Letter to the editor

Effects of inhaled nitric oxide in COVID-19-induced ARDS – Is it worthwhile?

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To the Editor,

I read with interest an article in your journal by Lotz et al.[1] They demonstrated that nitric oxide (NO) inhalation decreases pulmonary shunting and improves arterial oxygenation, leading to a therapeutic effect on coronavirus disease 2019 (COVID-19)-induced acute respiratory distress syndrome (ARDS). Inhaled NO (iNO) acts as a selective pulmonary artery vasodilator, alleviating lung ventilation/perfusion ratio. However, Lotz and colleagues assume that improved oxygenation is not the sole reason for survival benefits in patients treated with iNO, suggesting other modes of iNO action could have beneficial effects on systemic circulation. This may indeed be the case, because iNO has a wide range of systemic effects that reduce vascular endothelial inflammation, in addition to local pulmonary effects.[2,3] In plasma and erythrocytes, hemoglobin (Hb) immediately scavenges NO and oxidizes it to nitrite/nitrate, which are eventually excreted as inactive endo-products in urine. Therefore, iNO is unlikely to directly cause systemic effects. However, both plasma nitrite and S-nitroso-Hb (SNO-Hb) increase during NO inhalation (40 ppm, 15 min) in human volunteers.[4] Through active transport, plasma nitrite may be stored in peripheral tissues as an NO reservoir. In case of acidosis or hypoxia, xanthine oxidoreductase then reduces stored nitrite to trigger NO signaling. Furthermore, Hb can transport NO activity, forming S-nitrosothiols such as SNO-Hb in erythrocytes via less reactive intermediates such as N_2O_3. These intermediates subsequently dissociate, releasing NO^+ to cysteine residues of transcriptional factors and receptors related to COVID-19 progression.[5] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry to the host cells triggers molecular signaling cascades, and activates downstream transcriptional factors such as nuclear factor-kB (NF-κB). However, S-nitrosothiols nitrosate inhibitor of NF-κB kinase subunit beta (IKKβ) and suppresses NF-κB-mediated promoter activity and gene transcription responsible for vascular endotheliitis leading to platelet aggregation and thrombosis.[6] Mathru showed that iNO (80 ppm) significantly reduced NF-κB-mediated inflammatory response characterized by reduced expression of CD11b/CD18 (leukocyte adhesion molecule receptor) and P selectin (leukocyte adhesion molecule) in ischemia/reperfusion-induced human skeletal muscle injury.[2] Lotz and colleagues also speculate on angiotensin-II (Ang-II) involvement in COVID-19 progression.[1] Because angiotensin converting enzyme 2 (ACE2) is a receptor for SARS-CoV-2 entry to host cells, SARS-CoV-2 infection downregulates ACE2 expression by its internalization with virus particles from host cell surfaces. Thus, the original conversion of Ang-II to Ang (1-7) does not occur, resulting in Ang-II accumulation, increasing reactive oxygen species (ROS) production through Ang-II type 1 receptor (AT_1R), and endogenous NO consumption. AT_1R is a target for S-nitrosylation, a process that reduces binding affinity of AT1R with Ang-II and thus decreases subsequent ROS-induced systemic inflammation. This may be the mechanism underlying NO attenuation of Ang-II's deleterious effect on COVID-19.[7]

In closing, I note that in addition to the vasodilating action of cGMP-dependent iNO, plasma levels

of *S*-nitrosylated proteins, including SNO-Hb, continue to increase even after NO inhalation is discontinued. This observation might provide new clinical applications of iNO as nitrosating agent for treating COVID-19.

CONFLICT OF INTERESTS
The author declares no conflict of interests.

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