Gut microbiota and hyperbaric oxygen therapy

Daisuke Muroya*, Shinya Nadayoshi, Yutaro Kai, Shin Sasaki, Yuichi Goto, Kohji Okamoto

Hyperbaric oxygen therapy (HBOT) was originally developed to treat decompression sickness in divers, specifically for alleviating joint pain caused by nitrogen bubbles. HBOT involves inhaling 100% oxygen under increased atmospheric pressure, typically two to three times standard sea-level pressure (2.0–3.0 atmospheres absolute [ATA]). This process reduces tissue edema and supplies adequate oxygen to tissues that cannot be sufficiently oxygenated under normal atmospheric pressure.[1] At 2–3 ATA oxygen pressures, arterial oxygen levels exceed 2000 mmHg, and tissue oxygen concentration reaches approximately 400 mmHg. The increased pressure and oxygen concentration in plasma enables greater oxygen delivery to hypoxic tissues, promoting tissue healing.[2]

HBOT has been shown to have multiple beneficial pathways in both acute and chronic inflammatory conditions. For instance, it suppresses the production of inflammatory cytokines, enhances the synthesis of growth factors, and promotes the migration of stem cells from the bone marrow, thereby improving wound healing.[2] The scope of HBOT has expanded beyond its original indications of decompression sickness and arterial gas embolism. It is now employed in various domains, including the treatment of osteomyelitis to promote wound healing and angiogenesis, soft tissue infections, complications from radiation therapy, toxicological conditions such as carbon monoxide and cyanide poisoning, and brain stroke.[1] HBOT plays a primary role in the treatment of certain conditions such as decompression sickness, radiation-induced proctitis, and carbon monoxide poisoning. Furthermore, its high safety profile makes it particularly valuable as an adjunctive therapy that can be easily combined with other treatments for various diseases. While it may be associated with mild and transient side effects due to pressure and oxygen toxicity—middle ear barotrauma being a representative example—it is considered a relatively safe therapeutic modality.[1,3]

In the field of gastroenterology, chronic bowel dysfunction following pelvic radiation therapy is widely recognized worldwide as an indication for HBOT.[3] Recent studies have reported the effectiveness of HBOT in treating inflammatory bowel disease (IBD) and its association with the gut microbiota.[2] A registry-based cohort study utilizing a multicenter international registry reported that, despite being an off-label indication, HBOT was administered to 12.4% (47/378) of patients with ulcerative colitis and 10.6% (40/378) of patients with Crohn's disease among a total of 9726 patients.[4]

Hyperbaric oxygen therapy and gut microbiota (Figure 1): The gut microbiota is recognized as an endocrine organ with the ability to influence distant organs and associated biological pathways, and its homeostasis is increasingly recognized as essential for maintaining health. Dysbiosis of the gut microbiota has been suggested to affect the onset and progression of various diseases through the immune system, endocrine system, and metabolite pathways.[5]

HBOT is known to affect the intestinal flora, but the mechanism is unknown. Since hyperbaric oxygen conditions suppress anaerobic bacterial infections, oxygen supply likely affects anaerobic bacteria in the intestine, which is in a physiologically hypoxic state. It has also been hypothesized that HBOT promotes the production of oxygen radicals, which have strong oxidizing and bactericidal effects, thereby suppressing the growth of bacteria that perform oxidative metabolism and suppressing the expression of plasmids that control bacterial growth.[6] Additionally, studies on healthy individuals have reported that hyperbaric conditions alone can alter the gut microbiota.[7] While the effects of HBOT on a healthy gut remain unclear, dominant reports are showing favorable clinical outcomes in the gut with dysbiosis.[4-12] Since the gut microbiota is associated with various pathways, including the immune system, endocrine system, and metabolic pathways, the exact mechanism by which HBOT improves dysbiosis is yet to be determined at this point. Over 90% of the adult gut microbiota is composed of four phyla: Firmicutes, Bacteroides, Actinobacteria, and Proteobacteria. In particular, the colon is primarily composed of the densest and most metabolically active microorganisms. In addition to Actinobacteria, Proteobacteria, and Verrucomicrobia, an anaerobic microbiota consisting of the phyla Firmicutes and Bacteroidetes is predominant. An imbalance in the gut microbiota has been implicated in IBD, but the underlying mechanisms remain unclear. A study using Mendelian randomization analysis to assess the causal relationship between gut microbiota and IBD reported that three bacterial taxa—Verrucomicrobiaceae family, *Akkermansia* genus, and *Dorea* genus—may be associated with IBD. In patients with IBD, a reduction in the *Lachnospiraceae* family and a decrease in butyrate levels have been observed. *Akkermansia* is known as a commensal bacterium in the gut and may have anti-inflammatory properties; however, its levels tend to be lower in IBD patients. To maintain gut microbiota homeostasis, treatments such as probiotics, prebiotics supplementation, and fecal microbiota transplantation are commonly employed, and HBOT should be considered as a potential addition to these approaches. We have focused on the ability of HBOT to improve dysbiosis and reported its effectiveness in treating Clostridioides difficile-associated colitis.[8] Recently, its usefulness has also been reported in the context of intestinal dysfunction following traumatic brain injury.[13] Therefore, a promising direction for future research would be to investigate the efficacy of HBOT in diseases related to gut microbiota dysbiosis.

Inflammatory bowel disease: The efficacy of HBOT has been reported across the entire spectrum of IBD, including ulcerative colitis (UC), Crohn's disease (CD), and patients who have undergone ileal pouch-anal anastomosis. It has been shown to reduce the activity of severe UC, increase the remission rate, and lower the likelihood of requiring a colectomy during hospitalization. Additionally, up to 47% of patients undergoing ileal pouch-anal anastomosis or J pouch surgery after colectomy develop pouchitis, and HBOT has been reported to be effective in improving pouchitis. Furthermore, in CD, managing peri-anal fistulas can be particularly challenging, but HBOT has demonstrated promising results as an adjunctive therapy in the management of CD patients with peri-anal fistulas and extraintestinal manifestations.[2] A systematic review and meta-analysis examining 19 studies, including three randomized controlled trials, analyzed 809 patients. The reported clinical remission rates were 87% (95% *CI*, 10–100%) for ulcerative colitis, 88% (95% *CI*, 46–98%) for luminal CD, and 60% (95% *CI*, 40–76%) for perianal CD.[9] Currently, a large multicenter randomized controlled trial funded by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases is being planned.[10]

The mechanisms through which HBOT exerts its therapeutic effects in IBD primarily alleviate intestinal oxidative stress by enhancing oxygen supply and reducing inflammation. In IBD, microvascular damage leads to mucosal hypoxia, exacerbating oxidative stress and inflammation. HBOT increases oxygen availability by dissolving oxygen directly into the plasma, bypassing damaged blood vessels, and improving tissue oxygenation. This enhanced oxygenation reduces hypoxia-induced reactive oxygen species production and mitigates mitochondrial dysfunction, helping to break the cycle of oxidative stress and inflammation. Furthermore, HBOT enhances antioxidant enzyme activity, reducing oxidative damage to intestinal epithelial cells. By stabilizing the intestinal barrier and modulating immune responses, HBOT contributes to mucosal healing and the reduction of chronic inflammation in IBD.[11] Additionally, HBOT has been shown to decrease the production of inflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-α) and inhibit neutrophil adhesion. Additionally, HBOT acts on nitric oxide and vascular endothelial growth factor signaling pathways, promoting the upregulation of response pathways involved in hypoxia tolerance, such as the hypoxia-inducible factor and heme oxygenase pathways. These effects are thought to lead to improved tissue oxygen levels, a reduction in the inflammatory cascade, and ultimately, enhanced tissue healing.[2]

HBOT has emerged as a promising treatment for improving dysbiosis of the gut microbiota in patients with UC and CD. Dysbiosis is characterized by a decrease in strictly anaerobic bacteria and an increase in facultative anaerobic bacteria, playing a crucial role in the pathogenesis of IBD. HBOT increases oxygen delivery from the intestinal mucosal tissue to the lumen, promoting not only direct alterations in the microbiota composition but also facilitating microbiota reconstruction through modulation of the host immune system.

MEDICAL GAS RESEARCH
www.medgasres.com
https://doi.org/10.4103/mgr.MEDGASRES-D-25-00018
How to cite this article: *Muroya D, Nadayoshi S, Kai Y, Sasaki S, Goto Y, Okamoto K. Gut microbiota and hyperbaric oxygen therapy. Med Gas Res. 2025;15(4):548-549.*

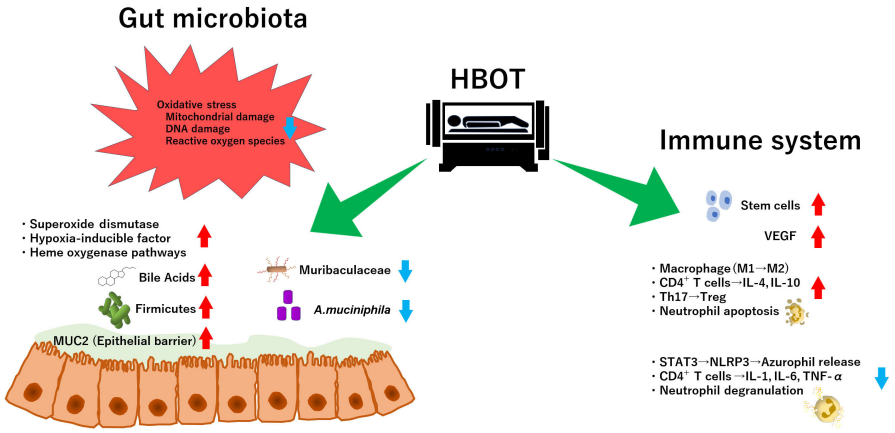

Figure 1 | The pathways through which HBOT influences the intestinal microbiota and immune system.
Created with Microsoft PowerPoint. *A. muciniphila*: *Akkermansia muciniphila*; HBOT: hyperbaric oxygen therapy; IL: interleukin; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; STAT3: signal transducer and activator of transcription 3; Th17: T helper 17; TNF: tumor necrosis factor; Treg: regulatory T; VEGF: vascular endothelial growth factor.

Proteomics analysis and digital spatial profiling have shown that HBOT suppresses neutrophil degranulation, with a specific effect on the reduction of azurophil granule-associated proteins. This action is associated with the suppression of inflammation through the regulation of the NLRP3 inflammasome via the signal transducer and activator of transcription 3 (STAT3) signaling pathway. Furthermore, HBOT has been found to decrease reactive oxygen species and MAPK signaling, while increasing neutrophil apoptosis. As a result, the release of inflammatory mediators is suppressed, and the levels of pro-apoptotic protein BIM and anti-apoptotic protein BCLXL are increased, enabling the modulation of the inflammatory response.

Moreover, HBOT induces significant changes in the gut microbiota composition. The impact of HBOT on the gut microbiota is thought to result in a significant decrease in Shannon diversity due to the reduction of mucin-degrading microbes Muribaculaceae and Akkermansiaceae, leading to a proportional increase in Firmicutes and subsequent elevation of bile acids.[8] The simplest speculated mechanism is that the oxygen supply induced by HBOT suppresses Muribaculaceae and Akkermansiaceae, which are obligate anaerobes, allowing a relative increase in Firmicutes, including facultative anaerobes.

Furthermore, MUC2 is a core structural protein of the inner mucus layer, and the weakening of this epithelial barrier is considered an early dysbiosis event in UC in both human and animal models. This MUC2-deficiency-associated dysbiosis is characterized by a decrease in Firmicutes and an increase in the Muribaculaceae and Akkermansiaceae families, which aligns with the aforementioned hypothesis. However, contradictory findings exist. Muribaculaceae has been reported to stimulate mucus secretion through the production of short-chain fatty acids via polysaccharide metabolism, activating signaling pathways and exerting anti-inflammatory effects. In IBD, a reduction in Muribaculaceae has also been observed.[12]

Moreover, dysbiosis in IBD is primarily characterized by a decrease in strict anaerobes and an increase in facultative anaerobes, and some studies suggest that the loss of Muribaculaceae abundance is directly linked to disease pathogenesis. Given these findings, the observed microbiota changes alone are insufficient to fully explain dysbiosis improvement via increased intestinal oxygen concentration. Thus, further research and careful interpretation are necessary to elucidate the impact of HBOT on gut microbiota dysbiosis. In animal models, changes in the microbiota due to HBOT have been shown to contribute to the reduction of colitis, likely through direct effects on the host neutrophil STAT3 pathway, leading to improvement in disease activity.[2]

Conclusion: HBOT has been applied to various diseases and, due to its safety, can be easily combined with existing treatments, making it a promising adjunctive therapy. In the field of gastroenterology, its effectiveness in IBD has been reported through multiple mechanisms, including improvement of the mucus layer, bile acid metabolism, and modulation of the gut microbiota. However, regarding the correction of dysbiosis by HBOT, conflicting reports exist concerning Firmicutes and Akkermansiaceae (particularly *Akkermansia muciniphila*). Therefore, further research and careful interpretation are required.

Daisuke Muroya*, Shinya Nadayoshi, Yutaro Kai, Shin Sasaki, Yuichi Goto, Kohji Okamoto

Department of Emergency, Kitakyusyu City Yahata Hospital, Kitakyusyu, Japan (Muroya D, Okamoto K)
Department of Clinical Engineering, Tobata Kyoritsu Hospital, Kitakyusyu, Japan (Muroya D, Nadayoshi S, Kai Y)
Department of Surgery, Kurume University Hospital, Kurume, Japan (Sasaki S, Goto Y)
***Correspondence to:** Daisuke Muroya, PhD, muroyadaisuke@gmail.com.
https://orcid.org/0009-0004-8064-5411 (Daisuke Muroya)

Date of submission: January 18, 2025
Date of decision: February 21, 2025
Date of acceptance: March 13, 2025
Date of web publication: April 29, 2025

References

1. Sen S, Sen S. Therapeutic effects of hyperbaric oxygen: integrated review. *Med Gas Res*. 2021;11:30-33.
2. Kaur H, Kochhar GS, Dulai PS. Role of hyperbaric oxygen therapy in patients with inflammatory bowel disease. *Curr Opin Gastroenterol*. 2023;39:263-267.
3. Monteiro AM, Costa DA, Mareco V, et al. The effectiveness of hyperbaric oxygen therapy for managing radiation-induced proctitis - results of a 10-year retrospective cohort study. *Front Oncol*. 2023;13:1235237.
4. Tanaka HL, Rees JR, Zhang Z, et al. Multicenter registry for hyperbaric oxygen treatment consortium. Emerging indications for hyperbaric oxygen treatment: registry cohort study. Interact J Med Res. 2024;13:e53821.
5. Wang MY, Sang LX, Sun SY. Gut microbiota and female health. *World J Gastroenterol*. 2024;30:1655-1662.
6. Chmelař D, Rozložník M, Hájek M, et al. Effect of hyperbaric oxygen on the growth and susceptibility of facultatively anaerobic bacteria and bacteria with oxidative metabolism to selected antibiotics. *Folia Microbiol (Praha)*. 2024;69:101-108.
7. Zhang ZJ, Qu HL, Zhao N, et al. Assessment of causal direction between gut microbiota and inflammatory bowel disease: a Mendelian randomization analysis. *Front Genet*. 2021;12:631061.
8. Muroya D, Nadayoshi S, Yamada K, et al. Effects of hyperbaric oxygen therapy for *Clostridioides difficile*-associated colitis: a retrospective study. *J Anus Rectum Colon*. 2023;7:264-272.
9. McCurdy J, Chin Koon Siw K, Kandel R, et al. The effectiveness and safety of hyperbaric oxygen therapy in various phenotypes of inflammatory bowel disease: systematic review with meta-analysis. *Inflamm Bowel Dis*. 2022;28:611-621.
10. Kaur H, Kochhar GS, Dulai PS. Role of hyperbaric oxygen therapy in patients with inflammatory bowel disease. *Curr Opin Gastroenterol*. 2023;39:263-267.
11. Chen L, Wang Y, Zhou H, et al. The new insights of hyperbaric oxygen therapy: focus on inflammatory bowel disease. *Precis Clin Med*. 2024;7:pbae001.
12. Zhu Y, Chen B, Zhang X, et al. Exploration of the muribaculaceae family in the gut microbiota: diversity, metabolism, and function. *Nutrients*. 2024;16:2660.
13. Yu X, Zhao W, Liu Y, et al. Hyperbaric oxygen therapy alleviates intestinal dysfunction following traumatic brain injury via mA regulation. *Int J Med Sci*. 2024;21:2272-2284.