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A narrative review on inhaled nitric oxide to treat Coronavirus Disease 2019.

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ABSTRACT

COVID-19-associated ARDS (cARDS) results from multiple pathogenetic mechanisms involving both parenchyma and circulation of the lungs. Despite authors described two pneumonia phenotypes according to lung elastance values, reported as Low and High phenotype, the evidence suggests that patients with cARDS have similar respiratory mechanics to patients with ARDS from other causes. Consequently, the proper management of patients with cARDS is the same as ARDS,consisting of protective mechanical ventilation strategy and prone position ventilation.However, the hypothesis that impaired alveolar perfusion could have a role in cARDS is interesting. Nitric oxide (NO) is a biatomic gaseous moleculeables to induce smooth muscle relaxation and vasodilation. So, inhaled nitric oxide (iNO) acts as a selective vasodilator because it only dilates vessels in areas participating in gas exchange, preserving hypoxic pulmonary vasoconstriction reflex and reducing ventilation/perfusion mismatch. With this narrative review we summarised the role of iNO for cARDS treatment to improve gas exchange. Furthermore, we briefly described its activity as an antiviral agent. In conclusion, although iNO administration can represent a valid theoretical therapeutic choice for the treatment of severe unresponsive hypoxemia in COVID-19 patients, data presented in the literature are scares and inconclusive, and several clinical trials are still ongoing. Further studies are needed to elucidate the pathogenetic mechanism of respiratory failure related to SARS-CoV-2 infection and inhaled NO role in patients with severe disease.

KEY WORDS: COVID-19, cARDS, nitric oxide.

Introduction

The most relevant clinical manifestation of Coronavirus Disease 2019 (COVID-19) is the development of interstitial pneumonia, ranging from mild to severe forms. It was estimated that about 5-15% of patients with COVID-19 required intensive care unit (ICU) admission to support respiratory function in severe forms, characterised by a pattern similar to Acute Respiratory Distress Syndrome (ARDS) [1].

Histopathological findings, mainly from postmortem examination, showed the presence of alveolar (diffuse alveolar damage, acute fibrinous and organising pneumonia) and vascular (perivascular inflammation, microthrombi, endothelial cell injury suggesting microangiopathy) damage [2]. These findings suggest that COVID-19-associated ARDS (cARDS) results from multiple pathogenetic mechanisms involving both parenchyma and circulation of the lungs.

Although Gattinoni et al. [3] described two pneumonia phenotypes according to lung elastance values (the Low and High phenotype), the evidence suggests that patients with cARDS have similar respiratory mechanics to patients with ARDS from other causes and that, for most patients, cARDS is, in the end, ARDS [1]. Consequently, the proper management of patients with cARDS is the same as ARDS [4], consisting of protective mechanical ventilation strategy and prone position ventilation. However, the hypothesis that impaired alveolar perfusion could have a role in cARDS is interesting. The administration of inhalation drugs to treat ventilation/perfusion (Va/Q) mismatch can represent a valid therapeutic strategy to improve gas exchange.

Nitric oxide (NO) is a biatomic gaseous molecule produced from arginine in mammalian cells by three enzymes that belong to the nitric oxide synthase (NOS) family: neuronal (nNOS), endothelial (eNOS), and inducible (iNOS) [5]. Notably, they are all expressed in the airways. Two of the three isoforms, nNOS, and eNOS, are constitutively expressed calcium-dependent enzymes. Contrary, iNOS expression is induced by inflammatory mediators (interleukin 1β, interferon γ, and interleukin 13), its activity is independent of the intracellular calcium concentration [6] and contributes to macrophages' antimicrobial activity [6, 7]. NO stimulates guanylyl cyclase and causes dephosphorylation of GTP to cyclic guanosine monophosphate, facilitating smooth muscle relaxation and vasodilation [8]. Inhaled nitric oxide (iNO)acts as a selective vasodilator because it only dilates vessels in areas participating in gas exchange, preserving hypoxic pulmonary vasoconstriction (HPV) reflex and reducing Va/Q mismatch.Once in the blood, NO is deactivated by haemoglobin, with a half-life of only 3 to 5 seconds. This mechanism prevents NO from becoming a systemic vasodilator. NO, thus, should not cause acute hypotension when inhaled [9].

Because of its strong vasodilator effect, iNO can significantly improve gas exchange in COVID-19 patients with interstitial pneumonia and cARDS. This narrative review aims to summarisethe role of iNO for cARDS treatment to improve gas exchange. Furthermore, we briefly described its activity as an antiviral agent.

COVID-19 and pulmonary perfusion

COVID-19 can alter pulmonary perfusion by two different mechanisms.The first is represented by pulmonary in situ thrombosis and embolism triggered by SARS-CoV-2 infection [10]. Pulmonary microthrombi observed with COVID-19 and cytokine storm are consistent with the existence of a bidirectional relationship between the immune system and thrombin generation during severe infection [11]. The use of anticoagulant therapy with heparin was associated with decreased mortality, especially in patients with significant sepsis-induced coagulopathy or markedly elevated D-dimer levels [12].

The second mechanism ables to alter alveolar perfusion is the impairment in HPV reflex. In healthy adults, HPV occurs in response to alveolar hypoxia. HPV diverts blood flow from poorly ventilated to well-ventilated alveoli, optimizing Va/Q [13]. When HPV is compromised, intrapulmonary shunts cause a decrease in oxygenation of the pulmonary venous blood flow, ultimately contributing to poor oxygen delivery, organ dysfunction, and failure. Severe cARDS patients can present alteration in HPV related to viral infection and inflammatory response, but this mechanism is still poorly understood [14].

Antiviral effects of iNO

The hypothesis that iNO could be helpful to treat SARS-CoV-2 infection derived from epidemiological observations.Hedenstierna et al. [15] hypothesised that intermittent bursts of high iNO concentration in cigarette smoke might protect against the virus. Despite smoking being listed as a risk factor for COVID-19, only a low proportion of smokers suffered from SARS in China in 2003 and COVID-19 in China, Europe, and the US. Mainstream smoke from cigarettes contains iNO at peak concentrations between 250 ppm and 1350 ppm in each puff compared to the medical use of no more than 80 to a maximum of 160 ppm. The diffusion of iNO through the cell wall to reach the virus should be significantly more effective at the very high iNO concentration in the smoke. Therefore, high iNO-dose intermittently administered in short bursts can represent an effective treatment without the health hazards associated with smoking.

In-vitro studies reported that NO had been shown to increase the survival rate of mammalian cells infected by Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). NO donors (i.e., S-nitroso-N-acetylpenicillamine) significantly increased the survival rate of SARS-CoV-infected eukaryotic cells, suggesting direct antiviral effects of NO [16]. In this study, NO significantly inhibited the replication cycle of SARS-CoV in a concentration-dependent manner. NO also inhibited viral protein and RNA synthesis. SARS-CoV shares most of the genome of SARS-CoV-2, indicating the potential effectiveness of iNO therapy in COVID-19 patients.Akaberi et al. [17] demonstrated that NO could inhibit the replication of SARS-CoV-2 in an in-vitro model, and they identified the SARS-CoV-2 main protease as a target for NO. Interestingly, non-canonical oxidative effects of NO were observed to inhibit the replication of SARS-CoV-2 by two proposed mechanisms:

1) reduced palmitoylation of nascent expressed spike (S) protein, which effectively diminishes the affinity of the viral receptor binding domain to ACE2;
2) chemical modification/inactivation of one or both of the cysteine proteases encoded by Orf1a of SARS-CoV-2 [18].

However, the main limitation of in-vitro studies is that NO is obtained by donor compounds (i.e., S-nitroso-N-acetylpenicillamine), while in humans NO is typically administered by inhalation route to ventilated alveoli, and pulmonary vasodilation occurs with a dose of approximately ten ppm [19]. Consequently, the NO concentrations able to inhibit viral replication could be too high, exerting collateral or toxic effects in in-vivo models. On this issue, further studies are needed to verify the NO ability to inhibit viral replication in in-vivo models and then in humans.

INO in spontaneous breathing patients

Several authors started the iNO administration in spontaneous breathing patients with COVID-19 as a rescue therapy to improve ventilation-perfusion matching, decrease pulmonary vascular pressure and provide breathless relief. Parikh et al. [20] observed that more than half of the 39 patients with COVID-19 did not require mechanical ventilation after iNO (30 ppm) therapy. They suggested that iNO therapy may have a role in preventing the progression of hypoxic respiratory failure in COVID-19 patients. Fakhr et al. [21] reported that high-dose iNO (160-200 ppm) was well tolerated and associated with improved oxygenation and respiratory rate in six awake and spontaneously breathing pregnant patients with severe or critical COVID-19. Systemic oxygenation improved immediately during the delivery of iNO, with rapid subjective relief of shortness of breath in all patients.Respiratory rates decreased, returning to being tachypneic 3 hours after the treatment.Heart rate and mean systemic arterial pressure were unchanged compared with baseline.Only one patient required intubation for cARDS and hemodynamic shock. Zamanian et al. [22] reported that after iNO therapy (20 ppm), physical activity and perfusion improved for a patient with vasoreactive pulmonary arterial hypertension and severe breathlessness from COVID-19. Wiegand et al. [23] performed a retrospective evaluation of COVID-19 patients in respiratory distress receiving iNO (160 ppm for 30 minutes twice per day via a face mask until resolution of symptoms, discharge, intubation, or the transition to comfort measures only) as rescue therapy.Five patients received iNO and the three patients that received multiple treatments (ranging from five to nine) survived and were discharged home. Patients tolerated the treatment exceptionally well and were often able to rest during inhalation, and their breathing effort was observed to decrease. Furthermore, the authors described a potential NO anti-inflammatory property in two patients.

Finally, it should be considered that NO can affect O_2 tissue delivery.Mortaz et al. [24], in a pilot study, demonstrated that COVID-19 patients showed higher levels of NO inside red blood cells (RBC) compared to non-COVID-19 hypoxemic patients. This is not due to the presence of hypoxia per se but may afford protection against the hypoxia seen in COVID-19 patients. RBC-derived NO causes the vasodilation of small vessels allowing oxygen to be readily released to tissues.

INO in mechanically ventilated patients

If spontaneous breathing patients seemed to present clinical advantages by iNO therapy, the data on mechanically ventilated patients are discordant. Furthermore, due to the lack of data derived by well-designed randomised controlled trials, the evidence to support or not iNO for the treatment of cARDS in mechanically ventilated patients derived by small observational studies. Table 1 reports the main characteristics of the current available literature on the topic [25-29], while table 2 showed trial registered on *clinicaltrial.gov*. In summary, not all patients trated with iNO showed gas exchange improvement and among those patients with improvement in gas exchange, the effect is quick but temporary. Further well-designed clinical trials can elucidate the role of iNO on gas exchange improvement and reduction in mortality rate in severe cARDS patients.

Table 1. The main characteristics of the current available literature about clinical evidence on iNO in mechanically ventilated patients with cARDS.

Author	Type of study	Sample size	iNO (ppm)	Results	Conclusion
Abou-Arab et al. [25]	Prospective	34	10	Response rate of 65% to iNO administration after 15 to 30 minutes. In the responder group PaO_2/FiO_2 improved	If iNO improves PaO_2/FiO_2 and ventilation/perfusion in most COVID-19 patients with severe pneumonia, the causes of unresponsiveness to iNO remain unclear.
Lotz et al. [26]	Retrospective	7	20	INO significantly improved oxygenation, but significant changes in pulmonary shunting were not observed	iNO could provide immediate help and delay respiratory deterioration in moderate to severe cARDS.
Longobardo et al. [27]	Retrospective case-control study	27	20	Only eight (40%) patients with cARDS had an increment in PaO_2/FiO_2 ratio >10%	More than half of patients with refractory hypoxaemia secondary to cARDS did not show an increase in PaO_2/FiO_2 in response to iNO. Moreover, this response was much lower when compared with a cohort with ARDS.
Ferrari et al. [28]	Retrospective	10	20	iNO administration did not significantly improve arterial oxygenation.	Further investigation is required to identify those patients who may benefit from iNO and the most appropriate dose to be used.
Robba et al. [29]	Prospective	9	20	The use of iNO increased PaO_2 and rSO_2.	In severe cARDS patients, ample physiologic variability was observed, with different early effects of rescue therapies on cerebral and systemic oxygenation.

Table 2. The clinical trials registered on clinicaltrial.gov about iNO as a prevention or therapy strategy for SARS-CoV-2 infection. Clinical trials are divided according to their current status as aviable on web-site.

Number	Title	Primary Objective	Sample size
Terminated			
NCT04388683	INO for preventing progression in COVID-19	To investigate the hypothesis that iNO will reduce clinical worsening of hospitalised, high-risk patients with early COVID-19 to progressive systemic de-oxygenation, intubation, or death	10
NCT04338828	INO therapy for COVID-19 infections in the ED	To determine whether iNO improves short term respiratory status, prevents future hospitalisation, and improves the clinical course in patients diagnosed with COVID-19 in the ED	47
NCT04421508	A Study to Assess Pulsed iNO vs Placebo in Subjects With Mild or Moderate COVID-19	To assess the efficacy and safety of pulsed iNO compared to placebo in subjects with COVID-19 who are hospitalised and require supplemental oxygen without assisted ventilation.	191
NCT03331445	INO Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections	To provide more data if NO therapy can reduce the bacterial load in the lungs, help the patients to breath better; and in the case of COVID-19, acts as a antiviral agent resulting in the reduction of incidence of oxygen therapy, mechanical assistance of BIPAP, CPAP, intubation and mechanical ventilation during the study period	13
Completed			
NCT04460183	A Study to Assess Efficacy and Safety of RESP301 Plus Standard of Care (SOC) Compared to SOC Alone in Hospitalised Participants With COVID-19	To evaluate the efficacy and safety of RESP301, a NO generating solution, plus SOC versus SOC alone in hospitalised patients with COVID-19 requiring supplemental oxygen	19
NCT04337918	NO Releasing Solutions to Prevent and Treat Mild/Moderate COVID-19 Infection	To evaluate the clinical efficacy of a novel Nitric Oxide Releasing Solution (NORS) treatment for the prevention and treatment of COVID-19 in healthcare workers at risk of infection	143
Recruiting			
NCT04601077	The Evaluation of NO Generating Lozenges on Outcome in Newly Diagnosed COVID-19 Patient of African Americans	To find out the side effects and ability to take the study drug, NO lozenges when taken twice daily by mouth	100
NCT04397692	INO for the Treatment of COVID-19 Caused by SARS-CoV-2 (US Trial)	To obtain information on the safety and efficacy of 80 ppm iNO given in addition to the standard of care of patients	20
NCT04606407	INO for the treatment of viral pneumonia in adults	To obtain information on the safety and efficacy of 150 ppm iNO given in addition to the standard of care of patients with viral pneumonia	90
Active, not recruiting			
NCT04383002	High dose iNO for COVID-19 (ICU Patients)	To test if high dose iNO is safe and can reverse virus burden and respiratory failure in patients on mechanical ventilation	21
NCT04476992	NO therapy for COVID-19 patients with oxygen requirement	To evaluate the safety of high concentration iNO with an adjunct of continuous low dose administration between the high concentration treatments in hypoxemic COVID-19 patients compared to the high dose treatment alone	20
NCT04305457	INO therapy for mild/moderate COVID-19	To test the effectiveness of iNO in preventing the progression of SARS-CoV-2 related disease when administered at an early stage	70
NCT04312243	NO prevention of COVID-19 for healthcare providers	To test efficacy and safety of iNO in healthcare providers for prevention of SARS-CoV-2 infection and COVID-19	24
NCT04306393	INO in Severe Acute RespiratorySyndrome in COVID-19	To determine whether iNO improves oxygenation in patients with hypoxic SARS-CoV2	200

Association of iNO with other vasoactive pulmonary drugs

Studies analysed the effects of iNO in combination or not with vasoactive pulmonary drugs administration, in detail almitrine bismesylate and inhaled epoprostenol [30-32]. Almitrine bismesylate is a selective pulmonary vasoconstrictor and can be an attractive therapeutic option to counteract the loss of HPV. Indeed, by decreasing the perfusion of nonventilated lung areas, almitrine decreases pulmonary shunt and indirectly reduces alveolar dead-space-to-tidal-volume ratio by increasing the perfusion of ventilated lung areas [33]. Cardinale et al. [30] retrospectively analysed data provided by 20 consecutive patients with COVID-19 pneumonia, fulfilling the Berlin criteria of ARDS with PaO_2/FiO_2 ratio <120 and treated with almitrine bismesylate or iNO (10-20 ppm) or both. When iNO was used alone, the median increase of PaO_2/FiO_2 ratio was 2.2%.When an iNO test dose was performed, no patient presented an increase in PaO_2/FiO_2 ratio ≥ 20%. The same effect was noted with almitrine bismesylate alone or with iNO. The authors concluded that pharmacological manipulation did not improve PaO_2/FiO_2 ratio in moderate to severe cARDS patients. In a monocentric preliminary pilot study in ten intubated patients with severe cARDS, Bagate et al. [31] analysed the effect of iNO (10 ppm) administration alone or in combination with almitrine (10 μg/kg/min). The median of PaO_2/FiO_2 ratio varied from 102 mmHg at baseline, to 124 mmHg after iNO (p-value not significant) and 180 mmHg after iNO and almitrine ($p < 0.01$). The authors concluded that iNO-almitrine combination was associated with rapid and significant improvement of oxygenation, which was not observed with iNO alone.

Epoprostenol is a synthetic prostacyclin that mimics the actions of natural prostacyclin, acting as a vasodilator. When administered by intravenous infusion, epoprostenol induces systemic hypotension and an increase of intrapulmonary shunts [34]. While inhaled epoprostenol has similar efficacy as iNO. DeGrado et al. [32], in a retrospective single-centre study, analysed the effect of inhaled epoprostenol in 38 patients.Eleven patients transitioned to iNO during their admission. The median starting dose of iNO was 20 ppm (20-30 ppm). The iNO dose was eventually increased to 80 ppm in seven patients (64%). There was a trend toward more significant improvements in PaO_2 and SpO_2 while receiving iNO than epoprostenol, but it was not statistically significant. In conclusion, both inhaled epoprostenol and iNO in cARDS patients with refractory hypoxemia, on average, did not produce significant increases in oxygenation.

INO in Critically Ill COVID-19 Patients with right ventricular impairment

Patients with right ventricular (RV) function impairment can represent a particular cluster in which iNO administration can play a crucial role. Garfield et al. [35], analysing the iNO effect on 35 consecutive patients, noted that responders had a significantly lower baseline PaO_2/FiO_2 ratio and higher baseline oxygenation index than non-responders.In addition, responders to iNO also had higher baseline brain natriuretic peptide (BNP). These data suggested the iNO may be beneficial in those patients with more severe hypoxaemia with raised BNP and troponin, likely suggestive of RV strain. Heuts et al. [36] described that iNO (starting dose 20 ppm, dose increase to 30 ppm) in cARDS patients with venovenous extracorporeal membrane oxygenation and dilated RV due to pressure overload, with severe tricuspid regurgitation, increased PaO_2.

However, after initial respiratory improvement, complications caused the patient death. Tavazzi et al. [37] reported their experience of iNO (20-30 ppm) administration in 16 COVID-19 mechanically ventilated patients with refractory hypoxemia and/or RV dysfunction. They showed that iNO did not improve oxygenation in the studied population. Only four (25%) patients were responders, of whom three have superimposed RV dysfunction.

A trend towards a larger improvement of oxygenation was observed in patients with RV dysfunction as compared with those without.In conclusion, iNO did not improve oxygenation in COVID-19 patients with refractory hypoxemia when administered as a rescue treatment after prone position. A subgroup of patients with RV dysfunction was better iNO responders, probably due to the hemodynamic improvement associated with RV unloading. Feng et al. [38] analysed whether iNO (10-20 ppm) was beneficial in the treatment of COVID-19 in five critically ill patients with pulmonary hypertension.Three patients received iNO based on pulmonary artery systolic pressure (PASP) and blood pressure.PASP returned normal upon iNO treatment in two patients, with an increase in PaO_2/FiO_2 and SpO_2, and survived.

However, despite iNO, PASP continued to fluctuate between 50 and 58 mmHg in one patient with improved gas exchange but died due to severe complications, including multiple organ failure and active thoracic haemorrhage. The other two patients who did not receive iNOS experienced RV failure and a sudden decrease of PASP and PaO_2/FiO_2, and then both died.

Conclusion

According to available data, we can highlight three aspects about the clinical effect of iNO administration. First, patients not requiring admission in the ICU seem to have a more favourable response to iNO, suggesting its role as prevention rather than treatment for severe cARDS.It is unclear if the early administration of iNO in patients spontaneously breathing could reduce ICU admission rate or mortality.It is possible that in non-ICU patients, iNO administration can impair viral replication, blocking damage cascade and cytokine storm, and slowing the clinical progression of the disease.In this setting, iNO can represent a strategy to limit lung injury.On this issue, further studies are needed to support the role of iNO administered in a different clinical setting from ICU.

Second, when used in ICU, not all patients showed gas exchange improvement. Among those patients with improvement in gas exchange, the iNO effect is quick but temporary, reaching the peak effect over 15-30 minutes. In patients with severe COVID-19 pneumonia requiring ICU admission, protective mechanical ventilation strategy and pronation cycles represent the primary step to treat cARDS. If the patient remains still severely hypoxic despite these treatments, an iNO trial administration can be performed. INO shows a relatively good safety profile, but the relationship between the magnitude of gas exchange improvement and mortality in COVID-19 patients is still unclear. About this aspect, well-designed clinical trials are needed.

Third, patients with RV function impairment can represent a particular cluster in which iNO administration can play a crucial role, suggesting a "*patient's tailored use*". Patients with RV dysfunction, evaluated by echocardiography, were better iNO responders, probably due to the hemodynamic improvement associated with RV unloading. It is unclear if iNO effects on RV function only improve gas exchange or reduce the mortality rate. Further well-designed clinical trials should be performed on this particular cluster of patients.

In conclusion, although iNO administration can represent a valid theoretical therapeutic choice for the treatment of severe unresponsive hypoxemia in COVID-19 patients, data presented in the literature are scares and inconclusive, and several clinical trials are still ongoing. Further studies are needed to elucidate the pathogenetic mechanism of respiratory failure related to SARS-CoV-2 infection and iNO role in ICU patients.

SUPPLEMENTARY INFORMATION

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