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POINT OF VIEW

Nitric oxide as the third respiratory gas. A new opportunity to revisit the use of oxygen therapy in clinical practice

Óxido nítrico como tercer gas respiratorio. Una nueva ocasión para revisar el empleo de oxigenoterapia en la práctica clínica

José Manuel Valencia-Gallardo[a,*], Felipe Rodríguez de Castro[b], Jordi Solé-Violán[c], José Carlos Rodríguez-Gallego[d]

[a] *Department of Respiratory Medicine, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[b] *Professor of Medicine, Department of Medical and Surgical Sciences, School of Medicine, University of Las Palmas de Gran Canaria, Spain*
[c] *Intensive Care Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[d] *Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain*

New drug development requires accurate evaluation of efficacy and understanding of the underlying physiology.[1] Old therapies, as oxygen therapy, should not be exempt from such demands. We have now the opportunity to consider a more rational use of oxygen therapy in clinical practice[2] focusing on the role of hemoglobin in improving oxygen delivery to tissues.

Almost twenty years ago, McNulty and colleagues[3] demonstrated that in patients with stable coronary artery disease, administration of 100% oxygen increased coronary vascular resistance and reduced coronary blood flow compared to breathing room air. This increase in vascular resistance could be explained by the oxidative degradation of endothelial nitric oxide (NO) caused by reactive oxygen species generated under hyperoxic conditions.

Moreover, there is strong evidence that NO bioactivity is not restricted to the vascular endothelium. Hemoglobin can also incorporate stable metabolites of NO into the red blood cell (RBCs) environment.[4] In pulmonary circulation, oxygenation of Hb facilitates NO uptake to form S-nitrosohemoglobin (SNO-Hb) while, in the peripheral circulation, deoxygenation facilitates the transfer of S-nitrosothiols (SNOs) out of RBCs.[5]

Since SNOs promote vasodilation, the release of NO from Hb to a hypoxic environment result in increased blood flow to hypoxic tissues and would explain the physiological significance of SNO-Hb improving tissue oxygenation (Fig. 1).[6] In other words, the bioavailability of NO in vivo could be directly and effectively coupled to the oxygen saturation of Hb, not PO_2, so oxyhemoglobin (SaO_2) would establish a dynamic regulation of oxygenated blood flow in the

* Corresponding author.
E-mail address: jvalgal@gmail.com (J.M. Valencia-Gallardo).

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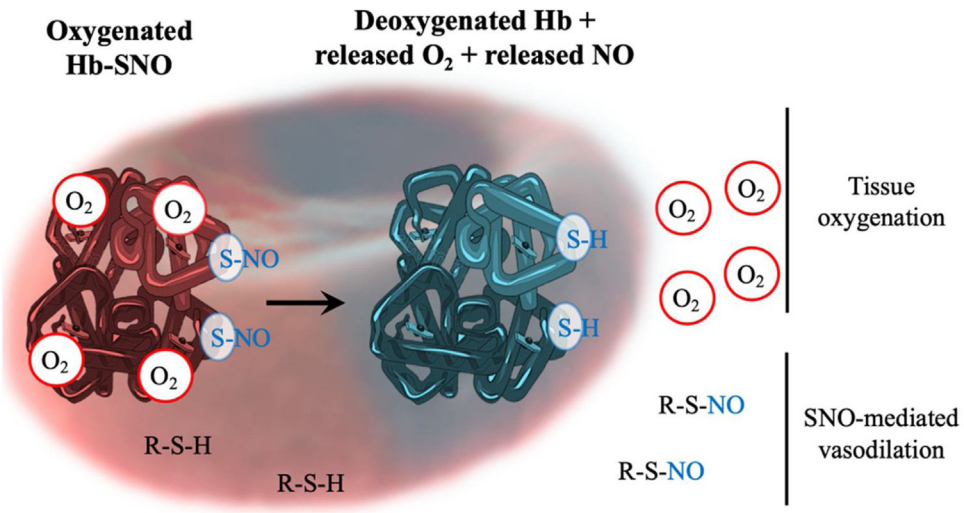

Figure 1 Allosteric linkage of Hb conformation to O_2 and SNO release. Left (Hb in red): cooperativity leads to Hb in the lung being able to bind oxygen molecules. Oxygenated Hb will also bind and stabilize SNO at Hb. Right (Hb in blue): upon reaching hypoxic tissues, Hb will cooperatively release oxygen molecules during transition to the deoxygenated state. Liberation of oxygen also causes the transfer of SNO from deoxygenated Hb to other erythrocyte thiols (R-S-H) and ultimately shuttling SNO out of red blood cells. Thus, Hb deoxygenation in tissues will lead to vasorelaxation (SNO-mediated vasodilation). Adapted from reference 6, with permission.

microcirculation.[4–6] This complementary activity of Hb provides a more efficient interpretation of its function. Rather than being considered a mere ''transporter'', Hb would now ensure an optimal tissue oxygen supply.

This alternative interpretation of the Hb role would promote the implementation of a targeted oxygenation with potential implications in clinical practice. In this regard, a judicious use of oxygen therapy would prevent the toxic effects of hyperoxia[2] and focus the clinician's concern on maintaining a SaO_2 value within a safety range.

As a result, two remarks should be taken account:

1 SaO_2 target of 100% should be avoided. Hemoglobin releases SNOs as blood becomes deoxygenated.[5,6] Therefore, a SaO_2 value far from 100% would preserve the vasodilator function of partial Hb deoxygenation.
2 The upper inflection point in the oxygen hemoglobin dissociation curve would represent the nadir in the optimal supply of O_2. Consequently, a SaO_2 value closer to 90% could be a safe threshold. Ideal SaO_2 have not been precisely established and may vary depending on clinical features,[7] but in terms of adverse outcomes, recent randomized clinical trials have demonstrated no superiority of maintaining higher values of SaO_2, and even fewer complications with the use of more restrictive oxygen therapy strategy among critically ill patients.[8,9] It is important to remember that not only PaO_2 is almost irrelevant in oxygen delivery (DO_2) to the tissues but also high PaO_2 values could increase mortality.[10]

In addition, to ensure adequate tissue oxygenation, a sufficient Hb level must be maintained. As with SaO_2, determining the optimal Hb level in specific clinical scenarios has been the goal of several guidelines[11,12] but discussion of this topic is beyond the scope of this paper. In any case, the decision to administer a blood transfusion should be based on clinical judgement of the individual's risk/benefit ratio, including risks associated with anemia and transfusion.[11]

All of the above would be consistent arguments for promoting automatic titration systems for oxygen therapy at bedside. Although it is a not widely implemented monitoring procedure, initial findings suggest an improvement in controlling target SO_2 compared with manual titration and could improve morbidity and mortality and reduce care costs.[7]

In short, scientific evidence supports a vasoactive role of Hb that would make it possible to better appreciate the tissue oxygenation optimizing function of Hb; it could also reinforce the prudent use of oxygen therapy if NO is considered as the third respiratory gas.

Author contributions

Conception and design: J.M. Valencia-Gallardo, F. Rodríguez -de Castro, J. Solé-Violán, J.C. Rodríguez-Gallego.

Collection, analysis and interpretation of the data: J.M. Valencia-Gallardo, F. Rodríguez de Castro, J. Solé-Violán, J.C. Rodríguez-Gallego.

Final approval of the article: J.M. Valencia-Gallardo, F. Rodríguez de Castro, J. Solé-Violán, J.C. Rodríguez-Gallego.

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Disclosures

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