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Potential poles of nitric oxide in COVID-19: A perspective

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Abstract

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a beta-coronavirus closely linked to the SARS coronavirus. COVID-19 patients present with hypoxemia linked to acute respiratory distress syndrome (ARDS). Reversing the hypoxemia prevalent in COVID-19 requires advanced mechanisms that facilitate the transportation of oxygen from alveoli to blood, as increased supplemental oxygen does not always lead to optimal oxygen saturation. Clinical and experimental evidence suggest a significant role for inhaled Nitric Oxide (NO) as a selective vasodilator, which has shown to restore oxygenation by helping to normalise shunts and ventilation/perfusion mismatch. NO has demonstrated the ability to suppress the replication of a respiratory corona virus, which is unique for NO among other vasodilators. These suggest a potentially significant role for NO in the clinical management of COVID-19, warranting urgent investigations into optimal methods of harnessing its potential in restoring pulmonary physiology.

Introduction

The pathophysiological conditions and clinical evidence associated with COVID-19 are rapidly being established, supporting the development of therapeutic solutions [1,2]. COVID-19 patients present with respiratory characteristics of acute respiratory distress syndrome (ARDS), which in accordance with The Berlin definition includes; new or worsening respiratory symptoms within one week of symptom onset; bilateral opacities on chest imaging not fully explained by effusions, atelectasis or nodules; respiratory failure from lung edema not fully explained by cardiac failure or fluid overload; and finally oxygenation impairment [3]. However, the ARDS presented with COVID-19 is recognised to be atypical as an alarmingly majority do not experience breathlessness and have relatively good lung compliance, whilst presenting with hypoxia [4-6]. Supplemental oxygen can partially improve oxygen saturation. However, hypoxaemia due to shunt does not respond well to supplemental oxygen [7]. High levels of supplemental oxygen can be toxic but can be prevented by titrating [8]. Invasive mechanical ventilation, which is considered when addressing the most severe cases continues to be associated with a higher incidence of adverse outcomes [9]. Therefore, there is currently an incentive to explore alternative methods of optimal management of patients in addition to widely practiced prone positioning [10]. Methods of reducing pulmonary resistance and resolving oxygenation with non-invasive therapy are of interest [11].

Hypoxia is known to cause vasodilation in systemic arteries whilst causing vasoconstriction in pulmonary arterioles. Nitric Oxide (NO) has a major role in regulating hypoxia and in healthy conditions it was found that NO can mediate adaptive mechanisms including modulation of vasodilation. Hypoxia regulation in extreme conditions such as high altitudes has shown a strong link to NO, with large population-based studies demonstrating NO upregulation as a physiological response [12]. Exhaled NO measurements associated with a range of respiratory disease conditions demonstrate specific variations in NO downregulation that correspond to an identifiable role in NO [13].

NO is a gaseous molecule and is primarily known for its role in regulating vascular compliance via cGMP pathway [14]. It is synthesised by the endothelial cells lining both healthy blood vessels, and platelets. NO prevents thrombotic complications by inhibiting blood coagulation and regulates blood flow. It is also synthesised in epithelial cells and is known for its potent antimicrobial properties as well as its ability to suppress the rate of viral replication [15,16]. NO synthesis is known to be impaired with co-morbidities that include metabolic syndrome and diabetes, thus it is arguable that impaired NO synthesis could be co-related to COVID-19 patient groups that are most severely affected [17,18].

The entry point of the coronavirus has been recognised to be Angiotensin Converting Enzyme 2 (ACE2) receptors, which are expressed in endothelial and epithelial cells [19]. ACE2 pathway is known to modulate a cascade of events including vascular compliance and vasodilation [20]. ACE2 has a direct effect in upregulation of Nitric Oxide Synthase demonstrated in ACE2 knockout mice with resulting vascular dysfunction and NO imbalance [21]. It would be beneficial to investigate whether potential therapeutic options to address COVID19, could be linked to this ACE2 –NO pathway.

This article presents the perspective that inhaled NO should be considered within the protocols in managing COVID-19, with the view that disruption to NO and related pathways may be leading complications related to COVID19. It is timely to evaluate the validity of this hypothesis and the results could be key, not only in managing COVID19, but also for the management of related hypoxic respiratory conditions.

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Nitric oxide improves oxygenation

Inhaled NO with a half- life of around 3-5 s diffuses from alveoli to vascular smooth muscle cells. These cells are adjacent (~1 μm) to the alveoli and causes selective pulmonary vasodilatation. This imparts an overall effect in pulmonary gas exchange, by increasing blood flow to well ventilated areas in the lung whilst simultaneously reducing the flow to areas of shunts [22,23]. NO has a high affinity to haemoglobin and gets deactivated upon binding to form methaemoglobin. In doing so it limits vasodilatory effects to ventilated areas of the lung [24]. Inhaled NO in the presence of superoxide is also converted into nitrogen dioxide, peroxy-nitrite and nitro-tyrosine. It should therefore be monitored and regulated to facilitate the positive effects of inhaled NO in reversing hypoxaemia. This could be done by controlling the dose and rate of inhaled NO introduction [25]. Pharmacological properties of inhaled nitric oxide can be linked to toxicological effects and should be considered when administering as therapeutic agent [26,27].

Haemoglobin within red blood cells that successfully take up oxygen from alveoli need to carry NO in order to facilitate oxygen delivery to relevant tissues. NO through protein S-nitrosylation and formation of S-nitrosothiol has shown a significant role in regulating ventilation during hypoxia [28]. Conditions such as diabetes and sickle cell disease, which affect allosteric properties of haemoglobin tetramer, are impaired in the ability to carry NO and therefore oxygen delivery to tissues becomes impaired [29]. It would be interesting to investigate if hypoxaemia in COVID-19 is related to such impairments in haemoglobin, and if there are related changes to the NO carrying capacity.

Independent of COVID-19, ARDS was recognised in need of suitable strategies in its clinical management with a reported relatively high rate of admissions in Intensive Care Units (ICU) and a high rate of mortality. Disease conditions that injure lungs such as infection or pneumonia can cause ARDS. ARDS, Chronic Obstructive Pulmonary Disorder (COPD) and pulmonary embolism are major conditions that result in arterial hypoxemia. Low ventilation-perfusion (V/Q) and shunt are recognised to be most common causes of clinical hypoxemia and shunt most common in ARDS. There are numerous studies that have investigated the application of NO in ARDS as well as its application in managing critically ill patients in ICU [30-38]. Whilst there is no strong evidence to support a role for NO in directly reducing mortality, inhaled NO has very strong experimental and clinical evidence with improved oxygenation, at least for 72 hr [38]. This could be a mortality determining factor in a resource limited COVID-19 situation and therefore inhaled NO could certainly be considered as a short-term rescue therapy to link with further management strategies [39-41]. Patients with greater baseline intrapulmonary shunt have demonstrated the most significant improvement in oxygenation and low dosed, (10-40 ppm) pulsed inhaled NO seem to be most effective [35-37]. Inhaled NO therefore should be considered prior to invasive ventilation and other treatment strategies such as extracorporeal membrane oxygenation for COVID-19 patients.

The effects of inhaled NO in COPD patients where hypoxemia is caused by low V/Q show a variable response within subgroups , within which the less consistent results are explained as a con-sequence of NO as a vasodilator reaching low V/Q regions. This in turn leads to greater arterial de-saturation. Unlike COPD, ARDS patients as well as those with acute severe pneumonia, have consistently and dramatically responded with a reduction in shunting and improved oxygena-tion [23]. Careful examination of systematic reviews that conclude an overall non-significant role for inhaled NO seem to base their conclusion with large variations in sub-groups. The authors themselves suggest caution to act on their conclusions and suggest further investigations would be beneficial. It is notable that even these systematic reviews have consistently highlighted a positive role of NO in oxygenation.

Blood clot formation

NO is well recognised for its role in inhibiting platelet aggregation and therefore its antithrombotic properties [42]. This could be yet another role for NO in managing COVID-19 patients who report increased D-dimer levels, and clot formation suggesting a pathological condition that could lead to thrombotic complications [43]. This is currently managed with prophylactic Heparin [10]. Prostacyclin such as Epoprostenol is known as a potent anticoagulant and inhaled Epoprostenol is known to be effective as a vasodilator in severe hypoxemia [44]. Unlike NO, which has a selective, local pulmonary effect, prostacyclin could lead to a more systemic vasodilatory effect due to rapid deactivation.

Nitric oxide's antiviral role

In addition to its vasodilatory and antithrombotic roles, NO has a key role in microbial infections particularly through its synthesis via inducible NO synthase (iNOS) [45]. A healthy airway epithelium can produce NO that acts as an antiviral agent in addition to providing a complex immune reactions in the pulmonary system [46-48]. Therefore, disease conditions that have impaired synthesis of NO could be salvaged with exogenous NO in the form of inhaled NO or NO releasing compounds, where innovative delivery mechanisms can be explored. SARS, which was caused by a Coronaviridae family virus had resulted in 774 deaths. NO has been shown to successfully inhibit its replication cycle by affecting its proteins and reduction in viral RNA [49-51]. Respiratory coronaviral infections have been recognised to induce epithelial cytolysis and NO releasing molecules, S-nitroso-N-acetylpenicillamine were able to preserve/restore rate of survival of SARS-Coronavirus infected cells.

Overall perspective

With an evident role in rapid re-oxygenation in ARDS, application of NO could be a mortality determining factor in a globally resource limited situation as COVID-19. Encouragingly, there are two clinical trials (as far as the author is aware of) underway to evaluate the effect of inhaled NO in managing COVID-19. "NO Gas Inhalation for Severe Acute Respiratory Syndrome in COVID-19 (NOSARSCOVID), NCT04290871" as well as a study led by Novoteris and Mallinckrodt with a high-concentration form of NO named Thiolanox. Dose and rate of NO administration as well as degree of exposure to superoxide could significantly vary the responses in addition to variations in pathological conditions that underlie a given respiratory condition and therefore need to be carefully documented. There are opportunities to develop systems that detect and respond to such changes where the process can be automated possibly through integrating machine learning and artificial intelligent systems. NO therapy is associated with relatively high costs, and this has been a determining factor in integrating its applications in routine therapy. However, this reasoning would not be relevant to its applications in COVID19, considering the global spending related to the disease. The evidence of NO's ability to have a positive impact, based on the fundamental biochemical role of NO in hypoxemia, platelets, and potentially corona viral replication, calls for greater efforts to delineate NO's role and harness its undeniable positive role in managing the current global COVID-19 crisis.

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