_1 receptors result in peripheral vasoconstriction and thus improved renal blood flow, and V_2 receptors have antidiuretic effects resulting in reabsorption of free water. This last mechanism has the potential to cause hyponatremia. In the Acker et al. series, they reported hyponatremia complications for the newborns that did not require ECLS, which they explain was due to differences in vasopressin doses used in the two groups. All 6 of the newborns experienced a decrease in serum sodium (average nadir 117.8 mmol/L, range 111-121) and were also treated for hyponatremia.[42] Mohamed et al. reported "negligible change in serum sodium" among their newborn series.[41] The degree of shock and mechanism of shock likely impacts the effect vasopressin has on sodium balance. For example, a review noted minimal or no cases of hyponatremia among studies of adults and children when vasopressin was used in settings of vasodilatory shock, however hyponatremia was commonly noted when vasopressin was used for indications other than vasodilatory shock.[45] None the less, use of vasopressin in neonates requires monitoring of serum sodium and research evaluating the

effect on serum sodium at varying doses and varying clinical indications in neonates may be helpful.

Hydrocortisone

Corticotrophin-releasing hormone (CRH), the hypothalamic peptide regulating the hypothalamus-pituitary-adrenal (HPA) axis in response to stress, is expressed in abundance in the human placenta and contributes to fetal cortisol during late gestation.[46] This source of CRH is lost following birth. Late preterm and term infants requiring vasopressor support have low cortisol levels but a normal response to exogenous ACTH.[47] Randomized trials to evaluate cortisol in term infants are warranted but are difficult to conduct.[48,49] The optimal indication and dose of hydrocortisone in neonatal hypotension is not clear.[48,49] However, cases demonstrating response to exogenous glucocorticoids in catecholamine-resistance hypotension are reported.[50]

The mechanisms of cardiovascular effects of hydrocortisone administration are not completely understood, but both genomic and nongenomic steroidal effects seem to play a role. [51] Hydrocortisone administration to preterm and term infants with vasopressor-resistant hypotension is associated with an improvement in BP, stoke volume (and a trend to increase in cardiac output) with a decrease in heart rate and need for vasoactive medications.[51] Genomic upregulation of cardiovascular adrenergic and angiotensin receptors and inhibition of inducible nitric oxide synthase and prostaglandins are potential mechanisms. In addition, non-genomic effects such as better capillary integrity, inhibition of catecholamine metabolism and increase in intracellular calcium may be mainly responsible for the rapid onset of the hydrocortisone-induced BP improvement.[51]

In addition to increasing blood pressure, glucocorticoids might have an effect on the lung in PPHN. Glucocorticoids may have beneficial effects in meconium aspiration syndrome[52] but there is a concern of exacerbation of infection and lack of multicenter randomized trials.[53] Animal studies have shown that high dose hydrocortisone inhibits phosphodiesterase 5 enzyme (PDE 5) and enhances oxygenation response in PPHN.[54,55] A single-center case series using 4 mg/kg loading dose followed by 1 mg/kg/dose q 6h in PPHN resistant to conventional therapy showed significant improvement in oxygenation and blood pressure with a reduction in the need for vasopressors.[56]

Special considerations

Infants born to mothers with diabetes (IDM) may have hypertrophic cardiomyopathy and impaired cardiac output that must be considered when choosing vasoactive medications. See Web Appendix for more.

Extracorporeal Life Support (ECLS)

Extracorporeal life support (ECLS) is a treatment option for newborns with PPHN, of which more information is in the Web Appendix.

CONCLUSION

PPHN may be characterized by a multitude of physiologic imbalances such an increased PVR to SVR ratio, or due to LV dysfunction or increased pulmonary blood flow that result in increased pulmonary artery pressure. Systemic hypotension is extremely common among infants with PPHN and should be identified early. Systemic hypotension is almost invariably a component of the clinical syndrome of PPHN but may have a variety of mechanisms that require thoughtful and targeted assessment and therapy. Further trials evaluating various vasoactive agents in PPHN are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEGMENTS

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Box 1.

Dopamine

Indication	Decreased cardiac function, hypotension, hypoxemia
Dose	2 to 20 mcg/kg/min (doses > 10-15 mcg/kg/min likely to have pulmonary vasoconstriction)
Precautions	May increase pulmonary pressure further adding to RV afterload; Watch for extravasation – (extravasation will need therapy with Phentolamine)
Contraindications	Supra-physiologic systemic pressures
Class of Recommendation	Class IIb – Usefulness/efficacy is less well established by evidence/opinion. May be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 2.

Norepinephrine

Indication	Hypotension without decreased cardiac function, hypoxemia
Dose	0.05 to 0.5 mcg/kg/min – occasionally may need up to 1 mcg/kg/min in PPHN with severe hypotension[24]
Precautions	Increased systemic vasoconstriction may decrease mesenteric perfusion and tolerance/safety of feeding Watch for extravasation – (extravasation will need therapy with Phentolamine)
Contraindications	Significant cardiac dysfunction unless using with an inotropic agent as well
Class of Recommendation	Class IIa – Weight of evidence/opinion is in favor of usefulness/efficacy. Should be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 3.

Epinephrine

Indication	Decreased cardiac function, hypotension, hypoxemia
Dose	0.05 to 0.3 mcg/kg/min
Precautions	Metabolic disturbances, arrhythmias
Contraindications	Potentially prematurity due to propensity to metabolic disturbances
Class of Recommendation	Class IIb – Usefulness/efficacy is less well established by evidence/opinion. May be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 4.

Dobutamine

Indication	Decreased cardiac function, hypotension, hypoxemia
Dose	2 to 25 mcg/kg/min (doses 10 > mcg/kg/min likely to have chronotropic effect)
Precautions	Arrythmias, tachycardia
Contraindications	Normal cardiac function
Class of Recommendation	Class IIa – Weight of evidence/opinion is in favor of usefulness/efficacy. Should be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 5.

Milrinone

Indication	Hypoxemia, decreased cardiac function, normal blood pressure or hypotension that is either mild or can be treated with another agent
Dose	0.25 to 1.0 mcg/kg/min (a loading dose is optional 25-75 mcg/kg and carries a higher risk of hypotension)
Precautions	May cause or worsen systemic hypotension due to vasodilation
Contraindications	Significant systemic hypotension or vasodilatory shock Renal dysfunction
Class of Recommendation	IIb[38] – Usefulness/efficacy is less well established by evidence or opinion
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 6.

Levosimendan

Indication	Decreased cardiac function with risk of arrhythmia
Dose	6 to 12 mcg/kg loading dose over 30 min followed by 0.1 mcg/kg/min for 6 h and then increase to 0.2 mcg/kg/min if tolerated
Precautions	Reduce milrinone dose if used concomitantly
Contraindications	Asphyxia due to potential altered affects in the pulmonary vasculature following asphyxia
Class of Recommendation	Class IIb – Usefulness/efficacy is less well established by evidence/opinion. May be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 7.

Vasopressin

Indication	Refractory pulmonary hypertension and systemic hypotension, however no literature in earlier use
Dose	0.1 to 2 milliunits (mU)/kg/min
Precautions	Hyponatremia, systemic vasoconstriction may affect mesenteric perfusion and tolerance/safety of feeding, and may be deleterious in the setting of LV dysfunction.
Contraindications	Hyponatremia
Class of Recommendation	Class IIb – Usefulness/efficacy is less well established by evidence/opinion. May be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Box 8.

Hydrocortisone

| Indication	Catecholamine-resistant systemic hypotension Refractory pulmonary hypertension not responsive to inhaled nitric oxide
Dose	Acute crisis: 1 mg/kg/dose q 6 h Maintenance: 1 mg/kg/day in divided doses Severe PPHN not due to infection – 4 mg/kg/dose x 1 followed by 1 mg/kg q 6h x 4 doses followed by maintenance
Precautions	Occult infection – fungal, viral (herpes simplex, CMV etc.,), bacterial can be exacerbated with steroid therapy
Contraindications	Known or suspected infection
Class of Recommendation	Class IIb – Usefulness/efficacy is less well established by evidence/opinion. May be considered
Level of Evidence	C – Consensus of opinion of the experts and/or small studies, retrospective studies, registries
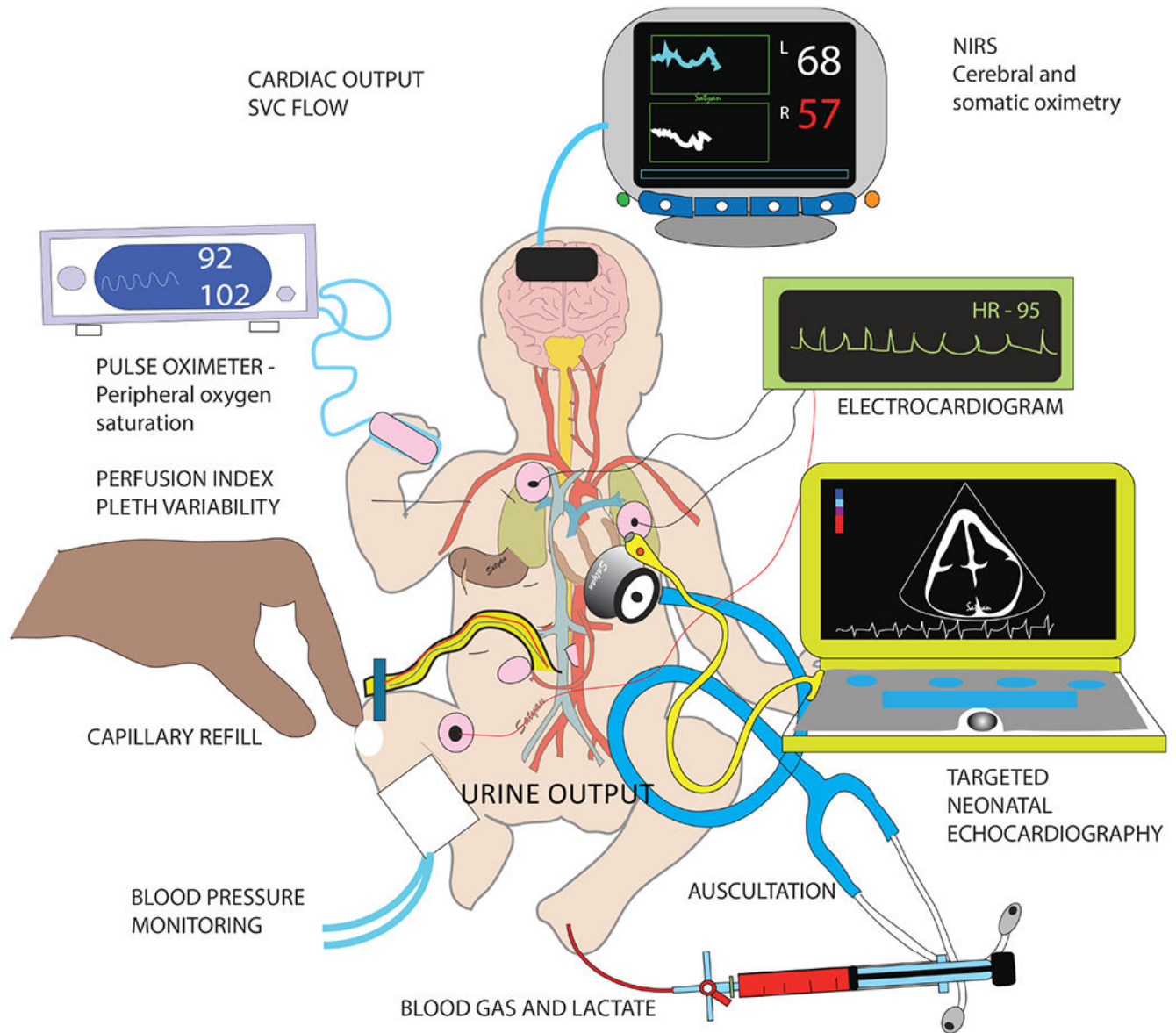
Figure 1. Cardiac pathophysiology in PPHN.

(A) A normal postnatal heart has left-to-right shunting at PFO and PDA with the interventricular septum (IVS) bulging to the right. (B) In mild-to-moderate PPHN, the IVS can be midline with bidirectional shunts at PFO/PDA. Increased right ventricular (RV) afterload is compensated by increased RV contractility. High velocity tricuspid regurgitation (TR) is observed. (C) In severe PPHN, the PFO and PDA shunt right-to-left with IVS bulging to the left decreasing left ventricular (LV) preload. Extremely high RV afterload leads to uncoupling of RV function leading to RV dilation. An open PDA might benefit the RV by providing a pop-off mechanism to reduce RV afterload. (D) When severe PPHN is associated with LV dysfunction, pulmonary venous hypertension and high pressure in the LA leads to left-to-right shunt at PFO but right-to-left shunt at PDA. Inhaled nitric oxide (NO), as well as other therapies that lower pulmonary vascular resistance, can precipitate

pulmonary edema in pulmonary venous hypertension if LV failure or other forward flow obstructions are present. In the setting of LV dysfunction, postductal systemic perfusion is supplemented by a transductal right to left shunt. Copyright Satyan Lakshminrusimha.
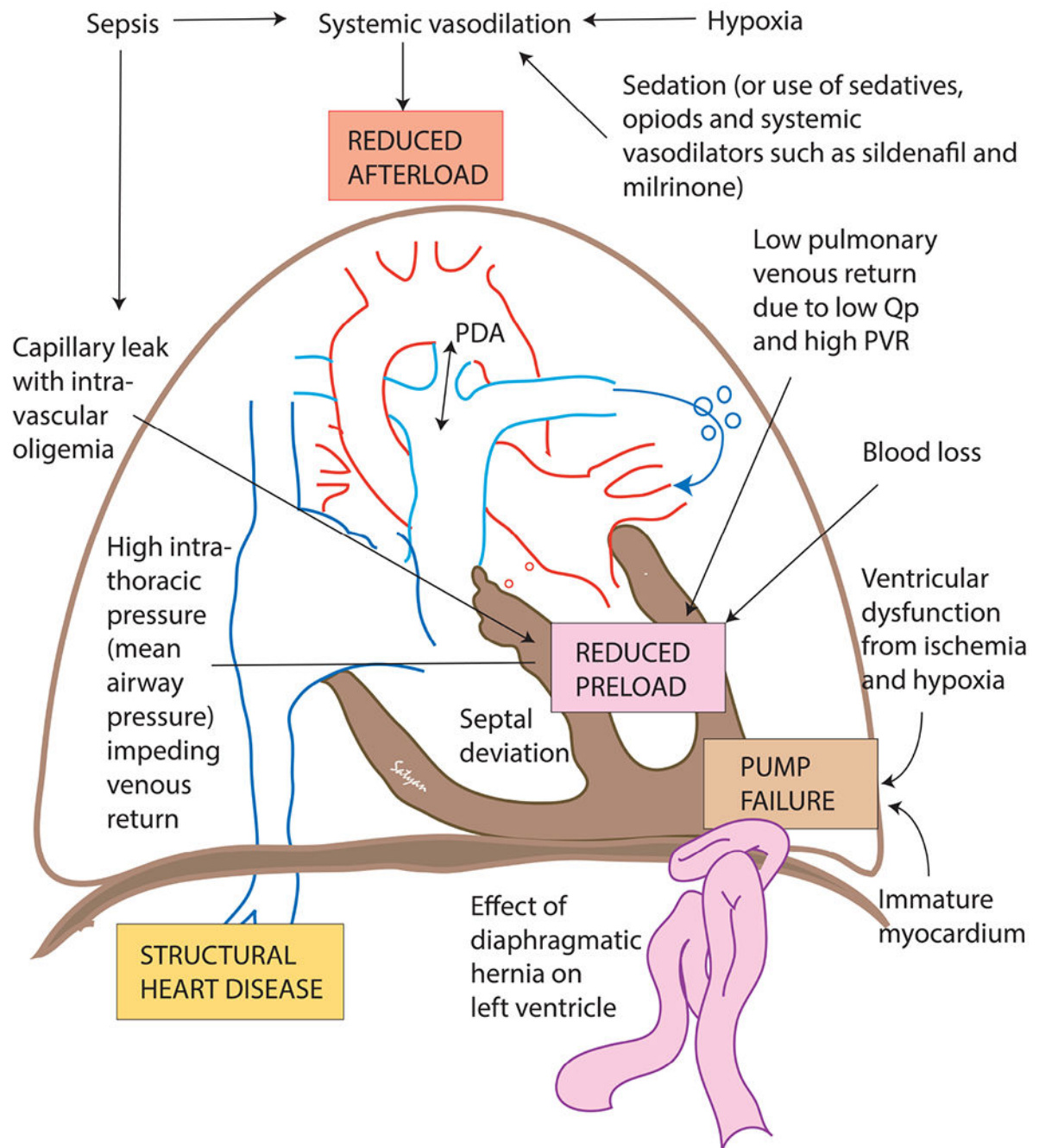
Figure 2. Assessment of perfusion:
clinical signs such as mental status (consciousness), capillary refill, blood pressure and urine output coupled with pulse oximetry, perfusion index, pleth variability index, targeted bedside echocardiography, electrocardiography (EKG), near-infrared spectroscopy (NIRS) and invasive monitoring with blood gas and lactate should be collectively interpreted to assess perfusion. Copyright Satyan Lakshminrusimha.
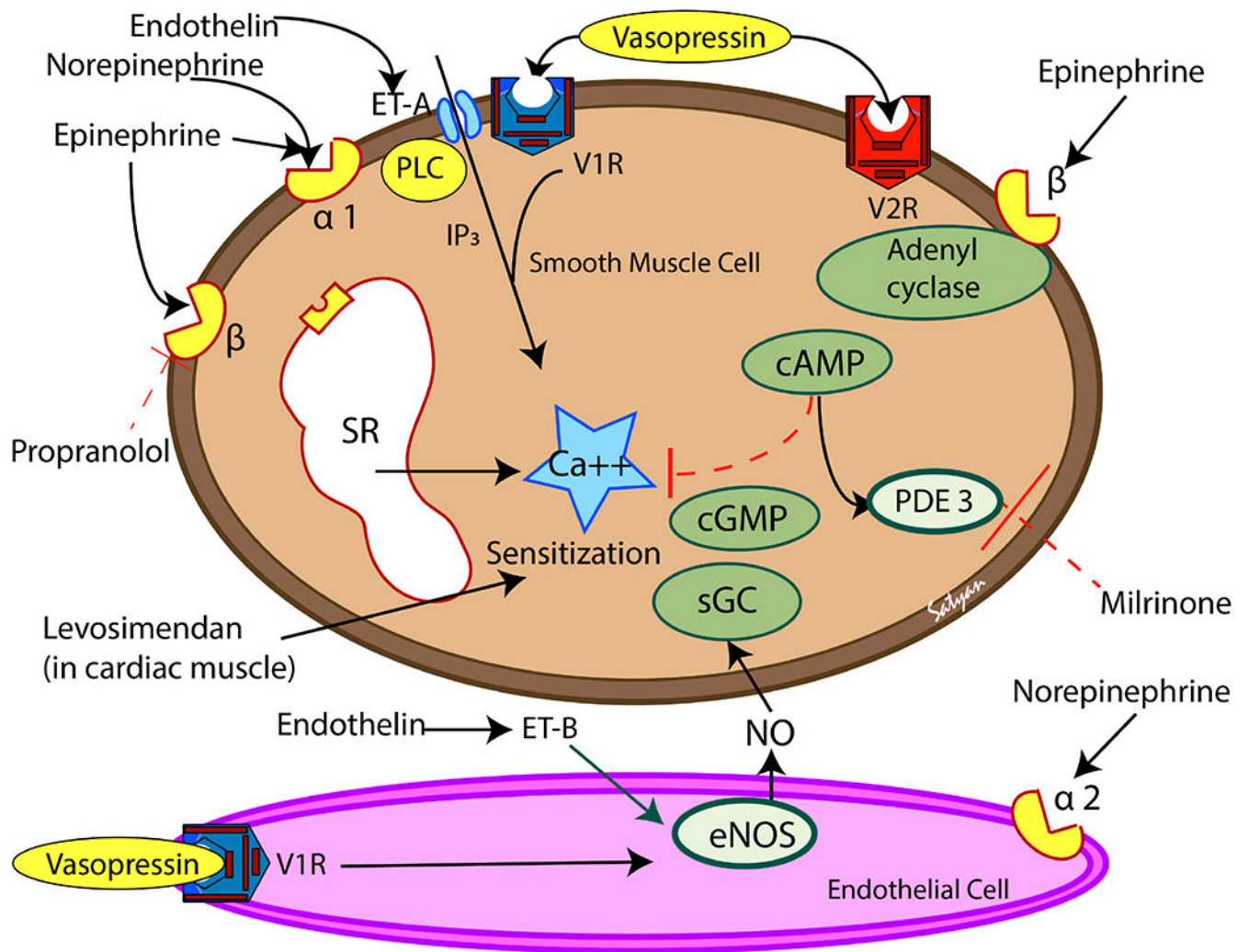
Figure 3. Etiology of systemic hypotension in PPHN.
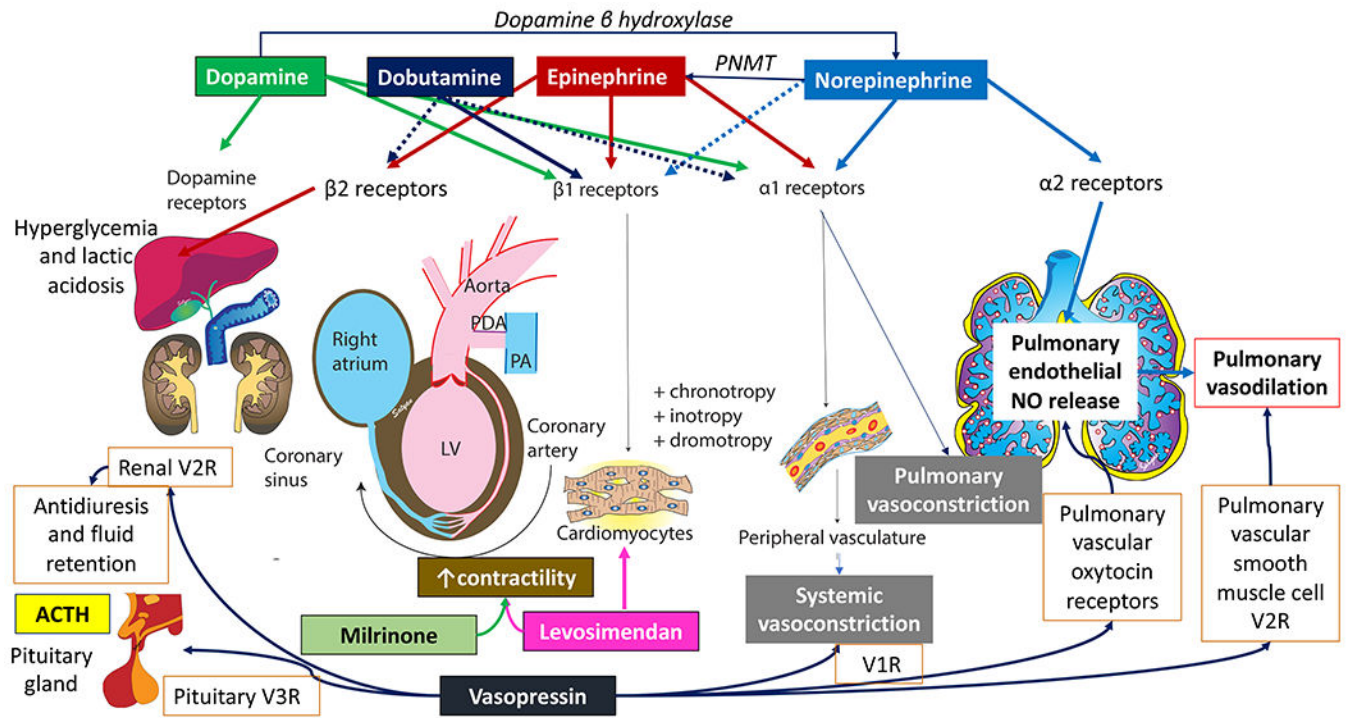Please see table 3 for details. Copyright Satyan Lakshminrusimha.

Figure 4. The vicious cycle of pulmonary hypertension, systemic hypotension and cardiac dysfunction in PPHN.

Selective pulmonary vasodilators to treat pulmonary hypertension, selective systemic vasoconstrictors to treat systemic hypotension and/or reducing afterload / optimizing preload are important strategies to interrupt this vicious cycle. Modified from an unpublished e-review by Dany Weisz, Patrick McNamara and Amish Jain. Copyright Satyan Lakshminrusimha.
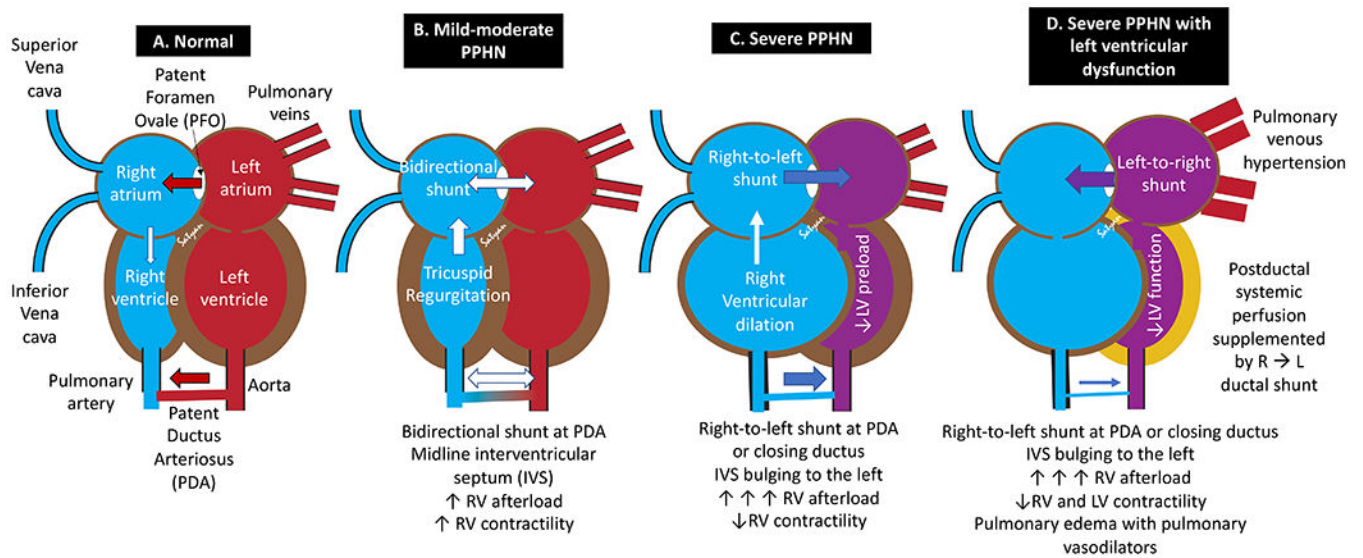
Figure 5. Mechanism of action of vasoactive medications in vascular smooth muscle (brown-top) and endothelial cell (pink-bottom).

V1R and V2R and vasopressin receptors. ET-A and ET-B are endothelin receptors, α_1, α_2, β_1 and β_2 are adrenergic receptors. PLC – phospholipase C, IP3 – inositol triphosphate; eNOS – endothelial nitric oxide synthase, NO – nitric oxide, sGC – soluble guanylyl cyclase, PDE3 – phosphodiesterase 3. Most of the vasoconstrictor mediators result in increase in cytosolic ionic calcium concentrations in the smooth muscle. Vasopressin (through V_1 receptors), endothelin (through ET-B receptors) and norepinephrine (through α_2 receptors) can act on pulmonary endothelium and stimulate NO production leading to pulmonary vasodilation. Copyright Satyan Lakshminrusimha.
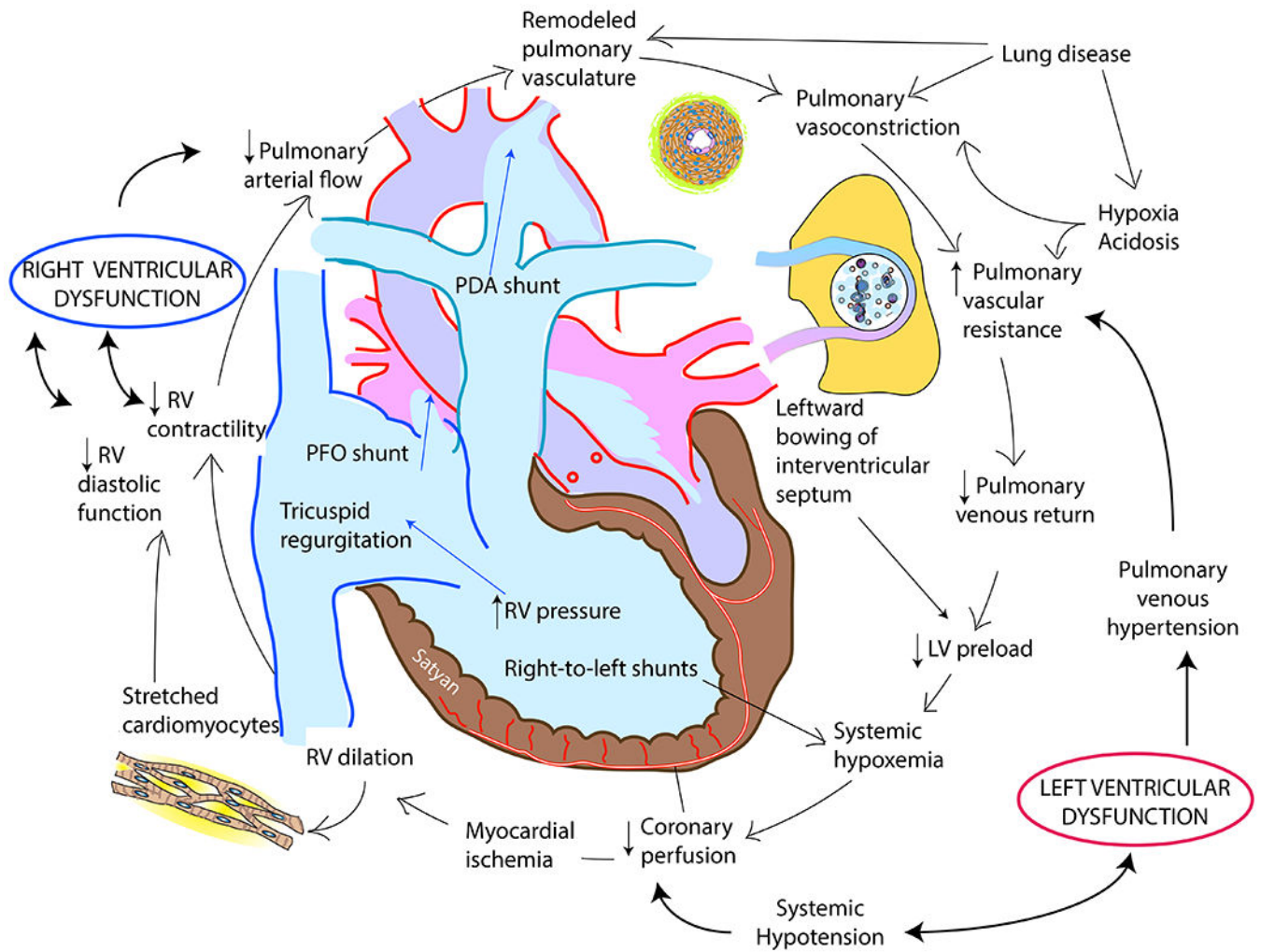
Figure 6. Vasoactive agents and their receptor distribution and action in various systems.
Dopamine is a precursor of norepinephrine. Norepinephrine is converted to epinephrine by Phenylethanolamine methyl transferase (PNMT). Dopamine has a dose-dependent effect on dopamine (D_1 and D_2) receptors, β_1 and α_1 receptors. Epinephrine is equally effective on β_1 and α_1 receptors. Norepinephrine predominantly acts on α_1 receptors causing systemic vasoconstriction. It is thought to stimulate α_2 receptors in pulmonary vascular endothelium and release NO leading to pulmonary vasodilation. Milrinone and levosimendan increases cardiac contractility. Vasopressin acts on V_1 receptors to induce systemic vasoconstriction, V_2 causing fluid retention in the kidneys and V_3 leading to pituitary stimulation to produce ACTH. Vasopressin also stimulates pulmonary vascular endothelial V_1 receptor and pulmonary vascular smooth muscle V_2 receptor to induce pulmonary vasodilation. Copyright Satyan Lakshminrusimha.

Table 1.

Cardiac function and shunt changes in persistent pulmonary hypertension of the newborn (see figure 1)

Parameter	Normal	Mild-to-moderate PPHN	Severe PPHN
RV afterload	Normal	↑	↑↑↑
RV contractility	Normal	↑↑ with RV hypertrophy	↓↓ (uncoupling) with RV dilation
RV diastolic function	Normal	Normal / ↓	↓↓ *
Septal position	Bulging to the right	Midline	Bulging to the left
PFO shunt	Left-to-right	Bidirectional or right-to-left	Right-to-left (or left-to-right with LV dysfunction) **
PDA shunt (if open)	Left-to-right	Bidirectional or right-to-left	Right-to-left (or closing ductus)
LV preload	Normal	Normal / ↓	Normal / ↓
Systemic blood pressure	Normal	Normal / ↓	↓↓↓

*
 In the presence of moderate to severe PPHN, RV diastolic function (lusitropy) is significantly reduced. In such states, it is important to avoid chronotropic agents (which will exacerbate diastolic dysfunction) and use agents which specifically target diastolic function (e.g. milrinone).

**
 In some patients with severe PPHN, a bidirectional atrial shunt or a left-to-right shunt may be observed even in the absence of LV dysfunction.[12]

Table 2.

Normal range of systemic blood pressure in mmHg in term infants (numbers in parentheses are 2 standard deviations below the mean; these can be considered the lower limit of normal during PPHN management).

Age	Systolic	Mean	Diastolic
6 to 18 h	80 ± 13 (54)	57 ± 12 (33)	43 ± 10 (23)
18 to 30 h	83 ± 12 (59)	60 ± 11(38)	46 ± 10 (26)
3 d ± 6 h [*]	84 ± 14 (56)	60 ± 12 (36)	48 ± 13 (22)
7 d ± 1 d	91 ± 15 (61)	67 ± 13 (41)	52 ± 11 (30)

[*] For practical purposes, systolic pressure of 55, mean of 35 and diastolic of 25 may be considered as lower limits of normal systemic blood pressure for term infants during the first postnatal week.

Table 3.

Etiology of systemic hypotension in persistent pulmonary hypertension of the newborn

Mechanism	Causes
Reduced LV afterload	systemic vasodilation from sepsis, hypoxia, sedation or vasodilators such as milrinone, prostacyclin analogs or sildenafil
Reduced LV preload	low pulmonary venous return, high intrathoracic pressure impeding venous return, blood loss, dehydration and septal deviation to the left
Pump failure	ventricular dysfunction from hypoxemia, acidosis, ischemia or inflammation
Structural heart disease	coexisting left ventricular hypoplasia with congenital diaphragmatic hernia (CDH) or severe asymmetric septal hypertrophy due to uncontrolled maternal diabetes