COVID/HBO_2 Synopsis

Participants on the call

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Invited Guests
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Introduction

This is a synopsis of a conference call between invited members of the Hyperbaric Oxygen Therapy committee, the American College of Emergency Physicians' Section on Undersea and Hyperbaric Medicine, and invited researchers with clinical trials on the use of HBO_2 and COVID-19. This is a synopsis of the discussion curated from a recording of the meeting.

Background

A case series of five patients has been circulated on the internet. This has drawn a lot of attention to the use of HBO_2 as a possible therapy for COVID-19. This has generated many questions that have been posed to the leadership of the UHMS.

Synopsis of Chen Case Series

This case series of five patients has not been published in the English literature, but may have been published in Chinese journals. This manuscript appears to have been translated into

English and disseminated informally to hyperbaric providers and policy members in the United States and abroad.

Study design

- 24-69 (mean 47.6) years old
- Chest CT showed typical pulmonary imaging changes of COVID-19
- Nucleic acid tests of SARS-CoV-2 were positive
- HBO_2 was started after routine treatments failed to stop deterioration of condition
- HBO_2 protocol
    - 2.0 ATA for first patient, then 1.6 ATA for subsequent patients
    - 90 minutes of oxygen breathing for first treatment, then 60 minutes after that

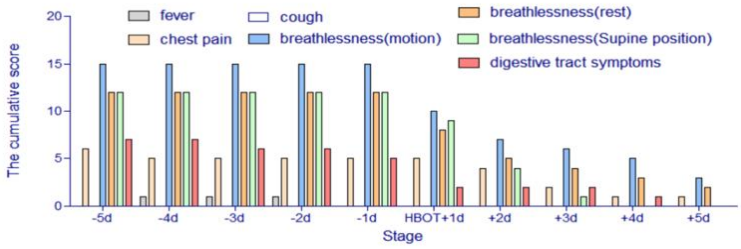
Table 1 the usage of oxygen therapy for 5 cases in the hospital

patient	sex	age	before HBOT treatment(d)			after first HBOT treatment(d)		HBOT(d)
			Nasal	Mask	Mech	Mask	Nasal	times
1#	M	69	2	14	-	3	15	8
2#	M	64	1	6	-	4	5	5
3#	M	28	2	12	2	0	2	4
4#	M	53	1	12	-	0	7	3
5#	F	24	1	16	-	0	9	3
mean		47.6	1	12	-	1.4	8	4.6

NOTE: nasal = nasal oxygen breathing with a flow of 3-5L/min; Mask = mask oxygen breathing with a flow of 5-8L/min; Mech = non-invasive mechanical ventilation

Results

- Clinical symptoms
    - Fever was not a persistent symptom
    - Always resolved after one course of routine therapy
    - Cough was not prominent symptom in these cases
    - All five patients had severe breathlessness
    - Symptoms of every case were “obviously mitigated” after first HBO_2 treatment
    - Breathlessness (supine position) disappeared three days later
    - Digestive tract symptoms five days later
    - All the symptoms were basically relieved except for mild breathlessness (motion) complained by every patient



Diagnostic Changes

SpO_2

- Each patient’s SpO_2 increased day by day
- Patients were transferred from the ward to the chamber without oxygen breathing
- SpO_2 outside the chamber reflects the true degree of hypoxemia under nature breathing state
- Pre- vs. Post-HBO_2 SpO_2 shows daily improvement after HBO_2 started

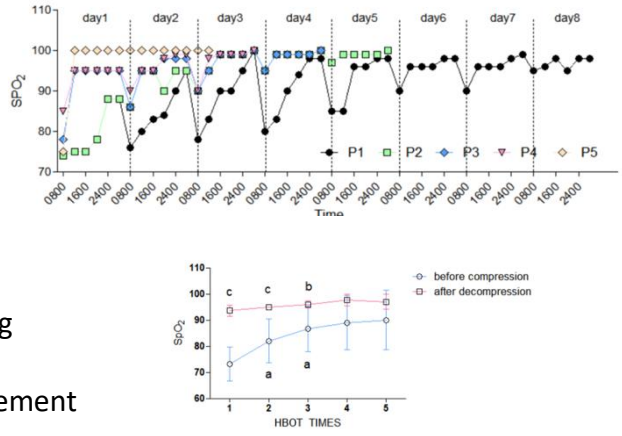


Figure 3 Changes of SpO2 beside the chamber before compression and after decompression

(a: P<0.05 vs first day before compression; b: P<0.05 vs first day after decompression; c: P<0.05 vs same day before

ABG

- PaO_2 and SaO_2 were significantly increased after HBO_2 treatments ($P<0.05$)
- Non-significant rise in $PaCO_2$ suggests that patients had a trend of over-ventilation with an inefficient oxygen uptake before introducing HBO_2
- Elevated lactate before HBO_2 was attributed to systemic anaerobic metabolism due to progressive hypoxia

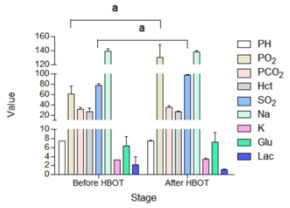


Figure 4 changes of ABG parameters before and after HBOT

CBC

- A recent paper of COVID-19 reported significantly decreased lymphocyte count in non-survivors
- Amount of lymphocyte and LYM% of each patient was obviously elevated after HBO_2 treatments
- Suggests that routine systematic addition of daily HBO_2 would reduce mortality

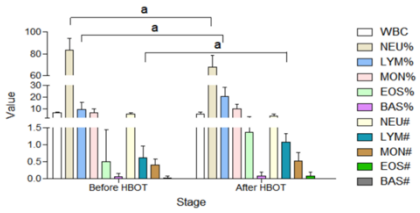
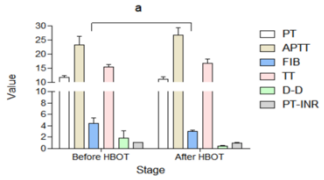


Figure 5 Changes of WBC count

Coagulation

- Fibrinogen (FIB) was increased before HBO_2, and significantly declined after HBO_2 treatment ($P<0.05$), as was D-Dimer (D-D).
- Activated partial thromboplastin time (APTT) was increased obviously after treatment.



Inflammatory markers

- Increased plasma CRP concentrations have been reported as an observed clinical feature of COVID-19
- CRP decreased after HBO_2

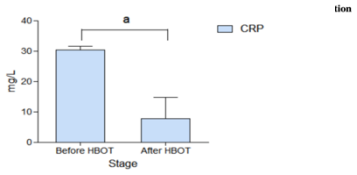
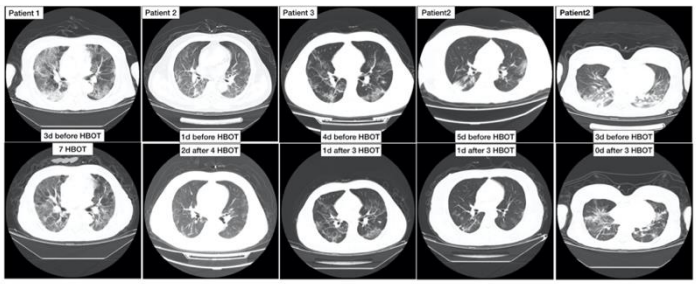


Figure 7 Changes of hs-CRP levels before and after HBOT

CT Finding

- All cases had previous imaging of mass shadows of high density in both lungs
- All Chest CTs obtained during or after HBO_2 showed significantly improved status



- Chest CT imaging suggested that the main pathological changes of COVID-19 pneumonia was inflammation of alveoli
- Patients had a loss of the lung gas exchange function larger than that of ventilatory function
- Decreased PaO_2 companied with decreased or normal $PaCO_2$

Claims

- It is suggested that HBO_2 provided the body an intermission of adequate aerobic metabolism, relieving the oxygen debt
- Two HBO_2 treatments might be enough for correcting hypoxia of most patients with severe COVID- 19
- Subsequent daily HBO_2 treatment could basically avoid hypoxemia of COVID-19 pneumonia patients with SpO_2 lower than 70%
- HBO_2 is a decisive treatment to the severe and critically ill patients with COVID-19 pneumonia
- Suggests that early additional HBO_2 may stop the patient's condition from deterioration when mask oxygen breathing could not prevent the decrease in SpO_2
- Routinely adding daily HBO_2 would reduce mortality

Comments and Critiques

- Selection criteria for hyperbaric treatment are not specified.
- The method of O_2 administration in the chamber is not described.
  - There is mention of the use of high-flow oxygen through a standard non-rebreather that would not be considered classic HBO_2 administration.
- The notion that a short period of HBO_2 will result in prolonged improvement in oxygenation is not substantiated by experience in other settings, where PO_2 decreases within minutes after decompression.
- In the case series, the decrease in lactate levels was statistically significant but was not clinically significant (only minimally elevated before HBO_2). Lactate itself does not say much about hypoxia since there are many reasons for elevation.
- The overall mortality of COVID-19 infection is less than 1%, and the usual course is clinical improvement. So, the observation that a small series of patients got better could perfectly well have been their normal course.
- Recommendations include a larger study/more case series that can draw conclusions regarding mortality and/or the possible therapeutic benefit of HBO_2.
- There is a question as to whether animal studies need to be completed since this case series has already shown that treatment was successful on humans.
- Although this case series did not show a level of evidence that one should go out and treat COVID-19 patients with HBO_2, it does warrant a larger organized trial that is well protocolized and well designed.
- This case study can be considered a feasibility report. HBO_2 has been successfully used to treat patients with COVID-19, and they did not acutely deteriorate in the chamber. The questions as to whether HBO_2 would induce pulmonary edema in these patients was not seen in this case series.

Rationale for HBO_2

Oxygenation

- PROs
  - COVID-19 disables the normal coupling of heme molecules therefore disrupting oxygenation. This functional hypoxia is similar to CO and cyanide poisoning, which are indications of HBO_2.
  - Patients with COVID-19-associated lung injury often present with severe hypoxemia and accumulated oxygen debt, in which HBO_2 could provide a reprieve.
  - Hyperbaric oxygen is likely to raise arterial PO_2 for the relatively brief period in which HBO_2 can be realistically administered.
- CONs
  - Arterial and tissue PO_2 rapidly decrease to baseline at the end of hyperbaric exposure; thus augmentation of blood and tissue oxygenation would only be transient

Attenuation of pulmonary inflammation

- PROs
  - There has been research to show that the polarization of macrophages reduces edema and in return can prolong the period of enhanced oxygenation.
  - HBO_2 could not only improve oxygen debt but also prevent the cytokine-mediated inflammatory state.
- CONs
  - The inflammatory issue is more theoretical in nature. We know that HBO_2 is anti-inflammatory in situations and indeed may be a mechanism of action. With COVID, there is no evidence for it yet.

Risks of HBO_2

- Pulmonary barotrauma
  - There is literature supporting that COVID-19 is presenting as an atypical ARDS with highly compliant lungs. There are discussions as to whether clinicians are causing lung injury secondary to the high pressures of ventilation.
  - Pulmonary barotrauma is unusual, provided any pneumothoraces have been identified and decompressed before initiating HBO_2
- Pulmonary oxygen toxicity
  - Extended exposure to above-normal oxygen partial pressures, or shorter exposures to very high partial pressures, can cause oxidative damage to cell membranes, which can lead to the collapse of the alveoli in the lungs. Tracheobronchitis and absorptive atelectasis can cause pulmonary edema, which would likely lead to acute deterioration in COVID-19 patients.
- Infection control

- Measures that have been discussed include:
    - Droplet precaution protocols
    - Patients transported to HBO_2 with oxygen via non-rebreather mask
    - All medical staff and hyperbaric technicians wear N95 masks and shields
    - Air breaks at the discretion of the supervising physician
    - Using a specific chamber for COVID-19 positive patients
    - Consider having staff pressurize in separate lock chamber to decrease exposure

Future Research

- Questions to be answered
    - How many treatments?
        - Chen case series reported two treatments to have beneficial effect on patient outcomes
        - Treatments should be limited to while the patient is hospitalized. NYU's protocol limits to a total of five treatments that can be extended for another five if clinically necessary.
    - What treatment pressure?
        - Chen case series used 2.0 ATA at 90 minutes for the first patient, and 1.6 ATA at 60 minutes for subsequent patients. There was no discussion as to why this specific protocol was chosen.
        - The NYU study will be treating patients at 2.0 ATA for 90 minutes.
        - Karolinska Institute/UCSD study will be treating patients at 2.4 ATA for 30 minutes.
    - How long for treatments?
        - Chen case series used 90 minutes for the first patient, and 60 minutes for subsequent treatments without explanation as to why.
        - NYU will be using 90 minutes.
        - Karolinska Institute/UCSD will be using 30 minutes; previous research conducted showed that gene expression changes in macrophages occurred within 15 minutes in healthy individuals.
    - How soon should HBO_2 be used?
        - There is currently no evidence to when HBO_2 should be trialed and how many treatments offered. Given the current situation of lack of ventilators, primary outcomes should include the prevention of respiratory failure and intubation.
        - However, this does not mean that HBO_2 would not work on intubated ICU patients.
        - Due to the presentation of COVID-19 patients with fulminant lung damage, timing of HBO_2 is critical and should be initiated within 3-10 days of symptoms onset if possible.
        - Protocols of current clinical trials focus on deteriorating but not yet intubated patients.

    - What is the outcome we want to effect?
        - Averting mechanical ventilation
        - Improvement of symptoms
        - Reduced mortality
        - Biochemical markers

Studies under way (see separate document listing all current studies under way)

- NYU
- Karolinska/UCSD
- Oschner
- NOLA

Position Statement

- No routine HBO_2 for COVID respiratory failure
- IRB-approved studies welcome