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Perspective

Promising gas therapies for severe COVID-19

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) pandemic is a worldwide catastrophe, thoroughly challenging the healthcare systems. A growing number of victims suffer from a remarkable acute respiratory distress syndrome (ARDS) that necessitates admission to the intensive care unit (ICU), but there are no satisfactory treatments. Various gas therapies including nitric oxide, ozone, hyperbaric oxygen, hydrogen, and heliox have been employed in the fight against the pandemic and have improved clinical outcomes. However, the potential roles of these gases in COVID-19 treatment need to be verified in well-designed randomized controlled trials. This paper reviews advances in gaseous therapy of COVID-19.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) initiated a devastating pandemic that posed an overwhelming threat to global health and challenged the researchers to explore effective treatments. As of January 28, 2021, more than 100 million people had been infected with SARS-CoV-2, and over 2 million have died [1]. The key clinical feature of patients with severe COVID-19 who require ventilation is acute respiratory distress syndrome (ARDS) due to the “proliferative activation of a network-immune-inflammatory crisis” (PANIC) [2]. COVID-19 pathogenesis is not fully understood, but the pathological picture in the lungs varies considerably in terms of diffuse alveolar damage and microcirculopathy that cause life-threatening hypoxia [3]. Approximately 30% of patients suffering COVID-19 require intensive care unit (ICU) admission, but no powerful clinical therapies are available [4].

Given the advantages of relative abundance, low cost, a reasonable safety profile, and low metabolic burden, gas therapy is a promising therapeutic strategy for fatal hypoxia in COVID-19 [Fig. 1]. Here, we present an overview of the progress made in the gaseous therapy for COVID-19.

Gas Therapies

Nitric oxide

Nitric oxide (NO) is a therapeutic gas that plays an important regulatory role in the vascular system by controlling vascular tone and blood flow following activation of soluble guanylate cyclase (SGC) within the vascular smooth muscle; it also affects mitochondrial oxygen consumption by inhibiting cytochrome c oxidase [5].

The observation of increased levels of intracellular NO in red blood cells indicates a possible clinical application for NO in COVID-19 patients with hypoxia [6]. NO may also be a competent candidate to alleviate hypoxic respiratory failure in COVID-19 due to its potential antiviral, anti-inflammatory, and mild bronchodilatory actions. Possible side effects of NO are due to the following two points: (1) the reaction product of NO with oxygen (NO_2) can induce airway inflammation and (2) oxidation of ferrous hemoglobin (Hb) to methemoglobin (Met-Hb) may impair the body's capability to transport and release oxygen to tissues. For these reasons, NO_2 and Met-Hb levels should be monitored and maintained at levels <2 ppm and 5%, respectively [7].

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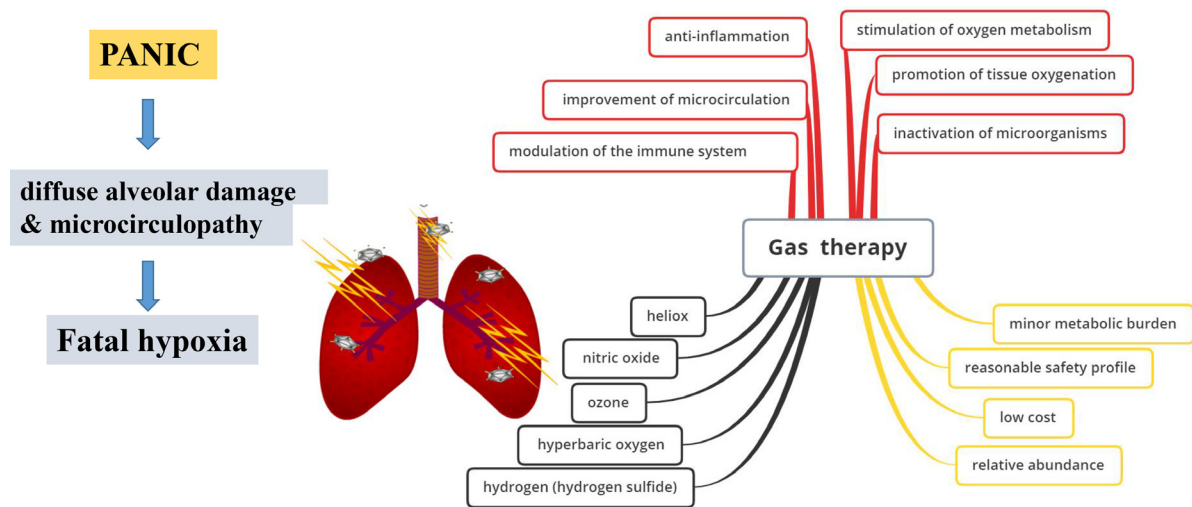


Fig. 1. Gaseous therapy is a promising strategy for fatal hypoxia in COVID-19 due to its effects on inflammation, oxygenation, and metabolism. COVID-19: Coronavirus disease 2019; PANIC: Prolific activation of a network-immune-inflammatory crisis.

Focusing on maternal rescue therapies, NO at 160–200 ppm was delivered by mask to treat 6 pregnant patients admitted with critical COVID-19. At a 28-day follow-up, NO was well tolerated, and treatment was associated with improved oxygenation and respiratory rate for pregnant patients, as well as the favorable condition of their newborns. No acute adverse effects were observed in any patient during the study [8].

Wiegand et al. [9] performed a retrospective evaluation of 5 coronavirus pneumonia patients in respiratory distress receiving NO gas at 160 ppm by mask. Three patients survived and were discharged home after full assessments. The inflammatory marker data of 2 participants showed a reduction or cessation of escalation after NO treatment. Their mean arterial pressure, heart rate, oxygenation, and the respiratory rate remained stable during and after NO treatment.

Lei et al. [10] released a multicenter randomized controlled trial protocol (Trial registration: Clinicaltrials.gov. NCT04306393) with a sample size of 200 subjects to investigate the clinical influence of inhaled NO gas (iNO) on COVID-19. Briefly, intubated patients with confirmed SARS-CoV-2 infection and severe hypoxemia will be enrolled to receive iNO at 80 ppm for the first 48 h. Oxygenation levels will be evaluated as the primary outcome. The results should add to and consolidate the evidence for the therapeutic potential of NO.

Ozone

Ozone is an allotropic form of oxygen, with a molecule composed of three oxygen atoms. The fact that the human body is capable of producing ozone to protect itself from diverse pathogens has been underlined [11]. Ozone also serves as nuclear factor- κ B (NF- κ B) and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) transcription agents, so it can exert anti-oxidizing and anti-inflammatory effects by modulating inflammation-related gene expression. Notably, Nrf2-mediated blocking of the fusion of SARS-CoV-2 spike protein with the angiotensin-converting enzyme 2 receptor effectively destroys the viral biology of SARS-CoV-2 [12]. Medical ozone (MO) therapy conventionally consists of a mixture of 1–5% ozone gas and 95–99% pure oxygen.

One case report enrolled three patients with critical respiratory failure who did not require invasive ventilation to test the potential role of ozone. The subjects were systemically treating by adding MO gas mixture to an autologous blood sample and then reinfusing it via the same vein. This “ozonated auto-hemotherapy” was followed by rapid clinical and laboratory recovery profiles. Early discharge to home was possible after 4–6 sessions of ozonated therapy, indicating the promising therapeutic power of ozone against this epidemic [13].

Franzini et al. [14] investigated the therapeutic impact of four cycles of oxygen-ozone in 50 elderly male COVID-19 patients undergoing non-invasive mechanical ventilation in ICUs. Detailed treatments were created with an ozone generator making a 45 μ g/mL oxygen-ozone mixture, which led to quick recovery from ARDS as demonstrated by improvements in major respiratory indexes and blood gas parameters.

The Italian Oxygen-Ozone Federation (Nuova FIO) designed a controlled, international, multicenter study to evaluate the beneficial effects of systemic administration of oxygen-ozone in the early phases of COVID-19 infection, before patients require tracheal intubation. This research will be performed through the ozonation of drawn blood at the volume of 1.5 g/kg and subsequent reinfusion into the patient’s venous circulation once every 24 h for 7 days. Patients will be followed for a total study duration of 14 ± 2 days to assess clinical progression including recourse to non-invasive ventilation, multi-organ failure onset, and mortality. This trial will offer concrete proof about whether oxygen-ozone therapy is effective for treating COVID-19 [15].

Hyperbaric oxygen

Standard oxygen-support care fails in COVID-19 patients due to increased diffusional resistance to oxygen. The vicious cycle where inflammation is tightly tied to hypoxia can only be halted when elevated oxygen concentrations are available to the tissue. During hyperbaric oxygen therapy (HBOT), the patient intermittently breathes nearly 100% oxygen inside a pressurized chamber of at least 1.4 atmospheres [16].

Zhong et al. [17] reviewed patient’s data including a seriously affected victim on a ventilator whose life was saved by the

Table 1
The detailed tips of gas therapy.

Gas	Timing	Dose	Duration	Side effect/risk/demerit	Countermeasure	Advantage
NO	Within 48 h after admission [8]	160–200 ppm	30–60 min per session (twice daily, until the desired endpoint)	Airway inflammation increase Oxygen-transport capability of Hb decrease	NO \leq 2 ppm Met-Hb \leq 5%	Regulating vascular tone Anti-virus Anti-inflammation Bronchodilatory action
	The beginning of enrolment [10]	80 ppm	48 h	Acute kidney injury	Monitoring kidney function	
	48 h after enrolment	40 ppm 160 ppm [9]	Until hypoxemia resolves 30 min per session (twice daily, until the desired endpoint)	Rebound pulmonary hypertension Oxygenation impairment Acute right heart failure	Gradual weaning	
Ozone	Early phase of COVID-19 [15]	Autologous blood (1.5 g/kg) ozonated by oxygen-ozone mixture (30 μ g/mL Ozone)	7 days (once daily)	Contraindication Glucose-6-phosphate dehydrogenase deficiency Antimalarials Hyperthyroidism		Anti-oxidization Anti-inflammation Anti-platelet Anti-edema Renal-protection effect Stimulate oxygen metabolism Destroy SARS-CoV-2's biology
	Within the first week of hospitalization [14]	Autologous blood (200 mL) ozonated by oxygen-ozone mixture (45 μ g/mL Ozone) Autologous blood (200 mL) ozonated by oxygen-ozone mixture (40 μ g/mL Ozone) [13]	30 min per session 5 days (once daily) 10 min per session 2–3 days (1–2 sessions per day)			
Hyperbaric oxygen		1.4 atmospheres [16]	Once-daily, until the desired endpoint	Cross-contamination of hyperbaric chambers	Strict infection control	Anti-inflammation Promoting growth and repair Anti-programmed cell death
Hydrogen [19]		Hydrogen-oxygen (66% hydrogen; 33% oxygen) at 6 L/min	Once-daily, until discharge			Anti-oxidization Anti-inflammation Anti-apoptotic Anti-allergy Airway resistance decrease
Heliox (coronavirus OC43) [22]		Helium-oxygen (70% helium; 30% oxygen) at 9 L/min	48 h	No treatment for underlying disease Lower cost-effectiveness	Just a bridge treatment	Airway resistance decrease

COVID-19: Coronavirus disease 2019; Hb: Hemoglobin; Met-Hb: Methemoglobin; NO: Nitric oxide; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

application of HBOT and four additional subjects with grievous respiratory failure who experienced sustained elevation of oxygen saturation, symptom improvement, and discharge from the hospital to home.

The preliminary evidence for HBOT underscores its significant potential to alleviate the COVID-19 pandemic, but strict infection control is mandatory to minimize cross-contamination of hyperbaric chambers.

Hydrogen or hydrogen sulfide (H_2S)

Existing basic and clinical research indicates that hydrogen is a vital physiological regulatory factor with anti-oxidative, anti-inflammatory, antiapoptotic, and anti-allergic effects. Beneficial effects of hydrogen have been reported in >38 diseases treated via inhaling hydrogen gas, drinking hydrogen-dissolved water, taking a hydrogen bath, and injecting hydrogen-dissolved saline [18].

The first open-label multicenter clinical trial involved 90 patients with laboratory-confirmed COVID-19 from seven hospitals in China that evaluated the treatment role of inhaling hydrogen-oxygen (66% hydrogen; 33% oxygen) at 6 L/min via nasal cannula daily until discharge. Hydrogen-oxygen inhalation rapidly decreased disease severity, dyspnea and cough scales, and chest distress. Furthermore, the increase in resting oxygen saturation was significant following hydrogen-oxygen inhala-

tion, supporting the efficacy and safety of hydrogen-oxygen inhalation in patients with COVID-19 [19].

Hydrogen sulfide (H_2S) is endogenously produced and has relevant physiological roles such as modulating the inflammatory and host responses to viral infections. Growing evidence suggests an inverse relationship between endogenous H_2S levels and several disorders (especially COVID-19), but verifications of the actual medical applications of H_2S in COVID-19 are lacking [20].

Heliox

Heliox is a helium–oxygen gas mixture that has been used for several decades to manage chronic obstructive pulmonary disease (COPD). Given the low density and high viscosity, heliox provides a solution to emergency airway problems and can significantly lower airway resistance (Raw) when an anatomic airway obstruction is present [21].

Besides its therapeutic role in acute asthma and COPD, the potential of using heliox in patients with COVID-19 was first described in a case report. An infected infant with severe acute respiratory distress responded immediately and significantly after inhaling Heliox followed by an improved respiratory and general condition. However, this gas mixture has lower cost-effectiveness because it may not treat the underlying disease or influence airway anatomy, so it should only be used as a

bridge approach to reduce Raw and respiratory muscle work until definitive therapies address the etiological factors. To date, heliox has not been recommended for routine clinical use [22].

Conclusion

The pulmonary viral pandemic induced by SARS-CoV-2 caused the healthcare system to collapse in many countries, demanding urgent rapid exploration of safe and effective therapeutic options. The growing tendency to use novel gas therapies to fight COVID-19 has achieved impressive success and the detailed tips of gas therapy above mentioned are compiled [Table 1]. Their therapeutic potential is associated with microorganism inactivation, immune system modulation, microcirculation improvement, anti-inflammatory action, oxygen metabolism stimulation, and greater tissue oxygenation. Gaseous treatment is a feasible and cost-effective adjuvant therapy while we develop new drugs or wait for widespread vaccine deployment. More large controlled clinical trials are required to clarify the efficacy and safety of gas therapy for COVID-19 in terms of the need for invasive ventilation and lengths of hospital and ICU stays.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] World Health Organization Coronavirus disease 2019 (COVID-19) Situation Reports. Available online: <https://covid19.who.int/>
- [2] Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020;20(10):1135–40. doi:10.1016/S1473-3099(20)30434-5.
- [3] Frohman EM, Villemarette-Pittman NR, Melamed E, Cruz RA, Longmuir R, Varkey TC, et al. Part I. SARS-CoV-2 triggered 'PANIC' attack in severe COVID-19. *J Neurol Sci* 2020;415:116936. doi:10.1016/j.jns.2020.116936.

- [4] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–62. doi:10.1016/S0140-6736(20)30566-3.
- [5] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130(5):2620–9. doi:10.1172/JCI137244.
- [6] Mortaz E, Malkomohammad M, Jamaati H, Naghan PA, Hashemian SM, Tabarsi P, et al. Silent hypoxia: higher NO in red blood cells of COVID-19 patients. *BMC Pulm Med* 2020;20(1):269. doi:10.1186/s12890-020-01310-8.
- [7] Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;34(5):646–56. doi:10.1016/s0196-0644(99)70167-8.
- [8] Fakhr BS, Wiegand SB, Pinciroli R, Gianni S, Morais CCA, Ikeda T, et al. High concentrations of nitric oxide inhalation therapy in pregnant patients with severe coronavirus disease 2019 (COVID-19). *Obstet Gynecol* 2020;136(6):1109–13. doi:10.1097/AOG.0000000000004128.
- [9] Wiegand SB, Fakhr BS, Carroll RW, Zapol WM, Kacmarek RM, Berra L. Rescue treatment with high-dose gaseous nitric oxide in spontaneously breathing patients with severe coronavirus disease 2019. *Crit Care Explor* 2020;2(11):e0277. doi:10.1097/CCE.0000000000000277.
- [10] Lei C, Su B, Dong H, Bellavia A, Di Fenza R, Safaei Fakhr B, et al. Protocol of a randomized controlled trial testing inhaled nitric oxide in mechanically ventilated patients with severe acute respiratory syndrome in COVID-19 (SARS-CoV-2). *medRxiv*; 2020. doi:10.1101/2020030920033530.
- [11] Rowen RJ. Ozone therapy as a primary and sole treatment for acute bacterial infection: case report. *Med Gas Res* 2018;8(3):121–4. doi:10.4103/2045-9912.241078.
- [12] Jiang HJ, Chen N, Shen ZQ, Yin J, Qiu ZG, Miao J, et al. Inactivation of poliovirus by ozone and the impact of ozone on the viral genome. *Biomed Environ Sci* 2019;32(5):324–33. doi:10.3967/bes2019.044.
- [13] Hernández A, Viñals M, Isidoro T, Vilás F. Potential role of oxygen-ozone therapy in treatment of COVID-19 pneumonia. *Am J Case Rep* 2020;21:e925849. doi:10.12659/AJCR.925849.
- [14] Franzini M, Valdenassi L, Ricevuti G, Chirumbolo S, Depfenhart M, Bertossi D, et al. Oxygen-ozone (O₂-O₃) immunocellular therapy for patients with COVID-19. Preliminary evidence reported. *Int Immunopharmacol* 2020;88:106879. doi:10.1016/j.intimp.2020.106879.
- [15] Marini S, Maggiorotti M, Dardes N, Bonetti M, Martinelli M, Re L, et al. Oxygen-ozone therapy as adjuvant in the current emergency in SARS-CoV-2 infection: a clinical study. *J Biol Regul Homeost Agents* 2020;34(3):757–66. doi:10.23812/20-250-E-56.
- [16] Harch PG. Hyperbaric oxygen treatment of novel coronavirus (COVID-19) respiratory failure. *Med Gas Res* 2020;10(2):61–2. doi:10.4103/2045-9912.282177.
- [17] Zhong XL, Niu XQ, Tao XL, Chen RY, Liang Y, Tang YC. The first case of hbot in critically ill endotracheal intubation patient with COVID-19. Beijing, China: Novel Coronavirus Pneumonia Research Network Sharing Platform of China Association for Science and Technology; 2020.
- [18] Ohta S. Molecular hydrogen is a novel antioxidant to efficiently reduce oxidative stress with potential for the improvement of mitochondrial diseases. *Biochim Biophys Acta* 2012;1820(5):586–94. doi:10.1016/j.bbagen.2011.05.006.
- [19] Guan WJ, Wei CH, Chen AL, Sun XC, Guo GY, Zou X, et al. Hydrogen/oxygen mixed gas inhalation improves disease severity and dyspnea in patients with Coronavirus disease 2019 in a recent multicenter, open-label clinical trial. *J Thorac Dis* 2020;12(6):3448–52. doi:10.21037/jtd-2020-057.
- [20] Citi V, Martelli A, Brancaleone V, Brogi S, Gojón G, Montanaro R, et al. Anti-inflammatory and antiviral roles of hydrogen sulfide: rationale for considering H₂S donors in COVID-19 therapy. *Br J Pharmacol* 2020;177(21):4931–41. doi:10.1111/bph.15230.
- [21] Kress JP, Noth I, Gehlbach BK, Barman N, Pohlman AS, Miller A, et al. The utility of albuterol nebulized with heliox during acute asthma exacerbations. *Am J Respir Crit Care Med* 2002;165(9):1317–21. doi:10.1164/rccm.9907035.
- [22] Morgan SE, Vukin K, Mosakowski S, Solano P, Stanton L, Lester L, et al. Use of heliox delivered via high-flow nasal cannula to treat an infant with coronavirus-related respiratory infection and severe acute air-flow obstruction. *Respir Care* 2014;59(11):e166–70. doi:10.4187/respcare.02728.