Bringing down the ROS: a new therapeutic approach for PPHN

Amy L. Firth and Jason X. -J. Yuan
Division of Pulmonary and Critical Care, School of Medicine, University of California, San Diego, La Jolla, California

Summary

Although infants with persistent pulmonary hypertension of the newborn (PPHN) experience some relief and therapeutic benefit from current therapies, over 50% have a limited or transient response and significant morbidity. There is no consistency in the best first line treatment throughout hospitals in the United States. Ventilation with high levels of oxygen or inhaled nitric oxide (NO) are typical strategies for improving the extracorporeal membrane oxygen, although they remain unproven to increase survival rates. While oxygen may stimulate endothelial nitric oxide synthase (eNOS) and NO production dilating the pulmonary vasculature, it also fuels the production of reactive oxygen species (ROS). ROS is likely to have counterproductive effects; in addition to stimulating vascular smooth muscle cell proliferation and increasing vascular tone, ROS may directly regulate eNOS and NO. The recent article by Farrow and colleagues (3) in AJP-Lung investigates the role of ROS on eNOS. By using recombinant human superoxide dismutase (rhSOD), they observed 1) increased eNOS activity and expression, 2) increased tetrahydrobiopterin (BH4), a cofactor critical to the function of eNOS, and 3) a decrease in oxidative stress, in addition to the stimulation of NO production and ultimately pulmonary vasodilatation. The observations they made may be paramount to increasing the survival of infants with PPHN and may lead to an adapted treatment regimen that addresses the pitfalls of current therapeutic approaches.

PPHN

When the pulmonary circulation fails to respond to natural stimuli, including increased oxygen tension, ventilation, and shear stress, it does not undergo the shift from the high resistance state in utero to a postnatal low resistance system, enabling efficient pulmonary gas exchange and oxygenation. Impaired NO-cGMP signaling has been shown to be critical to the regulation of pulmonary circulation in the newborn, and clinical strategies have involved administration of inhaled NO since the early 1990s (6, 10). While effective in immediate relief due to vasodilatation, the infants can enter an inhaled NO dependency state, and thus inhaled NO proffers poor long-term relief. The necessity for extensive research into the regulation of perinatal circulation and the changes that occur upon ventilation have led to improved and more specific therapeutic approaches for infants with PPHN over the past 30 years. Despite this, PPHN is still associated with significant short-term and long-term morbidity. Farrow et al. (3) strive to dissect the signaling pathways, determining the impact of ROS and elucidating the potential of decreasing oxidative stress as a therapeutic approach in PPHN. This study is published in a milieu of recent publications exploring the functional abnormals and associated signaling pathways, suggesting novel pharmacological approaches in the treatment of PPHN.

Reactive Oxygen Species

Current therapeutic strategies, while offering some symptomatic relief, fail to produce a significant survival rate in infants with PPHN. The data presented by Farrow et al. (3) ascertains a necessity to reduce oxidative stress to restore eNOS coupling as an alternative and more effective adjunctive treatment of PPHN. The authors convincingly demonstrated a hyperoxia-associated increase in oxidative stress in PPHN, a likely common side effect and drawback of oxygen therapy for PPHN. While the ups and downs of ROS stirring a debate in the pathogenesis of pulmonary arterial hypertension, a pertinent role for hyperoxia-induced increases in ROS in PPHN is seemingly assured. Previous work in animal models of PPHN from Steinhor et al. (12) showed that rhSOD decreased pulmonary vascular resistance by facilitating the actions of inhaled NO. Although interesting, this initial study failed to determine a mechanistic rationale for such beneficial effects. Before the publication of the “follow-up” study (3), other groups have investigated potential changes in ROS in PPHN. Wedgwood et al. (15) published two papers that revealed that 1) an increased level of oxidant hydrogen peroxide (H₂O₂) could be scavenged by catalase rescuing the vasodilatory response to inhaled NO in PPHN, and 2) H₂O₂ could decrease eNOS promoter activity, associated with an endothelin-1-mediated downregulation of eNOS expression (14). More recently, uncoupled eNOS was shown to increase superoxide radicals (SO⁻) impairing vasodilatation propensity in PPHN models (7).

In their recent study, Farrow et al. (3) addressed a potential detrimental effect of treating PPHN with high oxygen. Not only did they show that ventilation with 100% O₂ did not restore eNOS expression, cotreatment with inhaled NO showed a significantly lower enhancement of eNOS expression than did inhaled NO alone. Although on the surface, their current study reiterates their 2001 findings, the key and most interesting observation in the paper is that the rhSOD treatment enhanced eNOS, which is paralleled by an increase in key eNOS cofactor BH₄ expression. The upstream targeting of the vasodilatory pathway may prove to be a more successful and controllable means of treatment for infants with PPHN. It is apparent that treatment with rhSOD and 100% O₂ outweighs the adjunct treatment of inhaled NO with 100% O₂. It is interesting to consider that the conadministration of 100% O₂ with inhaled NO showed a comparable reduction in the DHE-detectable level of ROS to 100% O₂ and rhSOD; however, similar increases in eNOS and BH₄ expression were not observed. It is entirely possible that ROS, in the form of superoxide, combines with the inhaled NO to form a powerful oxidant peroxynitrite from which free radicals may cause peroxynitrite-related cellular damage.
Other Therapeutic Strategies

Other studies identify additional potential therapeutic targets in the eNOS signaling pathway including inhibition of phosphodiesterase 5 activity (5). Sildenafil is a cGMP-specific PDE inhibitor in clinical trials for infants; however, the safety and efficacy currently remains inconclusive (8, 11). Novel activator of guanylate cyclase, BAY 41-2272, causes potent pulmonary vasodilation in experimental models of PPHN (2) and recombinant human vascular endothelial growth factor, administered by intrapulmonary infusion, upregulates eNOS, and thus enables endothelium-dependent pulmonary vascular relaxation (4). Fasudil, a Rho-kinase inhibitor, has recently been shown to be effective in reducing high pulmonary vascular resistance in the fetal lung (13). Furthermore, decreased Ca\(^{2+}\)-activated K\(^+\) channel gene expression may factor in the reduced vascular reactivity in PPHN (1, 9).

The study by Farrow et al. (3) resources a potent and sustained vasodilation in animal models of PPHN by rhSOD. Its potential as a therapeutic strategy in PPHN should now be investigated clinically. It is essential to continue work to expand the therapeutic options for the treatment of PPHN, particularly those that are refractory to current therapeutic approaches.

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