Journal of Critical Care 51 (2019) 217–218

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Inhaled nitric oxide for safer use of hemoglobin-based oxygen carrier infusion (HBOC): A new indication?

From the historical publication made by Furchgott et al. [1] suggesting the "physiological" release of an endothelial derived relaxing factor (EDRF) to mediate the Acetylcholine-induced vasodilatation, the field was opened for a real nitric oxide (NO) saga. This topic had fascinated the scientific community for both basic scientist and clinicians. Similar to a TV series, the medical and scientific top journals have reported the knowledge related to this reactive, free radical gas molecule. The NO has a complex and ubiquitous biology that was admitted as major breakthrough [2] in Medicine. All ingredients were present to assure the success of the NO saga: the simplicity of the gas name; the multidisciplinary heroes (investigators) clever enough to open this difficult new topic; the discovery of a unique case in medical biology of a gaseous molecule having multitargets both intra and intercellularly controlling the cell biology;( ) the controversial list of the 1996 Nobel price winners given to 3 major contributors(R Furchgott, L Ignarro, and F Murad) excluding an unforgettable researcher (S Moncada) in this domain [3]; the implication in major medical fields with the potential of drug development for cardiovascular, inflammatory, neurologic, and many others diseases… [4] After the pioneer work the following major steps were reported: First, the demonstration that NO accounted for the biological activity of EDRF [5-8]. The radical NO gas was the unique gas demonstrating important role in mammalian biology [4]; Second, the NO was shown to be a key factor continuously released by the normal endothelial cell, exerting a tonic vasodilatation [5,7,8]. This concept introduced strong opposition with the classic view of tonic vasoconstriction. The reduction in NO release by endothelial cells (EC), whatever the mechanisms, reduces the vasodilation, an equivalent of passive vasoconstriction [4]; Third, the biological pathways for NO synthesis have been nicely dissected: NO is formed via the guanidino nitrogens of L-arginine. The reaction requires molecular oxygen as well as cofactors and is catalyzed by a family of enzymes called nitric oxide synthase (NOS). The type III NOS (cNOS in endothelial cells; (chromosome 7)) and type I NOS (neuronal nNOS; chromosome 12) are constitutively expressed. The type II NOS (iNOS; chromosome 17) is inducible in different acute inflammatory contexts, responsible for the release of large amount of NO. [2] When the concentration of L-arginine is low, NOS catalyzes the formation of superoxide radical anion (O_2^-) and hydrogen peroxide (H_20_2) [9]. The metabolic pathways for NO from the synthesis to the catabolism have been clarified. NO is characterized by a very short half-life (2 s in water, 2 ms in blood) [10], with a final elimination as NO_2 /NO_3 stable molecules; fourth, the very large spectrum of NO effects especially in platelets and smooth muscle cells were mediated mainly via a second cellular messenger. When NO reaches vascular smooth muscle, soluble guanylyl cyclase is its primary target producing cGMP, an essential intracellular step to induce vasorelaxation [11].

The NO molecule became a "star" in intensive care medicine for at least the two major reasons: 1- the demonstration of an excessive release of NO during the septic shock mediated by upregulation of iNOS in smooth muscle itself [12] leading to derangement in vascular smooth muscle function responsible for "vasoplegia". The effects of excessive NO production in sepsis patients may not be limited to uncontrolled vasodilation and/or vasoplegia, but concerns many organs and organelles dysfunction [2]; 2- the potential benefit to use the inhalation of NO to vasodilate pulmonary vessels, with consecutive improvement in gas exchange as P/F ratio and treatment of persistent pulmonary hypertension in neonates as well as in ARDS [13-19]. The case reported in the journal illustrates a mix of different properties of NO, particularly the substitution of NO scavenged by the artificial oxygen career product as Hemoglobin-Based Oxygen Carrier Infusion (HBOC) perfused when transfusion is contraindicated. [20]

The first report of the human use of inhNO (close to 20 ppm) was presented in severe hypoxemic ARDS patients in 1992, during the European Society of Intensive Care Medicine meeting in Barcelona [21,22]. The inhNO seemed to be safe at this dose and for a limited time of inhalation inducing a limited raise in methemoglobin. The P/F ratio increased in both studies, sometimes spectacularly, with no measurable negative impact on the left side hemodynamic effects [16]. After these pioneer studies, inhNO was tested in many adult or pediatric conditions to provide the best indications, the dose-response effect, the convenient delivery system, the adequate monitoring methods to alarm when excessive nitrite or nitrates are formed [23]. The publication of the 3 major RCTs on adult ARDS patients [24-26] and the recent meta-analysis [27] failing to demonstrate beneficial effect on reduction in mortality at day 28, disappointed the community and turned away the interest of inhNO as a drug to treat adult ARDS patients. However, the concern for inhNO therapy remains positive [28] for treating acute pulmonary hypertension in the context of cardiac surgery, especially when the right ventricular function is limited, and in pediatric acute situations [29-31]. In the present case report in this issue of the Journal [20] (JCRC_2018_194 should be placed. This editorial and the Case Report should be published together), another potential interest was tested, administrating pro-actively inhNO to limit the scavenging of endogenous NO by the perfused HBOC. This scavenging of endogenous NO by HBOC or other similar derivatives was shown to have severe consequences as vasoconstriction, ischemic organ dysfunction and intravascular coagulation, precluding the FDA registration as a substitute for blood transfusion [32]. The Authors decided to give high dose (80 ppm) of inhNO for a short time, followed by a lower inhNO dose (20 ppm) during the perfused HBOC. This strategy appeared very successful, since the hemodynamic data, the toxicity monitoring and the

https://doi.org/10.1016/j.jcrc.2019.01.019
0883-9441/

follow up after 6 months were not altered. This approach becomes very encouraging to render safer the use of HBOC, when blood transfusion is contraindicated in acute situation. The present case has to be seen as a proof of the valid strategy more than a successful treatment. Considering the cGMP as a second messenger mediating the vascular effects of NO [33], the measurements of plasma level of cGMP before, during inhNO treatment with HBOC might have been informative to detect a NO deficit or excess. This information could have been important to evaluate the potential combination of inhNO with the administration of a type V phosphodiesterase enzyme inhibitor [34] to maintain an adequate level of cGMP. This case motivates further development in the field of blood transfusion and artificial oxygen career, a fascinating topic for the future.

Disclosure

The Author had no financial disclosure to declare.

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