—**Review**—

Hyperbaric Oxygen Therapy in Japan, Now and in the Future

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The principles of hyperbaric oxygen therapy (HBOT) have been known since ancient times. Empirical knowledge regarding relief of decompression sickness (DCS) symptoms in divers re-entering a pressurized environment was reported as early as 4,500 BC. DCS was recognized as a disease after deep diving became possible because of diving helmets. DCS also occurs in high-pressure dry workspaces (caissons) developed to construct bridges and tunnels. After the discovery of oxygen in the 18th century, its administration was found to be beneficial in treating conditions that developed after rapid decompression, and HBOT is now established as a part of recompression therapy. This review describes the indications for HBOT in Japan and its effectiveness, as indicated by the author's experience with HBOT in the Department of Emergency Room and General Medicine at Nippon Medical School.

(J Nippon Med Sch 2025; 92: 242–247)

Key words: hyperbaric oxygen therapy, oxygen, decompression sickness, emergency services

Introduction

The principles of hyperbaric oxygen therapy (HBOT) have been known since ancient times. Empirical knowledge regarding the relief of decompression sickness (DCS) symptoms in divers re-entering a pressurized environment was reported as early as 4,500 BC. DCS was later recognized as a disease after deep diving became possible with the invention of breathing bags, diving bells, and diving helmets[1]. DCS also occurs in high-pressure dry workspaces (caissons) used to construct bridges and tunnels (called caisson disease)[1]. After the discovery of oxygen in the 18th century[2], its administration was recognized as a useful treatment for conditions that develop during rapid decompression. HBOT is now an established part of recompression therapy. Hyperbaric oxygen medicine and diving medicine were regarded as separate fields. However, as the treatments were similar or identical, researchers and clinicians now regard them as related. Current Japanese indications for HBOT are determined by the national insurance system. Herein, we describe the indications for HBOT in Japan and its effectiveness based on my experience with HBOT in the Department of Emergency Room and General Medicine at Nippon Medical School.

Indications for Hyperbaric Oxygen Therapy (Table 1)

Emergency Conditions

HBOT is recommended for many acute conditions, and initial support is particularly important. The two most common conditions requiring immediate attention are DCS and arterial gas embolism (AGE). DCS occurs when an inert gas dissolved in the body becomes supersaturated due to decompression. AGE is a similar condition that is difficult to differentiate from DCS. The symptoms are not simply caused by air bubbles in the blood vessels but by a reaction mediated by intravascular coagulation and inflammatory processes[3].

DCS

When breathing underwater while diving, the amount of inhaled gas dissolved in the bloodstream through the alveoli increases proportionally to the partial pressure, because 1 atm of pressure is added for every 10-m increase in depth. Consequently, the partial gas pressure in each organ (tissue) increases. However, when the environmental pressure decreases during a rapid ascent, bubbles and microgases may be generated in blood vessels and tissues because the amount of dissolved inert gas exceeds the amount that can be dissolved at that gas pres-

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https://doi.org/10.1272/jnms.JNMS.2025_92-311
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Indications for Hyperbaric Oxygen Therapy (HBOT) in Japan

1. For decompression sickness (DCS) or air embolism (AGE), HBOT should be performed within 1 month of symptom onset; seven sessions are available.
2. For the following conditions, 10 sessions are available:
(1) Acute carbon monoxide poisoning or other gas poisoning (including intermittent types).
(2) Critical necrotizing soft tissue infections (including gas gangrene and necrotizing fasciitis) or intracranial abscesses.
(3) Acute peripheral vascular disorders:
A. Severe burns or frostbite.
B. Extensive crush injuries or peripheral vascular disorders with complicated vascular tears.
C. Compartment syndrome or compression syndrome.
(4) Cerebral infarction.
(5) Impaired consciousness or cerebral edema due to head injury or craniotomy.
(6) Severe hypoxic-ischemic encephalopathy.
(7) Intestinal obstruction.
3. For the following conditions, 30 sessions are available:
(1) Retinal artery occlusion.
(2) Sudden sensorineural hearing loss.
(3) Malignant tumors treated with radiation or chemotherapy.
(4) Intractable ulcers accompanied by peripheral vascular disorders.
(5) Skin grafts.
(6) Spinal cord injuries.
(7) Osteomyelitis or radiation injuries.
4. Subacute myelo-optic neuropathy (SMON).

sure (supersaturation), which is known as DCS. Type I is mild DCS frequently causes skin redness, itching, joint pain, edema, swelling, and other symptoms. In contrast, Type II DCS is a severe form that often requires hospitalization and includes central nervous system-type symptoms, such as impaired consciousness, convulsions, paralysis, cranial nerve symptoms, and disorders of the sensory and motor nerves, as well as bladder and bowel dysfunction. The pulmonary type ("chokes") encompasses chest pain, cough, and shortness of breath. The inner ear type causes symptoms, such as dizziness, tinnitus, nausea, and hearing loss.

AGE

AGE occurs when a large volume of air enters a blood vessel during catheterization or surgery or from alveolar damage due to barotrauma during decompression. Symptoms have an acute onset and are related to the affected organs. The symptoms are useful for differentiating DCS from AGE. DCS and AGE are diagnosed based on contrast-enhanced computed tomography (CT) or magnetic resonance imaging scans showing visible gas in blood vessels or tissues, in conjunction with symptoms in the same organs. However, these diagnostic tests are often not sensitive[4]. Both conditions can be treated with HBOT, as indicated in treatment tables 5 and 6 of the DCS and AGE Treatment Guide of the US Navy Diving Manual (2018 Revision 7, Change A)[1]. Both of these treatment stages differ from the treatment table for the chronic condition (which is usually 90 min). Depending on the symptoms, treatment may require extended duration (treatment table 6 indicates a time of up to 4 h and 45 min for 10 sessions)[5]. The mechanism of action was detailed in a recent study[4].

Other Acute Conditions

Standard tables are often used for the following conditions.

(1) Acute carbon monoxide (CO) or other gas poisonings: CO poisoning, which is common during fires and is often associated with inhalation burns, is treated while the patient is intubated. The time required for CO-hemoglobin concentrations to decrease by half is 320 min at atmospheric pressure, which is reduced to 80.3 min with oxygen inhalation and significantly reduced to 23.3 min at 3 absolute atmospheres[6]. Some patients develop intermittent (delayed) CO poisoning, in which symptoms recur after complete resolution. This is believed to be due to residual cellular respiratory damage. Thus, it is important to repeat HBOT. However, the effect is controversial. Cyanide toxicants have been reported to be effective in HBOT as an adjunctive therapy when patients fail to respond to nitrous acid or sodium thiosulfate[7].

(2) Critical necrotizing soft tissue infections: The oxidative killing effect of HBOT is effective for treating severe cellulitis caused by bacteria. When gas gangrene and ne-

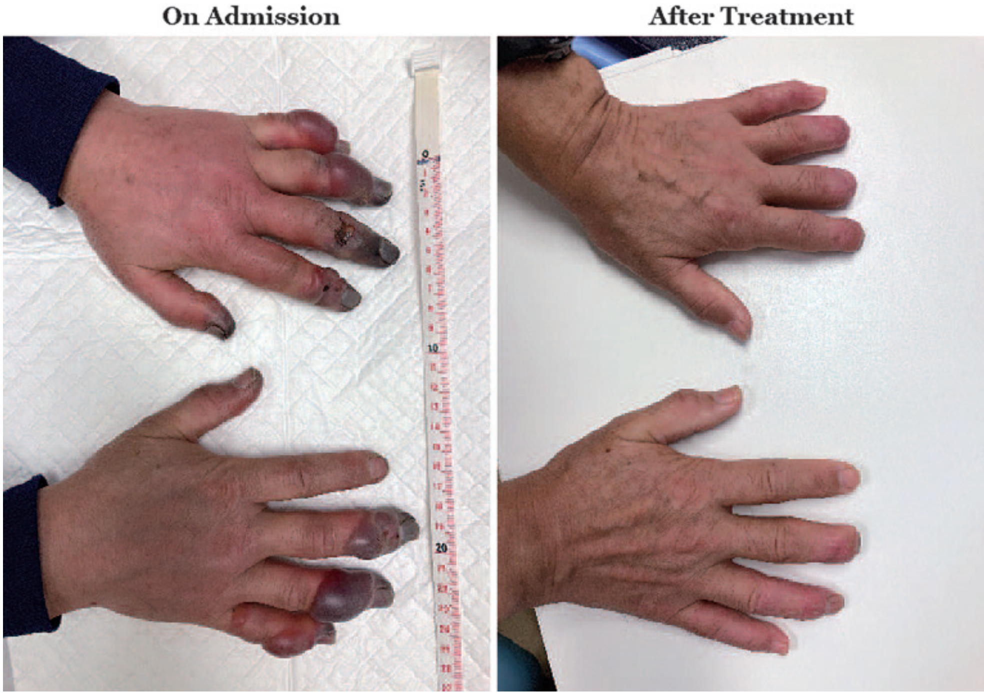

Fig. 1 Successful treatment of frostbite with HBOT

crotizing fasciitis develop because of the growth of anaerobic bacteria, limb amputation often needs to be considered. Under these conditions, early initiation and repetition of HBOT have long been recommended[8]. Treatment of intracranial abscesses is described in the same protocol.

(3) Acute peripheral vascular disorders:

A. Severe burns and frostbite cause delayed wound healing, and HBOT is used to prepare the wound bed. **Figure 1** shows an example of the effects of HBOT on a patient with frostbite in our hospital.

B. HBOT can be combined with surgical treatment in other cases, such as peripheral vascular disorders with extensive contusions or moderate / severe vascular tears.

C. Compartment syndrome or crush syndrome: Compartment syndrome develops when extravascular pressure exceeds capillary perfusion pressure[9]. To avoid neuropathy, compartment syndrome and crush syndrome[10] can be treated with HBOT in combination with surgical treatment, such as surgical decompression.

(4) Cerebral infarction: HBOT is indicated for acute stroke. Its effectiveness has also been demonstrated in the subacute phase, 1-5 d after symptom onset[11]. However, it is unclear if HBOT is indicated for all patients[12]. A recent approach for treating cerebral infarction is early intervention with thrombolytic therapy or catheterization, which does not allow sufficient time for HBOT. Similarly, in patients with myocardial infarction, HBOT may be useful in reducing the size of infarcts caused by reperfusion injury after catheterization[13].

(5) Impaired consciousness or cerebral edema from head injuries or craniotomies: Severe head trauma, which is often caused by traffic accidents or sports injuries, results in direct damage to the brain from high-energy injury. The main treatment goals are the surgical removal of the hematoma and reduction of intracranial pressure, which can be achieved with HBOT, use of an intracranial pressure reduction agent, and hypothermia. A recent randomized controlled trial reported that HBOT was effective in patients with head trauma[14]. HBOT is also effective after a craniotomy[15].

(6) Severe hypoxic-ischemic encephalopathy: We treated a child with hypoxic encephalopathy due to cardiopulmonary arrest after drowning. Because the patient required respiratory assistance, the treating pediatrician selected HBOT under manual ventilation. An individual treatment protocol was used for HBOT during the patient's short hospitalization[16].

(7) Intestinal obstruction: Mechanical intestinal obstruction can be improved by direct decompression of the gas located above the obstruction point. Additionally, HBOT enhances local blood circulation and reduces intestinal edema. HBOT can be provided under fasting conditions while gastric or ileus tubes are used. Symptoms often improve within a few days of HBOT. Even if surgery is necessary, HBOT may be continued during the perioperative

Fig. 2 Successful treatment of peripheral artery disease with HBOT

period.

Chronic Conditions

Despite the multiple indications for HBOT in progressive chronic conditions, such conditions are not always mild, and many patients do not improve, even after 10 HBOT sessions. Thus, 30 sessions are permitted under Japanese insurance guidelines, and treatment tables 5 and 6 are often used[1]. We modified table 5 to "2.8 ATA for 90 min".

(1) Retinal artery occlusion: Retinal artery occlusion, also known as central artery occlusion, is an acute condition that is treated with thrombolytic therapy and steroids. Initiation of HBOT at disease onset may contribute to improved vision. Although retinal artery occlusion is an acute condition, its treatment is allowed with a 30-session upper limit.

(2) Sudden sensorineural hearing loss: Sudden sensorineural hearing loss is an idiopathic condition that is usually unilateral and may be accompanied by dizziness and tinnitus. HBOT is highly effective if started within 14 d of symptom onset[17].

(3) Malignant tumors treated in combination with radiation or chemotherapy: HBOT is indicated for patients undergoing chemotherapy, regardless of the type of malignancy. We have experience in treating such patients; however, many had advanced metastases with ascites at the time of referral and often discontinued treatment because of difficulty in visiting the hospital for treatment.

(4) Intractable ulcers accompanying peripheral vascular disorders: I have been treating this condition for 20 years as a cardiologist (**Fig. 2**). Unlike pressure ulcers or ulcers associated with venous stasis, which do not involve ischemia, ischemic ulcers are difficult to treat. As they are particularly susceptible to ischemia, leg ulcers have been treated by major amputation (below or above the knee level) in Japan, which offers better wound healing. However, the mortality rate after limb amputation is extremely high[18,19]. The goal of adjunctive HBOT for these patients is to maintain the ability to walk. Foot ulcers due to diabetes mellitus are refractory to treatment, and management in combination with HBOT is expected to be effective[20,21]. In a Cochrane review, HBOT was shown to be effective in improving ulcers[22].

(5) Skin grafts: HBOT has been shown to increase the partial pressure of oxygen in ischemic skin grafts and is used in conjunction with skin grafts[23], including skin flaps, to promote skin graft survival[24].

(6) Spinal cord injuries: Our experience in using HBOT in spinal cord injuries was specifically as a perioperative adjunctive treatment for spinal cord surgery, especially in paralysis. Recent evidence suggests that HBOT may improve motor function and sensory function after spinal cord injuries[25].

(7) Osteomyelitis and radiation injuries: Osteomyelitis is often treated with a series of treatments for ischemic ulcer (these conditions are often concomitant). The onset of osteomyelitis is difficult to detect, and once CT or radiographic images indicate osteolysis, amputation should be considered. We developed an early diagnostic method using a combination of CT and gallium[67] scintigraphy and confirmed the therapeutic threshold of HBOT in these patients[26]. In contrast, in patients with malignancies, bloody stools (radiation proctitis) or hematuria (radiation cystitis) after radiation therapy developed several years after the radiation. HBOT is also effective in treating these delayed radiation injuries.

Other Indications

HBOT is indicated for patients with subacute myelo-optic neuropathy (SMON), a neurological condition that frequently occurred in Japan between 1950 and 1980 because of poisoning by the digestive medicine chinoform (clioquinol). Currently, approximately 2,000 patients re-

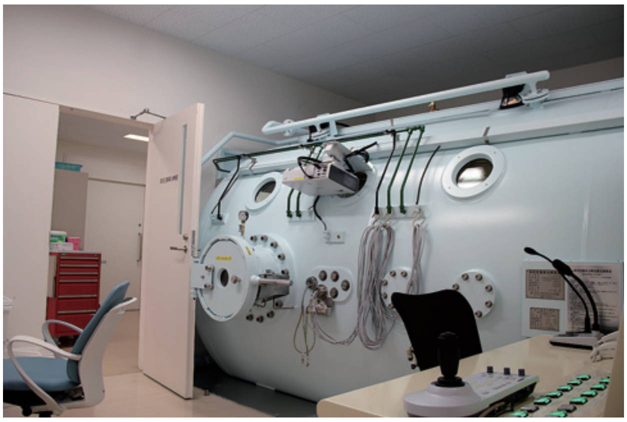

Fig. 3 Type 2 HBOT device (Barotech Hanyuuda Inc.)

ceive healthcare benefits from the Pharmaceuticals and Medical Devices Agency, and HBOT has proven effective in improving their symptoms[27,28]. Table 5 was often used, and 30 sessions are permitted under national insurance.

Complications of HBOT

The effects of fluctuations in ambient air pressure and high oxygen concentrations on the body cannot be avoided during HBOT. Therefore, prevention of these complications is important. Barotrauma occurs more frequently at the tympanic membrane, and while self-ear drainage is taught prophylactically, tympanostomy is performed in patients with impaired consciousness. Similarly, pneumothorax may occur because of lung injury. In principle, a history of spontaneous pneumothorax or the presence of giant bulla or blebs (cystic lung diseases) in the lungs is a contraindication for HBOT. Additionally, treatment should be withheld in patients with bronchial asthma because of the possibility of inducing an attack. Oxygen intoxication due to high oxygen concentrations can occur with Type 1 devices (isolation chambers), in which it is difficult to adjust the oxygen concentration[29]. Therefore, a protocol for administering oxygen via mask ventilation, with oxygen breaks, may be useful to avoid this complication, such as the use of Type 2 devices (chambers for multiple users; **Fig. 3**).

Conclusion and Future Applications of HBOT

Despite HBOT has limitations, such as side effects and their efficacy, we use HBOT to treat a wide range of conditions, with more than 1,000 sessions per year, and its effectiveness has been supported by recent evidence. Regarding indications, avascular necrosis (aseptic osteonecrosis) has recently been recognized, and the use of HBOT is recommended[30]. Also, current evidence suggests that HBOT prolongs telomere length[31], which is related to cellular aging, and HBOT is also effective as part of regenerative medicine[32,33]. If we can elucidate the mechanism of the new therapeutic effect, HBOT will likely benefit patients with many conditions that are not currently treated, such as refractory ischemic disease without ulcer, collagen disease, and cognitive dysfunction. In addition, because of individual differences in treatment efficacy, personalized treatment methods, such as protocols tailored to genetic characteristics, should be developed.

Conflict of Interest: None.

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(Received, January 20, 2025)

(Accepted, March 26, 2025)