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EDITORIAL

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Nitric oxide and COVID-19: Dose, timing and how to administer it might be crucial

Nitric oxide (NO) for inhalation has been a clinical option in the ICU since the early 1990s. Much has been written and claimed after the initial enthusiasm over an acutely improved arterial oxygenation in adult patients with ARDS. A few years ago, a meta-analysis[1] concluded that the regular use of inhaled NO (iNO) in patients with ARDS outside a clinical trial could not be recommended, as no benefit such as reduced mortality or time on the ventilator could be identified in published randomized studies. In *Acta Anaesthesiol Scand*, Lotz et al[2] describe gas exchange and haemodynamics from short-term exposure (15-30 min) of iNO 20 ppm (parts per million) in patients with ARDS caused by COVID-19 infection. The inhaled NO was considered "standard care" in this German ICU, and thus, the Institutional Review Board had waived the need for patient consent or an Ethics Committee approval for such exposure. Furthermore, the reported results only seem to highlight the beginning of an extended period of therapy with iNO in this group of patients. Thus, the results after a longer treatment period would also be relevant.

The reported findings of a certain improvement (34%) of arterial oxygen tension, with no clear lowering of elevated mean pulmonary artery pressure or pulmonary vascular resistance, reflect previously described effects from administering iNO in those with ARDS. As noted early in another study,[3] the dose of iNO needed for the maximum improvement of oxygen tension is much lower than the dose needed for a maximum reduction of mean pulmonary artery pressure. The absence of an effect on shunt by iNO, as reported by Lotz et al, is somewhat surprising. However, the authors refer to other mechanisms that may have improved oxygenation; they list effects on angiotensin II receptors, clotting, surfactant function, immune response, and direct effects on the virus. It is not clear to what extent any of these mechanisms may act within 15-30 min, if they act at all. However, in a recent experimental study, a NO-releasing substance *S*-nitroso-*N*-acetylpenicillamine (SNAP) inhibited the replication of the SARS-CoV-2 virus.[4] We do not know which dose of inhaled NO is optimal as an antimicrobial agent, and it may differ from those exerting effects on the oxygenation of blood. Ongoing clinical trials use higher doses of iNO at 80 ppm and even short periods of 200 ppm in a small group of pregnant patients infected with COVID-19 without reported side effects.[5] In addition, we do not know at which point in time the pharmacodynamic effect of iNO would be most beneficial. From an almost unwarranted and impugned observation, smokers seem to contract COVID-19 less often than non-smokers. Perhaps this is because of high NO concentrations in cigarette smoke or early exposure to NO_2.[6] Since beneficial effects of steroids in COVID patients have been shown,[7] it may be mentioned that a positive interaction between steroids and iNO has been demonstrated in experimental studies.[8] Furthermore, can iNO reach the entire lung and even further into the body? Potential combination approaches may be construed, combining an IV-administered NO-donor with iNO early in COVID-19 infection before intubation becomes inevitable. This highlights the need to study iNO further and explore combination approaches as yet another possible tool in the increasing armament directed against the coronavirus pandemic.

CONFLICT OF INTEREST

The author CF wishes to report financial interest in the development of a new intravenous NO-donor. The author GH has no conflict of interest to declare.

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