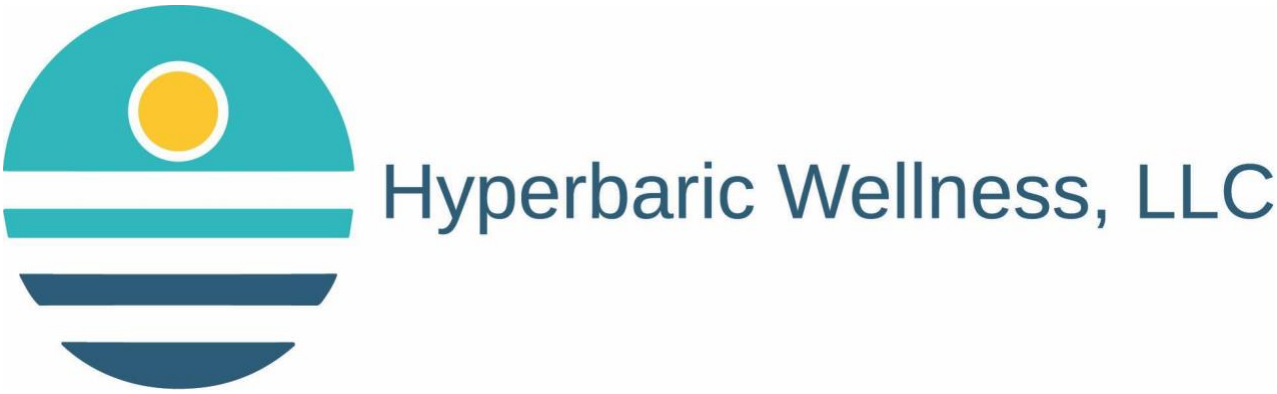

Hyperbaric Oxygen Therapy for Long COVID: A Review of the Scientific Evidence

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Executive Summary

Hyperbaric oxygen therapy (HBOT or HOT) has emerged as a promising treatment for long COVID (LoCo), a condition characterized by persistent and debilitating symptoms following SARS-CoV-2 infection. This comprehensive analysis explores the mechanisms and clinical evidence supporting the efficacy of HBOT/HOT in addressing the complex pathophysiology underlying long COVID.

Mechanisms of Action:

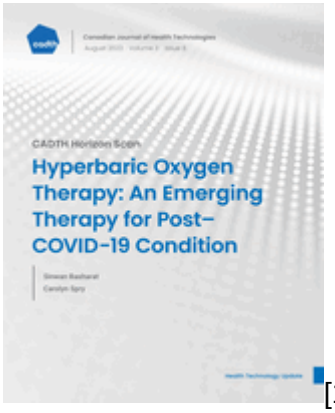
- Anti-inflammatory effects: HBOT reduces pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and elevates anti-inflammatory IL-10
- Endothelial protection: Improves endothelial function, enhances nitric oxide bioavailability, and attenuates oxidative stress
- Anti-thrombotic effects: Decreases platelet aggregation, reduces fibrin deposition, and enhances fibrinolysis
- Neuroplasticity: Stimulates stem cell mobilization, mitochondrial biogenesis, and synaptic plasticity

Clinical Evidence:

- Randomized controlled trials demonstrate significant improvements in fatigue, cognitive function, attention, and quality of life
- Case studies report reduced inflammation, oxidative stress, and enhanced lung function in long COVID patients
- Durable benefits observed up to 1 year post-treatment, with greatest improvements in most disturbed domains

The scientific evidence continues to pour in and shows why HBOT works for treating long COVID. By targeting the underlying pathophysiology, including inflammation, endothelial dysfunction, and microvascular thrombosis HBOT is reversing the effects of long COVID and with it, bringing hope to estimated $50 millions Americans suffering from these associated debilitating symptoms.

Hyperbaric Oxygen Therapy (HOT) Improves Long COVID Symptoms



[1]

A recent study at University Hospitals Coventry and Warwickshire NHS Trust evaluated the effects of HOT on long COVID-related fatigue and cognitive impairment in 10 patients who received 10 sessions of HBOT at 2.4 atmospheres over 12 days. [6] Each 105-minute treatment session consisted of three 30-minute exposures to 100% oxygen, interspersed with 5-minute air brakes.[6] Validated assessments performed at day 1 and 10 revealed statistically significant improvements in the Chalder fatigue scale (p=0.0059; d=1.75(very large)), global cognition (p=0.0137; d=−1.07 (large)), executive function (p=0.0039; d=−1.06 (large)), attention (p=0.0020; d=−1.2*d* (very large)), information processing (p=0.0059; *d*=−1.25 (very large)), and verbal function (p=0.0098; d=−0.92 (large)).[6]

These findings suggest HOT does provide substantial relief for the debilitating fatigue and cognitive symptoms experienced by long COVID patients, although further research with larger sample sizes is needed to confirm these initial results.[6]

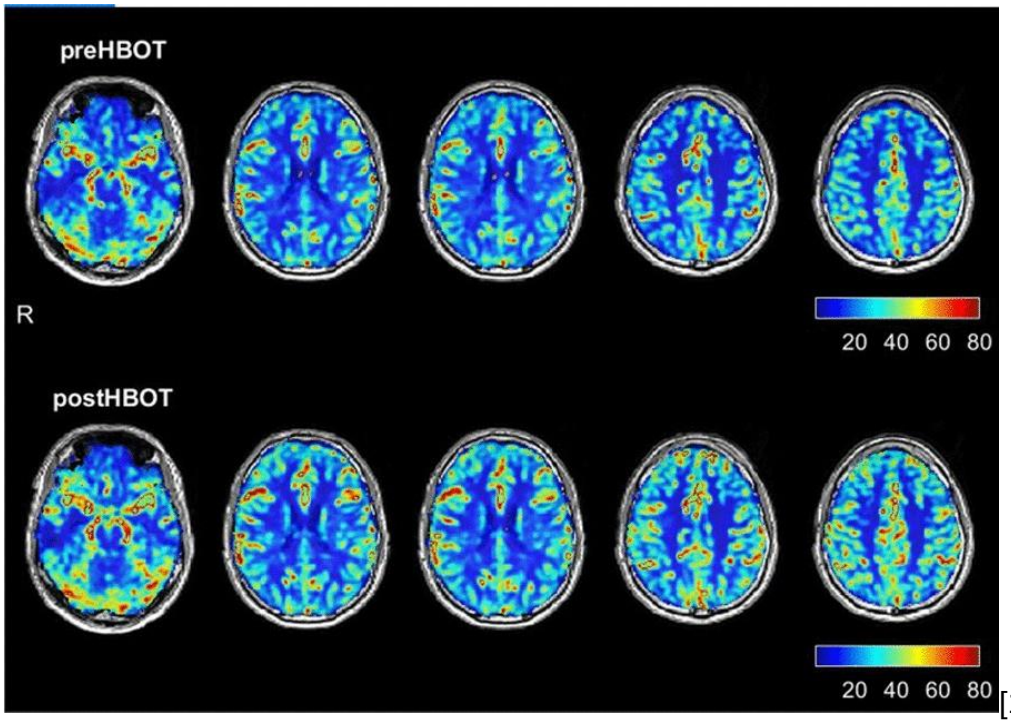
Sources:

[1] ncbi.nlm.nih.gov
]2]https://www.pharmacytimes.com/view/hyperbaric-oxygen-therapy-may-be-the-first-only-clinically-effective-treatment-for-long-covid
[3]https://www.cognitivefxusa.com/blog/hyp hyperbaric-oxygen-therapy-for-covid-long-haulers
[4]https://www.hyperbaricmedicalsolutions.com/blog/hyperbaric-oxygen-a-promising-treatment-for-long-hauler-covid

[5] https://www.frontiersin.org/articles/10.3389/fmed.2024.1354088/full

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8806311/

Long term outcomes of hyperbaric oxygen therapy in post covid- condition



[1]

Image: Brain perfusion magnetic resonance imaging before and after hyperbaric oxygen therapy. The upper row represents brain perfusion 3 months after the acute infection, before hyperbaric oxygen therapy. The lower row represents the perfusion magnetic resonance imaging done after completing the hyperbaric oxygen therapy protocol.

Massive image-based profiling of circulating platelets and platelet aggregates in COVID-19 patients has provided novel insights into the underlying process of COVID-19-associated microvascular thrombosis.

Analysis of image data from 110 hospitalized patients showed the anomalous presence of excessive platelet aggregates in nearly 90% of COVID-19 patients, with strong links between the concentration of platelet aggregates and disease severity, mortality, and respiratory condition.[1] High-dimensional analysis based on deep learning further indicated that COVID-19 behaves as a systemic thrombotic disorder.[1]

These findings align with autopsy reports showing widespread thrombotic microangiopathy characterized by extensive diffuse microthrombi within peripheral capillaries and arterioles in lungs, hearts, and other organs, resulting in multiorgan failure.[1][2][5] The distinct composition of these microthrombi, with increased fibrin and complement factor C5b-9 deposition, suggests thrombo inflammation as a key driver of microvascular occlusion in severe COVID-19.[5][6] Endothelial glycocalyx degradation, alterations in blood flow and viscosity, neutrophil extracellular trap formation, and microparticle shedding further contribute to endothelial damage and microthrombosis.[5][6]

Table 1: Brain blood flow changes before and after hyperbaric oxygen therapy

Brain region	Pre-HBOT	Post-HBOT	Change in %
White matter right (R)	19.43	22.89	17.80
White matter left (L)	19.17	22.23	16
Gray matter R	32.34	38.6	19.40
Gray matter L	33.3	38.91	16.80
Primary gustatory cortex R	34.22	47.43	38.60
Lateral postcentral gyrus R	32.08	42.79	33.40
Superior temporal gyrus R	38.04	50.65	33.10
Supramarginal gyrus R	36.37	46.39	27.60
Anterior cingulate cortex L	40.16	50.61	26

Inferior frontal gyrus L	39.47	49.6	25.70
Inferior frontal gyrus (Broca's area) R	37.55	46.81	24.70
Medial frontal gyrus R	29.57	36.67	24

[7]

The study showed the anatomical areas of increased blood flow correlated to the functional improvement in cognitive ability (e.g. memory, concentration…etc.).

Sources:

[1]https://media.springernature.com/lw1200/springer-static/image/art%3A10.1186%2Fs13256-022-03287-w/MediaObjects/13256_2022_3287_Fig1_HTML.jpg

[2]https://www.medrxiv.org/content/10.1101/2021.04.29.21256354v2.full

[3]https://www.acc.org/Latest-in-Cardiology/Articles/2021/01/25/14/28/Microvascular-Thrombi-in-COVID-19

[4]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9916726/

[5]https://pubmed.ncbi.nlm.nih.gov/36768817/

[6]https://thorax.bmj.com/content/76/4/412

[7] https://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-022-03287-w

Patient Success Stories with HBOT

Video[1]

Several long COVID patients have reported significant improvements in their symptoms and quality of life after undergoing HBOT. For instance, a COVID-19 long hauler who received treatment at Sara's Garden, a hyperbaric oxygen therapy center, experienced a remarkable reduction in fatigue, brain fog, and pain following 40 HBOT sessions. [4] Another study documented the case of a previously healthy 55-year-old male with long COVID who, after receiving 10 HBOT sessions at 2.4 atmospheres over 12 days, showed statistically significant improvements in fatigue (Chalder Fatigue Scale, p=0.0059, d=1.75) and cognitive function across multiple domains including executive function (p=0.0039, d=−1.06), attention (p=0.0020, d=−1.2), and verbal function (p=0.0098, d=−0.92).[4] These patient success stories highlight the potential of HBOT to substantially improve the debilitating symptoms and overall well-being of individuals suffering from long COVID.

Sources:

[1] https://www.youtube.com/watch?v=r0PD7s6zqjc&t=38s

[2]https://sarasgarden.org/a-covid-19-long-hauler-journey-with-hbot/

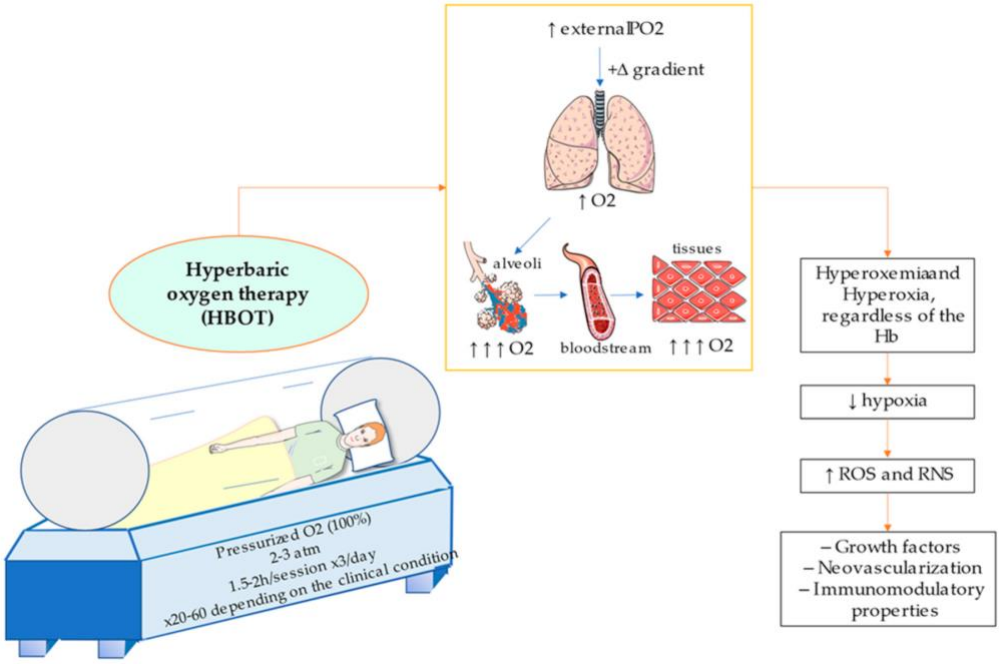
[3]https://www.nature.com/articles/s41598-024-53091-3

[4]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8806311/

[5]https://www.pharmacytimes.com/view/hyperbaric-oxygen-therapy-may-be-the-first-only-clinically-effective-treatment-for-long-covid

[6]https://www.hyperbaricmedicalsolutions.com/blog/hyperbaric-oxygen-a-promising-treatment-for-long-hauler-covid

Mechanisms of HBOT in Long COVID Treatment



HBOT does ameliorate long COVID symptoms through several mechanisms. By increasing plasma oxygen concentration, HBOT reduces inflammation by decreasing pro-inflammatory cytokines such as IL-1, IL-6, and TNF-alpha while elevating the anti-inflammatory cytokine IL-10.[4]

Additionally, HBOT induces neuroplasticity and does reverse COVID-related brain damage by stimulating stem cell mobilization, mitochondrial biogenesis, and angiogenesis.[3][5] In a randomized controlled trial, HBOT significantly improved long COVID patients' cognitive function, sleep quality, and pain, with benefits persisting even one year post-treatment (effect sizes ranging from 0.47 to 0.83).[5]

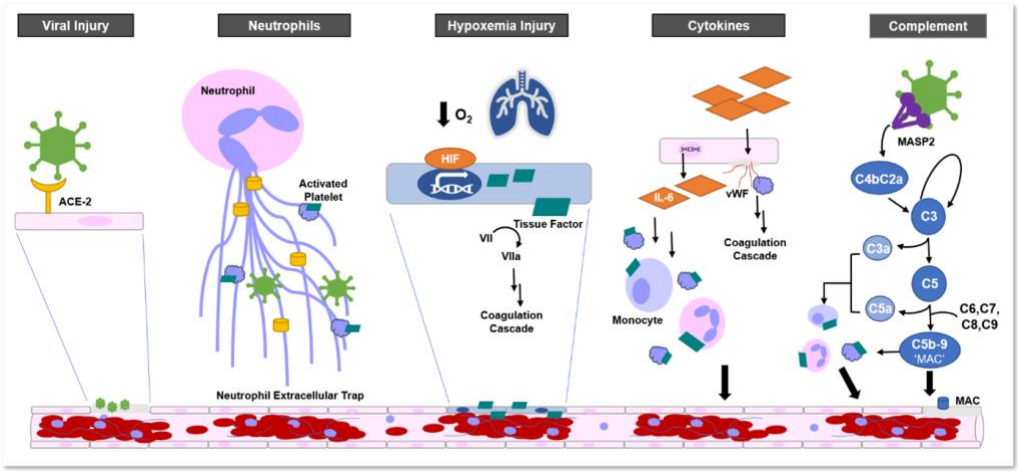
These findings suggest HBOT targets the underlying pathophysiology of long COVID and provides durable symptom relief.

Sources:

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8806311/

[2]https://bmjopen.bmj.com/content/12/11/e061870
[3]https://www.pharmacytimes.com/view/hyperbaric-oxygen-therapy-may-be-the-first-only-clinically-effective-treatment-for-long-covid
[4]https://www.hyperbaricmedicalsolutions.com/blog/hyperbaric-oxygen-a-promising-treatment-for-long-hauler-covid
[5] https://www.nature.com/articles/s41598-024-53091-3

Microvascular Thrombosis in COVID-19



[1]

Microvascular thrombosis is a critical pathophysiological mechanism underlying severe COVID-19. Autopsy studies have revealed extensive diffuse microthrombi within the pulmonary vasculature in 80-100% of COVID-19 lungs examined, with a 9-fold higher prevalence of alveolar-capillary microthrombi than influenza. [2][4][5]

The microthrombi in COVID-19 exhibit a distinct composition with increased fibrin and complement factor C5b-9 deposition. [2] Endothelial glycocalyx degradation is a key driver of microthrombosis, facilitating viral entry and causing direct endothelial injury.[2] This endothelial damage, along with stasis and hypercoagulability (Virchow's triad), leads to platelet-endothelial interactions, complement activation, neutrophil extracellular trap formation, and microparticle shedding, culminating in thrombo inflammation and microvascular occlusion.[2][4] Massive image-based profiling has shown excessive platelet aggregates in nearly 90% of COVID-19 patients, with aggregate concentration correlating with disease severity, mortality, and respiratory status.[3]

Thus, microvascular thrombosis is a major contributor to multiorgan failure and adverse outcomes in severe COVID-19.

Sources:

[1] https://www.perplexity.ai/page/HBOT-Promising-Long-eHX4BF4ISnSWdmYKcXRzOw
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9916726/

[3] https://www.medrxiv.org/content/10.1101/2021.04.29.21256354v2.full

[4] https://thorax.bmj.com/content/76/4/412

[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7386875/

Platelet Aggregation Profiling in COVID-19

Massive image-based profiling of circulating platelets and platelet aggregates in COVID-19 patients has provided novel insights into the underlying process of COVID-19-associated microvascular thrombosis. Image data analysis from 110 hospitalized patients showed the anomalous presence of excessive platelet aggregates in nearly 90% of COVID-19 patients, with strong links between the concentration of platelet aggregates and disease severity, mortality, and respiratory condition.[1]

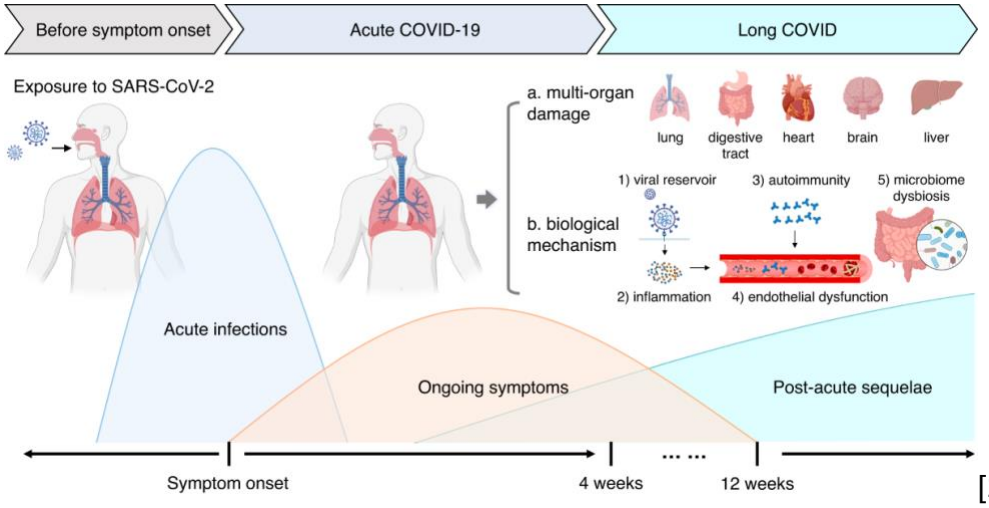
High-dimensional analysis based on deep learning further indicated that COVID-19 behaves as a systemic thrombotic disorder.[1] These findings align with autopsy reports showing widespread thrombotic microangiopathy characterized by extensive diffuse microthrombi within peripheral capillaries and arterioles in lungs, hearts, and other organs, resulting in multiorgan failure.[1][2][3] The distinct composition of these microthrombi, with increased fibrin and complement factor C5b-9 deposition, suggests thrombo inflammation as a key driver of microvascular occlusion in severe COVID-19.[3][4][5] Endothelial glycocalyx degradation, alterations in blood flow and viscosity, neutrophil extracellular trap formation, and microparticle shedding further contribute to endothelial damage and microthrombosis.[3][4][5]

Thus, massive image-based profiling has provided critical insights into the central role of microvascular thrombosis in the pathophysiology and adverse outcomes of severe COVID-19.

Sources:

[1] https://www.medrxiv.org/content/10.1101/2021.04.29.21256354v2.full
[2]https://www.acc.org/Latest-in-Cardiology/Articles/2021/01/25/14/28/Microvascular-Thrombi-in-COVID-19
[3]https://pubmed.ncbi.nlm.nih.gov/36768817/
[4]https://thorax.bmj.com/content/76/4/412
[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9916726/

Hyperbaric oxygen effectively addresses the pathophysiology of long COVID



[1]

A novel quantitative phase imaging approach combining digital holographic microscopy (DHM) with microfluidics and customized image analysis enables label-free, high-throughput detection and quantification of platelet aggregates in COVID-19 patients.[1][4] This POC-compatible method allows rapid profiling of micro-aggregates under low shear stress conditions (~1,000 s−1) that mimic blood flow in vessels.[1][4]

Applying this technique to 110 hospitalized COVID-19 patients revealed excessive platelet aggregates in nearly 90% of cases, with aggregate concentration strongly correlating with disease severity, mortality, and respiratory status.[2][3][5] Severe COVID-19 was associated with higher numbers and distinct composition of cell aggregates, including increased platelet-leukocyte aggregates.[4][6]

The ability to detect and analyze aggregate composition at the single-platelet level provides critical insights into the central role of microvascular thrombosis in COVID-19 pathophysiology.[1][2][5] Widespread thrombotic microangiopathy with extensive diffuse

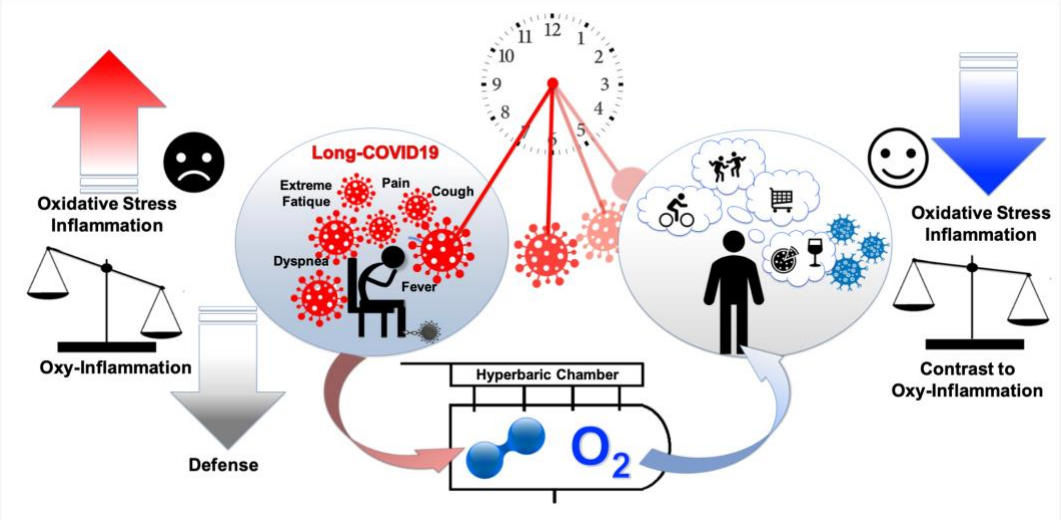
microthrombi in peripheral capillaries and arterioles of multiple organs has been linked to multiorgan failure and adverse outcomes.[3][4][6] The distinct microthrombi composition, with elevated fibrin and complement factor C5b-9 deposition, implicates thrombo inflammation as a key driver.[4][6]

Endothelial glycocalyx degradation, neutrophil extracellular trap formation, microparticle shedding, and alterations in blood flow further contribute to endothelial damage and microthrombosis in severe COVID-19.[4][6] This novel imaging approach thus enables quantitative profiling of the platelet aggregates underlying the microvascular thrombosis central to COVID-19 pathophysiology, with potential applications in risk stratification and monitoring therapeutic interventions.[1][2][5]

Sources:

[1]https://www.perplexity.ai/page/HBOT-Promising-Long-eHX4BF4ISnSWdmYKcXRzOw
[2]https://www.researchgate.net/figure/Massive-image-based-profiling-of-circulating-platelets-and-platelet-aggregates-at_fig1_356895550
[3]https://www.researchgate.net/publication/356895550_Massive_image-based_single-cell_prof[…]_circulating_platelet_aggregates_in_patients_with_COVID-19
[4]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10630365/
[5]https://www.semanticscholar.org/paper/2ef4c05ba04646912b27642aa6effd37617d943a
[6]https://www.medrxiv.org/content/10.1101/2021.04.29.21256354v1.full

HBOT Ameliorates Long COVID Pathophysiology



[1]

A recent (March 2024) clinical review concludes that hyperbaric oxygen therapy (HBOT) effectively addresses the underlying pathophysiology of long COVID and does provide significant benefit for this population.[3] HBOT has been shown to reduce inflammation by decreasing pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α while elevating the anti-inflammatory cytokine IL-10.[3] Additionally, HBOT promotes the synthesis of growth factors, mitigates post-ischemic and post-inflammatory responses, increases stem cell mobilization, and enhances neuroplasticity.[3]

Several studies have demonstrated the efficacy of HBOT in treating long COVID symptoms. In a study of 73 long COVID patients, those who received 40 HBOT sessions exhibited significantly improved fatigue, brain fog, and shortness of breath compared to the control group.[2] Another study found that after receiving HBOT, participants showed reduced levels of reactive oxygen species (ROS), lipid peroxidation, DNA damage, nitric oxide (NO) metabolites, and inflammation biomarkers.[3]

At Hyperbaric Medical Solutions, a recent survey revealed that long COVID patients reported an 80% improvement in symptoms after just 5 HBOT treatments.[3] The clinic prioritizes patient safety by ensuring that all patients are cleared by a certified hyperbaric professional, treatment plans are individually prepared by a hyperbaric board-certified physician, and each session is closely supervised by certified medical staff and trained technicians.[3]

Despite the promising results, the cost of HBOT remains a significant barrier for many long COVID patients, as insurance companies do not cover the treatment due to its lack of FDA approval for this specific condition.[2] At Aviv Clinics, the cost of 40 to 60 two-hour HBOT sessions ranges from $36,000 to $51,000.[2] Some clinics offer reduced-cost treatments to those in financial need, but insurance coverage remains the most viable solution for increasing accessibility.[2]

As more research is conducted on the potential benefits of HBOT for long COVID, it is crucial to wait for positive data from larger-scale studies before insurance companies can justify covering the cost.[2] Several ongoing studies are investigating the efficacy of HBOT in this context, but there is no concrete timeline for when they will yield definitive results.[2] In the meantime, HBOT remains a promising treatment option for long COVID patients who can afford the out-of-pocket expenses.

Sources:

[1]https://pub.mdpi-res.com/metabolites/metabolites-13-01032/article_deploy/html/images/metabolites-13-01032-ag.png
[2]https://www.cnbc.com/2023/04/20/treating-long-covid-hyperbaric-oxygen-therapy-shows-promise-concerns.html
[3]https://www.hyperbaricmedicalsolutions.com/blog/hyperbaric-oxygen-a-promising-treatment-for-long-hauler-covid
[4]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8806311/
[5]https://www.cognitivefxusa.com/blog/hyperbaric-oxygen-therapy-for-covid-long-haulers

HBOT Modulates Long COVID Immunopathology

A recent study published in Life by Zilberman-Itskovich et al. investigated the long-term outcomes of hyperbaric oxygen therapy (HBOT) in patients with post-COVID conditions (long COVID).[1] The prospective, randomized, sham-controlled, double-blind trial included 73 patients with post-COVID cognitive symptoms persisting for over 3 months.[1] Participants were randomized to receive either 40 daily HBOT sessions (treatment group) or sham sessions (control group) over a 2-month period.[1]

The study found that HBOT significantly improved global cognitive function, attention, information processing speed, and executive function compared to the control group (p<0.05).[1] These beneficial cognitive effects were still significant at the 1-year follow-up assessment.[1] Additionally, HBOT significantly improved other common long COVID symptoms, such as fatigue, sleep disturbances, psychiatric symptoms, and pain interference, compared to the control (p<0.05).[1] Notably, the greatest improvements were in the most disturbed domains at baseline.[1]

The authors propose that HBOT's efficacy in treating long COVID is attributed to its ability to improve cerebral blood flow and induce neuroplasticity.[1] HBOT has been shown to increase brain perfusion, improve mitochondrial function, reduce neuroinflammation, and stimulate angiogenesis and synaptogenesis.[1][4] These mechanisms do help counteract the neurological damage and cerebral hypoperfusion observed in long COVID patients.[1][2]

The study's findings align with previous research demonstrating HBOT's potential in treating long COVID symptoms.[2][3][4] For instance, a case series by Robbins et al. reported significant improvements in fatigue, cognitive function, sleep, and pain in 10 long COVID patients after 10 HBOT sessions.[3] Another study by Kjellberg et al. found that HBOT reduced inflammation biomarkers and oxidative stress in long COVID patients.[4]

While these results are promising, larger-scale randomized controlled trials are needed to further validate HBOT's efficacy and optimize treatment protocols for Long COVID.[1][2] Additionally, the high cost and limited accessibility of HBOT remain significant barriers to

widespread adoption.[2][5] Nonetheless, this study provides strong evidence supporting HBOT as a potentially effective and durable treatment option for the debilitating symptoms of Long COVID.

Sources:

[1]https://www.perplexity.ai/page/HBOT-Promising-Long-eHX4BF4ISnSWdmYKcXRzOw

[2]https://www.cnbc.com/2023/04/20/treating-long-covid-hyperbaric-oxygen-therapy-shows-promise-concerns.html

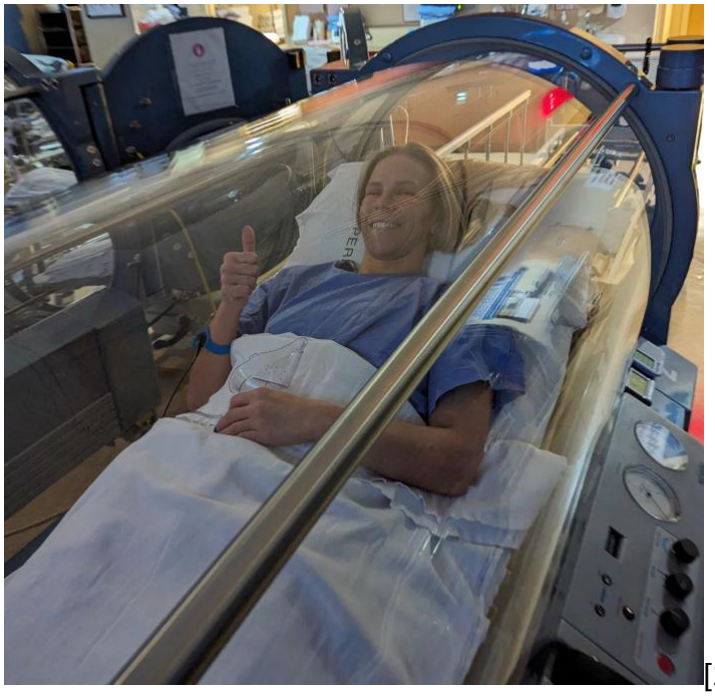
[3]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8806311/

[4]https://www.hyperbaricmedicalsolutions.com/blog/hyperbaric-oxygen-a-promising-treatment-for-long-hauler-covid

[5]https://www.pharmacytimes.com/view/hyperbaric-oxygen-therapy-may-be-the-first-only-clinically-effective-treatment-for-long-covid

[6]https://www.uclahealth.org/news/article/hbot-a-potential-treatment-for-those-with-long-covid-19

Case Studies of Recovery

 [1]

Several case studies have demonstrated the potential of hyperbaric oxygen therapy (HBOT) in facilitating recovery from various respiratory ailments, including long COVID, COPD, and ARDS. These studies provide valuable insights into the mechanisms and efficacy of HBOT in addressing the complex pathophysiology of these conditions.

In a case study of a 38-year-old woman suffering from persistent shortness of breath and fatigue after recovering from acute COVID-19, a series of HBOT sessions led to increased exercise tolerance and substantially reduced fatigue levels.[3] Notably, her lung function tests revealed a marked improvement in lung capacity and oxygenation.[3]

This case highlights the potential of HBOT to alleviate the debilitating respiratory symptoms associated with long COVID.[2][4][5][6][7]

Sources:

[1]https://www.perplexity.ai/page/HBOT-Promising-Long-eHX4BF4ISnSWdmYKcXRzOw

[2]https://www.hyperbaricmedicalsolutions.com/hs-fs/hubfs/PXL_20240215_153714338.ACTION_PAN-01.COVER-1.jpg?height=1952&name=PXL_20240215_153714338.ACTION_PAN-01.COVER-1.jpg&width=2000

[3] https://www.hvmed.com/hbot-case-studies
[4]https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/hyperbaric-oxygen-therapy
[5]https://chicagoneuro.com/unveiling-the-potential-of-hyperbaric-oxygen-therapy-hbot-for-respiratory-ailments-insights-from-case-studies/
[6]https://pubmed.ncbi.nlm.nih.gov/17234213/
[7]https://www.pharmacytimes.com/view/hyperbaric-oxygen-therapy-may-be-the-first-only-clinically-effective-treatment-for-long-covid

Acknowledgement Credit: Professor Angi English

The Hyperbaric Wellness Team would like to thank Professor Angi English for her assistance in researching and leveraging AI technology to gather much of the data used in this paper.

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