Effects of Volatile Gaseous Compounds induced by **Hyperbaric Oxygen**, in counteracting the SARS-CoV-2 virus in asymptomatic patients and COVID-19 infection in patients with mild symptoms

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I have **no relevant financial relationships with commercial interest** to disclose.
Asymptomatic patients positive to SARS-CoV-2 & patients with COVID-19 with mild symptoms

Treated with HBO$_2$ Therapy (5 sessions, 2 ATA, 76 minutes, 1 per day)

The main endpoint is the percent of the nasopharyngeal swabs who convert to negative (at least 50% is expected)
In birds and bats (where SARS-CoV-2 is likely to originate) it is shown that Nitric Oxide (NO) inhibits viral infections such as the Low Pathogenic Avian Influenza (LPAI) and the Avian infectious laryngotracheitis (ILT).

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Birds and some bats (frugivores) like to eat fruit (like cranberries, blueberries, strawberries, mango, pomegranate and watermelons), seeds and pollen from flowers that help increase Nitric Oxide production in their body.

According to an Italian NHS report published on June 11\(^{th}\), 2020\(^{(1)}\), most of the COVID-19 deceased patients were 20 years older than SARS-CoV-2 positive patients. \(82\%\) of them had a median number of 3 concomitant diseases, correlated with the iNOS polymorphism (up to OR = 2.74, 95% CI 1.78–3.85 for coronary heart disease).\(^{(2)}\)

\[
\begin{array}{c|c|c}
\text{Number of comorbidities} & \text{Number} & \% \\
\hline
0 comorbidities & 144 & 4.2 \\
1 comorbidity & 505 & 14.7 \\
2 comorbidities & 738 & 21.5 \\
3 comorbidities and over & 2051 & 59.7 \\
\end{array}
\]

Mean number of diseases was 3.3 (median 3, SD 1.9)


This subject has a \textbf{reduced endothelial NO synthesis} that could predispose to COVID-19. \textbf{The risk is greater if the patient is a smoker, hypertensive, hypercholesterolaemia}
In the presence of comorbidities, acting as inhibitors of the synthesis of iNOS, the NO concentration is significantly reduced and it is likely that the SARS-CoV-2 virus is facilitated in damaging the body.

<table>
<thead>
<tr>
<th></th>
<th>Apparent $K_m$ ppO$_2$ (In the presence of comorbidities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOS neuronal</td>
<td>$\sim 490$ mmHg</td>
</tr>
<tr>
<td>NOS inducible</td>
<td>$\sim 130$ mmHg</td>
</tr>
<tr>
<td>NOS endothelial</td>
<td>$\sim 38$ mmHg</td>
</tr>
</tbody>
</table>

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Nitration & Oxidation

Detrimental effects:
- Tissue injury
- Oxidative stress
- Cytotoxicity (apoptosis)
- Mutagenesis/carcinogenesis

Beneficial effects:
- Antimicrobial activity
- Anti-apoptosis
- Anti-inflammatory & antioxidant effects

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Akaike T. and Maeda H. (2000), Nitric oxide and virus infection. Immunology, 101: 300-308. doi:10.1046/j.1365-2567.2000.00142.x
Excessive “oxidative stress” could facilitate contagion

Up-regulation of the ACE2 receptors expression and Cytokines genes by reducing the DNA methylation (it's like releasing the brake)

Hypomethylation of Interferon-regulated genes, NFkB and Cytokine genes

Cytokines storm

Oxidative Stress

In addition, peroxynitrite (ONOO-), a free radical deriving from NO, can promote viral mutagenesis under selective pressure.

The repeated variation in partial pressure of oxygen (by HBO$_2$T) upregulates the Hypoxia Inducible Factor, HIF which promotes the expression of human antiviral peptides: defensins and cathelicidins (such as CRAMP) **effective to block the** coated, positive-sense, single-stranded RNA **virus** (such as SARS-CoV-2).

Therefore **it is important to alternate pure oxygen breathing with breaks in medical air.**
<table>
<thead>
<tr>
<th></th>
<th>0-10</th>
<th>10 meters / 2 ATA/ 196,13 kPa</th>
<th>10-0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depth (meters)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oxygen (minutes)</strong></td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Medical Air (minutes)</strong></td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Run Time (minutes)</strong></td>
<td>8</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

- Depth: 0-10 meters, 10 meters / 2 ATA/ 196,13 kPa, 10-0 meters
- Oxygen: 8, 12, 12, 12, 12, 12, 12, 8 minutes
- Medical Air: 4, 4, 4, 4, 4, 4, 4, minutes
- Run Time: 8, 20, 24, 36, 40, 52, 56, 68, 76 minutes
• the amount of NO supplied by nutrition (nutraceutical approach) is not efficient in patients with different comorbidities

• NO donors are difficult to use due to their short biological lifetime, instability during storage and potential toxicity (such as the production of methemoglobin which does not transport oxygen).

On the contrary, HBO₂T allows to finely modulate the synthesis of NO, without side effects.
The aim of the pilot study is to have patients:

- asymptomatic SARS-CoV-2 positive or with mild symptoms of COVID-19 infection,
- with genetic polymorphism of Nitric Oxide Synthase (NOS) and 2 or more comorbidities,
- with negative nasopharyngeal swabs and healed from mild symptoms after HBO₂T.
AIFA (Italian Medicines Agency) considers the idea acceptable but has not, at the moment, authorized the study claiming that the HBOT is not applicable on a national scale.

The scientific studies on which the project is based are public and we are available for collaboration with anybody in the World.

Thank you
Efficacy and Safety of Hyperbaric oxygen for patients with COVID-19

- rationale and protocol of the randomized controlled trial COVID-19-HBO

Anders Kjellberg, MD, DESA, EDIC

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Declaration of Competing Interests

- The authors have no relevant relationships with commercial interests to resolve.
Introduction- Background

- SARS-CoV-2 affects the innate immune response and activates an inflammatory cascade.
- Patients with risk factors such as diabetes and hypertension have increased risk of severe disease with inflammation out of control.
- Hyperbaric oxygen (HBO₂) has proven anti-inflammatory effects.
The Overall Hypothesis

- HBO₂ may reduce mortality, increase hypoxia tolerance and prevent organ failure in patients with COVID-19 pneumonitis by reducing the inflammatory response.
- Patients die from the inflammatory response not the virus.
Objectives

- **Primary objective:** evaluate if HBO₂ reduces the number of ICU admissions compared to best practice for COVID-19.
- **Main secondary objectives:** evaluate if HBO₂ reduces the load on ICU resources, morbidity and mortality in severe cases of COVID-19.
- **Other objectives** are to evaluate safety and evaluate if HBO₂ mitigates the inflammatory reaction in COVID-19.
The Clinical trial (NCT04327505)

- “A Randomized, Controlled, Open-Label, Multicenter Clinical Trial to explore Safety and Efficacy of Hyperbaric Oxygen for preventing ICU admission, Morbidity and Mortality in Adult Patients With COVID-19”

- Population: 200 adults, moderately severe COVID-19, admitted to hospital,
  → require oxygen (equivalent to Moderate ARDS without PEEP)
  → at least two risk factors for increased morbidity/mortality
Study design

Study design

Visit 1 2 3 4 5 6 7 8 9
HBO + Best practice N= 100

Day 1 2 3 4 5 6 7 14 30
Randomization End of trial
HBO HBO HBO HBO HBO HBO HBO

Treatments can be distributed differently depending on clinical effect and available resources.
Intervention

- Intervention: HBO\textsubscript{2} 1.6-2.4 ATA, 30-60 min, max 5 treatments in the first 7 days.
- Control: Best practice for COVID-19 pneumonitis
Endpoints

- **Primary endpoint:** ICU admission
- **Main secondary endpoints:** 30-day mortality, time-to-intubation, time-to-ICU, mean change in inflammatory response
- **Safety, other efficacy- and explanatory endpoints:** AE/SAE, change in vital parameters, oxygen requirement, change in biomarkers (clinical and experimental, including microRNA in plasma, RNA sequencing, lymphocyte- and macrophage profiling)
Strengths and weaknesses

- Online e-CRF (SmartTrial) and randomizing tool (Randomize.NET)
- ICH-GCP compliant
- "Dose-span" allow most centers to use "local routines"

- "Pragmatic design" - open label and no placebo
- Power calculation according to evidence available in March
- "Local routines" may produce heterogeneous data
Lessons learnt

- Expensive and time-consuming to plan multicenter RCTs
- Difficult to "sell in" to University hospitals
- More case series/ prospective cohort studies are needed
Conclusion

- RCTs are needed to prove the effect
- A positive result would make a strong argument to scale this treatment for general use against COVID-19
- A positive result of an RCT for COVID-19 would be a "once in a lifetime" opportunity to put hyperbaric oxygen into the limelight
Hyperbaric Oxygen Therapy in Preventing Mechanical Ventilation in COVID-19 Patients: A Multicenter Case Series

Kerry T. Thibodeaux, MD, FACS, CWSP, FAPWCA
“I have no relevant financial relationships with commercial interests to disclose”
NEW HYPERBARIC TREATMENT AVAILABLE FOR COVID PATIENTS
Objectives

- Review cases of HBOT & Covid-19 patients in Opelousas, LA
- Review number of centers and patients treated in multicenters
Processes & Protocol

- 13 Covid-19 patients treated with HBOT
- Initiated HBOT on April 13, 2020 - May 14, 2020 (12 patients)
- Patient 13 began June 13, 2020
- 64 HBO Treatments
- 9 fully recovered and discharged from hospital
- 3 deaths
- Age Range: 39-80
- 9 Females: 6 African American, 3 Caucasian
- 4 Males: 1 African American, 3 Caucasian
- Protocol: HBO consult sent from Hospitalist and Critical Care Pulmonologist—FI O2 >50 and tachypnea.
- HBOT: 2.0 ATA X 90 minutes daily
Covid-19 Case 1

- 47 y/o Female—Black/African American—OGHS Employee
- Comorbidities: HTN, Obesity, Sleep Apnea, Viral Pneumonia, Covid-19
- ICU
- Blood Type: AB Negative
- Tachypnea
- Vapotherm—FI O2 100% trended down daily
- D-Dimers: 21,079 down to 1,667
- CRP 23.6 down to 8.3
- 5 HBOT—2.0 ATA x 90 min
Covid-19 Case 2

- 62 y/o Female—Black/African American—OGHS Employee
- ICU
- Blood Type: O Positive
- Tachypnea—
- Vapotherm—Fi O2 100% trended down daily
- D-Dimers: 3,200 down to 785
- CRP 12.8 down to 0.6
- 3 HBOT—2.0 ATA x 90 min
Covid-19 Case 3

- 58 y/o Male—Caucasian
- Comorbidities: DM, HTN, Viral Pneumonia, Covid-19
- ICU
- Admit/Discharge—4/10/20—5/13/20
- Blood Type: O Negative
- Tachypnea
- Vapotherm—FI O2 100% trended down daily
- D-Dimers: 4,533 down to 1659
- CRP 30.3 down to 13.7
- Convalescent Plasma
- 11 HBOT—2.0 ATA x 90 min
Covid-19 Case 4

- 42 y/o Female—Black/African American
- Comorbidities: Obesity, Hypoxia, Covid-19
- Covid Isolation Unit
- Blood Type: O Positive
- Tachypnea
- O2 @ 4L/min---decreased to 2L/min after HBOT
- D-Dimers: 3,220 down to 1010
- CRP 102.75
- 1 HBOT—2.0 ATA x 90 min
Covid-19 Case 5

- 38 y/o Female—Caucasian
- Comorbidities: HTN, DM, Obesity, Hypoxia, Covid-19
- Covid Isolation Unit
- Admit/Discharge—4/17/20–4/20/20
- Blood Type: Unknown
- Tachypnea
- O2 @ 4L/min trended down to 2L/min after 2 HBOT
- D-Dimers: 483 down to 360
- CRP 8.6
- 3 HBOT—2.0 ATA x 90 min
Covid-19 Case 6

- 69 y/o Male—Caucasian
- Comorbidities: HTN, Obesity, Anemia, DVT, Viral Pneumonia, Covid-19
- ICU
- Admit/Discharge—4/19/20—5/1/20
- Blood Type: Unknown
- Tachypnea
- Vapotherm—FI O2 70% trended down daily
- D-Dimers: 60,208 down to 3,971
- CRP 20.5 down to 3.4
- 3 HBOT—2.0 ATA x 90 min
Covid-19 Case 7

- 79 y/o Female—African American
- Comorbidities: HTN, Obesity, Anemia, DVT, Viral Pneumonia, Covid-19
- ICU
- Blood Type: Unknown
- Tachypnea
- Vapotherm—FI O2 100%
- D-Dimers: 998 up to 4.59
- CRP 7.1 up to 16.3
- 2 HBOT—2.0 ATA x 90 min
- PE after second HBOT
Covid-19 Case 8

- 64 y/o Female—Caucasian
- Comorbidities: HTN, Obesity, Viral Pneumonia, Covid-19
- ICU
- Blood Type: O Negative
- Tachypnea
- Vapotherm—Fi O2 100%
- D-Dimers: 4,010 down to 4369
- CRP: 439 down to 4.1
- 8 HBOT—2.0 ATA x 90 min
Covid-19 Case 9

- 53 y/o Male—Caucasian
- Comorbidities: HTN, DM, Hyperlipidemia, Viral Pneumonia, Covid-19
- ICU
- Blood Type: A Positive
- Tachypnea
- Vapotherm—FI O2 100%
- D-Dimers: 2,204 down to 369
- CRP 21.4 down to 0.5
- 10 HBOT—2.0 ATA x 90 min
Covid-19 Case 10

- 71 y/o Female—African American
- Comorbidities: HTN, DM, Viral Pneumonia, Covid-19
- ICU
- Blood Type: A Positive
- Tachypnea
- Vapotherm—FI O2 100%
- D-Dimers: 1,336 up to 3,519
- CRP 4.4 up to 11.8
- 2 HBOT—2.0 ATA x 90 min
Covid-19 Case 11

- 71 y/o Female—African American
- Comorbidities: HTN, DM, Viral Pneumonia, Covid-19
- ICU
- Admit/Discharge—4/26/20—Died 5/04/20
- Blood Type: O Negative
- Tachypnea
- Vapotherm—Fi O2 90%
- D-Dimers: 911 up to 6,095
- CRP 27.5 up to 29.1
- 4 HBOT—2.0 ATA x 90 min
**Covid-19 Case 12**

- 59 y/o Female—African American
- Comorbidities: HTN, Asthma, PVD, DM, Viral Pneumonia, Covid-19
- ICU
- Blood Type: O Positive
- Tachypnea
- Vapotherm—FI O2 100%
- D-Dimers: 2,079 down to 294
- CRP 22.0 down to 8.5
- 7 HBOT—2.0 ATA x 90 min
Covid-19 Case 13

- 59 y/o Male—African American
- Comorbidities: HTN, Asthma, PVD, DM, Viral Pneumonia, Covid-19
- ICU
- Admit/Discharge—6/11/20—
- Blood Type: B Positive
- Tachypnea
- Vapotherm—FI O2 75%
- D-Dimers: 3,793 down to 2,084
- CRP 11.9
- 3 HBOT—2.0 ATA x 90 min
• Developed an app to collect HBOT_COVID data into the Tissue Analytics data base.

• 14 Sites Enrolled
• 3 active sites
Hyperbaric Oxygen Therapy for COVID-19: Treated Cases versus Propensity-Matched Controls

David C. Lee, MD, MS
NYU School of Medicine

Scott Gorenstein, MD
NYU Winthrop Hospital

Evidence Review for HBO2 Treatment of COVID-19 Webinar
The Undersea and Hyperbaric Medicine Society
June 20th, 2020
Disclosures

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• Jenica McMullen, MD
• Marcela Osorio, BA
• Christian Koziatek, MD
• David C. Lee, MD, MS
Study Design

- Single-center clinical trial of COVID-19 patients at NYU Winthrop Hospital from March 31 to April 28, 2020

- Cases received hyperbaric oxygen therapy at 2.0 ATM of pressure in monoplace hyperbaric chambers for 90 minutes daily for a maximum of five total treatments

- Controls identified using propensity score matching among COVID-19 patients admitted during the same time period

- Using competing-risks regression to perform a survival analysis, we studied our primary outcome of inpatient mortality and secondary outcome of mechanical ventilation
Preliminary Results

- 20 COVID-19 treated cases
  - Aged 30 to 79 with hyperbaric oxygen, with an oxygen requirement ranging from 2 to 15 liters on hospital days 0 to 14
  - Of these 20 patients, two (10%) were intubated and died, and none remain hospitalized

- 60 propensity-matched controls
  - Matched based on age, sex, body mass index, coronary artery disease, troponin, d-dimer, hospital day, and oxygen requirement
  - Of these 60 patients, 18 (30%) were intubated, 13 (22%) have died, and five (8%) remain hospitalized (two of whom are still on mechanical ventilation)
## Cases and Controls

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Treated Cases (20)</th>
<th>Matched Controls (60)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>58.4</td>
<td>60.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Median</td>
<td>58</td>
<td>62</td>
<td>0.42</td>
</tr>
<tr>
<td>Range</td>
<td>30 to 79</td>
<td>24 to 80</td>
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</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (90%)</td>
<td>55 (92%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (35%)</td>
<td>16 (27%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Black</td>
<td>3 (15%)</td>
<td>10 (17%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5%)</td>
<td>6 (10%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (45%)</td>
<td>28 (46%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body-Mass-Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>29.7</td>
<td>29.0</td>
<td>0.63</td>
</tr>
<tr>
<td>Median</td>
<td>28.0</td>
<td>28.5</td>
<td>0.72</td>
</tr>
<tr>
<td>Range</td>
<td>19 to 42</td>
<td>23 to 44</td>
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<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hypertension</td>
<td>10 (50%)</td>
<td>24 (40%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (30%)</td>
<td>27 (45%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (30%)</td>
<td>22 (37%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (5%)</td>
<td>2 (3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>2 (10%)</td>
<td>7 (12%)</td>
<td>1.00</td>
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<tr>
<td><strong>Hospital Day Before Treatment</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Average</td>
<td>3.0</td>
<td>2.8</td>
<td>0.83</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>1</td>
<td>0.71</td>
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<tr>
<td>Range</td>
<td>0 to 14</td>
<td>0 to 14</td>
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<tr>
<td>Day 0 to 1</td>
<td>10 (50%)</td>
<td>33 (55%)</td>
<td></td>
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<tr>
<td>Day 2 to 4</td>
<td>5 (25%)</td>
<td>14 (23%)</td>
<td></td>
</tr>
<tr>
<td>Day 5 to 14</td>
<td>5 (25%)</td>
<td>13 (22%)</td>
<td></td>
</tr>
</tbody>
</table>
## Cases and Controls

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<th>Treated Cases (20)</th>
<th>Matched Controls (60)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Oxygen Requirement</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Average</td>
<td>8.6</td>
<td>7.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Median</td>
<td>6.5</td>
<td>5.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Range</td>
<td>2 to 15</td>
<td>1 to 15</td>
<td></td>
</tr>
<tr>
<td>1 to 5 Liters</td>
<td>7 (35%)</td>
<td>32 (53%)</td>
<td></td>
</tr>
<tr>
<td>6 to 11 Liters</td>
<td>6 (30%)</td>
<td>8 (14%)</td>
<td></td>
</tr>
<tr>
<td>12 to 15 Liters</td>
<td>7 (35%)</td>
<td>20 (33%)</td>
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<tr>
<td>Baseline Laboratory Values</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Troponin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>20 (100%)</td>
<td>60 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>D-Dimer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>1142</td>
<td>1870</td>
<td>0.61</td>
</tr>
<tr>
<td>Median</td>
<td>375</td>
<td>389</td>
<td>0.66</td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Average</td>
<td>1490</td>
<td>1382</td>
<td>0.71</td>
</tr>
<tr>
<td>Median</td>
<td>1265</td>
<td>1151</td>
<td>0.46</td>
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<tr>
<td>C-reactive Protein</td>
<td></td>
<td></td>
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<tr>
<td>Average</td>
<td>120</td>
<td>137</td>
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<tr>
<td>Median</td>
<td>108</td>
<td>125</td>
<td>0.56</td>
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<tr>
<td>Lactate Dehydrogenase</td>
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<td></td>
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<tr>
<td>Average</td>
<td>496</td>
<td>475</td>
<td>0.70</td>
</tr>
<tr>
<td>Median</td>
<td>460</td>
<td>436</td>
<td>0.43</td>
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<tr>
<td>Other COVID-19 Treatments/Trials</td>
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<td></td>
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<tr>
<td>Azithromycin</td>
<td>16 (80%)</td>
<td>53 (88%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>18 (90%)</td>
<td>59 (98%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Anti-IL6 Immunomodulator</td>
<td>12 (60%)</td>
<td>26 (43%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Convalescent Plasma</td>
<td>4 (20%)</td>
<td>6 (10%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Inpatient Mortality Stratified by Oxygen Requirement

![Inpatient Mortality Graph](image)
Mechanical Ventilation Stratified by Oxygen Requirement

![Graph showing mechanical ventilation stratified by oxygen requirement.](image-url)
Survival Analysis

• Assuming, no further deaths among controls:

  • The adjusted subdistribution hazard ratio for inpatient mortality was 0.37 (p = 0.13, 95% CI of 0.10 to 1.37)

  • The adjusted subdistribution hazard ratio for mechanical ventilation was 0.26 (p = 0.046, 95% CI of 0.07 to 0.98)
Survival Analysis for Inpatient Mortality

[Graph showing cumulative incidence of inpatient mortality over study days for HBOT treated cases and propensity matched controls.]
Survival Analysis for Mechanical Ventilation

![Graph showing survival analysis for mechanical ventilation.](image-url)
Conclusions

• Our preliminary findings suggest that HBO2 may reduce the high mortality and the need for mechanical ventilation among COVID-19 patients

  • Cases treated with HBO2 who died highlight the importance of safety protocols to manage critically ill COVID-19 patients

• Further study of HBO2 for COVID-19 is needed through a multi-center randomized controlled trial
## Cases Treated with HBO2

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Past Medical History</th>
<th>Oxygen Needs Prior to HBO2 Therapy</th>
<th>Hospital Day of First HBO2 Therapy</th>
<th>HBO2 therapy Sessions Received</th>
<th>Patient Outcome or Current Status (Hospital Day)</th>
<th>Other COVID-19 Therapies Received</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>43 M</td>
<td>None</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Discharged (4)</td>
<td>AZITH, HCQ</td>
<td>Declined additional treatments</td>
</tr>
<tr>
<td>62 M</td>
<td>HTN, HLD, DM, ASTHM</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>Discharged (8)</td>
<td>AZITH, HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>54 M</td>
<td>None</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>Discharged (12)</td>
<td>AZITH, HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>56 F</td>
<td>HTN</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>Discharged (7)</td>
<td>PLASMA</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>79 M</td>
<td>HTN</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>Discharged (10)</td>
<td>HCQ, anti-IL6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>54 M</td>
<td>None</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>Discharged (9)</td>
<td>AZITH, HCQ</td>
<td>Limited sessions due to technician availability</td>
</tr>
<tr>
<td>57 M</td>
<td>HTN, HLD, DM</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>Discharged (12)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Discontinued due to ear pressure</td>
</tr>
<tr>
<td>30 M</td>
<td>None</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>Discharged (10)</td>
<td>AZITH, HCQ</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>54 M</td>
<td>None</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>Discharged (9)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>58 M</td>
<td>None</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>Discharged (4)</td>
<td>HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>55 M</td>
<td>DM</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>Discharged (12)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>67 M</td>
<td>HTN, DM</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>Discharged (12)</td>
<td>anti-IL6, PLASMA</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>55 M</td>
<td>None</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>Discharged (7)</td>
<td>AZITH, HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>75 M</td>
<td>None</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>Discharged (38)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Discontinued due to study pause and then deemed medically unstable</td>
</tr>
<tr>
<td>32 M</td>
<td>None</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>Discharged (9)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>58 F</td>
<td>HTN, CAD</td>
<td>15</td>
<td>1</td>
<td>3</td>
<td>Discharged (10)</td>
<td>AZITH, HCQ, anti-IL6, PLASMA</td>
<td>Discontinued due to study hold pending safety review for a different patient</td>
</tr>
<tr>
<td>60 M</td>
<td>HTN, HLD, CAD</td>
<td>15</td>
<td>15</td>
<td>4</td>
<td>Discharged (24)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Discontinued due to study hold pending safety review for a different patient</td>
</tr>
<tr>
<td>68 M</td>
<td>HTN, HLD, DM</td>
<td>15</td>
<td>0</td>
<td>5</td>
<td>Intubated (12), Death (35)</td>
<td>AZITH, HCQ, anti-IL6, PLASMA</td>
<td>General anesthesia for removal of large thromboembolism</td>
</tr>
<tr>
<td>73 M</td>
<td>HTN, HLD, DM</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>Discharged (14)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Discontinued due to epistaxis</td>
</tr>
<tr>
<td>77 M</td>
<td>HTN, HLD</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>Intubated (3), Death (25)</td>
<td>AZITH, HCQ, anti-IL6</td>
<td>Hypoxic arrest while off oxygen</td>
</tr>
</tbody>
</table>
The recent COVID-19 pandemic produced extreme demands for hospitalizations and equipment, with depletion of critical care resources. Current therapies provide limited clinical relief and a robust vaccination program is not yet available. Therefore, several empirical investigations were initiated with intermittent hyperbaric oxygen therapy (HBO2) to overcome the relentless and progressive hypoxemia that is often refractory to maximal ventilator support of intubated patients. However, more recently, less severe patients at the edge of impending hypoxemia were exposed to HBO2, which prevented intubation and obtaining the rapid resolution of symptoms. With this summary we illustrate the possible biological mechanisms of action of HBO2 in COVID-19 patients.

We performed a scoping review, gathering the most valuable evidences supporting mechanisms of action of HBO2 and possible overlaps with COVID-19 pathophysiology.

**Introduction**

The recent COVID-19 pandemic produced extreme demands for hospitalizations and equipment, with depletion of critical care resources. Current therapies provide limited clinical relief and a robust vaccination program is not yet available. Therefore, several empirical investigations were initiated with intermittent hyperbaric oxygen therapy (HBO2) to overcome the relentless and progressive hypoxemia that is often refractory to maximal ventilator support of intubated patients. However, more recently, less severe patients at the edge of impending hypoxemia were exposed to HBO2, which prevented intubation and obtaining the rapid resolution of symptoms. With this summary we illustrate the possible biological mechanisms of action of HBO2 in COVID-19 patients.

**Materials and methods**

We performed a scoping review, gathering the most valuable evidences supporting mechanisms of action of HBO2 and possible overlaps with COVID-19 pathophysiology.

**Results and Discussion**

HBO2 acts increasing the amount of oxygen in the plasma and peripheral tissues. Possible direct effects of HBO2 on viruses are still uncertain but, in COVID-19 patients, hyperoxia could mobilize stem cells, block the inflammatory cascade, interfere with interstitial fibrosis development in the lungs, delay the onset of severe interstitial pneumonia, and reduce the risk of MOF due to an overall abated SARS-CoV-2 viral load. HBO2 proved to reduce interleukins levels, specifically of IL-1 beta, IL-6, IL-8, and TNF-alfa, all involved in the development of pulmonary fibrosis. Moreover, the increased production of nitrogen oxide during HBO2 can increase vasodilation and reduce platelets activation, potentially hampering the pro-coagulant state encountered by COVID-19 patients. HBO2 also seems to preserve the antioxidant capacity of lymphocytes, thus protecting the resilience of the immune system that is known to be impaired in COVID-19 cases. Potential, known adverse effects of HBO2 – such as oxygen pulmonary toxicity, hyperoxic seizures, or transient visual impairment – are preventable and rare at pressures currently used.

**Conclusions**

In this period, it seems reasonable to take every possible method into account to take care of COVID-19 patients. Despite its possible beneficial effects, the role of HBO2 in COVID-19 patients still need to be demonstrated with properly designed trials. Therefore, when using HBO2, clinicians should weigh possible benefits with potential damages and risks.