PROPOSED TRIAL OF HYPERBARIC OXYGEN THERAPY TO SUCCESSFULLY TREAT COVID-19 PATIENTS AND REDUCE NEED FOR MECHANICAL VENTILATION

SPECIFIC AIMS:

To successfully treat COVID-19 patients with hyperbaric oxygen therapy to prevent them from needing mechanical ventilation and to **save lives**.

INTRODUCTION:

The Nation lacks a curative treatment for COVID-19, and this has created a growing crisis resulting in suffering and strain on national resources. We are fighting a pandemic. COVID-19 is a rapidly spreading virus with **A HIGH DEATH RATE**. To date we do not have a treatment. Although many patients with COVID-19 have a mild/benign course, up to 15-20% of the patients require hospitalization, most frequently with **lung issues**. Approximately 1/3rd of hospitalized COVID-19 patients experience advancing pulmonary dysfunction related to progressive inflammation that frequently results in needing mechanical ventilation. Many of these patients with immediate need for intubation who may **require** mechanical **ventilation do not survive**. **Simply put, despite a ventilator, we cannot get enough oxygen to their tissues. Bottom line, patients are dying due to lack of oxygen because their lungs are inflamed due to the reaction to COVID-19.**

Hyperbaric oxygen therapy (HBOT) has a long history of clinical usage with an excellent safety record and known anti-inflammatory effects. **Previous studies have shown HBOT can disrupt progressive pulmonary inflammation similar to what is seen with COVID-19 patients. HBOT gets oxygen to the tissues.** In this crisis, HBOT treatment has been used with benefit in a small series of critical COVID-19 patients in China (discussed below). Based on the clinical rationale and our early experience, we propose a trial to study the use of HBOT as treatment for hospitalized patients with COVID-19 to limit progression requiring mechanical ventilatory support. We will base further trials on the success of these early results, addressing the needs for both healthcare workers as well as critically ill, ventilator dependent patients **and save lives**.

Treating patients with COVID-19 early, will prevent the need for mechanical ventilation in the majority of patients. Preventing the disease progression, will **save the lives** of many patients who are at high risk. Most importantly, we will demonstrate a treatment which will **allow** people to **return to work sooner** and **relieve hospital overcrowding**. America would not able to take care of her people should any additional strain be put on the system, such as a minor terrorist attack.

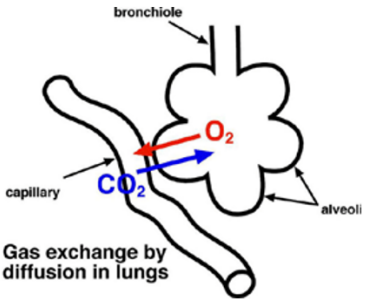
HYPERBARIC OXYGEN THERAPY:

HBOT consists of breathing 100% oxygen in either a monoplace (single person) or multiplace (multiple people or ICU bed capable) chamber. The chamber is pressurized with either oxygen (monoplace) or air (multiplace, patients have individual oxygen masks) to a range of increased atmospheric pressures, like flying in an airplane. The increase in pressure allows increased

oxygen saturation of the hemoglobin. More importantly HBOT increases the amount of dissolved oxygen in the plasma! **A 500-1200% increase in plasma oxygen (Po2)**.

NORMAL LUNG CONDITIONS

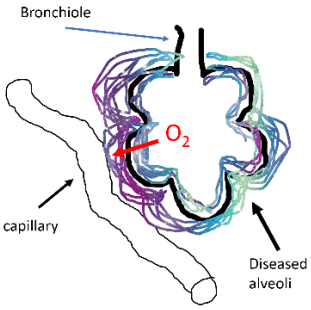
In the lungs, the balloon like alveoli fills with air from breathing. The cells are very thin, and gases easily exchange across the membrane around the alveoli and the membrane of the capillary.



COVID-19 PNEUMONITIS

The alveoli of the lungs thicken with inflammatory cells and the area between the alveoli and the capillary thickens.
Gas exchange is greatly diminished because oxygen cannot diffuse through the degree of thickening.

Patients ultimately die due to lack of oxygen throughout the body, especially the heart. Patients whose hearts work harder prior to COVID, like diabetics, patients with high blood pressure, and the elderly, are less prepared for this even greater additional work, but now with even less oxygen.



The oxygen cannot cross the diseased alveoli to get into the blood stream.

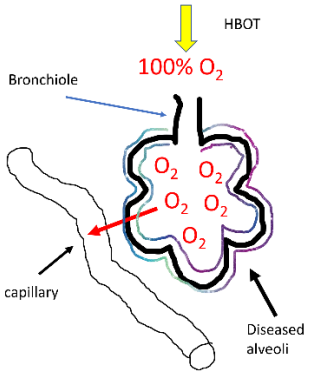
Illustration taken: https://mathbench.umd.edu/modules/cell-processes_diffusion/page23.htm

WITH HYPERBARIC OXYGEN THERAPY:

Breathing 100% oxygen under greater than atmospheric pressure increases the amount of oxygen dissolved.

Therefore the distance that oxygen can travel increases and it can cross the thickened alveoli. The oxygen distance is increased multiple fold, therefore the oxygen in the capillary is increased.

The higher than normal oxygen level also decreases the inflammatory response, helping to resolve the amount of inflammatory tissue that has to be crossed.



Oxygen gets across the thickened tissue but also decreases the thickening.

Pneumonitis, such as develops in patients due to COVID-19, prevents oxygen from being able to get into the blood stream. In this disease dissolved oxygen plays a **life-saving role,** increasing the O_2 levels in the tissues to hyperoxic, or higher than normal levels. These high oxygen levels during HBOT treatment, creates **profound anti-inflammatory responses** in the body. **HBOT works** through various pathways, especially inducible nitric oxide synthase and **HIF-1a** (hypoxia inducible factor-1alpha), **to not only mitigate the inflammatory response but also to reverse the tissue damage.**

Currently HBOT is FDA approved for 14 indications. These include carbon monoxide poisoning, compartment syndrome, osteomyelitis, diabetic foot ulcers delayed soft tissue injuries after radiation, and recently sudden hearing loss to name a few.

HBOT is readily available. There are an estimated 3,500 HBOT chambers available and ready to **start treating patients within a week or less**. Once protocols are optimized, and infectious disease protocols are in place, HBOT chambers across America can be put into action.

Additionally, large multiplace chambers can be rapidly put together in convention centers like New York and Chicago to begin treating in these field hospitals.

HBOT has been shown to treat other viruses. According to work done with the HIV virus, "Hyperbaric Oxygen Therapy (HBOT) increases the production of ROI's (reactive oxygen intermediates) throughout the body, **leaving no safe harbor for the virus to hide** outside the genome." ***(Baugh, 2000)(12).*** ROI's repeatedly have been shown to be virucidal against enveloped-viruses, like the human immunodeficiency virus (HIV)." HBOT was shown to be effective with **another virus, the BK virus.** In a study of 16 patients with hemorrhagic cystitis due to BK virus after a hematopoietic stem cell transplant, 15 of 16 patients showed **complete resolution** of the hematuria with decline of the viral titers after hyperbaric treatment ***(Savva-Bordalo, Pinho Vaz, Sousa, et al. 2012)(13).***

PRELIMINARY DATA IN HBOT USE FOR COVID-19:

A recent **report from China** has described the use of HBOT for serious/critical patients with COVID-19: "*Demonstration report on inclusion of hyperbaric oxygen therapy in treatment of COVID-19 severe cases*" from the Department of Hyperbaric Oxygen in Wuhan Yangtze River Shipping General Hospital in Wuhan, China **(1,2).**

The report presents a case series of 5 COVID-19 patients already requiring mechanical ventilation who were treated successfully with hyperbaric oxygen (2 of the patients were deemed "critical," and 3 were deemed "severe"). Their HBOT protocol used was 95-120-minute sessions once a day at 1.4-1.6 ATA for 5 days. The HBOT treatment was conducted in addition to existing comprehensive treatment in ICU, including mechanical ventilation. The report claims that "***the THERAPEUTIC EFFECT [of HBOT treatment] of 5 patients was VERY SIGNIFICANT, and both the subjective and objective clinical indexes showed that the deterioration of hypoxia was interrupted immediately and then the whole body recovered gradually after the first HBOT***."

(It is worth noting that this proposal is to treat patients ***prior*** to their need of mechanical ventilation. Our hypothesis is aggressive **early treatment will prevent the progression** of this disease. **However, toxicity is more commonly seen with prolonged exposure to 100% normobaric oxygen (Jan, 1989) (3).**

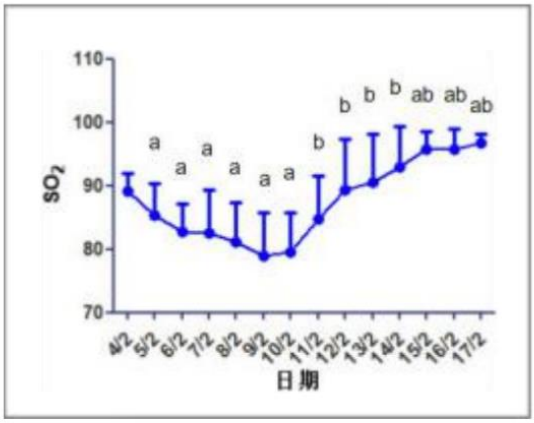
The mechanism of HBOT oxygen therapy as reported by Wuhan team:

- Oxygen transport is improved by oxygen under high pressure in the hyperbaric chamber
- HBOT has a higher diffusion rate and distance.
- HBOT increases the partial pressure of oxygen more effectively.
- HBOT is more effective than ECMO at improving cell tissue oxygen uptake.
- HBOT involves natural breathing without physical interference into the airway.
- HBOT is within the current clinical guidelines or methodologies.

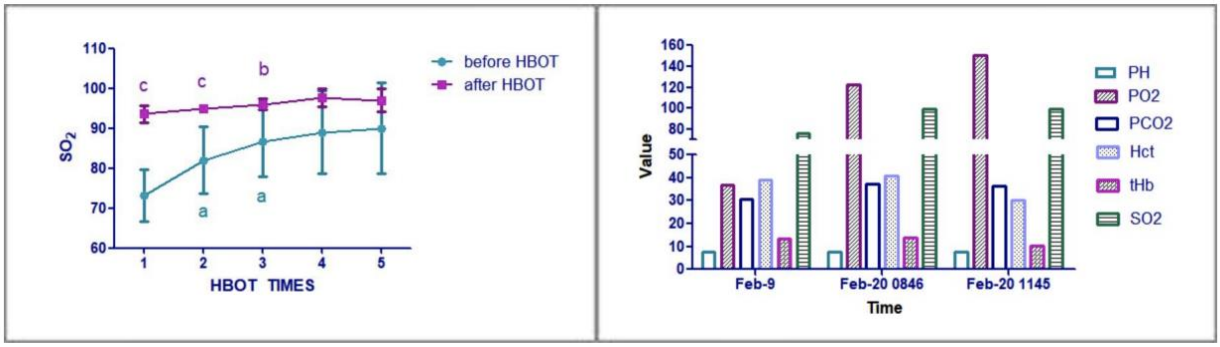
Results of the Preliminary Report from Wuhan:

The pre-HBOT treatment arterial blood PaO_2 values (with oxygen masks) of the 5 patients were 37, 65, 60, 78, and 68 mmHg respectively.

- SO_2 daily average back to 95% by the 5th day of HBOT treatment (pic 1)
- Significant upward trend in SO_2 each day (pic 2)
- Each treatment resolved total hypoxia (pic 2 left)
- Arterial blood gas index recovered (pic 2 right)
- CT scans performed 6-11 days after initial HBOT show decreased inflammation.



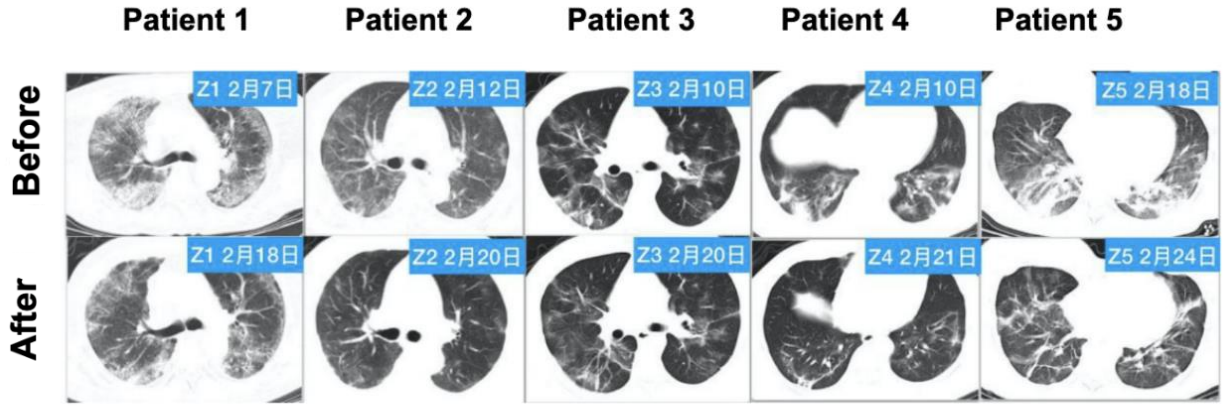
(pic 1)Changes of critical patients' SO2 before and after HBOT (11/2)



(pic 2) SpO2 daily changes and Arterial blood gas analysis of 5 patients before and after HBOT

Lung recovery per CT imaging:

"Lung CT after treatment showed that lung inflammation in all 5 patients was significantly improved"



(pic 4) CT changes before and after 4-7 HBOT in 5 patients

Other Reported Improvements:

- Relief of hypoxic symptoms, reversal of "general state"
- GI symptoms reduced; appetite restored
- Headaches relieved, "mental state improved"
- "Differential blood count… recovered gradually"

PRELIMINARY DATA IN COVID-19 WITH CONVALESCENT PLASMA:

Online in **JAMA Network, the Preliminary Communication March 27, 2020**, was the article featured in the news: "***Treatment*** *of 5 Critically Ill Patients* ***With*** *COVID-19 With* ***Convalescent Plasma****."* The article reports the response of 5 critically ill patients. At the time of publication, 2 were still hospitalized **37 days** after their dose of plasma! The other three were **discharged on day 51, 53 and 55 days**! Patients received the treatment on day 10-22, and were **still hospitalized at least 30 days after treatment**. While we do not know the full details for hospital discharge, America cannot afford the hospital beds and ventilator support for the durations of this type of treatment!

BACKGROUND RATIONALE FOR THIS PROTOCOL:

SAFETY: ***HBOT is a safe therapy***. Two studies of adverse events from 2009-2010 involved 17,267 patients, 463,293 HBOT treatments total. **The overall event rate was 0.37%.** The events and numbers are as follows: ear pain 928 patients; confinement anxiety 407 patients; hypoglycemic event 244 patients; shortness of breath 112 patients; seizure 88 patients; sinus pain 66 patients; and chest pain in 25 patients. It is worth noting that the HBOT treatments for this data were 90 minutes at 2.4 ATA. There have been no reported (oxygen toxicity) seizures for the depth and duration we propose for treatments of COVID-19 patients. Additionally, oxygen toxicity seizures are self-limiting and do not require additional work-up or treatment. Patients recover by returning to the less than 100% oxygen environment. Any patient determined to be at greater risk of a seizure can be given an air brake, which is standard procedure in all hyperbaric units.

RESPIRATORY COMPLIANCE: HBOT treatment has been **shown to improve pulmonary conditions** without impacting respiratory compliance in the treatment ranges proposed for this trial.

PULMONARY OXYGEN TOXICITY: Pulmonary oxygen toxicity is always a concern to physicians when discussing breathing 100% oxygen. **However, toxicity is more commonly seen with prolonged exposure to 100% normobaric oxygen (Jain, 1989)(3)**. Furthermore, HBOT preconditioning improved the side effects of hyperoxia that normobaric 100% oxygen can induce, as well as decreasing oxidative products and increasing antioxidant enzymes. This further supports the **anti-inflammatory effect** of **HBOT.**

RESPIRATORY INSUFFICIENCY: HBOT treatment has been shown to improve respiratory insufficiency and reverse hypoxemia, acid base disfunction, and respiratory acidosis. In a study exploring the impacts of HBOT treatment on 16 patients with restrictive or obstructive lung disease, HBOT at 1.3-1.5 ATA for 40-60 min **eliminated** hypoxemia, **rebalanced** acid-base and eliminated acidosis **in all patients (Lukich, Filimonova, and Bazarova, 1978)(6).**

INFLAMMATORY PROCESSES: HBOT treatment at 1.5 ATA has also been shown to have no adverse effects on **acute inflammatory pneumonia** with some benefit in chronic cases **(Ermakov and Barksy, 1981)(8).** Notably the authors cautioned against the use of HBOT in cases of hypercapnia. HBOT treatment also produced **positive results** of recovery **for 194 children**, ages 3 days to 3 years, with severe **pneumonias (Zhdanov et al. 1991)(9).** A combination of HBOT and antioxidants (unithiol and alpha-tocopherol) was used in a complex intensive therapy that **yielded excellent and good results in 75.8%** of patients, was ineffective in 17% of cases, and produced signs of oxygen toxicity in 7.2% of patients **(Zhdanov et al. 1991)(9).** Finally, HBOT treatment has been shown to be beneficial in lung injury in rat models. **Sahin et. al (2011)** showed that HBOT treatment at 2.4 ATA in 90-minute intervals led to a significant reduction in the activity of inducible nitric oxide synthase and a rise in the expression of surfactant protein D in lung tissue **(10).** The study further backed the potential for clinical use of HBOT **treatment for chronic inflammatory processes.**

BRIEF SUMMARY OF PROPOSED TRIAL:

The initial goal is to demonstrate in a pilot trial that HBOT can be safely and successfully used in hospitalized COVID-19 patients to (1) avoid/**reduce** the **need** for mechanical **ventilation** and (2) to thereby **reduce the overall mortality of this disease**. If the pilot trial is successful, we anticipate rapid expansion to multiple hospital based hyperbaric centers already open and functional. Based on **decades of science and clinical experience**, we believe hyperbaric oxygen (HBOT) can provide benefit to COVID-19 patients through improvement in the ability to oxygenate tissues and mitigate the inflammatory process in the lungs and **save lives**. The progressive inflammatory process in COVID-19 is the driver for the progressive pulmonary dysfunction which too frequently leads to needing mechanical ventilation. HBOT **can reduce the need** for patients requiring **mechanical ventilation** and mitigate the disease process and **address the growing nationwide ventilator shortage**. There are an estimated 3,000 monoplace hyperbaric chambers in use in the United States today that could **begin treating patients immediately.**

Once optimal treatment for preventing patients from requiring ventilator support has been established, centers with expertise in providing HBOT for intubated patients can address this patient population. Discharge dates, like those published in the convalescent plasma trial of 37 to 55 days, will be markedly reduced, **freeing up hospital beds.**

A second trial would provide our protocols for outpatient centers to **prevent patients from requiring hospitalization**. **Treating first responders** and healthcare personnel in a prophylactic way will also be an option, based on our results.

METHODS:

Study Design: A prospective repeated measures and outcome design, phase I trial.

Participants: Documented COVID-19 positive patients

The inclusion and exclusion criteria for participants will be as follows:

Inclusion Criteria:

- COVID-19 positive patients

Exclusion Criteria (any ONE of the following):

- Ventilator dependent
- Presenting to the ER in extremis
- Patients requiring immediate intubation with less than 90% or 92% oxygen saturation
- Dependent on oxygen prior to admission due to previous pulmonary disease
- Bullous lung disease
- Congestive heart failure
- Non-removable implanted devices not designed for HBOT
- Emphysema, Hypercapnia

Procedures:

1. Patients COVID-19 positive are assessed to assure not in imminent need of intubation.
2. Patient has initial lab and radiology consisting of (but not limited to)
    a. Subjective difficulty of breathing score [use FACES scale 0-10]
    b. Incentive spirometer
    c. Pulse oximetry
    d. CT scan to r/o bullous disease and be used as comparison to untreated patients
    e. ABG
    f. Chemistry, LFTs, CBC per norm
    g. Cytokine analysis if available
3. Patients/family are informed and consented.
4. Patient has HBOT treatment. Start with 1.5-2.0 ATA for 60-90 minutes. **Protocol optimized for each individual patient as is typical.**
5. After HBOT treatment, the patient has a repeat incentive spirometer, subjective pain/difficulty of breathing score. Patient is followed with a continuous pulse oximetry.
6. Plan for additional treatments 2-3 times a day as needed, watching the pulse oximetry, difficulty in breathing/respiratory rate, and incentive spirometer as guidelines with a plan to return for treatment prior to the patient's pneumonitis progressing.
7. Wean treatment frequency as tolerated and indicated. Expect patients to require only 1-5 treatments prior to being able to be discharged from the hospital.

Data Analysis:

Items of interest will be (again, not limited to):

1. Duration of each treatment.
2. Optimal depth of each treatment, or a stepwise protocol
3. Frequency of treatments
4. Total number of treatments required until resolution of symptoms (patient will not need mechanical ventilation)
5. Number of patients who do progress to need for mechanical ventilation
6. Potentially repeat CT scan at some point to objectively demonstrate improvement radiographically (not needed for all)
7. Subjective data pre and post each HBOT treatment for work of breathing
8. Pulse oximetry numbers for duration of study for each patient, comparing pre and post treatments
9. Comorbid conditions to compare to randomized or non-treated matched controls
10. Length of time until hospital discharge
11. Cost per patient compared to non-treated controls
12. Longevity study to see if fatigue and other subjective complaints resolve sooner with HBOT treatment
13. Cytokine analysis where available
14. Viral loads and immunity
15. Cost per patient compared to Hydroxychloroquine/ Plaquenil treated patients.

Timeline:

Begin immediately to curve the ventilator shortfall crisis. We should be able to recruit over 3,000 HBOT chambers in facilities across the United States with HBOT physicians educated about the protocols via webinar.

Budget:

$1 million for initial site. Anticipate 20 million to facilitate the aggressive rollout which will be a multi-institutional study at 20 sites.

PARTNERSHIPS:

We have an organization of hyperbaric providers who we will partner with to educate members and disseminate our test protocols. Expect education to be done by webinar with 24/7 availability of trained physicians to answer any questions from other facilities.

We also have exclusive agreements with two manufacturers of hyperbaric chambers capable of producing monoplace and multiplace chambers within 3 weeks of placed orders and significant numbers of used chambers that are available almost immediately.

We will explore partnerships with private investor sources to help with global outreach, and to facilitate anticipated governmental support in putting America back to work again!

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