REVIEW ARTICLE

Treatment of persistent pulmonary hypertension of the newborn

Cleide Suguihara*

Abstract

Objective: to review the medical literature, emphasizing the new scientific advances in the treatment of persistent pulmonary hypertension of the newborn.

Sources: literature review using Medline and Cochrane library.

Summary of the findings: persistent pulmonary hypertension of the newborn (PPHN) is characterized by an increase in pulmonary vascular resistance associated with right to left shunting via the oval foramen and/or ductus arteriosus, leading to marked hypoxemia and respiratory failure. The balance between the vasoconstrictor (endothelin) and vasodilator (nitric oxide and prostaglandin I2) mediators plays an important role in the regulation of the transition from fetal circulation with high pulmonary vascular resistance to postnatal circulation with low pulmonary vascular resistance. In addition to general management, cardiovascular support, the treatment of the cause of the PPHN, and the use of selective pulmonary vasodilator such as inhaled nitric oxide (iNO) are indicated. Furthermore, the combined therapy with iNO and high-frequency oscillatory ventilation significantly improved the oxygenation of patients who were refractory to iNO therapy and conventional ventilation. The practice of hyperventilation and the administration of nonspecific pulmonary vasodilators (tolazoline) should be avoided. On the other hand, the administration of surfactant to patients with PPHN due to meconium aspiration should be considered. However, if all these therapies fail, extracorporeal membrane oxygenation (ECMO) should be considered as rescue therapy.

Conclusions: the mortality due to PPHN has significantly decreased with the use of new therapies, and the major concern today is the quality of life of these patients, especially in terms of neuropsychomotor development.


Introduction

(The incidence of persistent pulmonary hypertension of the newborn (PPHN) is estimated to be approximately of 1.9 per 1,000 livebirths.1 PPHN is characterized by increase in pulmonary vascular resistance (PVR) associated with right-to-left (R-L) shunting via the oval foramen and/or the ductus arteriosus. It is also associated with a mismatch in ventilation-perfusion that, consequently, results in significant hypoxemia.

PPHN is a clinical syndrome that occurs together with numerous cardiorespiratory diseases such as meconium aspiration syndrome, sepsis, pneumonia, acute respiratory distress syndrome, perinatal asphyxia, congenital diaphragmatic hernia, and pulmonary hypoplasia.

* Associate Professor of the Department of Pediatrics. Director, Neonatal Physiology Laboratory.
Despite the latest advancements in perinatal healthcare, PPHN continues to be an important clinical problem that contributes significantly to the mortality and morbidity of premature and term newborn babies. In order to offer adequate treatment to these patients, it is fundamental to understand the mechanisms that regulate fetal and postnatal pulmonary vascular tonus.

During fetal life, PVR is increased causing the pulmonary circulation to receive only 5 to 10% of cardiac output; consequently, most of the oxygenated blood of the right ventricle goes to the aorta via the ductus arteriosus. As the gestation advances, pulmonary artery pressure and blood flow increase progressively. The increase in pulmonary vascular tonus occurs mainly at the end of the gestation and seems to be modulated by low oxygen tension, low baseline production of vasodilators such as prostacyclin (PG I2) and nitric oxide (NO), increase in production of vasoconstrictors such as endothelin-1 and leukotrienes, and altered reaction of smooth muscle cells (myogenic tonus).2

The mechanisms that contribute to alterations in pulmonary vascular response during development are still unknown. It is known, however, that these alterations are associated with the maturing of endothelial cell function, mainly related to NO. Nitric oxide is produced in the vascular endothelium through the conversion of l-arginine and l-citruline by the nitric oxide synthase enzyme (Figure 1). As soon as NO is produced, it is rapidly diffused into smooth muscle cells and causes vasodilation due to soluble guanylate cyclase stimulation, thus increasing the production of cGMP.3 NO synthase enzyme expression is influenced by numerous factors, such as oxygen tension, hemodynamic forces, hormone stimulation, availability of substratum, and cofactor in superoxide production (inactivates NO).

It is interesting to note that exogenous NO can dilate fetal pulmonary circulation especially during the beginning of pregnancy. This probably explains the clinical finding of pulmonary vessels of extremely premature newborns being more sensitive to administration of inhaled nitric oxide (iNO).

In addition to the soluble guanylate cyclase enzyme, two other enzymes are important for the vascular response to NO: phosphodiesterase type 5 and cGMP kinase.

Prostaglandin I2 also participates in the regulation of baseline fetal pulmonary vascular tonus, but its effect is of a smaller magnitude than that of NO. In order to counterbalance the effect of vasodilator mediators there are vasoconstrictor mediators such as endothelin-1 (ET-1), thromboxane A2, leukotrienes, and the platelet-activating factor.

Thromboxane is an important vasoconstrictor after birth and in cases of infection by group B streptococcus, but it does not seem to influence baseline fetal pulmonary vascular tonus. The leukotrienes, in turn, seem to be important for control of the baseline pulmonary vascular tonus of the fetal lung. The most potent vasoconstrictor and mitogenic peptide produced by the vascular endothelium is ET-1. It causes vasoconstriction through ET-A receptors but can also have an opposite effect causing vasodilation when affecting ET-B receptors.

A few minutes after birth pulmonary artery pressure reduces drastically due to the increase in production of vasodilators such as NO and PG I2, which occurs as a response to stimulation such as rhythm distention of the lungs, caused by breathing, increase in O2 tension and pulmonary tension. Despite the fact that NO is not responsible for the whole decrease in PVR at birth, the activity of NO synthase seems to be important for postnatal adaptation of pulmonary circulation. The release of adenosine also contributes to the reduction of PVR at birth, though its activity is partially mediated by the release of NO.
When some of these factors do not operate together appropriately, the transition from fetal to postnatal life is not harmonious, and the pattern of fetal circulation may last until after birth, resulting in the clinical syndrome of PPHN.

Despite the fact that the increase in PVR is common to all causes of PPHN, pathological alterations can vary from anatomically normal pulmonary vessels, but with vascular hyperresponsiveness, arteries with excess smooth musculature and vascular remodeling, to pulmonary hypoplasia associated with reduction of the pulmonary vascular bed. Clinically, many of these conditions are characterized by alterations in both structure and function. In the case of congenital diaphragmatic hernia, there is a possibility that vascular hyperreactivity and alteration of vessel structure may occur with remodeling and alteration of vascular growth. But not all PPHN patients present alteration of vascular structure, such as in the case of sepsis caused by group B streptococcus, in which case, as a response to an acute insult, the only consequence is an increase in vascular reactivity.

However, it seems that PPHN is not explained solely by lower production of pulmonary vasodilators, but also by the increase in production of vasoconstrictors such as ET-1. This vasoconstrictor can also participate in vascular remodeling because of its mitogenic effect. In corroborating the action of ET-1, recent studies verified that patients with severe PPHN present increased plasmatic levels of ET-1, which are positively correlated with the severity of PPHN; it was also verified that levels of ET-1 decreased during recovery.

**Treatment**

In general, PPHN is a transient condition in which pulmonary artery spasms last a maximum of 5 to 7 days, with the exception of that in patients with congenital diaphragmatic hernia. Consequently, if newborns with this condition are adequately treated during this period, without the condition being deteriorated by lesion to the pulmonary parenchyma, there is a considerable increase in chances of survival.

In the treatment of PPHN, general care is as important as the specific treatment with pulmonary vasodilation.

**General care**

Whenever possible, it is important to correct the basal cause of PPHN; for example, if the newborn has a history suggestive of infection and x-ray compatible with the diagnosis of pneumonia, antibiotics should be administered to the patient. Metabolic problems such as hypoglycemia, hypocalcemia, and hypomagnesemia, among others, should be corrected. Moreover, environmental stimulation should be minimized.

It is also important to maintain normal blood perfusion and arterial pressure correcting cases of systemic arterial hypotension with restoration of vascular volume and use of vasopressor drugs. In general, the treatment used is intravenous infusion of fluids and/or albumin and vasopressors such as dopamine or dobutamine. The dosage of dopamine varies from 1 to 20 micrograms/kg/minute. The effects of dopamine (dopaminergic, beta-1 adrenergic, alpha-1 adrenergic) are determined by the dosage.

The dosage of dobutamine varies from 2.5 to 25 micrograms/kg/minute and its effect is predominantly beta-1 agonist. Differently from dopamine, dobutamine does not increase endogenous production of norepinephrine and does not affect dopaminergic receptors. Dobutamine is indicated in cases with cardiac failure.

Dopamine has been reported to be more effective than dobutamine in the treatment of arterial hypotension in premature babies with respiratory distress syndrome.

The side-effects of dobutamine and dopamine are tachycardia, arrhythmia, arterial hypertension, and tissue necrosis - in cases of overflow of the drug.

Newborns with pulmonary hypertension, during mechanical ventilation, are frequently sedated with phentanyl or morphine to minimize the effects of environmental stimulation, of pain, and of the discomfort characteristic to the treatment. Phentanyl can be administered through slow, intravenous infusion with bolus technique at every 2 to 4 hours and 1-4 micrograms/kg, or through continuous infusion of 1-5 micrograms/kg/hour. The dosage of morphine is of 0.05-0.2 mg/kg intravenously, intramuscularly, or subcutaneously; the dosage can be repeated at every 4-6 hours or from 10-15 micrograms/kg/hour by continuous infusion. In addition, these drugs can also reduce systemic arterial pressure.

The use of drugs that cause muscle palsy in ventilated patients with PPHN is still controversial. That is because these drugs can cause cardiovascular alterations, change the relation ventilation-perfusion and, also, make ventilator weaning more difficult. Recently, a study by the National Institutes of Health (NIH) analyzed the factors that contribute to the mortality of PPHN patients who were not treated with iNO. Results indicated that mortality was lower in neonatal ICUs where muscle palsy was significantly less applied to ventilated patients. Thus, the indication for muscle palsy should be limited to patients who are still struggling with the ventilator despite receiving appropriate respiratory assistance and general treatment measures (sedation and minimization of environmental factors).

**Pulmonary vasodilator**

Drugs that cause non-selective vasodilation of pulmonary vessels, such as tolazoline, prostacyclin, isoproterenol, adenosine and its derivatives such as ATP-MgCl, calcium channel blockers, and nitroprusside have been indicated for
PPHN treatment.\textsuperscript{6-9} Tolazoline is the most widely used vasodilator; despite attenuating pulmonary hypertension, however, this drug also causes significant systemic arterial hypotension in over 50\% of patients.\textsuperscript{6}

The introduction of inhaled nitric oxide (iNO) has allowed for effective and selective pulmonary vasodilation in PPHN newborns without systemic repercussions.

\textbf{Nitric Oxide (NO)}

Nitric Oxide is produced by blood vessel endothelial cells and it soon diffuses to the adjacent smooth muscle (Figure 1). Nitric oxide can dilate pulmonary and cardiac circulation, but when administered through inhalation, it diffuses from the airways into pulmonary vessel walls, causing their dilation. Next, it is rapidly connected to the hemoglobin in the vessel lumen and inactivated; as a consequence, the pulmonary circulation is connected to the hemoglobin. That is why iNO does not have a significant effect on systemic circulation, thus acting selectively on pulmonary vessels. In addition to this effect, the iNO can also optimize the relation between ventilation and perfusion - which is explained by the fact that NO acts predominantly on blood vessels that perfuse the better-ventilated alveoli. As a result, NO can be beneficial in the treatment of a variety of pulmonary diseases in addition to pathologies associated with severe vasoconstriction.

As for the clinical effect of iNO in PPHN patients, the first two multicentered, randomized, controlled studies were published in 1997. The first study, by Roberts et al., evaluated 58 newborns with over 37 weeks’ gestation or birthweight greater than 2.5 kg, selected with the condition of presenting \(\text{PaO}_2\) less than 55 torr during conventional ventilation treatment with 100\% oxygen.\textsuperscript{10} In the study, high-frequency ventilation was not used for patients with unsuccessful conventional ventilation treatment. The initial dose of iNO was of 80 ppm, which was later reduced according to patient response. Immediate successful response was established when 20 minutes after beginning of therapy, patients presented \(\text{PaO}_2\) greater than 55 torr, no systemic arterial hypotension, and oxygenation index less than 40 (\(\text{OI} = \frac{\text{MAP} \times \text{FiO}_2 \times 100}{\text{PaO}_2}\)). Inhaled nitric oxide successfully doubled systemic oxygenation in 53\% of patients, whereas conventional therapy without inhaled nitric oxide increased oxygenation in only 7\% of controls. Extracorporeal membrane oxygenation was required in 71\% of the control group and only 40\% of the nitric oxide group.

The second study is that of the Neonatal Inhaled Nitric Oxide Study Group with 235 newborns.\textsuperscript{11} The population included infants born after 34 weeks’ gestation or more and whose oxygenation index was 25 or higher on two measurements. Patients could be either on conventional or high-frequency ventilation. The initial iNO dose was of 20 ppm with the possibility of being increased up to 80 ppm if oxygenation did not improve. Results of the study indicated immediate response after administration of iNO. OI reduced from 43 to 29 during iNO, \(\text{PaO}_2\) increased to 58 torr, and there was a 30\% reduction in newborns who required ECMO. In turn, patients with congenital diaphragmatic hernia did not respond to iNO.\textsuperscript{12} This finding was corroborated by more recent studies that show that iNO has not affected the evolution of diaphragmatic hernia.\textsuperscript{13}

In the NIH study, there was no indication of increase in intracranial, pulmonary, or gastrointestinal hemorrhages in patients who received iNO in comparison to controls.\textsuperscript{12} There was also no difference on the incidence of bronchopulmonary dysplasia, in duration of mechanical ventilation, in duration of hospital stay, and in mortality.

All clinical results were confirmed by the metaanalysis published by the Cochrane library in 1999 with 8 randomized, controlled studies.\textsuperscript{13} The review concluded that oxygenation improved in approximately 50\% of patients treated with iNO and that the need for ECMO reduced. However, the authors observed that mortality did not change and treatment was unsuccessful in patients with diaphragmatic hernia. The study suggests an initial dosage of 20 ppm for term or near-term newborns; still, more studies should be carried out to follow-up the pulmonary aspect and long-term neuropsychomotor development.

An important question in the iNO therapy is: What would be the best way to ventilate patients with iNO? with high-frequency or conventional methods?

While the NIH study did not indicate a difference between conventional and high-frequency ventilation in improving oxygenation, the randomized, multicenter study by Kinsella et al. suggests that patients with severe PPHN, who did not respond to either high-frequency oscillatory ventilation (HFOV) or conventional ventilation combined with iNO, responded with significant improvement in oxygenation when receiving iNO combined with HFOV.\textsuperscript{14} The treatment combining iNO and HFOV was more effective especially in the case of patients with PPHN associated with severe parenchymatous disease. This finding is probably a consequence of improvement in intrapulmonary shunt following recruitment and maintenance of pulmonary volume, which favors the release of NO in the area of action.

\textbf{Dose}

The initial recommended dose of iNO is of 20 ppm and should be reduced to 5 ppm as soon as possible.

Recently, Davidson et al. carried out a dose-response study with iNO in term newborns with respiratory problems.\textsuperscript{15} In the study, patients were randomly administered 0 (placebo), 5, 20, or 80 ppm iNO. In comparison to placebo, oxygenation increased with each dose of iNO; there were no significant differences between the different doses of iNO. Elevated methemoglobin (greater than 7\%) was observed in 35\% of the 80 ppm NO group, there was also a 19\% increase in nitrogen dioxide (greater than 3 ppm). These results, and the fact that the 80 ppm
dosage was not more effective in improving oxygenation in comparison to 5 and 20 ppm dosages, corroborate the recommendation that PPHN term newborns should be given an initial dosage of 20 ppm of iNO. Though very short-term exposure to high doses of iNO (40 to 80 ppm) seems safe, the prolonged use should be avoided due to the side-effects that may occur.

iNO weaning should be aggressive and start as soon as the patient presents adequate, stable levels of PaO₂. The reduction of the initial dosage from 20 to 5 ppm can be made as soon as the patient has maintained a good oxygenation for 6 to 12 hours. This usually occurs during the first 24 hours of treatment. The reduction from 20 to 5 ppm can be carried out rapidly and at once. It can also be carried out gradually (20 to 10 to 5 ppm) at every 4 to 6 hours, as long as oxygenation remains stable; if oxygenation deteriorates, however, it is necessary to immediately restore the previous concentration of iNO. Weaning iNO at 5 ppm should be carried out slowly, with 1-ppm reductions at every 4 to 6 hours. These cautions with weaning iNO are aimed at avoiding rebound pulmonary hypertension.

iNO toxicity

Despite the advantages in the use of iNO, initial studies have suggested that it can have a toxic effect to the lungs. NO can combine with O₂ to form NO₂, and with the superoxide to form peroxynitrite; these metabolites are responsible for NO lung toxicity.

The use of iNO can lead to an increase in methemoglobinemia. However, elevated methemoglobinemia (greater than 5%) was observed only with high iNO doses (80 ppm) and presented a tendency to be resolved rapidly when NO was interrupted.

Nitric dioxide can decrease serum glutathione peroxidase activity, thus increasing the risk for oxidative lesion to the lungs. Experimental studies have shown that peroxynitrites are oxidizing agents capable of damaging lipids in biological membranes, thus affecting pulmonary surfactant production and its proteins.

In turn, clinical studies with the use of iNO have shown methemoglobin levels between 2 and 5%; more recently, experimental and clinical studies suggested that the use of low dose iNO does not present toxicity to the lungs.

Another undesirable effect of iNO involves platelet function. iNO inhibits platelet aggregation and adherence; however, different studies indicated no differences regarding the occurrence of intracranial, pulmonary, or gastrointestinal hemorrhage in newborns treated with iNO in comparison to controls.

Patients treated with iNO, even with doses of 20 ppm, should be monitored for methemoglobin during the first 4 to 6 hours after the beginning of treatment and subsequently at every 24 hours. If iNO therapy fails and the patient requires transfer to an ECMO center, it will be necessary to provide iNO ventilation during patient removal in order avoid acute deterioration (rebound pulmonary hypertension) caused by abrupt weaning of iNO.

Mechanical ventilation

Conventional ventilation

For many years, pulmonary hyperventilation was used to cause hypocapnia together with respiratory alkalosis and, thus, improve systemic oxygenation and reduce pulmonary artery pressure. However, experimental studies with mechanically-ventilated newborn lambs suggest that increased arterial pH, not hypocapnia attenuates pulmonary vasconstriction. In addition, others have shown an increase in complications related to volutrauma and neurodevelopmental sequelae following hypocapnia. Consequently, most neonatal ICUs have abandoned the use of hyperventilation and adopted administration of sodium bicarbonate in order to increase blood pH.

In a noncontrolled study, Wung et al observed a greater survival rate in patients with PPHN submitted to more conservative ventilation and acceptable hypercapnia. This finding was confirmed by a retrospective study carried out by Dworetz et al, in which results indicated a smaller mortality rate in the group of patients submitted to a more conservative approach (PaO₂ of 60 to 80 torr; PaCO₂ of 35 to 45 torr; and pH of 7.45 to 7.50 - sodium bicarbonate was administered if necessary) than in the group of hyperventilated patients (PaO₂ greater than 90 mmHg and PaCO₂ of 20 to 25 mmHg).

High-frequency oscillatory ventilation (HFOV)

HFOV has been used empirically in PPHN patients at numerous neonatal ICUs; however, there are few studies evaluating the use of HFOV in a randomized, controlled manner.

In a study by Clark et al., 79 newborns with gestational age greater than 34 weeks and respiratory failure were randomly submitted to HFOV or conventional ventilation. In case of failure of the randomly assigned treatment, patients could be submitted to a different type of ventilation. A total of 60% of patients assigned to conventional ventilation met treatment failure criteria compared with 44% of those assigned to HFOV; this difference was not statistically significant. Of patients in whom conventional ventilation failed, 63% responded to HFOV, whereas only 23% of patients in whom HFOV failed responded to conventional ventilation; this difference, in turn, was statistically significant.

In the treatment of PPHN patients, it is reasonable to start respiratory assistance with conventional ventilation, and HFOV when patients do not respond to conventional ventilation. The combined use of iNO with conventional ventilation or HFOV was discussed previously in this review.
**Liquid ventilation**

In partial liquid ventilation, perfluorocarbon is instilled into the lungs until it fills the functional residual capacity. Ventilation with O\(_2\) at 100% is carried out with a conventional ventilator.\(^{26}\)

Perfluorocarbon has more solubility in O\(_2\) and CO\(_2\) than blood and, thus, can be used to deliver oxygen to the alveoli. It has low surface tension and can act as a surfactant, as well as in recruiting collapsed alveoli for a more uniform ventilation. Yet, when partial liquid ventilation is used, the lungs become full of liquid and gas during inspiration, thus establishing an air-liquid interface. This interface causes the surface tension to increase and, consequently, high inspiratory pressure may be necessary. This therapy has been successfully applied to animals with pulmonary hypertension as a result of tracheal instillation of meconium; however, the use of partial liquid ventilation has not been systematically researched in newborns with severe pulmonary hypertension.\(^{26}\)

**Extracorporeal membrane oxygenation (ECMO)**

ECMO functions as a rescue therapy when all other measures have failed in the treatment of PPHN. The use of ECMO is based on the idea that vasospasms are transitory and, until they are resolved, it is possible to maintain adequate oxygenation. In sum, ECMO is a bypass technique in which a catheter is placed in the jugular vein and advanced into the right atrium in order to remove unsaturated blood. The blood is then anticoagulated and pumped to an oxygenation membrane, where O\(_2\) is added and CO\(_2\) removed. The oxygenated blood returns to the patient via the carotid artery. Currently, there is also veno-venous ECMO where blood is removed and reinfused through the vein, avoiding carotid artery catheterization.

ECMO is an extremely expensive therapy that involves specialized teamwork. It is indicated for newborns with severe respiratory failure, ventilated less than 10 to 14 days, and who despite maximum therapeutics, present oxygenation index > 40 in consecutive gasometries. Its use is restricted to newborns with gestational age greater than 34 weeks and weight greater than or equal to 2.0 kg due to technical limitations of catheterization in premature babies and to the greater risk for bleeding.

A total 180 PPHN patients were evaluated according to treatment administered. Ninety patients were treated with ECMO and the other 90 receive conventional treatment. Survival was of 71% in the ECMO group and only of 42% in the conventional therapy group.\(^{27}\)

In the United States, the use of ECMO peaked in 1992, when it was administered in 1,500 cases. Since then, there has been a progressive decrease in the number of cases that require ECMO. This finding is probably related with the use of HFOV, surfactants, and iNO.\(^{28,29}\)

In addition, there has been a change in the population of patients treated with ECMO who currently are, in their majority, newborns with surgical complications such as congenital diaphragmatic hernia. This occurred while actual clinical cases of pulmonary hypertension have responded to the new therapeutics.

Despite the improved prognosis for patients treated with ECMO, there is still a great concern related to intracranial hemorrhage in ECMO and to long-term neuropsychomotor development. Glass et al., carried out a study with 103 patients at age 5 years and treated with ECMO; the authors reported that approximately 15% of patients presented severe sequelae, with most cases of mental retardation being of mild to moderate nature.\(^{30}\) The IQ of children treated with ECMO was lower than that of children in the control group, but within the normal limits.

Considering all of the above aspects, ECMO should be indicated for reversible cases of PPHN in patients who do not respond to conventional treatment and to combined iNO and HFOV.

**Pulmonary surfactant treatment**

Surfactant administration has been indicated for term newborns with pulmonary hypertension caused by meconium aspiration. On the one hand, Findlay et al. demonstrated that surfactant replacement therapy, if started within 6 hours after birth and administered in 1 to 4 doses (150 mg of phospholipids/kg), significantly improves oxygenation and reduces the incidence of air leak syndrome, the need for ECMO, the duration of oxygentherapy and of hospital stay.\(^{30}\) On the other hand, Loetze et al. examined the effects of surfactant administration at 100 mg/kg in PPHN patients due to meconium aspiration syndrome or sepsis.\(^{31}\) In that study, the authors observed a significant improvement in oxygenation and reduction in the need for ECMO therapy, but there were no differences regarding the incidence or air leaks and pulmonary hemorrhage, or in the duration of oxygentherapy and mechanical ventilation.

The referred studies indicated that surfactant replacement therapy benefits patients with PPHN, but the adequate dosage is still not well-established. It is possible to administer surfactant to PPHN patients via meconium aspiration during the first 6 hours of life; up until 4 doses may be necessary if PaO\(_2\) is less than 60 to 70 torr with a FiO\(_2\) of 1.0.

**Future advancements in PPHN treatment**

Before finishing this review, it is important to mention new possibilities for PPHN treatment. These new approaches are aimed at searching for drugs with selective effect on pulmonary vasculature.

Up until now, the drug with selective vasodilator effect is iNO. However, only approximately 50% of PPHN patients...
respond to this therapy. The possibility of increasing the production of endogenous NO by inhibiting NO deterioration (Figure 1) should be considered. One of the ways to do this is inhibiting the activity of 5-phosphoesterase. The drugs zaprinast, dipyridamole, and sildenafil (viagra) can inhibit the activity of 5-phosphoesterase, but only dipyridamole was approved by the FDA for use with the treatment of pulmonary hypertension in adults and children. Children aged more than 1 year with pulmonary hypertension were treated with dipyridamole and results indicated a significant attenuation of pulmonary hypertension; this effect, however, was associated with significant systemic arterial hypotension.

The effects of zaprinast and sildenafil were evaluated in lambs with pulmonary hypertension. Both drugs reportedly allowed for significant attenuation of pulmonary hypertension, and zaprinast caused more systemic hypotension than sildenafil. When these drugs were administered in combination with iNO, the authors observed that zaprinast prolonged the effect of iNO, which did not occur in the case of sildenafil. Evidently, the fact that these drugs can attenuate pulmonary hypertension alone is not enough to indicate these drugs to patients; more studies should be carried out in the sense of verifying whether the benefits of these drugs are more important than short and long-term undesirable effects.

Another group of NO donors that are being studied experimentally are the soluble substances belonging to the NONOates, which present the advantage of being administered via inhalation or directly via the trachea. Experimental studies with these drugs have shown that they cause selective dilation of pulmonary circulation and have no effect on systemic circulation. These studies are still incipient, and it is necessary to carry out more research in order to evaluate (in addition to hemodynamic effects) the short and long-term side effects.

It is still not possible to state that the future of PPHN treatment will be the combined use of NO donors with very low dose iNO; there is still the need for more research in order to definitively understand the efficacy and safety of this treatment, both short and long-term, and to understand the clinical applicability of the treatment.

References