

Nitric oxide therapy

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There is not much use for the lungs during the fetal life. At such stage, the function of the lungs is carried out by the placenta through the umbilical cord. Fetal life is characterized by a high pulmonary vascular resistance (PVR) with pulmonary blood flow being restricted to a less than 10% lung-directed cardiac output. Blood vessels that connect the heart and the lungs are constricted, sending the circulating blood back to the heart through the ductus arteriosus, a blood vessel that functions only in fetuses. In other words, the lungs in the fetal stage are bypassed.

At birth, when the lungs finally assume the function of gas exchange, the PVR decreases, allowing for an increase in pulmonary blood flow. The blood vessel that is previously constricted, favoring blood flow to the ductus arteriosus is now relaxed, simultaneously with the permanent closure of the ductus arteriosus. This happens as the lungs become ventilated and the alveolar oxygen tension is increased.

Persistent Pulmonary Hypertension occurs when at birth, the lung circulation fails to achieve the normal drop in PVR, preventing the transition from fetal to newborn circulation. This failure results in the continuous functioning of the ductus arteriosus which impairs the flow of blood from the heart to the lungs and limits the amount of oxygen that can be picked up by the blood to be delivered to the different parts of the body. The blood that flows back to the heart remains in an unoxygenated state which could lead to the development of refractory hypoxemia, respiratory distress and acidosis.

It is only in 1987 when nitric oxide (NO) was recognized as a key endothelial-derived vasodilator molecule. From then, research has been expanded to establish the role of NO throughout the body, and to discover its therapeutic

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potential. To appreciate the effects of NO in alleviating pulmonary hypertension, it is important to gain understanding of its chemistry and mechanism of action.

Nitric Oxide is a gaseous compound that rapidly diffuses across membranes and has a single unpaired electron. This explains its high reactivity, especially to Hemoglobin (Hb) in the blood. This nature of the compound accounts for its noted biological significance. It has been discovered to function as stimulant in the release of hormones; as neurotransmitter; a significant participant in the magnification of synaptic actions and learning processes; and an inhibitor in platelet aggregation, which makes it a marvel in the field of cardiology.

In the field of pulmonology, nitric oxide is valued for its vasodilatory effect in the blood vessels. This effect can be explained by the mechanism involving the compound's diffusion from the vascular endothelial cells to the subjacent smooth muscles of the pulmonary vessels. From here, NO activates the enzyme guanylate cyclase to change conformation to promote smooth muscle relaxation by converting GTP to cGMP. This vasodilatory effect signals the mechanism to modulate blood flow and vascular tone.

Given the mechanism of action, it is easy to surmise how NO can be utilized as a therapeutic agent in the management of blood-vessel-related diseases such as those related to the heart (hypertension), the reproductive system(erectile dysfunction) and in this case, the lungs (Persistent Pulmonary Hypertension in infants (PPHN)).

Before NO, treatments used in infant PPHN are hyperventilation, continuous infusion of alkali, tube vasodilation and vasodilator drugs. A study on the effects of these various treatments was done by Ellington, Jr., et. al., (2001) showing no specific therapy clearly associated with the reduction in mortality in infants. In determining whether therapies were equivalent, the study showed that hyperventilation reduced the risk of extracorporeal membrane oxygenation (ECMO) with no oxygen increase at 28 days, while alkali infusion increased the use of ECMO as well as an increase in the use of oxygen at 28 days (Ellington, Jr., et. al., 2001). ECMO is a highly invasive procedure that requires major surgery, performed in serious cases of PPHN when patients fail to respond to treatments.

It is only after post-lab studies were able to identify the role of NO-cGMP signaling in the regulation of lung circulation that NO therapy was developed for PPHN (Channick, R., et. al., 1994). Like previous treatment methods, NO therapy improves oxygenation as well as reduces the risk of ECMO in infants with PPHN (Oliveira, et. al., 2000). But because nitric oxide is capable of acting on its own upon inhalation to relax the blood vessels and improve circulation, it is considered as a less invasive procedure in the management of infants with PPHN compared to the previous treatments mentioned in the preceding paragraphs.

The efficiency of the treatment procedure can be determined by observing its effect on the patient's ventilation and blood flow, which is a determinant of the efficiency of transpulmonary oxygenation and partial pressure of oxygen in the systemic arterial blood (Ichinose, et. al., 2004). NO therapy enhances the mechanism by which blood flow is redistributed toward regions

in the lungs with better ventilation and higher intra-alveolar partial pressure of oxygen (Ichinose, et. al., 2004).

Other treatments used in the management of PPHN such as tube ventilation, alkalosis and intravenous vasodilators were shown to be effective in ameliorating pulmonary hypertension in some infants, but in many instances, it does not, as ECMO almost always becomes a necessity in saving the life of the infants (Ichinose, et. al., 2004). A type of hyperventilation has been proven not to increase the risk of ECMO, but unlike NO-therapy (Ellington, Jr., et. al., 2001), it is invasive as to require a tube inserted inside the infant's trachea.

In patients with moderate PPHN, there is an improvement in arterial p_aO_2 , reduced necessity of ventilator support and low risk of progression to severe PPHN (Sadiq, et. al., 2003) and this, without the risk of increasing the incidence of adverse outcomes when the age of 1 year is reached (Clark, et. al. 2003). Inhaled NO is able to rapidly increase the arterial oxygen tension and increase the blood flow in the lungs without causing systemic hypotension (Roberts, 1992; Kinsella, 1992). No apparent increase in morbidity has been shown after one year of treatment with NO (Aparna and Hoskote, 2008). For high-risk infants with PPHN, inhaled NO has been found to lessen the risk of pulmonary hypertensive crisis (PHTC) after congenital heart surgery (Miller, et. al. 2000).

Studies on the role of NO in the management of PPHM show that while it is therapeutic, it also prevents the occurrence of chronic lung disease which affects morbidity. Vascular cell proliferation and pulmonary vascular disease have been shown to decrease with NO in the newborn (Roberts, et. al., <https://assignbuster.com/nitric-oxide-therapy/>

1995). In addition, while NO treatment can be more costly, it is the most cost-effective among other methods because of the reduced need for ECMO (Angus, et. al. 2003). For these reasons, it is understandable why NO therapy seems to have taken over in the area of PPHN treatment.

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