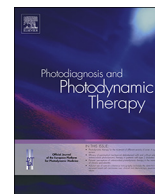




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Letter to the editor

Photodynamic and sonodynamic therapy of acute hypoxemic respiratory failure in patients with COVID-19



To the Editor – COVID-19 has infected more than 12 million people and claimed nearly 600,000 lives worldwide. Numerous case series reports and observational studies have described the clinical course and outcomes of patients who have contracted SARS-CoV-2 and were subsequently hospitalized. A majority of moderate-to-critically ill patients required high flow nasal cannula or mechanical ventilation. A proportion of those patients were treated with different off label or investigational drugs and convalescent plasma therapy [1–3]. However, only two pharmaceuticals demonstrated efficacy. Remdesivir has been shown to reduce the total amount of time in ICU required per patient [4], and dexamethasone had reduced deaths by 35 % in patients who needed treatment with invasive ventilation and by 20 % in those needing supplemental oxygen [5]. In this letter we propose the exploration of using photodynamic therapy (PDT) and Sonodynamic Therapy (SDT) to treat acute hypoxemic respiratory failure (AHRF) in patients with COVID-19 (Fig. 1).

Several recent studies have argued that severe-critically ill COVID-19 patients develop acute hypoxemic respiratory failure (AHRF) and therefore cannot be successfully treated using established ICU protocol [6,7]. The unique challenges of COVID-19 were demonstrated in early radiological studies presenting bilateral interstitial lung inflammation and fibrosis, characterized by ground glass opacity, crazy-paving pattern, and consolidation in lung CT scans [8]. Beyond COVID-19 related complications, invasive ventilation can do more harm than good, including air leaks due to high ventilation pressures (barotrauma), pulmonary edema due to large tidal volumes (volutrauma), atelectasis due to the repetitive opening and closing of the lungs (atelectrauma), and oxytrauma from free oxygen radicals [9]. The damaging effects of intubation combined with the complications of severe COVID-19 may explain the large mortality rates in intubated COVID-19 patients. In an outcomes study examining over 2600 discharges/deaths in New York City area hospitals, among those who died, 88 % received mechanical ventilation [10]. This alarmingly high mortality rate may indicate a failure in established ICU protocols, though it could be confounded by the overreliance of intubation/ventilation therapy. However, there is a growing consensus that intubation should serve as a last resort for the most ill patients. Therefore, many hospitals are now transitioning to the use noninvasive ventilation and/or low-volume ventilation [6,7].

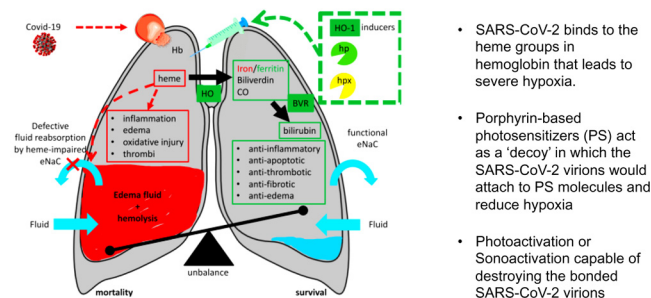
The challenges posed by COVID-19-induced AHRF had lead physicians to rethink the characterization of these effects to indicate a different mechanism of respiratory distress. [6,7,9,11], A recent study performed conserved domain analysis, homology modeling, and molecular docking on SARS-CoV-2 pathogenesis, which proposed that SARS-CoV-2 binds to the heme groups in hemoglobin, leading to severe hypoxia. Porphyrins, a ring-like organic compound, make up Heme and attach to iron atoms. Iron atoms bind to oxygen as the blood travels between the lungs and the tissues. It was hypothesized that several nonstructural proteins (orf1ab, ORF10, and ORF3a) target the 1-beta

chain of hemoglobin, which dissociates iron to form porphyrin (Fig. 1). This attack causes a disruption in the passage of hemoglobin-carrying-oxygen between the alveoli and capillaries [12]. While the study is in pre-print and some have criticized the study design, SARS-CoV-2-mediated attack on hemoglobin could explain the lack of efficacy with intubation therapy [13]. The attack on hemoglobin leads to desaturation, which coupled with the proliferation of pro-inflammatory cytokines cause the alveoli to become filled with fluid, white blood cells, mucus, and the detritus of destroyed lung cell. The attack on hemoglobin and the lung tissue can lead multi-organ failure.

Considering the unique challenges of AHRF in patients with COVID-19, we propose the use of Photodynamic Therapy (PDT). The earliest understanding that photonic energy in visible light could be harnessed through the presence of a photoreactive substance to promote a biological, photodynamic effect in an oxygenated tissue is attributed to the work of Professor von Tappeiner on xanthene derivatives, first published in 1900 [14]. Early photodynamic agents were naturally-derived porphyrins such as hematoporphyrin and typically were mixtures of many porphyrins leading to inconsistent biological results. Through many decades of purification, and ultimately the synthesis of new single-entity photoreactive agents with tissue-selective localization, together with advances in light sources and photonics, the versatility of PDT has been clinically validated in a wide range of pathologies from esophageal and certain lung cancers, to uses in treating age-related macular degeneration in the eye and in tumor margin identification during brain cancer surgery. Evidence for the antimicrobial effects of PDT have been shown (i.e. destruction of bacteria, viruses, protozoa, and fungi) [15–17]. Unlike antibiotics, there is little to no risk for the formation of resistance following repeated exposures to PDT, which could be useful to treat opportunistic infections in patients with COVID-19.

We propose to treat AHRF by the injection of porphyrin-based photosensitizers (PS) systemically or locally into the lungs either through the pulmonary artery and/or bronchial arteries using a Swan Ganz or micro catheters. Initially, and without the need for photoactivation, the PS molecules act as a ‘decoy’ in which the SARS-CoV-2 virions would attach to PS molecules instead of healthy lung tissue or hemoglobin. The therapy may improve clinical performance and increase oxygenation. However, to reduce viral load, illumination of the target lung tissue using fiberoptic catheter to deliver low-power light of a characteristic absorption wavelength for the photosensitizer (typical range 450 – 800 nm), causes photoactivation yielding a highly reactive oxygen species capable of destroying the bonded SARS-CoV-2 virions to the PS molecules through peroxidation. The predominant mechanism in PDT involves generation of singlet oxygen (1O_2). The diffusion distance of 1O_2 is around 0.01 – 0.02 μ before being quenched so the PS must be associated intimately with the target substrate for maximal impact. [18] Thus, the SARS-CoV-2 affinity for the heme structure of the PS,

PHOTODYNAMIC AND SONODYNAMIC THERAPY



- SARS-CoV-2 binds to the heme groups in hemoglobin that leads to severe hypoxia.
- Porphyrin-based photosensitizers (PS) act as a 'decoy' in which the SARS-CoV-2 virions would attach to PS molecules and reduce hypoxia
- Photoactivation or Sonoactivation capable of destroying the bonded SARS-CoV-2 virions

Fig. 1. Proposed pathway of SARS-CoV-2 targeting the heme groups of hemoglobin and the subsequent formation of hypoxic effects of COVID-19. Adapted from: Wagener and colleagues. Targeting the Heme-Heme Oxygenase System to Prevent Severe Complications Following COVID-19 Infections. *Antioxidants* 2020, 9, 540.

predicts high viral destruction titers limited to the zone of photoactivation. The application of nanoparticle technology may provide opportunities to enhance delivery, bioavailability, selectivity, and functionality of currently available PS while reducing side-effects. In the absence of specialized photonics or in resource-limited settings, some PS may be activated using transthoracic continuous wave ultrasound (sonodynamic therapy). In some clinical settings there may be incremental benefit in combining PDT and sonodynamic therapy (SDT). PDT does not preclude the use of conjunctive pharmacologic treatment of COVID-19 disease, in fact, PDT and/or SDT combined with an existing therapy may prove the most effective approach. However, pre-clinical and clinical studies are planned to examine early feasibility, safety, and efficacy of this approach.

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Declaration of Competing Interest

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