EDITORIAL COMMENTARY

# Hyperbaric oxygen as a treatment for COVID-19 infection?

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Recently the internet has been abuzz with new ideas to treat COVID-19, including hyperbaric oxygen ($HBO_2$) therapy, undoubtedly driven by the fact that until recently there have been few therapeutic options for this highly contagious and often lethal infection. A series of five patients from Wuhan, China, has been reported to the UHMS and their features summarized [1]. Some groups have subsequently promoted $HBO_2$ for COVID-19 infections, largely based upon two possible rationales. The first is treatment of hypoxemia, which is the major indication for endotracheal intubation in this condition. The second proposed rationale for hyperbaric oxygen is its potential anti-inflammatory effect.

Refractory hypoxemia is certainly treatable with hyperbaric oxygen due to the obvious effect of increasing inspired oxygen partial pressure ($PO_2$), the major reason for using $HBO_2$ for its established indications. However, the length of time during which patients can safely be administered $HBO_2$ inside a chamber is limited, due to practical issues of confinement and isolation from other necessary medical interventions, but also because of oxygen toxicity.

A sub-argument for using $HBO_2$ for treatment of critically ill patients such as those with COVID-19 is to accelerate resolution of "oxygen debt" or "systemic hypoxia." In addition to previously documented systemic effects of sepsis it has been suggested that the COVID-19 virus can induce tissue hypoxia by attacking the hemoglobin molecule and reducing the number of oxygen binding sites from four to three. This could induce tissue hypoxia due to a functional anemia and leftward shift of the hemoglobin-oxygen dissociation curve, but this appears unlikely since it would generate a mismatch between arterial $PO_2$ and hemoglobin-oxygen saturation (inappropriately low Hb-$O_2$ saturation in the face of normal or high $PO_2$), and we are unaware of any such reports. Nevertheless, blood lactate elevation has been observed in COVID-19 infections. Elevated blood lactate, so the argument goes, indicates tissue hypoperfusion and hypoxia, for which a short period of normalization of blood oxygenation or indeed hyperoxemia may be beneficial. However, tissue hypoxia is an uncommon cause of elevated blood lactate level in sepsis, particularly after adequate initial resuscitation [2,3]. Other sepsis-related reasons for elevated lactate include impaired oxygen use due to mitochondrial dysfunction, which is not ameliorated by an increase in oxygen delivery [4], and stress-related increase in glucose metabolism and impaired lactate clearance [2-4], neither of which is likely to respond to hyperoxemia.

Anti-inflammatory effects of $HBO_2$ at 2-2.5 atmospheres absolute (ATA) for two hours have been demonstrated in animal models [5,6] and at 2.4-2.5 ATA in human clinical disease [7,8]. It has been suggested that the efficacy of $HBO_2$ in other conditions such as sudden sensorineural hearing loss may be related to its ability to attenuate inflammation [9]. Unlike corticosteroids $HBO_2$ does not seem to be an immunosuppressant; therefore it may have some advantage in treating inflammatory conditions.

Whether $HBO_2$ at 1.5 ATA might reduce inflammation in the lung due to COVID-19 infection is an open question. However, pulmonary oxygen toxicity itself is an inflammatory process [10], and it is possible that administration of high inspired $PO_2$ to a lung with gas exchange impairment due to the host response to infection could cause additional damage.

Enter Dr. Guo, et al. with a report of two cases of moderately severe COVID-19 infection, each of whom was treated in a hyperbaric chamber at 1.5 ATA for one

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hour each day for one week [11]. These patients, ages 57 and 64 years, received at least 95% oxygen at 1.5 ATA, providing an inspired $PO_2$ of 1.4-1.5 ATA. For patients with normal lungs, arterial $PO_2$/alveolar ratio ($PaO_2$/$PAO_2$) = 0.85, and arterial $PCO_2$ = 35 mmHg, predicted $PaO_2$ under these conditions would be 830-880 mmHg [12]. For the two patients in this case report baseline gas exchange was respectively: $PaO_2$ 60 mmHg ($O_2$ by mask at 15 L/minute); $PaO_2$ 66 mmHg ($O_2$ by mask at 10 L/minute). Their estimated $PaO_2$/$PAO_2$ ratios were therefore in the range 0.11-0.14 (P/F ratios 60-80 mmHg), for which $PaO_2$ in the hyperbaric chamber would be predicted at 135-150 mmHg [12]. Since this method tends to underestimate measured $PaO_2$ [13], one might speculate that their actual $PaO_2$ during the initial treatment would not have been significantly higher than 200 mmHg, although since oxygenation improved over the next few days it may have been higher in subsequent treatments.

What information can be derived from these two cases? It is highly probable that these two COVID-19-infected patients would have survived irrespective of active therapy; thus it is not possible to conclude anything about the effect of $HBO_2$ on outcome. It does appear that an uptick in blood oxygenation coincided with the start of hyperbaric treatment, so it is tempting to infer that $HBO_2$ changed the course of their disease. However, both patients were also receiving a variety of medications including moderately high doses of corticosteroids, in addition to supportive care. With predicted arterial $PO_2$ only in the mildly hyperoxemic range even for 1 ATA, it is difficult to conclude that $HBO_2$ has much therapeutic effect in COVID-19 infections based only on these two cases. Although one might propose that high intrapulmonary oxygen tension has a direct positive effect, in other forms of sepsis and lung injury published evidence thus far supports the opposite view [14,15].

Is it possible that $HBO_2$ could be toxic to this virus, or could interfere with viral adhesion or other adverse effects caused by COVID-19? We do not know, and this supposition is speculative without supporting information.

While Guo's cases do not provide sufficient evidence to recommend routine $HBO_2$ for COVID-19 patients his observations have provided a service: He has contributed preliminary assurance that hyperbaric hyperoxia may be minimally toxic to the lung, at least at this dose. Thus there is now at least some reassurance regarding safety for investigators who are planning appropriately powered prospective trials.

A position statement by the Undersea and Hyperbaric Medical Society recommends that $HBO_2$ should be offered only to COVID-19 patients if enrolled in Institutional Review Board clinical trials [16].

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