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REVIEW

Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm neonates

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Recent advances in our understanding of neonatal pulmonary circulation and the underlying pathophysiology of hypoxemic respiratory failure (HRF)/persistent pulmonary hypertension of the newborn (PPHN) have resulted in more effective management strategies. Results from animal studies demonstrate that low alveolar oxygen tension (PAO_2) causes hypoxic pulmonary vasoconstriction, whereas an increase in oxygen tension to normoxic levels (preductal arterial partial pressure of oxygen (PaO_2) between 60 and 80 mm Hg and/or preductal peripheral capillary oxygen saturation between 90% and 97%) results in effective pulmonary vasodilation. Hyperoxia (preductal $PaO_2 > 80$ mm Hg) does not cause further pulmonary vasodilation, and oxygen toxicity may occur when high concentrations of inspired oxygen are used. It is therefore important to avoid both hypoxemia and hyperoxemia in the management of PPHN. In addition to oxygen supplementation, therapeutic strategies used to manage HRF/PPHN in term and late preterm neonates may include lung recruitment with optimal mean airway pressure and surfactant, inhaled and intravenous vasodilators and 'inodilators'. Clinical evidence suggests that administration of surfactant or inhaled nitric oxide (iNO) therapy at a lower acuity of illness can decrease the risk of extracorporeal membrane oxygenation/death, progression of HRF and duration of hospital stay. Milrinone may be beneficial as an inodilator and may have specific benefits following prolonged exposure to iNO plus oxygen owing to inhibition of phosphodiesterase (PDE)-3A. Additionally, sildenafil, and, in selected cases, hydrocortisone may be appropriate options after hyperoxia and oxidative stress owing to their effects on PDE-5 activity and expression. Continued investigation into these and other interventions is needed to optimize treatment and improve outcomes.

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INTRODUCTION

Term and late preterm newborns with respiratory failure requiring mechanical ventilation represent a high-risk population with significant morbidity and mortality.[1] Respiratory failure at this gestational age is frequently complicated by persistent pulmonary hypertension of the newborn (PPHN).[2,3] PPHN occurs in diverse settings and encompasses a wide spectrum of diseases, including but not limited to respiratory distress syndrome, meconium aspiration syndrome (MAS), pneumonia, sepsis and primary pulmonary hypertension (Figure 1).[2,3] PPHN reflects the failure of the pulmonary vasculature to relax at birth, which results in increased pulmonary arterial pressure and pulmonary vascular resistance (PVR), leading to right-to-left shunting of deoxygenated blood from the pulmonary to systemic circulation (Figure 1).[4,5] PPHN is a neonatal emergency that requires timely and precise intervention to prevent severe hypoxia and short- and long-term morbidities. Appropriate clinical management of PPHN in term and late preterm newborns requires a full understanding of the pathogenesis of PPHN and recognition that pulmonary circulation differs from systemic circulation in structure, function and regulation (for example, hypoxia causes pulmonary vasoconstriction but dilates the systemic circulation).

This article discusses translational science and current challenges, as well as best practices, in the management of hypoxemic respiratory failure (HRF) and PPHN in term and late preterm neonates. It is part of a series summarizing presentations and discussions from a roundtable discussion that focused on HRF in neonates (see the Introduction to this issue).

INHALED THERAPY AND VENTILATION

Optimizing oxygenation: avoid both hypoxemia and hyperoxemia

Ensuring adequate oxygen delivery to the brain and other tissues represents the mainstay of PPHN therapy via therapeutic modalities, such as oxygen supplementation, mechanical ventilation and inhaled nitric oxide (iNO). Oxygen delivery is dependent on blood flow and arterial oxygen content (CaO_2) (Figure 1).

Oxygen use at birth

During the intrauterine period, the fetus is in a state of physiological pulmonary hypertension, partly secondary to relative hypoxemia. At birth, following ventilation of lungs with air, a rise in oxygen tension contributes to rapid pulmonary vasodilation. In normal term neonatal lambs, use of 21% oxygen during initial ventilation led to a decrease in PVR in the immediate postnatal period.[6] Although initial ventilation with 100% oxygen marginally enhanced the decrease in PVR at birth, it also impaired pulmonary vasodilation in response to a subsequent exposure to iNO.

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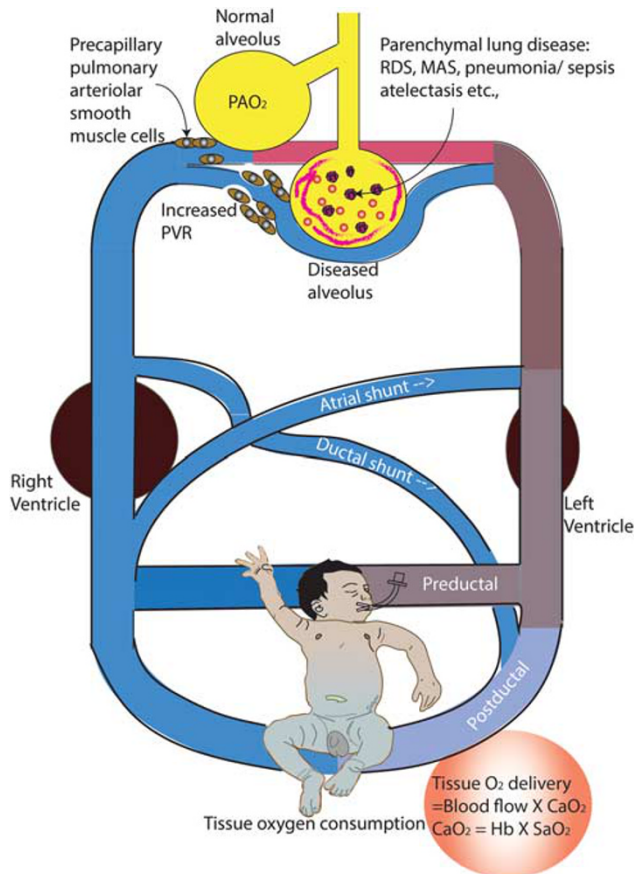E-mail: slakshmi@buffalo.edu

Figure 1. Pathophysiology of persistent pulmonary hypertension of the newborn (PPHN)—precapillary pulmonary arteriolar smooth muscle cells are considered to be the primary oxygen sensors in the pulmonary vasculature. Their partial pressure of oxygen (PO_2) is mainly regulated by alveolar oxygen tension (PAO_2). In PPHN, increased pulmonary vasoconstriction secondary to various causes, including parenchymal lung disease such as respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS) and pneumonia/sepsis, results in increased pulmonary vascular resistance (PVR). This leads to right ventricular hypertrophy and right-to-left shunt across the patent foramen ovale (atrial shunt) and ductus arteriosus (ductal shunt) leading to hypoxemia. A ductal shunt results in differential cyanosis with preductal oxygen levels higher than postductal oxygen levels. The goal of therapy in hypoxemic respiratory failure (HRF) and PPHN is to optimize tissue oxygen delivery. (Copyright: Dr Lakshminrusimha, Dr Konduri and Dr Steinhorn). CaO_2, arterial oxygen concentration; O_2, oxygen; SaO_2, arterial oxygen saturation.

Similar results were seen in a neonatal lamb model of PPHN with remodeled pulmonary circulation induced by antenatal ligation of the ductus arteriosus[7] (Figure 2) and in a neonatal lamb model of acute pulmonary hypertension secondary to perinatal asphyxia.[8] These studies suggest that, while high concentrations of inspired oxygen may induce short-term pulmonary vasodilation, they may also impair subsequent vasodilator response to iNO. The mechanism of hyperoxia-induced impairment of NO-mediated vasodilation is most likely related to inactivation of NO by superoxide anions and/or superoxide anion-mediated enhancement of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE-5) activity (see next section). These findings support the recommendation of the Neonatal Resuscitation Program to use 21% oxygen for the initial resuscitation of term neonates.[9,10]

Optimal oxygenation during management of a neonate with HRF in the neonatal intensive care unit

It has been recognized for some time that alveolar hypoxia and hypoxemia increase PVR and contribute to the pathophysiology of PPHN. PVR is regulated predominantly by pulmonary arterial smooth muscle cells (PASMCs) in small resistance precapillary pulmonary arterioles (Figure 1). The oxygen tension in these PASMCs is determined by alveolar oxygen tension (PAO_2) and pulmonary arterial (or mixed venous) partial pressure of oxygen, although PAO_2 is considered to be the more important factor.[11]

In clinical practice, preductal arterial partial pressure of oxygen (PaO_2) is measured and used to calculate PAO_2. The relationship between PVR and PaO_2 was first described in a study of healthy newborn calves, which found a precipitous increase in PVR as the PaO_2 fell below 45 to 50 mm Hg.[12] A similar relationship between PaO_2 and PVR was later described in an ovine model of PPHN.[7] Healthy control lambs in this study had an acute increase in PVR with preductal $PaO_2 < 52.5$ mm Hg (Figure 3a). In PPHN lambs, hypoxic vasoconstriction was greatly exaggerated with two PVR change points: severe hypoxemia with $PaO_2 < 13.9$ mm Hg resulted in a steep increase in PVR (up to 6 mm Hg/mL/kg/min), whereas resistance declined more gradually at $PaO_2 > 59.6$ mm Hg (Figure 3b). Within clinically relevant ranges of preductal oxygen saturations (80% to 100%), PVR increased below capillary oxygen saturation (SpO_2) of 85% and also as oxygen saturation exceeded 98% (Figure 3d). Similar change points were observed in acute PPHN induced by perinatal asphyxia and MAS (Figure 3c). Moreover, in both groups, an increase from 50% to 100% inspired O_2 did not produce any further decrease in PA pressure or PVR.[7] These observations suggest that the lowest PVR can be maintained with preductal peripheral SpO_2 in the 90% to 97% range with preductal PaO_2 between 60 to 80 mm Hg in these newborn sheep models (Figure 3d).

Findings from these ovine models have clinical relevance to the management of PPHN, as traditional practice often involved hyperoxic ventilation during the acute phase. Such an approach has not been shown to produce persistent clinical benefit in PVR, and the animal studies suggest that this approach paradoxically impairs the subsequent response to iNO.

The mechanisms underlying the hemodynamic effects of hyperoxia reflect, in part, increased oxidative stress (Figure 4). Ventilation with 100% oxygen promotes formation of reactive oxygen species (ROS), such as superoxide anions that enhance vasoconstriction in the neonatal pulmonary circulation,[13–15] and inactivate NO through formation of peroxynitrite.[15–18] In addition, ROS decrease endothelial nitric oxide synthase activity and soluble guanylyl cyclase activity resulting in reduced cGMP levels[19] with consequent vasoconstrictor effects. Decreased responsiveness to iNO is reflected in decreased intracellular cGMP response as well as increased PDE-5 cGMP-hydrolytic activity.

The role of ROS in pulmonary vasoconstriction is further supported by demonstration that activation of xanthine oxidase produces acute pulmonary vasoconstriction.[20] An increase in superoxide anion production has been reported following ventilation of PPHN lambs with 100% oxygen, which could be reversed by administration of superoxide dismutase.[15,21] Superoxide dismutase also improved oxygenation, suggesting that ROS formation impairs vasodilation to endothelium-independent agents, such as NO.

Overall, the evidence from animal models indicates that hypoxia causes pulmonary vasoconstriction and normoxia results in pulmonary vasodilation. However, hyperoxia (especially when the fraction of inspired oxygen (FiO_2) exceeds 0.5, and PaO_2 exceeds 80 to 100 mm Hg) does not cause further pulmonary vasodilation. Hyperoxemia promotes ROS formation and interferes with the function of various enzymes of the NO pathway and reduces cGMP
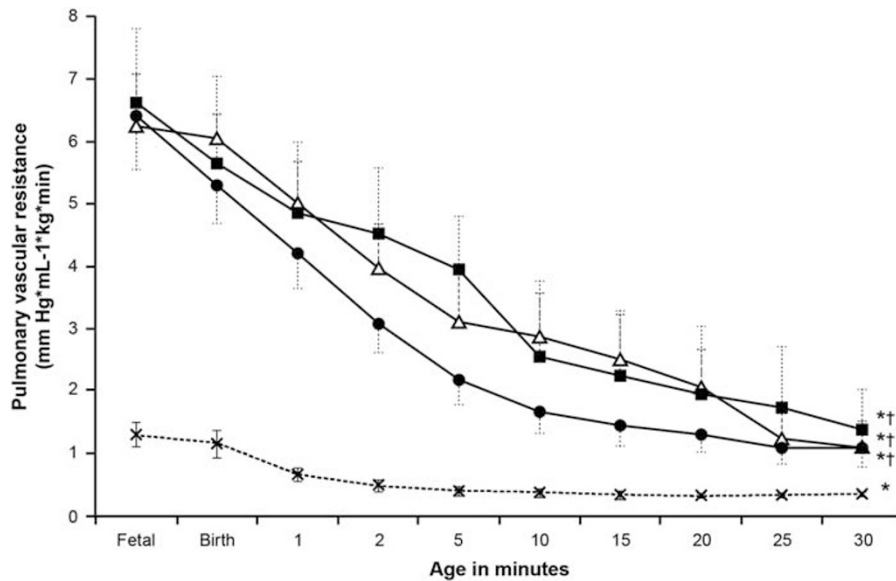
Figure 2. Changes in pulmonary vascular resistance (PVR) (mean ± s.e.m.) during fetal life, at birth and during the first 30 min of life in persistent pulmonary hypertension of the newborn (PPHN) lambs ventilated with 21% (black squares), 50% (white triangles) or 100% O_2 (gray circles) ($n = 6$ each). Similar changes in PVR in four control twin lambs without PPHN ventilated with air are shown for comparison (dashed line). (*$P < 0.05$ by analysis of variance (ANOVA) over time; $^†P < 0.05$ compared with control by repeated-measures ANOVA). Adapted with permission from Lakshminrusimha et al.[7]

formation (Figure 4). Therefore, avoiding hyperoxemia is potentially as important as avoiding hypoxemia in the management of PPHN. Clinicians should recognize that oxygen is a drug and should be used accordingly in the therapeutic context taking into account potential benefits as well as side effects.

Relationship between pH, PaO$_2$ and pulmonary vascular response to hypoxia

Early studies in animal models showed that lower pH exaggerates the pressor response to hypoxia (vasoconstriction and increased PVR).[12] An acceptable PaO_2 range, which avoids an hypoxic vasoconstrictor response, is dependent on the acid–base status. Therefore, avoiding acidosis may offer some protection against pulmonary vasoconstriction in response to hypoxia. There is a tendency in clinical practice, however, to compartmentalize pH and PaO_2 using different ventilator controls, which artificially separates these two inter-related parameters. Maintaining arterial pH ⩾ 7.3 appears to reduce the intensity of hypoxic pulmonary vasoconstriction.[12] There have been many advances in the understanding of mechanisms underlying changes in minute ventilation in response to PaO_2 and pH targets (such as tachypnea in response to hypoxia or hypercarbia). However, the endogenous compensatory mechanisms that determine optimal PaO_2 or oxygen saturation still need to be defined (that is, what mechanisms, such as increased cardiac output, allow the newborn to establish appropriate PaO_2 target set points in the presence of low CaO_2).

BENEFITS OF EARLIER INTERVENTION

Inhaled nitric oxide

Ventilator- and hyperoxia-induced changes in the pulmonary vasculature are seen very early at the subcellular and gene expression levels. Supporting evidence has been derived from analysis of pulmonary artery endothelial cells and lung homogenates isolated from PPHN and control lambs. These samples showed that mitochondrial electron transport chain complex proteins levels are decreased in PPHN, suggesting a disruption in

energy metabolism.[22,23] Furthermore, there was a drastic reduction in the mitochondrial complex proteins when PPHN lambs were ventilated with 100% oxygen, indicating that mitochondria were undergoing injury and disappearing from the lung. In contrast, preservation of mitochondria and increase in electron transport chain complex proteins occurred in PPHN lambs weaned to a FiO$_2$ target range and treated with iNO. These findings provide a theoretical rationale for early intervention with iNO (ameliorating deleterious subcellular changes), which could translate into clinical benefits. Initiating therapy before alveolar atelectasis from lung disease or ventilator-induced barotrauma or oxygen toxicity could potentially lessen the lung injury with consequent reduction in the duration of respiratory support and/or length of hospital stay.

Initial clinical trials of iNO for HRF enrolled newborns with advanced respiratory failure, with many of them already meeting extracorporeal membrane oxygenation (ECMO) criteria at the time of enrollment and randomization (oxygenation index (OI) > 40).[24–26] Although the response to iNO was consistently favorable, many newborns who were critically ill with severe lung disease and vascular dysfunction were unresponsive to therapy.

Results from later trials suggested the advantages of introducing this intervention in infants with moderate PPHN.[27–29] For example, the Franco-Belgium Collaborative NO trial randomized neonates to early iNO or control ventilation therapy without iNO, stratified by gestation age (< 33 or ⩾ 33 weeks). In 107 term and late preterm infants with moderate respiratory failure (median OI 25.9), iNO use led to a decrease in OI at 2 h, the primary endpoint.[27] Although methodologically limited, analyses of data from this cohort also suggested that babies assigned to early iNO therapy spent fewer days on mechanical ventilation and less time in the neonatal intensive care unit. Other findings were not significant.

A trial conducted in Chile in a setting where ECMO was not available randomly assigned 56 newborns with moderate respiratory failure (OI 10 to 30) at ⩽ 48 h after birth to early iNO or conventional mechanical ventilation with oxygen.[28] Newborns in the control group who reached OI > 40 were treated with iNO. Respiratory variables at baseline were similar, including FiO$_2$ and
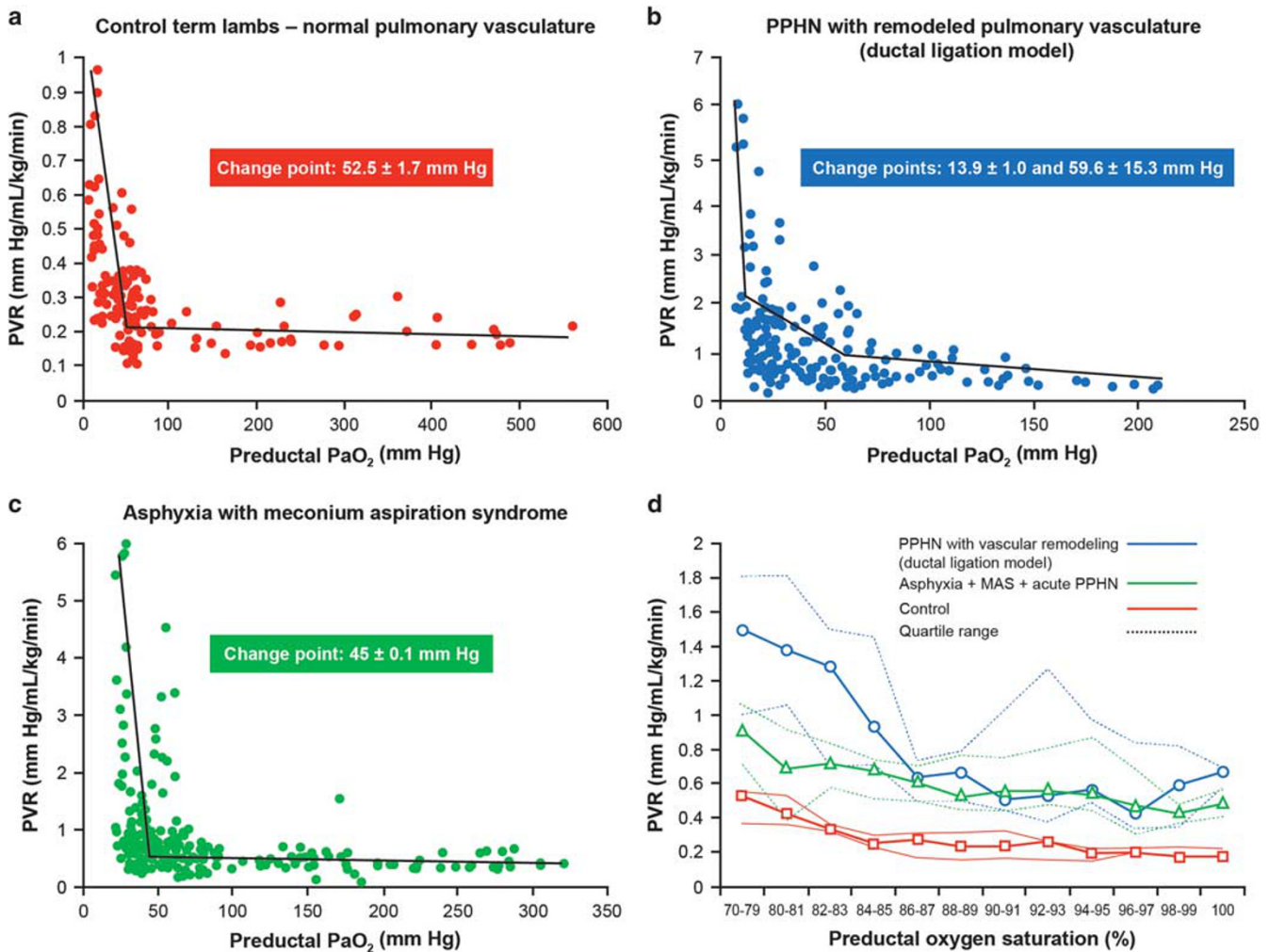
Figure 3. Scatterplots showing pulmonary vascular resistance (PVR) and arterial partial pressure of oxygen (PaO_2) in control (**a**), persistent pulmonary hypertension of the newborn (PPHN) with vascular remodeling (**b**) and asphyxia+meconium aspiration lambs (**c**). The two regression lines for the control lambs demonstrate a change point of 52.5 mm Hg of PaO_2. The three regression lines for the PPHN lambs correspond to mean PaO_2 change points of 13.9 ± 1 and 59.6 ± 15.3 mm Hg. The two regression lines in lambs with meconium aspiration demonstrate a PaO_2 change point of 45 ± 0.1 mm Hg. Panel (**d**) demonstrates the median and inter-quartile range (dashed lines) of PVR plotted against a clinically relevant range of oxygen saturations (70% to 100%) in control (**a**) and PPHN with remodeled pulmonary vasculature induced by antenatal ductal ligation (**b**) and acute PPHN induced by asphyxia and meconium aspiration (**c**) in lambs. Adapted and modified with permission from Lakshminrusimha et al.[7] MAS, meconium aspiration syndrome.

OI. The OI decreased in the early iNO group from 22 at baseline to 19 at 4 h ($P < 0.05$ vs baseline) and remained lower at all subsequent time points. In contrast, OI increased in the control group and remained significantly higher ($P < 0.01$ vs early iNO group) during the first 48 h of the study (Figure 5).[28] Significantly fewer newborns receiving early iNO (25%) compared with conventional therapy (61%) developed OI>40, defined as the primary endpoint of treatment failure ($P < 0.05$), although mortality, days of mechanical ventilation and rates of chronic lung disease did not differ. Along with improved oxygenation, newborns on early iNO had a reduction in duration of oxygen exposure ($P < 0.03$ vs controls). These results with early iNO are consistent with a potential decrease in disease progression in newborns with moderate respiratory failure.

Additional evidence for the benefit of early intervention can be derived from the multicenter Neonatal Inhaled Nitric Oxide Study Group trial that randomized 299 term and late preterm neonates (gestational age ⩾ 34 weeks) with moderate respiratory failure (OI 15 to 25) to early iNO or placebo.[29] The study population had a wide variety of diagnoses (primary PPHN, MAS, respiratory distress syndrome, pneumonia/sepsis, lung hypoplasia), and all study infants (including controls) were eligible to receive standard iNO therapy if HRF progressed to OI ⩾ 25. The trial failed to show a difference between the early iNO group and the control group for the primary outcome of ECMO/death (16.7% vs 19.5%, respectively; $P = NS$). However, the overall incidence of ECMO/death in this trial was noticeably lower than that observed in earlier randomized trials in newborns with more advanced disease.[29] In addition, there was limited separation between the two study groups as the mean OI at the time of enrollment in the trial was nearly 20 and control infants were eligible to receive iNO at an OI of 25. Nevertheless, arterial oxygen tension increased by > 20 mm Hg in 73% of early iNO neonates compared with 37% of control neonates ($P < 0.001$).[29] Thus infants earlier in the course of respiratory failure responded favorably to iNO although one-third remained unresponsive.

In the Konduri et al. trial, a post-hoc analysis found that OI < 20 ($P = 0.031$) and prior surfactant use ($P = 0.008$) were significantly associated with decreased risk of ECMO/death.[30] Irrespective of exposure to iNO, use of surfactant therapy prior to target OI of 15

to 25 in the infants with parenchymal lung disease was associated with a striking threefold reduction in the risk of this endpoint ($P < 0.001$). The decrease was primarily observed in infants with MAS ($P = 0.04$), respiratory distress syndrome ($P = 0.04$) or pneumonia/sepsis ($P = 0.03$) and not in infants with PPHN ($P = 0.43$). In the early iNO group, exposure to iNO at OI < 20 decreased ECMO/
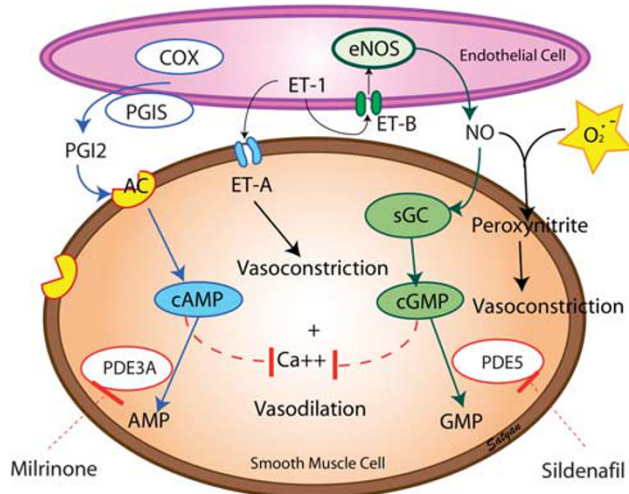
death (odds ratio 0.25, confidence interval CI 0.08 to 0.67; $P = 0.01$) compared with infants at an OI 20 to 25, suggesting that intervention with iNO was more effective at OI < 20.

Although this was a *post-hoc* analysis, the results suggest that early use of surfactant and iNO in moderate respiratory failure could lead to improved outcomes. Early treatment with iNO at an OI < 20 was also associated with decreased length of stay, compared with control infants who presented at the same OI and received standard iNO at OI > 25 (18 vs 27 days). Supplementing these findings, a pharmacoeconomic analysis of this population suggested that early use of iNO (at OI $\geqslant$ 15 to < 20) was associated with lower total cost of care relative to standard iNO ($88 518 ± 7574 vs $92 581 ± 9664) based on costs of hospital care, iNO and ECMO at the time of analysis.[31]

Figure 4. Alterations in biochemical and enzyme pathways in persistent pulmonary hypertension of the newborn (PPHN) and effect of hyperoxia on these pathways. See text for details (Copyright: Dr Lakshminrusimha).[4,5] AC, adenylate cyclase; AMP, adenosine monophosphate; Ca, calcium; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; ET-A, endothelin-A; ET-B, endothelin-B; GMP, guanosine monophosphate; NO, nitric oxide; O_2, oxygen; PDE3A, phosphodiesterase 3A; PDE5, phosphodiesterase 5; PGIS, prostacyclin synthase; PGI2, prostaglandin I2; sGC, soluble guanylyl cyclase.

Surfactant

Randomized clinical trials have confirmed that surfactant therapy is effective in reducing the immediate need for respiratory support and improving clinical outcome. Moreover, there is evidence that early selective surfactant administration given to newborns requiring assisted ventilation leads to better outcomes. A pilot study in 40 neonates with MAS, which evaluated surfactant (beractant) instilled every 6 h compared with control, found that mean arterial-to-alveolar partial pressure of oxygen ratio values increased modestly after the first dose of surfactant and that oxygenation improved significantly and cumulatively after the second and third doses of surfactant.[32] Although not the primary outcome, there was also a significant reduction in the need for ECMO and duration of oxygen therapy and hospitalization with surfactant therapy ($P < 0.05$ for each).

A large multicenter trial compared surfactant (beractant) ($n = 167$) versus control ($n = 161$) in neonates (gestational age $\geqslant$ 36 weeks) with HRF prior to ECMO treatment.[33] Neonates were stratified by diagnosis (PPHN, sepsis, or MAS) and OI (15 to 22, 23 to 30, 31 to 39), as a surrogate for severity or stage of disease. This trial reported an approximate 10% absolute reduction in ECMO rate in the surfactant-treated group ($P = 0.038$), with the principal
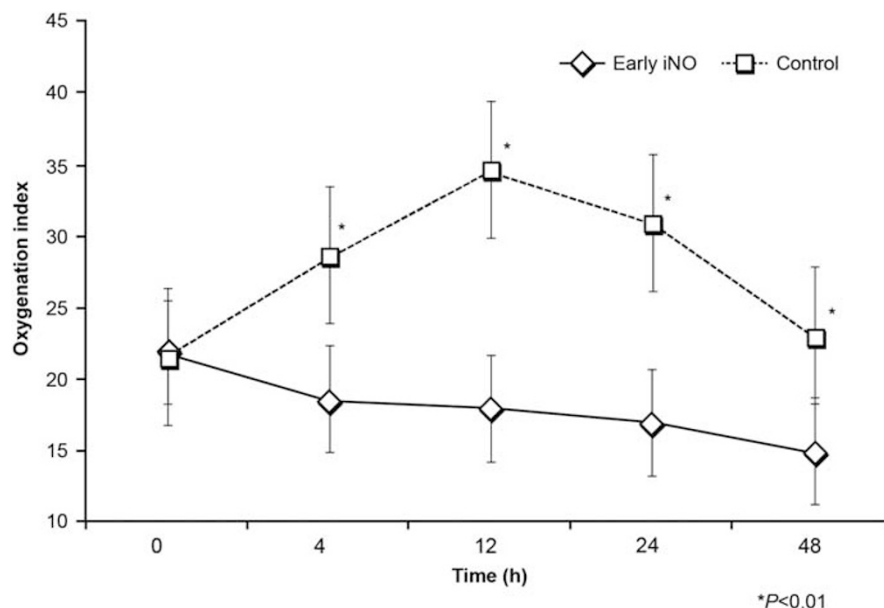

Figure 5. Change in oxygenation index (OI) over time in newborns with moderate respiratory failure (OI between 10 and 30) randomized before 48 h postdelivery to early treatment with 20 p.p.m. inhaled nitric oxide (iNO; early iNO group, $n = 28$) or conventional mechanical ventilation with fraction of inspired oxygen (FiO$_2$) of 1.0 (control group, $n = 28$). Points represent mean ± s.e.m. The OIs were significantly higher after baseline in the control group ($P < 0.01$). This figure was used with permission from Gonzalez *et al.*[28] Adapted by permission from Macmillan Publishers: *J Perinatol* 2010;30:420–424.

effect in the lowest OI stratum. Neonates enrolled late in the course of HRF (OI 31 to 39) experienced no benefit and those with a moderate degree of respiratory failure (OI 23 to 30) had a modest reduction in ECMO rate. In contrast, there was a highly significant ($P = 0.013$) threefold reduction in the ECMO rate when surfactant was administered in less severe or early disease (OI 15 to 22).

Although the use of iNO and surfactant in the management of HRF and PPHN has been well documented through clinical trials, other potential treatment approaches, including those that follow, are under active consideration based on their potential physiological effects.

Prostacyclin vasodilators

Prostacyclin (PGI_2) mediates vasodilation by activating adenylate cyclase and increasing cyclic adenosine monophosphate (cAMP) in the PASMC. The use of inhaled PGI_2 (epoprostenol) is well established for acute adult pulmonary hypertension and has been described in a case series of term neonates with HRF and PPHN refractory to iNO.[34] Oxygenation rapidly improved after inhalation of PGI_2 in all four neonates, although the condition of one neonate subsequently deteriorated owing to alveolar capillary dysplasia. The authors speculated that neonates with PPHN and inadequate response to iNO may have impaired cGMP-mediated pulmonary vasodilation and might benefit from PGI_2, which acts through cAMP (Figure 4). Successful use of inhaled Iloprost, a PGI_2 analog, has also been reported in combination with iNO for intractable PPHN.[35,36] Although a synergistic effect with iNO has been suggested based on translational studies, there are no randomized controlled trials evaluating the effect of PGI_2 vasodilators in term and late preterm neonates.

SYSTEMIC AGENTS: INOTROPES, VASODILATORS, AND 'INODILATORS'

Dopamine

Dopamine is commonly used to increase systemic blood pressure to reduce right-to-left shunting in neonates with high pulmonary arterial pressure. The effect of dopamine on systemic arterial pressure and pulmonary arterial pressure has been studied in newborn lambs with PPHN and control twins with normal pulmonary vasculature.[37,38] In control lambs, systemic blood pressure was higher than pulmonary arterial pressure and increased relatively selectively in response to low doses of dopamine. In contrast, both systemic and pulmonary blood pressure were similar in PPHN lambs and increased in parallel suggesting that remodeled pulmonary arteries might have higher sensitivity to dopamine. These studies indicate that dopamine is not selective to the systemic circulation in the setting of remodeled pulmonary arteries and suggest the need for frequent echocardiography to evaluate pulmonary arterial pressure in patients with PPHN receiving dopamine therapy (especially at doses > 10 mcg/kg/min).

Milrinone

Infants with HRF and PPHN typically have right-to-left shunting, but left-to-right shunting at the atrial level can occur in the presence of left ventricular dysfunction and/or hypoplasia owing to increased left atrial pressure.[37] Milrinone may have a role in improving left ventricular function and reducing pulmonary venous hypertension as it inhibits PDE-3A in both cardiomyocytes and pulmonary arterial smooth muscle cells, thereby increasing the level of cAMP resulting in improved ventricular diastolic function as well as pulmonary vasodilation (Figure 4). In newborn lambs with PPHN, intravenous milrinone reduced PVR by 22% and increased pulmonary blood flow by 18%.[39]

Milrinone and iNO may act synergistically as they signal through separate pathways (cAMP and cGMP, respectively), yet both interact with PDE-3A. A study in rat PASMCs showed that the NO-donor, S-nitrosoglutathione, modulates PDE-3A gene expression via mechanisms dependent upon cGMP synthesis and gene transcription.[40] Consistent with a synergistic interaction, the vasodilatory effects of milrinone were found to be most pronounced in vessels from lambs with the highest PDE-3 activity, such as lambs ventilated for 24 h with 100% oxygen plus 20 p.p.m. iNO.[41] From a clinical perspective, case series have described the effectiveness of milrinone in improving oxygenation in term and late preterm neonates with iNO-resistant PPHN.[42,43] Together, these findings suggest that milrinone may be a unique agent with optimal benefit when used in conjunction with iNO or in patients with prior NO exposure, especially in the presence of ventricular dysfunction.

PDE-5 inhibitors

Both oral and intravenous sildenafil, a PDE-5 inhibitor, have been studied in term and late preterm neonates with PPHN and found to improve oxygenation and survival.[44,45] In a dose–response study, intravenous sildenafil improved oxygenation in neonates with and without concurrent iNO treatment,[45] suggesting a role for sildenafil in patients with partial or poorly sustained responses to iNO. Hypothetically, sildenafil may also be effective in neonates with PPHN following prolonged hyperoxic ventilation, as PDE-5 expression and activity are increased following ventilation with high concentrations of oxygen and exposure to ROS (Figure 4).[19] The availability of sildenafil as an enteral preparation makes it feasible for long-term therapy for infants with chronic lung disease.[46,47] A multicenter, randomized clinical trial is underway to test the efficacy of sildenafil in iNO-resistant PPHN (NCT01720524).[48]

ET-1 inhibitors

Endothelin-1 (ET-1) is synthesized by vascular endothelial cells and is a potent vasoconstrictor that acts through two receptors (ET_A and ET_B) mediated by endothelium-derived NO. The nonspecific ET-1 receptor blocker, bosentan, has been principally used to treat pulmonary hypertension in adults. A placebo-controlled trial ($N = 47$) conducted in a single center without access to iNO or ECMO demonstrated that bosentan was more effective than placebo in improving oxygenation and well tolerated in term and late preterm neonates with PPHN.[49] A recent multicenter trial ($N = 21$) among neonates with persistent respiratory failure despite iNO treatment did not demonstrate improved outcome versus placebo, possibly owing to higher baseline OI.[50]

Glucocorticoids

Glucocorticoids have potent anti-inflammatory properties and have been shown to reduce the duration of oxygen dependence in neonates with MAS.[51] There is anecdotal evidence that hydrocortisone improves oxygenation in neonates with PPHN, and it is used in some centers as a rescue strategy prior to ECMO. Recent evidence derived from animal models of PPHN suggests a potential role for glucocorticoids in restoring normal pulmonary vascular function. In a neonatal lamb model of PPHN, hydrocortisone significantly improved arterial-to-alveolar ratios and attenuated oxidative stress, in part by increasing superoxide dismutase activity.[52] Hydrocortisone increased cGMP by normalizing soluble guanylyl cyclase and PDE-5 activity and by attenuating abnormalities induced by oxidative stress. Generally favorable results from studies have indicated that glucocorticoids may be beneficial, particularly in severe MAS in the presence of lung edema, pulmonary vasoconstriction and inflammation.[53]

Caution must be exercised when considering hydrocortisone therapy, as it could mask the signs of infection.

The nature of vascular dysfunction that underlies a lack of response to iNO therapy has become the subject of intense investigation.[30] A number of alterations in endothelial and smooth muscle cell function in PPHN contribute to impaired vasodilation and vascular remodeling. As previously described, these alterations include increased oxidative stress, increased PDE-5 activity, decreased levels of NO and PGI_2 and increased ET-1 release. These changes also lead to impaired angiogenesis, which contributes to increased PVR. These studies support the use of iNO as well as PDE inhibitors, inhaled or intravenous PGI_2 analogs, ET-1 antagonists and antioxidants. In addition, recent studies in the ductal ligation model identified dysfunction of endothelial AMP-activated protein kinase and peroxisome proliferator-activated receptor-γ and depletion of tetrahydrobiopterin as important contributors to impaired angiogenesis in this model.[54,55] The potential use of AMP-activated protein kinase agonists (for example, metformin), peroxisome proliferator-activated receptor-γ agonists (for example, rosiglitazone) or tetrahydrobiopterin analogs (sepiapterin) to restore angiogenesis requires further investigation.

CONCLUSION

In summary, greater insights into the neonatal pulmonary circulation and underlying pathophysiology of HRF and PPHN have improved the treatment protocols and allowed adoption of more effective interventions for PPHN. In the current treatment era, oxygen should be considered a drug and administered accordingly. Avoiding hyperoxia is as important as avoiding hypoxia in the management of HRF. There is also evidence that surfactant and iNO use at a lower acuity of illness may reduce the progression of HRF–an approach that could improve outcomes.[31] Understanding the abnormalities in the signaling pathways in PPHN helps to optimize management of this condition through the most appropriate choice and integration of therapies. For example, milrinone may be particularly beneficial following prolonged exposure to iNO plus oxygen because it inhibits PDE-3A, whereas hydrocortisone and sildenafil might be appropriate options in the settings of hyperoxia and oxidative stress owing to their effects on PDE-5 activity and expression.

Despite the progress in the management of HRF and PPHN, several issues remain to be explored. These include the integration of NO and other therapies, use of iNO prior to ventilator-induced hyperoxia and barotrauma and defining alternate outcomes. Noninvasive strategies are needed to recognize ROS formation or lung injury in a timely manner. The effect of iNO on long-term outcomes also requires further investigation. Finally, defining future clinical trials in HRF and identifying meaningful and achievable study outcomes remain important goals.

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