Hyperbaric Oxygenation Therapy

Molecular Mechanisms and Clinical Applications

Nariyoshi Shinomiya
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Preface

Hyperbaric oxygen (HBO) therapy is a well-known traditional treatment method for patients with tissue hypoxia. It improves tissue oxygen levels and brings increased capacity of wound healing/tissue remodeling. It also revitalizes the cell activity to increase survival and modulates anti-inflammatory/immunological function of immune cells, which leads to the recovery of hosts from severe infection. The application of HBO therapy has a wide range of choices including carbon monoxide poisoning, infectious diseases refractory to regular antibiotics treatment such as necrotizing soft tissue infections, gas gangrene and osteomyelitis, traumatic ischemia, crush injury, diabetic foot, and so on. It can also be applied for curing diving-related disorders such as gas embolism and decompression illness; in such cases, HBO is used as a specialized method of treatment named recompression therapy. However, HBO therapy is not a dream-like therapy but a complementary one to support other treatment methods or express effects in cooperation with other treatment options. Then why does HBO bring successful outcome in patients with such complicated situations? To understand the effectiveness of HBO, it is essential to clarify basic mechanisms how HBO improves the cellular function of hypoxic tissues and which players are involved in the process of the recovery of cell function. To this end, this book focuses on basic molecular mechanisms of HBO as well as hyperbaric stress itself. Also it introduces how HBO can be applied to the treatment of intractable diseases.

In the first half of this book (Part I), basic molecular mechanisms of HBO and their potential applications for clinical activities are outlined. Chapter 1 describes physiological and molecular basis of HBO therapy. Chapter 2 introduces hosts response against not only HBO stress but also hyperbaric stress itself. Chapter 3 shows a unique concept of HBO preconditioning which might be used for artificial induction of neuroprotection. In the latter half (Part II), the rational how the HBO therapy should be introduced into suitable clinical cases is described with successful clinical reports. Chapter 4 introduces current situation of HBO treatment for strokes and ileus in Japan with the concept of guidelines. Chapter 5 shows basic overview of the treatment of refractory osteomyelitis by HBO with the provision of typical clinical cases. Chapter 6 introduces the fundamental concept how severe soft

tissue injuries should be managed and how HBO therapy can be applied to those cases. Chapter 7 is a unique review that raised a question about the evaluation of HBO therapy as a first-line treatment for carbon monoxide poisoning. Chapter 8 describes basic as well as applied recompression therapies for diving-related disorders such as decompression sickness and arterial gas embolism.

HBO therapy has been proved to show strong effectiveness on several specific diseases based on the clinical evidences, but understanding of precise indication of this regimen how it should be applied to which cases is not clearly achieved. This book provides clear evidences on this issue and answers fundamental questions from the viewpoints of basic physiology and molecular biology.

This book is written primarily for HBO clinicians, but it is also useful for physiologists and basic research scientists. It may also attract clinicians who have an interest in this field and think of starting HBO therapy. We hope systematic knowledge provided by this book will enhance the readers' understanding about HBO therapy and related medical topics so that the HBO therapy becomes more popular and establishes a solid position in modern medicine.

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Contents

Part I
Stress Responses of the Cell Under Hyperbaric/Hyperoxic Environment

Chapter 1
Molecular Mechanisms of Hyperbaric Oxygen Therapy

Nariyoshi Shinomiya

1.1 Introduction

Hyperbaric oxygenation/hyperbaric oxygen (HBO) therapy is a treatment option in which tissue hypoxic condition is improved by providing high pressure oxygen to increase tissue oxygen tensions. It is used for a wide variety of diseases or disorders that are caused by hypoxic conditions, poor tissue oxygen supply due to vascular damage or circulation insufficiency, tissue damages because of injuries or infections, and impairment of tissue recovery. In most cases, HBO therapy is used as adjunctive therapy, but in some diseases such as decompression sickness and arterial gas embolism it is chosen as first-line therapy because of dramatic recovery in clinical cases.

HBO improves oxygen supply to hypoxic tissues because dissolved oxygen can permeate via tissue fluid even if damaged tissues have poor blood circulation. Basic mechanisms of HBO is very simple by just increasing dissolved oxygen, but an increase in the tissue oxygen tensions brings several beneficial effects; it provides the wound with a more favorable environment for repair and facilitates healing [1]. HBO is shown to aid the healing of ulcerated wounds and demonstrated to reduce the risk of amputation in diabetic patients by up-regulation of angiogenesis and collagen synthesis [2]. Ischemia-reperfusion injury is a suitable state for HBO application [3], and the effects of HBO on brain oxygenation, cerebral blood flow, and intracranial pressure [4, 5] are also well described. HBO improves oxygen supply of the ischemic penumbra [6] as well as the cellular bioenergetic metabolism [7]. From the view of molecular mechanisms, HBO suppresses apoptotic cell death pathways by activating the activity of mitochondria and modifying the cellular hypoxia sensor HIF-1α and its downstream pathways. Thus, HBO therapy can be applied to

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prevent injured or infected tissues from damage progression and improve tissue viability against various sorts of histopathological conditions. In this overview, the mechanisms how HBO exhibits its effects are described not only from physiological aspects but also from the viewpoints of molecular mechanisms. Also, clinical indications of HBO therapy and unsolved issues are mentioned.

1.2 General Mechanisms of Hyperbaric Oxygenation

In a word, the main mechanism of hyperbaric oxygenation is to increase the amount of dissolved oxygen and re-oxygenize the tissues in which circulation is disturbed and oxygen supply is decreased. Historically, HBO therapy was first tested in 1662 by an English physician named Henshaw [8], a mobile hyperbaric operating room was introduced in 1879 by Fontaine, and in 1928 an anesthesiologist, Cunningham built a sanitarium for HBO therapy. But HBO therapy had not really taken root in the clinical field until the latter half of twentieth century since the academic basis of the effectiveness of HBO was very weak. Boerema et al. first established a new concept called "life without blood" [9] which consists the most basic part how HBO treatment acts on the body (Fig. 1.1) and explains the clinical value of HBO therapy in the true sense.

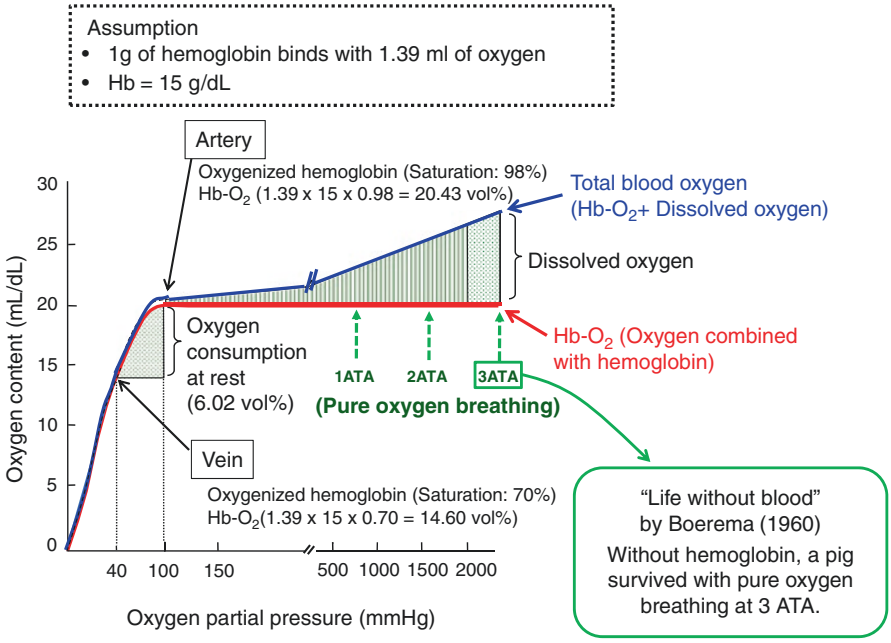

Fig. 1.1 Oxygen transport in the blood. This figure is modified from MGR training Text, vol. 2, p. 174 (2016) with some modification. The original design was provided by Dr. Shinya Suzuki

1.2.1 Basic Physiological Mechanism of Oxygen Transport

HBO is helpful because it provides an excess of dissolved oxygen, which not only can sustain life in the absence of hemoglobin [10] but also stimulates tissue metabolism by activating respiration at cellular levels.

Oxygen existing in the blood consists of two components; one is binding oxygen which directly binds hemoglobin (Hb) and is conveyed to peripheral tissues by blood circulation, and the other is dissolved oxygen which directly dissolved into plasma fluid and can permeate peripheral tissues via direct diffusion. Assuming that 1 g of Hb binds with 1.39 mL of oxygen and blood Hb level is 15 g/dL, the amount of oxygen combined with Hb (Hb-O_2) in the arterial blood (provided oxygen saturation is 98%) is estimated as follows:

1.39 mL/g × 15 g/dL × 0.98 = 20.43 mL/dL (= 20.43 vol%)

Similarly, Hb-O_2 in the venous blood (provided oxygen saturation is 70%) is estimated as follows:

1.39 mL/g × 15 g/dL × 0.70 = 14.60 vol%

Next, dissolved oxygen in the arterial blood at regular condition is calculated as follows when oxygen solubility coefficient to the plasma is assumed as 0.0031 vol%/mmHg and oxygen partial pressure in the alveolus is postulated to be 100 mmHg:

0.0031 vol%/mmHg × 100 mmHg = 0.31 vol%

Similarly, partial pressure of oxygen in the venous blood is assumed as 40 mmHg, so dissolved oxygen in the vein becomes as follows:

0.0031 vol%/mmHg × 40 mmHg = 0.12 vol%

Accordingly, total amount of oxygen in the artery or vein is calculated, respectively, as follows:

Artery: 20.43 vol% + 0.31 vol% = 20.74 vol%
Vein: 14.60 vol% + 0.12 vol% = 14.72 vol%

Oxygen consumption at rest is calculated as a result of subtracting the value of total oxygen in the venous blood from that in the arterial blood:

20.74 vol% − 14.72 vol% = 6.02 vol%

Therefore, 6.02 vol% is considered to be the minimally required blood oxygen level in order to sustain basic metabolism of the body. Once Hb is 100% saturated with oxygen, the increase of Hb-O_2 cannot be expected anymore because an upper limit of oxygen binding capacity for Hb is 1.39 mL/g. However, HBO therapy can increase the oxygen supply according to Henry's law in which the amount of dissolved oxygen increases in proportion to the increased level of partial pressure of oxygen (Fig. 1.1). If pure oxygen is breathed at 3 ATA (≈ 2280 mmHg), dissolved oxygen reaches 6.02 vol% thereby providing theoretically sufficient oxygen

to maintain the life. The fact reported by Boerema et al. that a pig under a severe anemic condition survived with pure oxygen breathing at 3 ATA [9] supports a theoretical part of the effectiveness of dissolved oxygen increased by HBO although it is somewhat an early study.

1.2.2 Physiological Effects of HBO

Physiological effects of HBO are roughly divided into three categories: (1) increase of oxygen partial pressure, (2) direct effect on blood vessels, i.e., vasoconstriction, and (3) increase of physical pressure (Table 1.1).

Table 1.1 Physiological effects of HBO

Direct effect of HBO	Action mechanisms	Physiological effects	Medical conditions for HBO therapy
Increase of oxygen partial pressure	Increase of dissolved oxygen	Increase of blood oxygen content, increase of oxygen transport, oxygenation of circulating blood	Circular disturbances, hypoxic conditions, hypoxia by shunt
	Tissue oxygenation	Enhancement of wound healing, enhancement of tissue regeneration	Refractory osteomyelitis, decompression sickness, arterial gas embolism, ileus
	Increase of tissue oxygen tension	Improvement of tissue hypoxia	Shock, anemia, ischemia, CO intoxication
	Washout of toxic gases	Enhancement of the clearance of toxic gases	CO intoxication, air embolism, decompression sickness, ileus
	Neovascularization	Oxygenation of surrounding tissue, proliferation of fibroblasts	Skin graft, radiation osteonecrosis, chronic wound, obstructive vasculitis
	Stimulation of fibroblast proliferation	Enhancement of wound healing, remodeling of fibrotic scars	Chronic wound, radiation ulcer
	Increase of reactive oxygen species in leukocytes	Enhancement of bacterial killing by free radicals	Clostridial gas gangrene, necrotizing soft tissue infection (necrotizing fasciitis, etc.), chronic osteomyelitis
	Suppression of ICAM-1 expression on endothelial cells, suppression of β_2-integrin expression on leukocytes	Inhibition of leukocyte adhesion on vascular endothelial cells	Ischemia-reperfusion injury, intermittent type CO intoxication

Table 1.1 (continued)

Direct effect of HBO	Action mechanisms	Physiological effects	Medical conditions for HBO therapy
Direct effect on blood vessels	Vascular constriction	Reduction of edema	Crush injury, burn (acute phase), compartment syndrome
Increase of physical pressure	Compression of gases	Reduction of the size of tissue bubbles	Decompression sickness, arterial gas embolism, ileus

Increase of oxygen partial pressure in circulating blood is brought by a condition of increased partial pressure of oxygen in breathing gas unless alveolar function is disturbed. HBO increases oxygen diffusion from the alveolar space to capillaries that surround alveoli, thereby increasing the amount of dissolved oxygen in the pulmonary veins and ultimately in the peripheral arteries after cardiac output. Increased oxygen tension/dissolved oxygen in the blood results in tissue oxygenation and provides improved oxygen supply to damaged tissues, which leads to various subsequent actions including washout of toxic gases [11], neovascularization [12], stimulation of fibroblast proliferation [13], enhancement of bacterial killing [14] by increasing reactive oxygen species, suppression of inflammation by inhibiting adhesion of leukocytes on to the endothelium [15], and so on. Increased blood oxygen content recovers the tissues from hypoxic conditions or circular disturbances, and enhances wound healing, regeneration of damaged tissues, and improves the remodeling of fibrotic scars. It also shows effectiveness in improving refractory infections such as osteomyelitis, infection associated with radiation-induced bone necrosis, and diabetic foot often compromised by vasculitis and infections.

Vascular constriction by HBO therapy is often used for the reduction of edema in cases of crash injuries and compartment syndrome [16, 17]. It is also effective in acute phase burn injuries by removing the edema and improves the circulation of damaged tissues.

Reduction of the size of circulating/tissue bubbles by gas compression effect in HBO is applied to arterial gas embolism [18] as well as ileus [19]. HBO not only improves the circulation by removing obstructive gas bubbles from the blood vessels but also has an effect to re-oxygenize hypoxic tissues.

1.3 Molecular Mechanisms of HBO Actions

In addition to physiological roles of HBO as mentioned above, it stimulates wound healing/tissue repair by promoting the expression of several genes that are involved in fibroblast proliferation, cell migration, and angiogenesis. Also, cells exposed to

a condition of high oxygen concentration produces cytokines or growth factors that regulate the proliferation of surrounding fibroblasts and recruit endothelial progenitor cells.

1.3.1 Gene Expression and Cytokine Production in Wound Healing/Tissue Repair

The effect of HBO on gene expression is characterized by the up-regulation of a series of genes that are mainly involved in cell growth/proliferation, migration, and tissue remodeling (Table 1.2). HBO enhances wound healing by stimulating fibroblast proliferation [13], epithelial cell growth [12], and the production of extracellular matrix [20]. It also has an effect to suppress inflammatory responses [21, 22] that may bring more damages to injured tissues and prevent them from smooth tissue repair. Anti-inflammatory response is mediated by the down-regulation of cytokines such as TNF-α, TGF-β_1, IL-6, and IL-10 [20–22]. In diabetic chronic wound, HBO reduces neutrophil recruitment through the changes in endothelial and neutrophil adhesion molecule expression and function [15]. Also, HBO enhances the mobilization of endothelial progenitor cells from the bone marrow into peripheral blood in the patients with diabetic foot [23]. In that case NOS-NO cascades play important roles in HBO-mediated gene reactions. Hypoxia and hyperoxia is known to intercurrently play an important role in wound healing, and hypoxia-inducible factor 1 (HIF-1) plays a crucial role in wound healing [24]. HBO has a synergistic effect with growth factors by up-regulating HIF-1. Also HIF-1 is involved in ischemic/hypoxic tolerance and HBO has an effect to augment this tolerance [25, 26].

1.3.2 Effect on Vasculogenesis

Vasculogenesis/angiogenesis is an important factor when thinking about advantageous effects of HBO on wound healing. HBO can maximize the viability of compromised skin graft and reduce the need for repeat grafting. Though several mechanisms, including hyper-oxygenation, fibroblast proliferation, and collagen deposition are raised as key roles of HBO, angiogenesis and vasculogenesis are one of the most important factors to make the grafts successful [27].

Vascular endothelial growth factor (VEGF) is the main angiogenic regulator and stimulates the growth of endothelial cells during the tissue repair stage. Since AP-1 sites exist in the promoter region of VEGF and affect its gene expression levels, the status of the upstream pathways, namely stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) and extracellular signal regulated kinase (ERK) pathways plays a key role in effective production of VEGF. Using human umbilical vein endothelial cells, it has been reported that HBO up-regulated the gene expression of VEGF by simultaneously activating SAPK/JNK and ERK pathways [28].

Table 1.2 Molecular mechanisms of HBO in wound healing/tissue repair

Disease/application	Effects of HBO	Molecules involved[a]	Reference
Tendon laceration	Increase collagen synthesis	Pro-alpha1 (I)	[57]
Wound healing	Angiogenic action	VEGF	[58]
In vitro analysis	Fibroblast proliferation	bFGF, VEGF	[13]
Wound healing	Synergistic effect of systemic hyperbaric oxygen and growth factors	HIF-1	[24]
Wound healing	Enhance wound healing by damping pathological inflammation	TNF-α and endothelins ↓ PGE_2 and COX-2 ↓ VEGF ↑	[21]
Diabetic foot	Enhance the mobilization of endothelial progenitor cells from the bone marrow into peripheral blood	eNOS-NO cascade/ SDF-1α	[23]
Impaired wound healing	Effectively reverse the negative effect exerted by macrophage reduction on wound epithelialization and neovascularization	TNF-α, MMP-9, and TIMP-1	[12]
Wound healing	Promotes both angiogenesis and nitric oxide production, decrease in endothelial IL-8	Angiogenin	[59]
Diabetic chronic wounds	Reduce neutrophil recruitment, through changes in endothelial and neutrophil adhesion molecule expression and function	iNOS	[15]
Wound healing in colonic anastomosis	Anti-inflammatory effects	TNF-α, IL-6, and IL-10 ↓	[22]
Periodontitis	Quick regeneration of extracellular matrix, quicker resolution in both soft tissue and bone remodeling	Collagen expression ↑ $TGF\text{-}\beta_1$ and alkaline phosphatase ↓	[20]

[a]*VEGF* vascular endothelial growth factor; *bFGF* basic fibroblast growth factor; *HIF-1* hypoxia-inducible factor 1; *TNF-α* tumor necrosis factor alpha; *PGE_2* prostaglandin E_2; *COX-2* cyclooxygenase 2; *eNOS* endothelial nitric oxide synthase; *NO* nitric oxide; *SDF-1α* stromal cell-derived factor-1α; *MMP-9* matrix metalloprotease 9; *TIMP-1* tissue inhibitor of matrix metalloproteases 1; *iNOS*-inducible nitric oxide synthase; *IL-6 and IL-10* interleukin 6 and interleukin 10

HBO is also reported to induce placental growth factor (PlGF) expression in human bone marrow-derived mesenchymal stem cells [29]. PlGF is a growth factor that stimulates revascularization of ischemic tissues. Since the production of PlGF as well as the induction of migration and tube formation was significantly blocked by the addition of N-acetylcysteine, the oxidative stress-related pathways are considered to be involved in HBO-induced vasculogenesis.

HBO stimulates the growth and differentiation of vasculogenic stem cells by activating a physiological redox-active autocrine loop. This activation of thioredoxin

system leads to elevations in hypoxia-inducible factors (HIF-1/2) followed by synthesis of HIF-dependent growth factors such as VEGF and stromal cell-derived factor-1 [30]. Thus, HBO stimulates vasculogenesis not only by directly activating vasculogenic stem cells but also promoting the autocrine system to enhance their proliferative reaction.

1.3.3 Effect of HBO Against Infections

Classically, HBO has been proven to have a direct bactericidal or bacteriostatic effect on anaerobic organisms. Therefore, clostridial infections were considered as the most suitable indications for HBO therapy among various infectious diseases [31–33]. However, HBO is also proven to be effective for nonclostridial infections [34]. Necrotizing fasciitis, sometimes called Fournier's gangrene, when it is seen around the perineal region is caused not only by anaerobic bacteria but also by aerobic bacteria or the cases are often mixed infection of both organisms. Besides having anti-bacterial effects, HBO suppresses inflammatory responses and mitigates tissue damage which is caused by infection. HBO also enhances wound repair by improving tissue oxygenation and removing edema. In addition to those pre-evaluated effects, recently HBO is reported to be effective on the bacteria that have poor ability to repair oxidative damage to DNA such as *Vibrio vulnificus* [35]. Also, HBO seems to augment the killing effect of some antibiotics [36, 37].

1.3.4 Stimulation of Stem Cell Recruitment

HBO treatment mobilizes bone marrow-derived stem/progenitor cells by a free radical mediated mechanism. Interestingly in 2005, it was reported that endurance training increases the number of endothelial progenitor cells (EPCs). According to the report a significant increase in circulating EPCs was positively correlated with the increase of NOx synthesis [38]. At the same period, it was reported that HBO-induced elevation in stem cell factor and circulating stem cells in the peripheral circulation and the NO was an important factor to induce this phenomenon [39]. In knockout mice lacking genes for eNOS, stem cell mobilization did not occur. Besides, pretreatment of wild-type mice with a NOS inhibitor prevented the HBO-induced elevation in circulating stem cells. Thus, the importance of NOS-NO system in stem cell recruitment was recognized, which dramatically enhances wound repair in the patients receiving HBO therapy.

Using a mouse model, HBO has been proven to exert a trophic effect on vasculogenic stem cells [30]. Also, it was shown that skin wounds from diabetic patients undergoing HBO therapy exhibited higher expression of CD133, CD34, hypoxia-inducible factor-1, and thioredoxin-1 than those without HBO therapy [40]. This

clearly suggests that HBO therapy stimulates vasculogenic stem cell mobilization from bone marrow of diabetics and more cells are recruited to skin wounds.

Recently, it has been reported that putative progenitor cell mobilization seems to be significantly higher in those treated at 2.5 ATA than those treated at 2.0 ATA [41]. Although higher oxygen stress has toxic effects and sometimes harmful on damaged tissues, it induces more NO radicals and those NO radicals may act in the promotion of tissue regeneration by recruiting endothelial progenitor cells. This may be an important effect to be considered when we use HBO therapy.

1.3.5 Flow of the Molecular Mechanisms of HBO Actions

Taken together, the flow of the molecular mechanisms of HBO actions is drawn as Fig. 1.2 [42]. Hyperbaric oxygenation improves oxygen environment/conditions surrounding damaged tissues, and this induces subsequent gene reactions. The basis of molecular actions after HBO are supported by the up-regulation of growth factors, stem cell recruitment, HIF-1 response to hypoxia, improvement of phagocytic functions of neutrophils, chemotaxis of phagocytic cells to the tissue, and

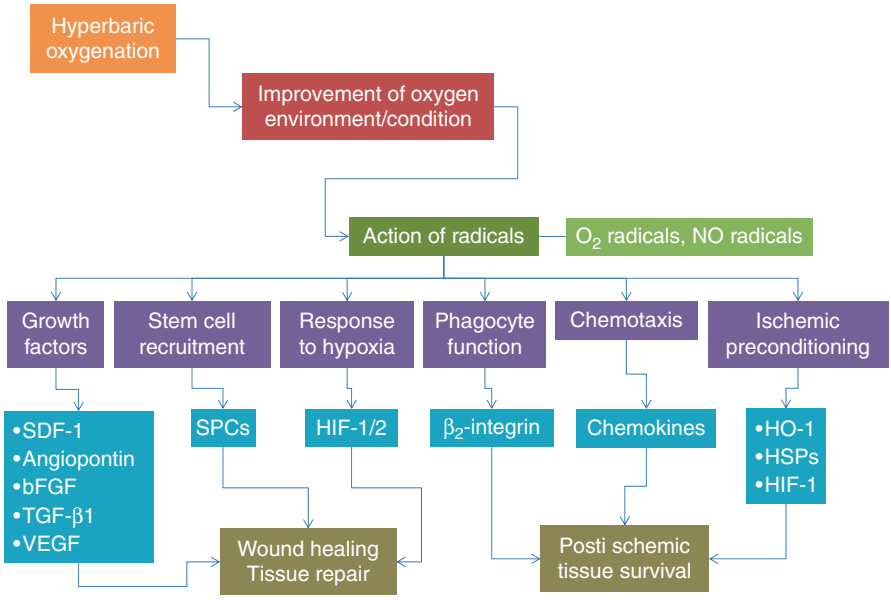

Fig. 1.2 Flow of the molecular mechanisms of HBO actions. This figure is modified from the concept of Thom, S. R. [42]. *NO* nitric oxide; *SDF-1* stromal cell-derived factor-1; *bFGF* basic fibroblast growth factor; *TGF-β1* transforming growth factor beta 1; *VEGF* vascular endothelial growth factor; *SPCs* stem/progenitor cells; *HIF-1/2* hypoxia-inducible factor 1/2; *HSPs* heat shock proteins

preconditioning of the ischemic wound to enhance the resistance to hypoxic conditions; all of those gene responses are regulated via the production of reactive oxygen species (ROS; O_2 radicals) or NO radicals.

1.4 Hyperbaric Oxygenation and Molecular Biology

1.4.1 Gene Expressions

Godman et al. performed a genome-wide microarray analysis of gene expression using human microvascular endothelial cells (HMEC-1) exposed to HBO [43]. Highly up-regulated genes included immediate early transcription factors (Fos, FosB, and JunB) and metallothioneins. Six molecular chaperones working in protein damage control were also up-regulated immediately after HBO treatment. Pathway analysis programs identified the Nrf-2-mediated oxidative stress response as one of the primary responders to HBO. They concluded that those gene expression changes in endothelial cells may be beneficial for improving current HBO protocols.

1.4.2 HIF-1

A hypoxia-related factor, HIF-1 is one of the most important molecules that are closely involved in the enhancement of wound healing/tissue repair as well as acquiring resistance ischemic stresses when patients receive HBO treatment. The neuroprotection induced by HBO preconditioning is mediated by an up-regulation of HIF-1 and its target gene is recognizes as erythropoietin [25]. In the treatment of osteonecrosis, HBO inhibits osteoclast formation and bone resorption. The action of HBO is reported to be at least in part mediated through a reduction in RANK, NFATc1, and Dc-STAMP expression and inhibition of HIF-1 [44]. Activated HIF-1 by HBO therapy also contributes to improved wound healing in a diabetic condition [45].

1.4.3 N-*Methyl-*D*-Aspartate (NMDA) in the Brain*

Although HBO is used for the treatment of brain damages such as CO toxicity, global brain ischemia, and cerebral infarction, it sometimes induces convulsions and deteriorates the treatment results. The reason for the neurotoxic effects of HBO is considered to be an activation of *N*-methyl-D-aspartate (NMDA) receptors and production of NO [46, 47]. To overcome such adverse effect, HBO therapy with NMDA antagonist is being tried and restored neurologic scores are reported [48]. The mechanism underlying the neuroprotective effects of the combined treatment

is, therefore, considered to lie in alleviated blood–brain barrier permeability, inhibited inflammatory response, and up-regulation of the antioxidant enzyme activity.

1.4.4 Wnt, JNK, and MMP Pathways

HBO treatment is also reported to increase other signal pathways. Wnt processing, secretion, and signaling is involved in osteogenic differentiation of mesenchymal stem cells [49]. Regarding the JNK signaling pathway, HBO therapy suppresses its activation and attenuates ischemia-reperfusion testicular injury [50], whereas it is up-regulated when human coronary arterial endothelial cells were exposed to HBO, resulting in an increase in the production of adipocytokine, visfatin which is involved in endothelial angiogenesis [51]. Little is known about the impact of HBO treatment on matrix metalloproteinase (MMP) production. Recently, HBO has been reported to reduce MMP in ischemic wounds through a redox-dependent mechanism [52]. HBO increases the expression of antioxidant enzymes, such as Cu/Zn-superoxide dismutase, catalase, and glutathione peroxidase, but it decreases pro-oxidant enzyme levels, such as iNOS and gp91-phox. This suggests that HBO reduces tissue degradation and improves ischemic wound healing by regulating the ROS/MAPK/MMP signaling axis.

1.5 Clinical Indications for HBO Therapy

HBO therapy is a well-known treatment method which improves the patients with tissue hypoxia. Recent reports have also shown that it brings successful outcome in patients with complicated infections or in those with diabetes and other immunocompromised status. Some reports show it is effective as an adjunctive therapy for severe infection with extensive tissue damage. These reports will open a new way for HBO applications. Although HBO therapy is a very effective and promising treatment method for the improvement of tissue ischemia/hypoxia, tissue injury by increased production of reactive oxygen species that have adverse effect such as DNA damage, lipid peroxidation, and inactivation of enzymes (Fig. 1.3). Therefore, the effect of HBO should be taken into account as a result of the balance between tissue injury and treatment effect.

Here, standard clinical indications for HBO therapy which are accepted by most medical communities and research societies are displayed with specific concepts for clinical applications (Table 1.3). The indications include 14 diseases/disorders authorized by UHMS and four additional diseases. Most diseases have been authorized by all of four areas (UHMS: USA, ECHM: Europe, ANZHMG: Australia/New Zealand, JACHOD/JSHUM: Japan), but some are not because of controversial results of clinical studies. For example, regular oxygen breathing and blood

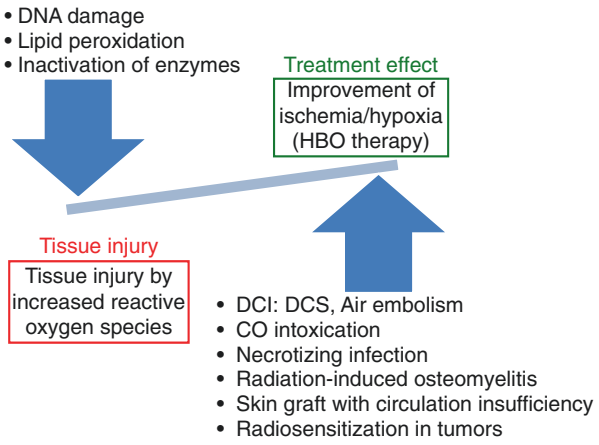

Fig. 1.3 Effect of HBO as a balance between tissue injury and treatment effect. HBO improves tissue ischemia or hypoxia by increasing the blood oxygen content, thereby applying for the treatment of various diseases as shown here. At the same time, HBO increased the production of reactive oxygen species which cause DNA damage, lipid peroxidation, and inactivation of enzymes, all of which induce tissue injury and damage the organs. Therefore, the effect of HBO is expected as a result of balance between tissue injury and treatment effect

Table 1.3 Clinical indications for HBO therapy

Diseases	Specific descriptions	Authorization by societies/groups[a]			
		UHMS	ECHM	ANZHMG	JACHOD, JSHUM
Air/gas embolism	Usually called recompression therapy; use US Navy Treatment Table 6A or 6	Yes	Yes	Yes	Yes
Carbon monoxide poisoning	Suitable HBO treatment table for CO poisoning is still controversial	Yes	Yes	Yes	Yes
Clostridial myositis and myonecrosis (gas gangrene)	Preferred therapy is a combination of debridement, antibiotics, and HBO (HBO is an adjunct therapy)	Yes	Yes	Yes	Yes
Crush injury, compartment syndrome, and other acute traumatic ischemias	Oxygen tensions in the tissue fluids greater than 30 mmHg are required for the indication of HBO therapy	Yes	Yes	Yes	Yes

Table 1.3 (continued)

Diseases	Specific descriptions	Authorization by societies/groups[a]			
		UHMS	ECHM	ANZHMG	JACHOD, JSHUM
Decompression sickness	Usually called recompression therapy; use US Navy Treatment Table 5, 6, 6A, 4, 7, or other treatment tables	Yes	Yes	Yes	Yes
Arterial insufficiencies					
Central retinal artery occlusion	HBO therapy must be initiated before the retinal tissue is irreparably damaged	Yes	Yes	Yes	Yes
Enhancement of healing in selected problem wounds	Indications in this area include diabetic foot ulcers	Yes	Yes	Yes	Yes
Severe anemia	Normobaric oxygen is considered a class I indication while HBO may be a class IIb indication	Yes	No	No	No
Intracranial abscess	Patients for HBO therapy should be carefully selected	Yes	No	Yes	Yes
Necrotizing soft tissue infections	HBO is an adjunct therapy to surgical debridement, antibiotic therapy, and critical care for infections	Yes	Yes	Yes	Yes
Osteomyelitis (refractory)	HBO therapy is considered an American Heart Association class II recommendation	Yes	Yes	Yes	Yes
Delayed radiation injury (soft tissue and bony necrosis)	HBO can mobilize stem cells by increasing nitric oxide (NO)	Yes	Yes	Yes	Yes
Compromised grafts and flaps	HBO therapy at 2.0 ATA enhances the survival of flap and graft skins	Yes	Yes	Yes	Yes

(continued)

Table 1.3 (continued)

Diseases	Specific descriptions	Authorization by societies/groups[a]			
		UHMS	ECHM	ANZHMG	JACHOD, JSHUM
Acute thermal burn injury	HBO contributes to vascular permeability and improves phagocytic and killing function of neutrophils	Yes	Yes	Yes	Yes
Idiopathic sudden sensorineural hearing loss	Steroids, vasodilators, and HBO are used for treatment; the evidence level is class IIa	Yes	Yes	Yes	Yes
Ileus	HBO reduces gas load and improves intestinal circulation; HBO therapy should not be used for strangulation ileus	No	No	No	Yes
Adjunct to radiotherapy (in treatment of solid tumors)	HBO prior to radiation increases oxygen tensions inside tumors and enhances radiotherapeutic effects	No	No	Yes	Yes
Global brain ischemia/brain edema/cerebral infarction (acute phase)	Although HBO has neuroprotective mechanisms, the effect on global brain ischemia is still controversial	No	Optional/ non-accepted	No	Yes
Myocardial infarction/ischemia	In animal experiments, HBO decreases the necrotic area, but clinical effects remain to be investigated	No	No	No	Yes

[a]Information about the societies and groups are as follows: Undersea and Hyperbaric Medical Society (UHMS) (https://www.uhms.org/resources/hbo-indications.html). The European Committee for Hyperbaric Medicine (ECHM): seventh European Consensus Conference on Hyperbaric Medicine, Lille, December 3rd–4th 2004; ECHM "recommended" indication for HBO therapy, ECHM Workshop report [60]. The Australia and New Zealand Hyperbaric Medicine Group (ANZHMG) accepted indications [61]. Japanese Association for Clinical Hyperbaric Oxygen and Diving Medicine (JACHOD): http://square.umin.ac.jp/jachod/pdf/guideline_pdf/guideline_vr1.pdf. The Japanese Society of Hyperbaric and Undersea Medicine (JSHUM): http://www.jshm.net/P01/tekiou_160818.pdf

transfusion is first-line therapy for severe anemia in most countries, whereas the UHMS suggests it as class IIb indication. In contrast, ileus except a strangulation case is a popular indication for HBO therapy in Japan but not in other countries. Also, HBO has neuroprotective mechanisms on stroke and brain diseases but the effectiveness is still controversial.

1.6 Challenges Remain Unsolved

Although the mechanisms how HBO exhibits the effectiveness on the indicated diseases are analyzed in both basic and clinical studies and in most of them clear explanations have been made, clinical cases often result in poor outcomes. This is a difficult point in which dissociation clearly exists between theoretical background and actual clinical practices.

For example, HBO therapy for carbon monoxide (CO) poisoning is officially recognized as an effective therapeutic approach by the societies dealing with hyperbaric medicine. However, a systematic review report on the effectiveness of HBO for CO poisoning by Buckley et al. [53] concludes *"Existing randomised trials do not establish whether the administration of HBO to patients with carbon monoxide poisoning reduces the incidence of adverse neurologic outcomes. Additional research is needed to better define the role, if any, of HBO in the treatment of patients with carbon monoxide poisoning. This research question is ideally suited to a multicenter randomised controlled trial."* This shows a very difficult aspect of clinical activities. Even if Weaver et al. designed and performed an excellent double-blinded randomized control study and showed the effectiveness of HBO therapy for CO poisoning [54], many other negative clinical studies deny HBO effects. Therefore, the approach by systematic review has some sort of limitations to prove the true effectiveness in case right clinical patients are selected for right regimen. A similar story exists in the management of necrotizing fasciitis [34] and other severe soft tissue injuries.

The other challenge for us is to chase more precise mechanisms of HBO actions, which gives us a chance to understand the pathophysiology of diseases. HBO treatment is considered to be effective in the prevention of delayed neurological sequela that frequently occur after exposure to CO, but the mechanisms of the disorder has not been clearly elucidated yet. A hypothesis presented by Thom et al. that HBO prevents immune-mediated delayed neurological dysfunction following CO poisoning [55] provides a unique viewpoint. Also, Kilicaslan et al. showed that tau protein levels were significantly higher in patients with severe neurological symptoms [56], indicating a possibility of the development of new diagnostic system for predicting the severity of CO poisoning. These are just examples in the research field of CO poisoning, and there remain a lot of subjects about HBO to be investigated.

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Chapter 2
Host Response Against Hyperbaric Diving Stresses

Nariyoshi Shinomiya

2.1 Introduction

Diving is an underwater activity which is used for many different directions, such as recreational purposes, fishing, scientific research, military operations represented by mine-sweeping, commercial dives for oil drilling in the offshore oilfield, and resource development under water. Since diving is used for a wide variety of purposes, various types of diving methods as well as diving apparatus have been developed. Because underwater environment is quite different from regular atmospheric condition, to safely reach a certain amount of depth and perform intended underwater activities for a scheduled period of time there are several physiological problems to be solved. Among those, air/oxygen supply and protection from hydrostatic pressure changes are two most important issues in diving physiology. Others include changes in breathing gas density in deep depth which may affect divers' breathing capability, hypothermia in cold water, narcotic effect of inert gases, psychological stress, and so on. Also decompression after work at the bottom is a major issue to keep safe diving. Thus divers are exposed to a series of diving-related stresses most of which are attributed to underwater condition. In exploratory activities using a submersible vehicle near atmospheric condition is guaranteed for crew members, but they only can see things through the observation window or monitor camera. On the contrary, divers can touch underwater things directly and perform precise work at their request. Here how various hyperbaric diving stresses affect human bodies will be discussed from the viewpoint of host responses by looking over the physiological, biochemical, and immunological mechanisms.

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2.2 Various Types of Diving and Their Stresses

There are various kinds of diving activities and each of them has very unique characteristics that may affect the responses of human bodies. The factors include types of diving themselves, types of gas supply systems, and types of breathing gases.

2.2.1 Types of Diving

Diving is classified into several different types according to the purpose. Because risks and physiological effects may vary depending upon the types of diving, first we need to well understand which type of diving has what characteristics (Table 2.1).

One of the most important differences among those types of diving is whether divers are provided with breathing gas during diving or not. In the breath-hold type diving, divers can only breathe just before diving, thereby oxygen consumption becomes the limiting factor of duration time and diving depth. Hyperventilation before diving decreases the blood carbon dioxide content, which enables breath-hold divers to stay down longer but is very dangerous because they do not feel the need to breathe until the arterial oxygen tension has fallen to levels which stimulate the carotid chemoreceptors [1].

Other types of diving have breathing gas supply while divers go into the water. This brings the dissolution of inert gases into the blood stream or body tissue while divers are exposed to pressure. During the phase of decompression, dissolved inert gas may become oversaturated and make bubbles inside the body, which causes circulatory disturbance and tissue damage. This is called decompression sickness (DCS) or decompression illness (DCI), and the existence of a patent foramen ovale is a risk factor for the divers [2, 3].

Most of the names of diving come from the equipment or system that divers use, such as SCUBA (self-contained underwater breathing apparatus) diving, helmet diving, and PTC (personnel transfer capsule) diving. But saturation diving is quite unique in the physiological point that divers are saturated with inert gas during diving, which enables them to stay the bottom as much time as they want. In this type of diving, decompression time is not affected by the bottom time but only by the saturation depth. Thus, the deeper the saturation depth becomes, the longer the decompression time needs.

2.2.2 Types of Gas Supply Systems

Air (or diving gas depending upon the types of diving) supplying system is important for divers to decide how deep and long they can stay underwater.

Table 2.1 Various types of diving and their characteristics

Type of diving	Used gases[a]	Diving depth	Diving purposes	Characteristics
Breath-hold diving	Air	<20 m	Recreation, fishing	Usually use a mask, a snorkel, and fins
Freediving (breath-hold)	Air	>100 m[b]	Competing diving depth (a kind of sport diving)	Use special weight and device to quickly reach deep depth; very dangerous, a minor trouble may lead to death
SCUBA diving	Air, Nitrox	<40 m	Recreation, fishing, scientific research, military purposes such as mine-sweeping and explosive ordinance disposal (EOD) activities	Open-circuit scuba is popular, but semi-closed or closed-circuit diving apparatuses (rebreathers) are also used depending upon the purposes
Technical diving	Air, Nitrox, Heliox, Trimix	40–150 m	Recreation, scientific research	Requires diving skills and complicated decompression tables
Helmet diving	Air, Nitrox, Heliox	40–100 m	Salvage, fishing, research of seabed, military purposes (mine-sweeping, etc.)	Divers are connected with an umbilical hose that supplies air or other breathing gases
Pneumatic caisson working	Air, Nitrox, Heliox, Trimix	<100 m	Construction of bridges, subways, city infrastructure, etc	Divers (caisson workers) work in a dry condition
PTC diving	Air, Nitrox, Heliox, Trimix	<150 m	Salvage, research of seabed, military purposes	Use a personnel transfer capsule (PTC) for conveying divers to the diving depth; divers' decompression is performed in a deck decompression chamber
Saturation diving	Air, Nitrox, Heliox, Trimix	<300 m[c]	Salvage, research of seabed, commercial purposes (oil excavation, etc.), military purposes (submarine rescue, etc.)	Once divers are saturated with the environmental breathing gas, the length of bottom time does not affect the decompression profile

[a]Nitrox (N_2-O_2), Heliox (He-O_2), Trimix (He-N_2-O_2)
[b]Depth record in "No limit" genre is 253.2 m (established by Herbert Nitsch on June 6, 2012) [77]
[c]Depth record is 701 m (H_2-He-O_2 was used as breathing gas)

Breath-hold diving is the simplest type of diving with very brief equipment. Divers usually wear a mask, a snorkel, and fins. There is no mechanical air supply, so diving range, i.e., depth and time, basically depends on divers swimming/diving skill.

The development of SCUBA has dramatically improved divers' activity range and now it is widely used for recreational diving. The most popular SCUBA is an open-circuit form that releases used gases into the open water. Other types of

SCUBA include semi-closed or closed-circuit diving apparatuses (rebreathers) which are often used for special covert operations such as mine-sweeping/explosive ordinance disposal (EOD) activities because they produce very small or no bubbles during an operation. In a simple SCUBA diving, compressed air is usually used. In semi-closed or closed-circuit type diving, Nitrox (mixture of nitrogen and oxygen at a fixed ratio) gas as well as air is used. In a special form of SCUBA diving named "technical diving", very complicated usage of air and other types of gases such as Nitrox, Heliox (mixture of helium and oxygen), or even Trimix (mixture of those three gases) is employed.

Surface-supplied diving is a form of diving in which the breathing gas is supplied from the surface boat. Divers are connected with the breathing gas hose and all the diving procedures are well controlled. This type of diving is not suitable for recreational purposes but often applied for fishing, salvage, and military purposes. Helmet diving is one of this type.

For PTC diving or saturation diving, a large sophisticated system specially designed for its purpose is required (Fig. 2.1). First divers are pressurized to the intended depth in a deck decompression chamber (DDC), and then they move to a PTC (sometimes the capsule is called "diving bell" but it is remnant from the days when bell-shaped diving apparatus was actually used in the very beginning of this type of diving). In an actual diving activity PTC is pulled down from the support vessel and transferred into the deep sea. When the PTC reached the scheduled depth, divers open the hatch and go out for work. Diving gas is supplied from the support vessel to the PTC, and divers breathe the gas via an umbilical hose that

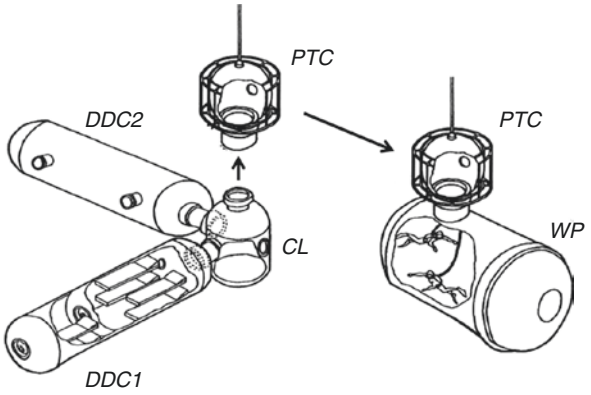

Fig. 2.1 Deep diving simulator. Deep diving simulator is a training system for PTC diving and saturation diving. Divers are pressurized to the scheduled depth and live in a deck decompression chamber (DDC). In this figure, the system has two DDCs, DDC1 and DDC2, as its backup. In the diving activity, the divers move into a personnel transfer capsule (PTC) through a center lock (CL), and then the PTC is disconnected from the CL. The PTC goes down into the deep sea to reach the desired depth. In a diving simulation, wet pot (WP) is used for an alternative of deep sea environment. In a regular PTC diving, three members make one team (one leader and two divers). In actual diving operation, this type of system is equipped on the diving support vessel

anchor them to the PTC. Since divers live mostly in a dry environment in a chamber and go out for diving like a short trip, such diving process is called “excursion diving”. Defining difference between PTC diving and saturation diving is that the former finishes the entire process of diving within 1 day and the divers are not saturated with inert gases, whereas the latter takes much longer time. Because PTC diving is used for deep (up to 150 m/500 ft. depth) and short term diving, sometimes it is also called “bounce diving”.

2.2.3 Types of Breathing Gases

The choice of breathing gas is also an important limitation factor for diving types. Compressed air is the cheapest and the most frequently used breathing gas, which is generally applied for SCUBA. Because nitrogen in the air has high solubility in the body tissue fluid and produces an anesthetic effect to cause nitrogen narcosis, the air is not suitable for the diving deeper than 30 m. Also nitrogen is not utilized for physiological metabolism, i.e., physiologically inert, thereby becoming a main causative factor for decompression sickness. Therefore, mixed gas of nitrogen and oxygen to reduce the composition of nitrogen named “Nitrox” or “Oxygen-enriched air” is preferably used for the diving deeper than 30 m depth. In deeper and longer diving situation such as technical diving and helmet diving, to reduce disadvantageous effects of nitrogen as well as respiratory resistance mixed gas of helium and oxygen named “Heliox” is usually used. It is essential to use Heliox as a breathing gas in the system diving such as PTC diving or saturation diving in which divers have to work in an extremely deep underwater condition. Since helium is very expensive, to reduce the cost of breathing gas “Trimix” the mixed gas of helium, nitrogen, and oxygen is often used for pneumatic caisson working, but this makes decompression schedule more complicated. In a very special occasion such as the deepest manned saturation dive performed by a French diving company Comex in 1992 (HYDRA 10), gas mixture of hydrogen, helium and oxygen (Hydreliox) was used, and one of three divers reached 701 m seawater depth (7.11 MPa) [4, 5].

2.3 Physiological Stress of Diving

Diving induces various stresses depending upon its type (Table 2.2). Also many risk factors associated with various types of diving modify the pathological process of diving-related disorders. Therefore, symptoms or diseases as the result of diving stress may be diverse and cannot be explained by a simple reason. Stressors associated with diving include hypoxia (in case of breath-holding underwater), high pressure or pressure changes, hyperbaric oxygenation, inert gas accumulation, bubble formation in the body tissue associated with decompression, and so on.

Table 2.2 Diving types and their stresses to human

Types of diving	Risks and stresses	Diseases/disorders
Breath-hold diving	Cerebral hypoxia	Shallow water blackout
	Air bubble formation due to repetitive dives	Taravana syndrome [78, 79] (a form of decompression sickness)
Scuba diving	Inert gas bubble formation due to poorly managed decompression	Decompression sickness (DCS)/ decompression illness (DCI)
	Rapid ascent, pulmonary barotrauma	Arterial gas embolism
Technical diving	Complicated decompression operation, wrong decompression profile	Severe DCS/DCI
	Gas trouble, oxygen poisoning	Drowning
Helmet diving	Hard work in the deep followed by unregulated decompression	DCS/DCI
	Blow up	Arterial gas embolism
PTC diving	Diving process is well regulated by the staff and risk is low. Long decompression time may be psychological stress for divers	DCS/DCI (low risk)
Saturation diving	Unusually high pressure, rapid compression	High pressure nervous syndrome, high pressure arthralgia, hyperbaric bradycardia
	Humid and relatively high oxygen partial pressure condition	Ear infection (otitis externa)

2.3.1 Bubble Formation Associated with Decompression

Under a hyperbaric condition, inert gas such as nitrogen in the regular diving or helium in the system diving accumulates in the tissue depending upon the solubility. When divers ascend to the surface, the ambient pressure decreases and the inert gas becomes an oversaturation status. Then excess inert gas makes bubbles and cause tissue damage, blood flow disturbance and inflammation. This is considered to be the cause of the clinical manifestations named DCS.

Generally, bubbles produced in the peripheral tissue return to the pulmonary circulation in which most of them are trapped by the capillaries and absorbed. But when many bubbles are produced, they may accumulate in the peripheral tissue or directly obstruct blood vessels and cause serious tissue damage. Accumulation of bubbles in the joints of extremities may cause pain only disease (Type I DCS), whereas those in the spinal cord/brain or lung induce more serious symptoms including neurological, inner ear and cardiopulmonary symptoms (Type II DCS). As shown elsewhere, patent foramen ovale (PFO) (Fig. 2.2) helps the transition of bubbles from right-sided circulation to left-sided circulation and may modify the symptoms more like arterial gas embolism (AGE). The term of DCI is often used for the disorder which result in overlapping sets of symptoms of DCS and AGE. Therefore, decompression disorder in which PFO may be involved is commonly called DCI rather than DCS. The presence of PFO and its size correlates well with the risk of developing DCI [3] and also corresponds to more severe phenotypes [6].

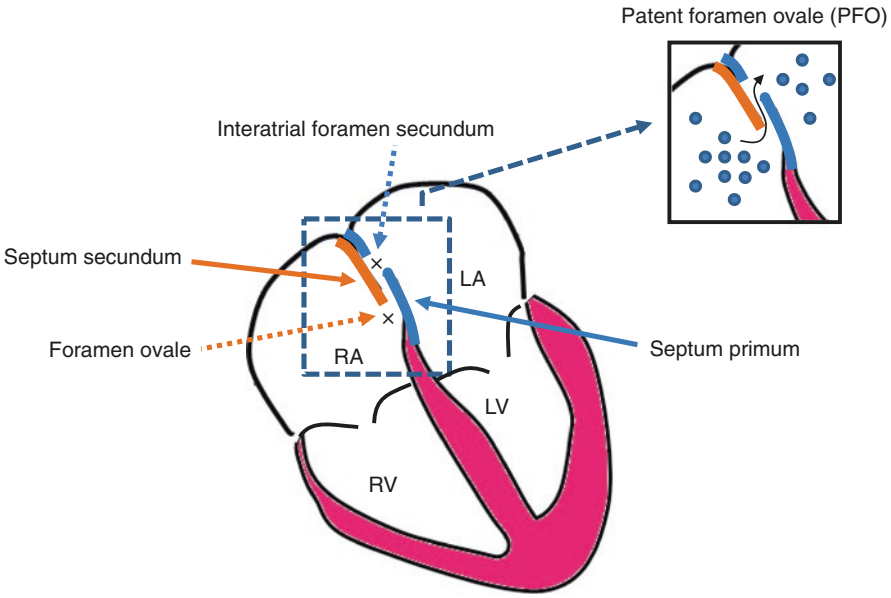

Fig. 2.2 Anatomy of the heart and patent foramen ovale (PFO). The existence of patent foramen ovale (PFO) may be a risk factor for DCI because bubbles can translocate from right atrium to left atrium (upper right box) and ultimately be conveyed to central nervous system through arteries, which causes arterial gas embolism. Thus, bubbles associated with decompression in an individual having PFO may cause not only DCS like symptoms but also AGE-like symptoms. *RA* right atrium; *RV* right ventricle; *LA* left atrium; *LV* left ventricle

In addition to the circulatory obstruction, bubbles associated with decompression induce complement activation [7] especially the alternate pathway in which C3a and C5a are more involved [8, 9]. Therefore, a reduction in complement levels such as total Ca3 after exposure to dives may be a good tool for a high estimated risk of DCS [10]. The complement activation also upregulates the function of polymorphonuclear leukocytes [11], which accelerates tissue inflammatory responses and induces the aggregation of platelets and clot formation, leading to further obstruction of microcirculation and tissue damage [12]. It has also been reported that circulating vascular gas bubbles cause endothelial dysfunction [13].

Both audio Doppler ultrasound and echocardiographic techniques are useful tools for bubble detection. Bubble levels after decompression may be a good indicator to predict the risk of DCS development [14] but it is also well known that the bubble score does not necessarily correlate with the incidence of DCS. So far Doppler technique has not been considered to be of diagnostic value in the absence of other clinical information [15]. Bubble grades are affected by personal factors like with age, weight, maximal oxygen uptake and body fat percentage [16]. Such bubbles that do not cause overt DCS are called “silent bubbles”, so the development of methods to accurately investigate the load and size of bubbles developed will be required [17].

Because DCS has a probabilistic nature, it is almost impossible to completely avoid this disorder. The best way to prevent DCS is to keep the body in good health condition and obey the safety rules about decompression schedule. Also use of oxygen inhalation just before or during the decompression process is theoretically supported because it has a beneficial effect for bubble reduction by enhancing the washout of tissue nitrogen load [18]. Compared to air breathing, oxygen brings wider "oxygen window" that causes a partial pressure difference of inert gas between the inside and outside of decompression bubbles [19]. In addition, provision of oxygen reduces platelet activation, thereby suppressing inflammatory response induced by tissue damage [20].

Recently it has been reported that oxygen inhalation prior to diving reduces the risk of DCS via nitric oxide production in a rat model [21]. Oxygen preconditioning also induces heat shock proteins such as Hsp70, which is involved in tissue protection [22]. In human studies have suggested that endurance exercise in a warm environment, oral hydration, and normobaric oxygen breathing is a good measure for preventing bubble formation and ultimately reduces the risk of DCS [23, 24]. More recently, pre-dive whole-body vibration is reported effective for DCS risk reduction [25].

2.3.2 Host Stress Response in Deep Saturation Diving

Saturation diving is a special form of diving in which divers stay in a hyperbaric (pressurized) environment for more than 24 h, which makes inert gas saturated and equilibrated inside the body fluid. Divers live in a dry condition when they are not working. Because divers go into a transfer capsule named PTC and move to the underwater working place like a short trip, diving operation in the wet environment is called excursion diving. Although decompression requires much longer time than other types of diving, divers can work at very deep condition for a long period of time. Exposure to extremely high pressure condition brought by saturation diving such as deeper than 150 msw (>1.57 MPa) induces quite unique stresses to human body.

2.4 Physiological Effects of Hyperbaric Stress

2.4.1 Nitrogen Narcosis

Nitrogen has an anesthetic effect in a high pressure condition. Divers breathing air under an environment deeper than 30 m feel euphoric, and if they dive much deeper neurological signs and symptoms including delayed response, laughter and loquacity tendency, hallucinations, etc. become more obvious and ultimately lead to unconsciousness. To reduce the risk of those neurological manifestations and

improve diving operability, use of nitrogen should be avoided in the diving deeper than 50 m. Narcotic potency of helium is 1/22 times as small as that of nitrogen. That is why helium is commonly used as an alternative inert gas to nitrogen. Trimix gas is preferably used for caisson workers or technical diving divers and Heliox is used for helmet diving, PTC diving and saturation diving.

2.4.2 High Pressure Nervous Syndrome (HPNS)

High pressure nervous syndrome or high pressure neurological syndrome (HPNS) is first described as "helium tremors" in 1960s [26]. This type of neurological manifestations is observed in helium compressed divers at depth more than 150 m. Typical HPNS is characterized by tremor, somnolence, and electroencephalogram (EEG) changes. Especially the appearance of slow waves, i.e., increased slow wave (θ, 4–8 Hz) and decreased fast wave (α, 8–13 Hz) activity well describes the changes in EEG [27].

Gamma-aminobutyric acid (GABA) transmission is well known to be involved in some seizure disorders, thereby its activity has been implicated in HPNS-related tremors. Using isolated synaptosomes suppression of GABA efflux at high ambient pressure was observed, and it has been postulated that alteration in synaptic transmission in the central nervous system with the inhibitory neural pathways may be affected in HPNS situation [28]. It is also suggested that both NMDA (*N*-methyl-D-aspartate)-related events and GABA inhibition are involved in the helium pressure-induced hyperexcitability [29].

The severity of symptoms depends on the compression rate and the diving depth. Therefore, introducing slow rates of compression or adding some compression stops is considered to be effective to prevent HPNS development [30]. Also, the usage of Trimix gas at a nitrogen concentration of up to 5% may be effective to prevent HPNS since nitrogen has a narcotic effect that could suppress the neurological symptoms during saturation diving [31].

2.4.3 High Pressure Arthralgia

High pressure arthralgia or compression arthralgia is caused by exposure to high ambient pressure at a relatively high compression rate [32]. Most frequently affected joints are knees, shoulders, back, and hips, but other joints are also included. Pain onset commonly occurs more or less 60 m depth. Because compression speed in saturation diving is much slower than that of other types of diving, saturation dives usually do not feel joint pain at shallow depth. Divers often feel discomfort or roughness other than pain. Gas pressure inside the joint may cause a form of osmosis and fluid shift, but exact etiology remains unknown. Compression arthralgia is generally well distinguished from DCS because it occurs during compression or

staying at the bottom and pain is relieved by decompression. Similar to the case of HPNS the use of Trimix breathing gas could reduce the symptoms of high pressure arthralgia [33].

2.4.4 Hyperbaric Bradycardia

Hyperbaric bradycardia is the status in which diver's heart rate (HR) drops while they are exposed to high pressure. Generally, diver's HR at rest in a normal pressure condition shows 60–80/min, but it may drop to 30–40/min in a pressurized condition. In an animal model that were compressed to high pressure with Heliox, a decrease in spontaneous HR and prolonged P-R and Q-T intervals of the electrocardiogram (ECG) associated with significantly increased ventricular contractility was observed [34]. Because marked bradycardia rapidly appears at the beginning of compression [5], increased oxygen tension in the breathing gas is considered to be the main reason for this bradycardia. But in much deeper situation, changes in duration of myocardial cell repolarization due to increased intrathoracic pressure changes with dense-gas breathing may also affect the HR. It is actually reported that hydrostatic pressure contributed to bradycardia in divers pressurized to the depth as deep as 5.5 bar (550 kPa) [35] The effect of hyperoxia on decreased HR is more obvious in an HBO condition. The role of autonomic nervous system in hyperoxic bradycardia evaluated by using the power-spectral analysis of heart-rate variability revealed the fact that 100% oxygen breathing under pressurized condition caused marked increase in parasympathetic tone compared with 21% oxygen at the same pressure [36]. Although HR is a good parameter of static work load, it might underestimate the work load at the hyperbaric environment due to hyperbaric bradycardia, and also overestimate it after decompression because of the so-called decompression tachycardia [37].

2.4.5 Breathing Gas Resistance

The resistance of breathing gas increases as the pressure increases, and the increase in resistance is about linear with gas density in saturation diving to 457 m [38]. Air or Nitrox is not suitable for deep diving because of its high specific gravity in addition to narcotic effect. To solve such a problem, using helium instead of nitrogen as an inert gas (in an actual situation breathing gas is Heliox) is introduced to deep saturation diving. Because specific gravity of nitrogen (= 0.967) as compared to air is 7 times higher than that of helium (= 0.1381), respiratory resistance is much reduced in Heliox breathing. Yet, gas density of Heliox in saturation diving for example at 350 m (3.6 MPa) depth corresponds to 5 times as heavy as that of air in 1.0 ATA (0.1 MPa) environment. Therefore, saturation divers working in deep depth are forced to do labored breathing even if they are provided with relatively

light gas. In very deep dives such as a series of HYDRA projects pressed forward by French diving company COMEX, hydrogen (actually Hydreliox) was used as divers' breathing gas [39] and 701 m dive was performed in HYDRA 10 project in 1992.

Helium has a very special phonetic property and it causes voice to become high-pitched so-called Donald Duck voice. Divers under hyperbaric conditions often experience a marked deterioration in speech intelligibility that is caused by the changes in speaking fundamental frequency [40]. Communication between saturation divers inside the pressurized chamber and supporting team members on the deck is performed through the voice changer which translates the helium voice into understandable voice conversation according to the phonetic property. However, conversation between saturation divers at deep depth environment is often very difficult, which makes them very stressful.

2.4.6 Other Stresses Associated with Saturation Diving

Other types of stress associated with saturation diving includes biochemical changes in circulating blood and peripheral tissues. Precise cause is unknown, but most of the cases are considered to be caused by the combination of hyperoxic and hyperbaric conditions. A reduction in hemoglobin concentration and an increase of ferritin concentration after saturation dives has been reported, but the changes are too small to be of clinical significance [41]. Liver dysfunction after saturation diving is also reported [42, 43]. Supplementation of anti-oxidants may help resume liver function during saturation diving [44].

2.5 Diving Stress and Immune Function

2.5.1 Types of Diving and Immune Function

Diving-associated infection has been frequently reported [45–47] and one of the reasons is ascribed to diving-associated situational immunosuppression [48]. An early study showed the elevation of basophilic granulocytes and atypical lymphocytes at the end of a series of dives, which suggests some kind of inflammatory changes induced decompression-associated venous bubbles [49]. Potential immunological changes associated with diving mostly include a decrease in $CD4^+$T cells and CD4:CD8 ratio. There may also be an increase of neutrophils and an activation of the complement pathways during decompression [50]. Using a rat model with repetitive exposure to 7-ATA air diving, it has been shown that key lymphocyte activities such as $CD3^+$ and $CD4^+CD3^+$ lymphocyte subsets in peripheral blood and spleen, plasma IL-2 levels, and the responses of splenic lymphocytes to concanavalin A (ConA) stimulation were all decreased [51]. Recent studies also supported

the involvement of bubbles after decompression on the suppression of lymphocyte functions and reciprocal activation of neutrophils/macrophages [52] as well as the upregulation of inflammatory cytokines such as NF-κB, IL-6, and TRL4 [53].

Freediving is a special field of diving in which divers compete in diving depth, horizontal distance, or time of apnea depending upon the type of discipline. Freedivers hold their breath while diving, thereby causing hypoxia and hypercapnia. One of the recent reports on the effect of apnea associated with freediving has indicated a temporary increase of neutrophil granulocytes, and a decrease of cytotoxic lymphocytes such as $CD8^+$T cells and NK cells [54]. It also shows temporary activation and recruitment of neutrophil granulocytes with the upregulation of MMP9, TLR3, TLR 2, and IL-8 genes.

Although the phenotypes of immunological changes somehow seem to be similar to those in other types of diving (Table 2.3), diving stress during saturation dives is considered quite different from those types of stress because immunosuppressive changes mainly occurs in the high pressure stages and not during or after decompression [55, 56]. Divers exposed to unusually high pressure show the decrease in lymphocytes and monocytes and reciprocal increase in polymorphonuclear leukocytes. A decrease in T cells especially in $CD4^+$T cell fraction is remarkable and thus CD4:CD8 ratio is significantly suppressed during the bottom period. On the contrary, NK cells, which play an important role in innate immunity, show a dramatic increase in their fraction and cytotoxicity [55–57]. This type of immunosuppression might be caused by the combination of hyperbaric stress, hyperbaric oxygen, and psychologic stress (Fig. 2.3) [58]. Because lymphocyte subset changes are strongly affected by the deep pressure and/or pressurizing speed [59], hyperbaric stress is considered to be the most important factor among them. Figure 2.4 is the summary of the changes in T cell and $CD4^+$T cell fractions in eight saturation dives that were performed in Japan Maritime Self Defense Force Undersea Medical Center. The results clearly show a positive correlation between the diving depth and suppressive effect on T/$CD4^+$T lymphocytes. Confinement and isolation, which is a very unique situation in saturation diving, does not seem to affect divers' immune function [60, 61] and a decrease in T/$CD4^+$T cell fractions was not obvious in saturation dives shallower than 150 m, which is quite similar to the threshold of HPNS; Compression-related increase in θ activity and reduction of fast α and β frequencies in EEG was obvious in the depth deeper than 150 m, and tremor appeared at 305–350 m which became marked at 480 m [62]. Thus, lymphocyte subset changes could be used as biomarker for hyperbaric stress detection in human. However, these immune changes associated with saturation diving are considered at least partially offset by acclimatization, and so far seem to have little clinical significance.

2.5.2 Diving-Associated Oxygen Stress on Immune Function

In any kind of diving, divers breathe the gas containing higher partial pressure of oxygen than air at ambient pressure (= 0.21 ATA, 21 kPa). Thus, diving is always associated with oxygen stress. In HBO therapy, to improve tissue oxygenation pure

Table 2.3 Changes in immune function associated with diving

Types of diving	Diving depth	Duration	Decompression	Changes in lymphocyte subsets				Reference
				T/B	CD4/CD8	NK cells	Others	
Repetitive air diving	150 ft. sea water gauge for 30 min	12 consecutive days	Standard U.S. Navy decompression	N.D.	N.D.	N.D.	Elevation of basophilic granulocytes and atypical lymphocytes	Eckenhoff and Hughes [49]
Saturation diving (Heliox)	440 m	30 days	Duke-GKSS	T↓	CD4↓ (CD4:CD8 ratio↓)	NK↑	Increase in polymorphonuclear leukocytes, decrease in monocytes, γ/δT cells↑	Shinomiya et al. [55]
Saturation diving (Heliox)	4.1 MPa (400 msw)	39-day	Duke-GKSS	T↓	CD4↓ (CD4:CD8 ratio↓)	NK↑	N.D.	Matsuo et al. [56]
Heliox saturation diving	2.64 MPa (254 msw)	19.3 days	During decompression PO_2 was ~50 kPa, except for 8 h around each of the first 10 6-h Night-stops, when Po 2 was reduced to; 35 kPa	N.D.	N.D.	NK cell cytotoxicity↑	N.D.	Krog et al. [57]
Nitrogen-oxygen (Nitrox) saturation dive	30 m (400 kPa)	9 days		N.D.	N.D.	NK↓	CD69↓ Granulocytes↓	Shimamiya et al. [80]

(continued)

Table 2.3 (continued)

Types of diving	Diving depth	Duration	Decompression	Changes in lymphocyte subsets				Reference
				T/B	CD4/CD8	NK cells	Others	
Scuba diving	50 m	Total time of 35 min	A decompression of 3 min at a depth of 6 m and another one of 6 min at 3 m	N.D.	N.D.	N.D.	NF-kB, IL-6, TLR4 gene expression ↑ (inflammatory and immune response of neutrophils)	Sureda et al. [53]
Scuba diving	18 msw	Stayed at the bottom for 47 min, performing light physical exercise	Ascended to the surface at a linear rate of 9 m per min	N.D.	Activated T cells↓: CD8+ CD45.1+	NK cells↓: NK1.1+ TCRb− Ly49H+ NK cells↓: NK1.1+ CD3− Ly49C/I+	Neutrophils↑: CD11b+ Ly6-G+ Macrophages↑: CD45+ F4/80+ CD11b+ Classical monocytes↑: HMCII-, CD115+ B220− CD43+ Ly6C+	Eftedal et al. [52]

N.D. not determined

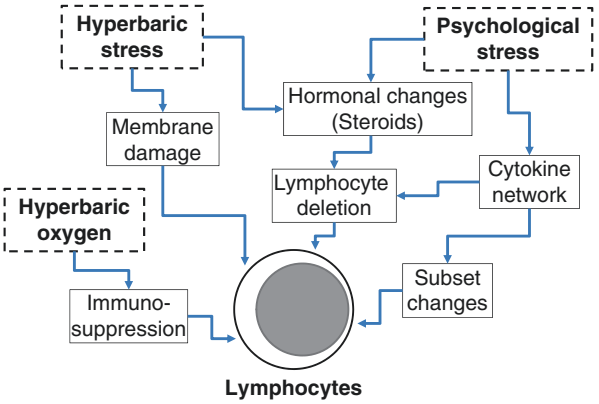

Fig. 2.3 Immunosuppressive mechanism during deep saturation diving. A model for immunosuppressive mechanism during deep saturation diving is proposed. This scheme has been modified from the original figure [58] with some modification

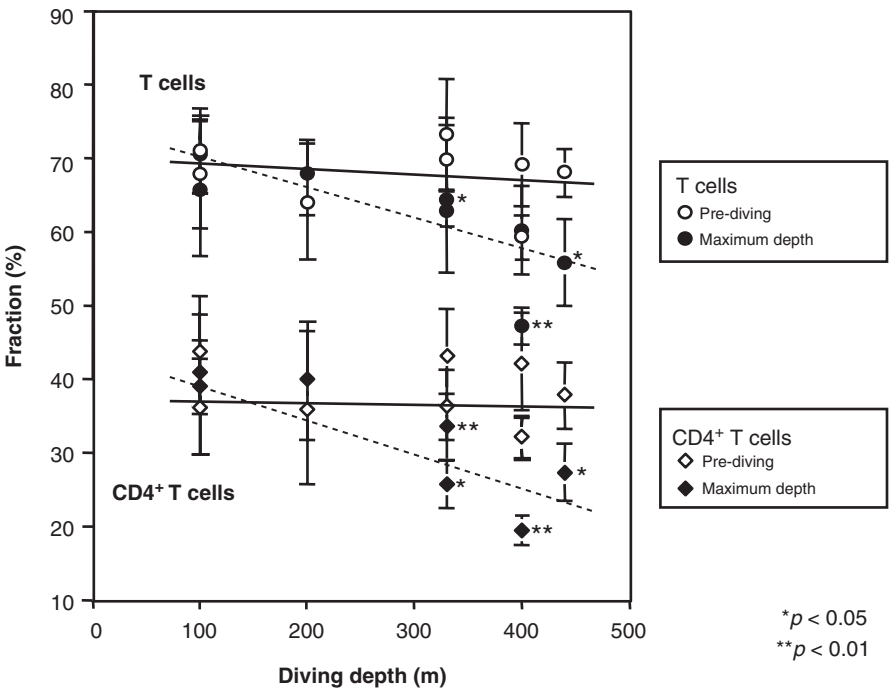

Fig. 2.4 Changes in lymphocyte fraction during saturation diving. Relationship between diving depth and the lymphocyte fraction of T cells or $CD4^+$T cells was investigated in eight saturation dives which consist of two 100 m (1.1 MPa), one 200 m (2.1 MPa), two 330 m (3.4 MPa), two 400 m (4.1 MPa), and one 440 m (4.5 MPa) depth dives, respectively. In each diving, five to six divers served as test subjects. As the diving pressure increases, a decrease in T cells and $CD4^+$T cell fraction becomes remarkable. $*p < 0.05$; $**p < 0.01$. Correlation curves represent T cells in pre-diving (solid line): $y = -0.006x + 69.474$ ($r = 0.177$), T cells at maximum depth (broken line): $y = -0.042x + 73.854$ ($r = 0.765$), $CD4^+$T cells in pre-diving (solid line): $y = -0.005x + 39.938$ ($r = 0.167$), and $CD4^+$T cells at maximum depth (broken line): $y = -0.045x + 45.241$ ($r = 0.820$), respectively

oxygen up to 3.0 ATA (294 kPa) may be used, but to perform advantageous decompression and avoid oxygen toxicity partial pressure of oxygen in the breathing gas in diving is restricted to be less than 1.4 ATA (137 kPa). Therefore, oxygen stress in diving if any is not considered as strong as that in HBO therapy.

As mentioned above upregulation of NF-κB, IL-6, and TLR4 gene expression after a dive at 50 m depth has been reported [53]. But bubbles are not the only cause of this immune change because neutrophil nitrite levels as indicative of inducible nitric oxide synthase (iNOS) activity progressively increased after diving, suggesting the involvement of oxygen. Diving-associated oxygen stress is also reported to induce DNA double-strand breaks dose dependently (tested at 100, 240, 400, and 600 kPa) [63]. Interestingly, peripheral blood mononuclear cells separated from oxygen diver seemed more resistant to oxygen stress, suggesting the induction of tolerance after exposed to repetitive diving conditions. The effect of HBO on lymphocyte function may be affected by oxygen load. It has been reported that cytotoxic T lymphocyte activity stimulated by ConA was enhanced by exposure to low dose of HBO (100–150 kPa), but was inhibited by exposure to higher pressure-durations [64]. Animal experiments suggest that lymphocyte functions are suppressed by HBO conditions caused by diving stress. 7 ATA air (= 1.47 ATA oxygen) has a temporary immunosuppressive effect and pretreatment with N-acetylcysteine, a potent-free radical scavenger and antioxidant attenuated this effect [51]. Since HBO is known to cause cytokine down-regulation and growth factor upregulation [65], cellular response including lymphocyte subset changes might be affected by such environmental changes inside the body.

2.6 Diving (Hyperbaric) Stress and Heat Shock Protein (HSP) Responses

Heat shock proteins (HSPs) are a series of ubiquitous proteins that control various stress responses at cellular levels. When cells are exposed to micro-environmental stress, e.g., heat shock, hypoxia, and oxidative stress, the production of HSPs is upregulated, which assist intracellular protein transport and degradation of old useless proteins. They also assist protein folding process as molecular chaperones and some of them help transport proteins to be expressed on the cellular membrane and stimulate immune function. We first described that hyperbaric stress associated with saturation diving induces lymphocyte subset changes and heat shock protein expression [56]. Since then the relationship between diving-associated stress and HSP expression has been analyzed in various ways.

Hyperoxia associated with diving may lead to the production of reactive oxygen species (ROS) and affect several biochemical parameters such as HSP70 and glutathione that may play important roles in the mechanisms against the adverse effects of diving [66]. Using DCS animal models, heme oxygenase-1 (HO-1) and HSP70 have been reported to increase in the brain, and HO-1, early growth response protein-1

(Egr-1), and inducible nitric oxidase synthase (iNOS) have proven to increase in the lungs [67], which suggests that they can be used as stress markers for DCS. HSP70 seems to have protective effects against DCS, whereas nitric oxide (NO) seems to be related to bubble formation and endothelial dysfunction that are closely related to the development of DCS. Although the production of HSPs may have a negative effect on endothelial function, it is suggested that HBO preconditioning to increase the HSP levels beforehand could be used to confer cardio-protective effect against venous gas emboli to the host [68]. Using the serum samples from divers involved in saturation dives ranging from 100 to 450 msw, we found that the expression of transthyretin and alpha-1-acid glycoprotein 1 was elevated during the high pressure period in saturation diving [69]. These proteins have a common function as antioxidants, thereby functioning to neutralize the ROS and counteract the effects of hyperbaric/hyperoxic conditions during saturation diving.

A recent report said that heat stress had decreased the NOS activity but hyperoxia (40 kPa) at saturation dives had not affected the NOS activity, suggesting a limited role of hyperoxia in divers' physiological functions during saturation diving [70]. Nowadays saturation diving is performed under a well-regulated condition and it is thought to be a reasonably safe method compared to other types of diving in terms of endothelial integrity and low DCS incidence [71]. Yet, we still have limited knowledge about the effect of diving on the host responses, so many important questions to be solved about pathophysiological mechanisms of diving-associated hyperbaric/hyperoxic stresses have left behind.

2.7 Problems to be Clarified in the Future

To reduce the stresses associated with diving, more sophisticated method to predict DCS should be developed. From a safety perspective, flexible decompression measures depending upon the diving situation will be needed. Regarding the mechanisms of immunological changes during deep saturation diving or in hyperbaric stress conditions, precise pathways how they are controlled are still unclear. We showed Th2 type cells were more easily affected than Th1 type cells in the situation of diving-associated $CD4^{+}$T cell depletion [72]. But the precise mechanism as well as its role in host immune response is unknown. Also, oxygen preconditioning and prevention of diving-related disorders is definitely one of the most important issues to be investigated.

While diving is a very stressful condition for human body, diving capability of marine animals, e.g., sea turtles, whales, and seals is quite different from humans. For examples, sperm whales can dive in average as deep as about 1000 msw and as long as 45 min with a 9 min surface interval [73]. Weddell seals can remain underwater for more than 90 min with no neurological or behavioral impairment [74]. They have a striking difference in globin levels, which facilitates oxygen transfer into neural tissue. Differences between the diving capacity may be ascribed to

the production of ROS and antioxidant levels inside the body, which successfully maintains redox balance [75]. Another mechanism is the late upregulation of HSPs during anoxia, which suggests that stress proteins play a role in promoting long-term anoxia tolerance [76]. Those analyses will help understand the mechanisms of diving stress and may lead to develop the measures for avoiding diving-related disorders in humans.

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Chapter 3
Hyperbaric Oxygen Preconditioning-Induced Neuroprotection

Kojiro Wada

3.1 Ischemic Tolerance

Neuron is considered to be one of the most vulnerable types of cells in the body. Even brief global cerebral ischemia causes irreversible damage to neurons in rodents. This neuronal damage can be reduced by various pretreatment or diverse environmental changes, such as nonlethal hyperthermic stress, nonlethal ischemic stress, oxidative stress, tumor necrosis factor α, and thrombin. The phenomenon of providing resistance to ischemia has been designated "ischemic tolerance" and the pretreatment that induces ischemic tolerance is called preconditioning [1]. It has been suggested that reactive oxygen species (ROS) generated during and after cerebral ischemia play an important role in the development of ischemia-induced neuronal damage. Generally, rodents have the regulation of cellular defense against ROS. But once excessive ROS is generated beyond the ability of endogenous scavenging system after ischemia, neuronal damage may occur. Conversely, if the ability of defense system against ROS is upregulated, the extent of neuronal damage may be reduced. Indeed, the defense system against ROS is upregulated in the brain provided with ischemic tolerance. So far several preconditioning methods have been reported, but it is difficult to apply them to actual clinical conditions because of several obstacles.

Hyperbaric oxygen (HBO) has been used in human for the treatment of stroke, CO poisoning, air embolism, and decompression sickness without any severe side effect. It is well known that the elevation of inspired partial pressure of oxygen enhances ROS production, thereby increasing the risk of oxidative stress to each organ. Oxygen partial pressure of more than 1.4 ATA has a possibility to cause central nervous system (CNS) oxygen toxicity of, but it is not critical unless the oxygen partial pressure exceeds 3.0 ATA [2]. Therefore, the partial pressure of oxygen for

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disease treatment is usually set 2.0 ATA to 2.8 ATA with air break, which greatly reduces the risk of severe CNS oxygen toxicity. Here, we hypothesized that HBO might induce ischemic tolerance by greatly changing the host environment through the generation of ROS at nonlethal level, so an experiment using animal models was conducted to verify it.

3.2 HBO Preconditioning Induces Ischemic Tolerance in the Brain

To determine whether repeated HBO administrations can induce ischemic tolerance in the hippocampus a histological analysis using experimental animals was performed. HBO at 2.0 ATA was administered for 1 h to male Mongolian gerbils either for a single session or every other day for five sessions. Two days after final HBO pretreatment, they were subjected to 5 min of forebrain ischemia by occluding both common carotid arteries under anesthesia. Seven days after recirculation, neuronal density per 1-mm length of the CA1 sector in the hippocampus was significantly better preserved (50% of normal) in the five-session HBO pretreatment group (Fig. 3.1c) than in the ischemic control group (8% of normal) (Fig. 3.1b). This was the first report that demonstrates repeated administration of HBO induces ischemic tolerance in gerbil hippocampal neurons [3].

3.3 Preferable Condition for Ischemic Tolerance Induction by Repeated HBO

To see which condition is more suitable to induce ischemic tolerance, we compared different types of HBO preconditioning; 2.0 ATA HBO once every other day for one, three, or five sessions, 2.0 ATA hyperbaric air (HBA) once every other day for five sessions, or 3.0 ATA HBO once daily for 10 sessions. After each preconditioning the gerbils were

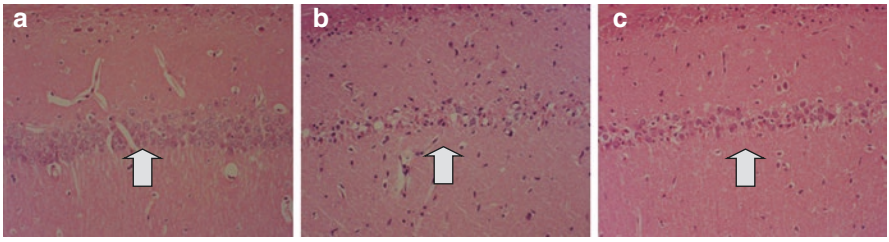

Fig. 3.1 Hippocampal CA1 pyramidal neurons stained by Hematoxylin and Eosin. (**a**) sham operation, (**b**) no pretreatment, and (**c**) 5 times HBO pretreatment. Neuronal density per 1-mm length of the CA1 sector in the hippocampus was significantly better preserved (50% of normal) in the five-session HBO pretreatment group (**c**) than in the ischemic control group (8% of normal) (**b**)

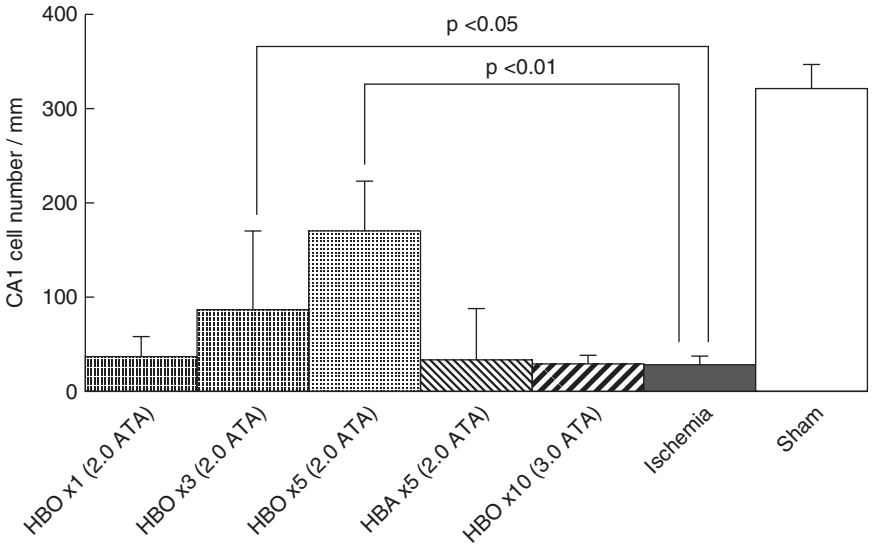

Fig. 3.2 Effect of various HBO pretreatments on the number of CA1 pyramidal neurons in the hippocampus. Pretreatment of HBO at 2.0 ATA increased the number of CA1 cells (induction of ischemic tolerance) depending on the number of sessions (x1, x3, or x5). However, HBO at 3.0 ATA for 10 times did not induce ischemic tolerance

processed for 5-min forebrain ischemia, and histological examinations were performed 7 days later. Ischemic tolerance was induced in the group of pretreatment with HBO at 2.0 ATA once every other day for three or five sessions. However, the induction of ischemic tolerance was not observed in the groups of pretreatment with HBO at 2.0 ATA for one session and HBA at 2.0 ATA once every other day for five sessions (Fig. 3.2). The oxygen partial pressure under 2.0 ATA HBA is estimated 0.42 ATA. Since CNS oxygen toxicity usually requires more oxygen stress than oxygen partial pressure of 1.4 ATA, these results suggest that HBO may promote ischemic tolerance via the production of oxygen radicals under a high oxygen partial pressure condition but not through a simple environmental pressure change. In contrast, the group of HBO at 3.0 ATA once daily for 10 sessions did not induce ischemic tolerance (Fig. 3.2) [4]. Besides, HBO at 3.0 ATA might lead to cerebral vasospasm, suggesting that oxygen radicals may have both beneficial and detrimental effects depending upon the produced amounts.

3.4 HBO Preconditioning in Different Models and Different Organs

The induction of ischemic tolerance using HBO preconditioning may be strain-dependent because HBO preconditioning has been reported to induce ischemic tolerance in SV129 mice but not in C57BL/6 mice [5]. The application of HBO to

induce ischemic tolerance has also been tested using rat models with mid-cerebral artery (MCA) focal and global cerebral ischemia [6, 7]. Neuroprotective effect of HBO preconditioning is also reported in the studies using traumatic and surgical brain injury models [8, 9] and neonatal hypoxia-ischemia. Furthermore, beneficial effects of HBO preconditioning in other organs are reported such as spinal cord [10], heart [11], small bowel [12], optic nerve [13], and liver [14]. In the clinical standpoint, Yogarantnam et al. [15] and Li et al. [6] reported the usefulness of HBO preconditioning in the coronary artery bypass surgery in human.

3.5 Mechanisms of Ischemic Tolerance Induced by HBO Preconditioning

We demonstrated that five-session HBO pretreatment increases the production of 72-kDa heat shock protein (HSP-72) in the hippocampus of gerbil carotid artery occlusion models by immunostaining study [3]. HSP-72 is a well-known protein that is induced in response to a wide variety of stress conditions including brain injury, status epilepticus, cerebral ischemia, and hyperthermia. It has an effect to assist fold proteins correctly, maintain the tertiary structure of normal or partially denatured proteins, and increase the cellular resistance against stressful condition. The upregulation of HSP-72 tends to be observed selectively in the neurons subjected to sub-lethal stress, whereas lethal ischemic damage can be ameliorated by preceding exposure to hyperthermia, brief ischemia, or moderate oxidative stress, all of which can induce HSP-72 response.

Mitochondria are considered a major subcellular source of ROS, and SODs are the most effective endogenous scavenging enzymes involved in the regulation of cellular defense against ROS. Three types of SODs are known: cytosolic copper-zinc SOD, mitochondrial Mn-SOD, and extracellular SOD. Regarding the localization of Mn-SOD immunostaining in the hippocampus, CA1 pyramidal cells are weakly positive under physiological conditions, whereas strong reaction to Mn-SOD is observed in CA3 pyramidal cells. So, the Mn-SOD immunostaining status may be related to the vulnerability of CA1 to ischemia. We showed that the pretreatment of animals with HBO at 2.0 ATA once every other day for five sessions but not with HBO at 3.0 ATA once daily for 10 sessions significantly increased the immuno-reactivity to Bcl-2 and manganese superoxide dismutase (Mn-SOD) in the CA1 sector (Fig. 3.3). Thus, the increase of Mn-SOD levels by repeated HBO pretreatments may play an important role in the induction of ischemic tolerance. Bcl-2 has been demonstrated to keep the mitochondrial membrane integrity and inhibit apoptosis, thereby promoting cell survival. Therefore, the upregulation of Bcl-2 is considered to contribute to the protection of neurons from ischemia. Thus, it is conceivable that HBO pretreatment induced an increased production of anti-apoptotic proteins, which prevented neuronal cells from apoptosis and consequently reduce neuronal cell death.

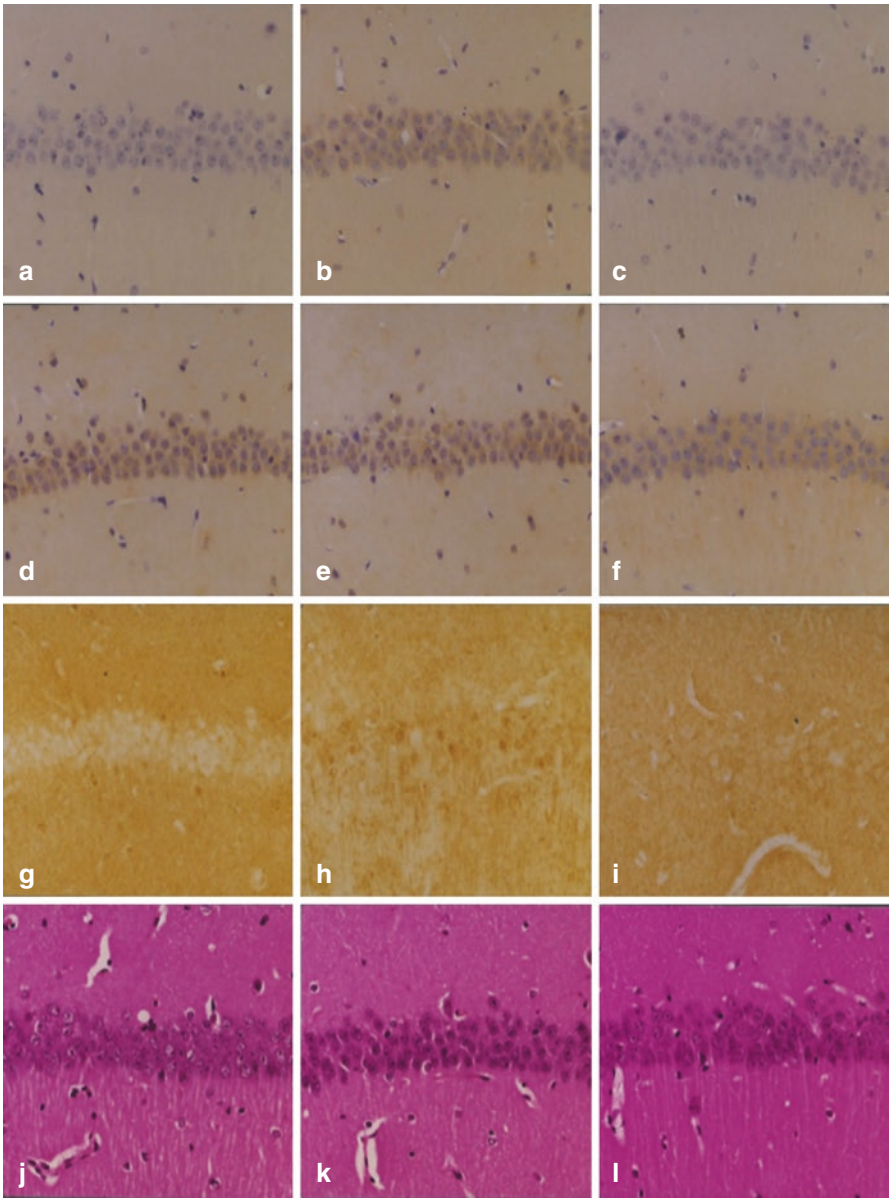

Fig. 3.3 Immunohistochemical study of Bcl-2 (**a**–**c**), Bax (**d**–**f**), Mn-SOD (**g**–**i**). Pretreatment with HBO at 2.0 ATA once every other day for five sessions (**b**, **e**, **h**), but not with HBO at 3.0 ATA once daily for 10 sessions (**c**, **f**, **i**), significantly increased Bcl-2 (**b**) and manganese superoxide dismutase (**h**) immuno-reactivity in the CA1 sector compared to sham treatment (**a**, **d**, **g**). Hippocampal CA1 pyramidal neurons stained with Hematoxylin and Eosin (**j**, **k**, **l**) did not show any significant sign of neurological damage

Precise mechanisms involved in HBO preconditioning-induced ischemic tolerance have not been fully determined. Several candidate pathways have been suggested including the upregulation of hypoxia-inducible factor-1α and its downstream adaptive genes [16, 17], the inhibition of neuronal apoptotic pathways (blockage of caspase-3 and caspase-9 activities) [18] (some reference should be cited), a reduction of early apoptosis [19], the upregulation of antioxidant enzymes [4, 20] (some reference should be cited), or anti-inflammatory mechanisms [21].

3.6 Other Possible Mechanisms of Ischemic Tolerance Induced by HBO Preconditioning

Murry et al. have shown that a brief episode of ischemia slows the rate of ATP depletion during subsequent ischemic episodes to the myocardium [22]. Sarcolemmal K_{ATP} channel opening during brief ischemia of the myocardium appears to be the crucial role. Recently, Heurteaux et al. have shown that activation of K_{ATP} channels is a key step in the beneficial effects of ischemic preconditioning and has been proposed as a way to acquire neuroprotection against brain ischemia [23]. K_{ATP} channels are located in the brain, particularly in hippocampus, and play an important role in controlling neurotransmitter release [24]. K^+ channel openers prevent neurons from ischemia-induced neuronal death by inducing the expression of a variety of genes such as immediate early genes, genes for heat shock protein including HSP70, amyloid P-protein precursor, and growth/neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF).

Here, we asked a question if ATP-sensitive potassium channels are involved in HBO preconditioning. If so, can HBO preconditioning at 2.0 ATA open the K_{ATP} channel and induce ischemic tolerance? To examine this, we tested animal models; just after HBO preconditioning at 2.0 ATA, 3.0 ATA, or sham preconditioning, gerbils were processed for 4 min of forebrain ischemia, and histological examinations were performed at Day 7. Both HBO pretreatment at 2.0 ATA and at 3.0 ATA showed significant more neuronal damage in hippocampus CA1 compared to the sham pretreatment with ischemia group (Fig. 3.4). The result seems HBO cannot induce early ischemic tolerance, not to mean that HBO preconditioning is concerned in K_{ATP} channel opening. However, Quock et al. have reported that HBO-induced acute antinociception might be due to activation of a K_{ATP} channel pathway [25]. Their HBO condition was 5-min breathing of 100% oxygen at 3.5 ATA and quite different from our experimental condition. Therefore, to clarify whether K_{ATP} channel pathway is involved in HBO preconditioning or not, the role of HBO preconditioning at different conditions needs to be investigated.

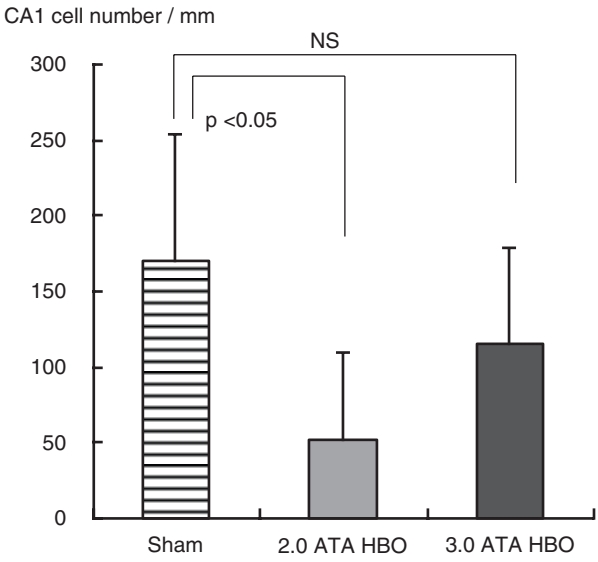

Fig. 3.4 CA1 neuronal density (/mm) after nonlethal ischemia with HBO. HBO at 2.0 ATA once just before 4-min forebrain ischemia did not induce ischemic tolerance. HBO 3.0 ATA once just before 4-min forebrain ischemia also did not show ischemic tolerance, but more survival neurons were observed in this group

3.7 Postconditioning with HBO

Although extensive studies have shown that many neuroprotectants reduce infarction size and improve neurologic functions in animal stroke models, translational studies aiming at clinical applications have suggested only few neuroprotectants can offer practical approaches for substantial protective effects. This necessitates the exploration of novel therapeutic approaches and ischemic postconditioning has recently emerged as a strategy to overcome the problem. Initially ischemic postconditioning was defined in the field of myocardial ischemia research as a series of brief mechanical occlusions and reperfusions, and it has recently proved to be also effective against cerebral ischemia. Its protective effect has been shown to be comparable to that of ischemic preconditioning, which refers to a brief sub-lethal ischemia that prevents ischemic injury caused by a subsequent prolonged lethal ischemia the promotion of neurogenesis and angiogenic remodeling [26]. HBO can also promote neurogenesis [27], and angiogenesis [28], so postconditioning with HBO might have a neuroprotective effect. Postischemic hypothermia has a protective effect in patients with cerebral ischemia [29]. However, ischemic deterioration such as brain swelling during rewarming has been reported as a notable complication after successful implementation of therapeutic cerebral hypothermia. We investigated the effect of HBO as a postconditioning treatment on ischemia during rewarming using a gerbil model. The group of hypothermia with HBO (Hypo + HBO) showed significant preservation of CA1 pyramidal neurons in the hippocampus compared to the sham treatment group which is the group of ischemia without hypothermia nor HBO and the

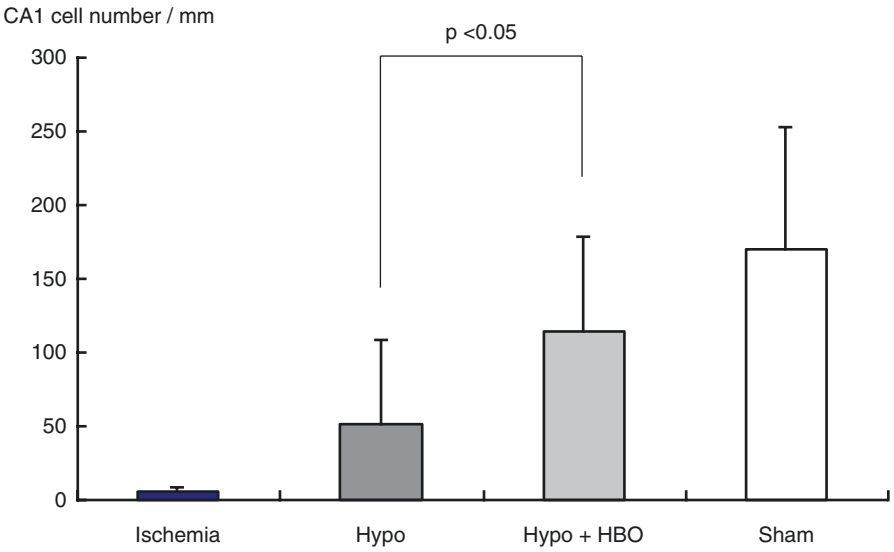

Fig. 3.5 CA1 neuronal density after hypothermia with or without HBO. Treatment with hypothermia just after 5-min forebrain ischemia protected hippocampal CA1 neurons from ischemic damage. This protective effect was enhanced by HBO post-treatment during rewarming

group of hypothermia only (Fig. 3.5). These results suggest that HBO works as a postconditioning effect during rewarming after hypothermia therapy against ischemic neuronal damage.

3.8 Preconditioning for the Prevention of Decompression Sickness

Preoxygenation has been reported to reduce decompression sickness risk during extravehicular activity in space [30]. Pretreatment with hyperbaric oxygenation has also been reported to reduce bubble formation after decompression in human during diving. Even normobaric preoxygenation showed decreased bubble scores in diving. Oxygen pre-breathing before each dive resulted in the highest reduction in bubble scores measured after the second dive compared to the control condition. These findings provide evidence that normobaric oxygen pre-breathing decreases venous gas emboli formation with a prolonged protective effect over time. This procedure could therefore be beneficial for multi-day repetitive diving. In the near future, the role of preconditioning with HBO or NBO in diving will be proven.

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Part II
Application of Hyperbaric Oxygen to the Treatment of Intractable Diseases

Chapter 4
Hyperbaric Oxygenation as an Adjunctive Therapy

Yasufumi Asai and Hiroshi Dohgomori

4.1 Hyperbaric Oxygen Therapy for Stroke/Brain and Other Diseases

4.1.1 Indication of Hyperbaric Oxygen Therapy

In Japan, the following diseases are permitted for this therapy:

Acute carbon monoxide poisoning/Caisson disease/Gas gangrene/Air embolism/Acute peripheral arterial diseases/Acute myocardial infarction /Cerebral embolism/Severe head injury/Hypoxia-related brain functional disorder/Ileus/Disturbance of consciousness after the craniotomy or serious brain edema/Retinal artery obstruction /Spasmodic deafness, etc. [1].

HBO is widely applied for caisson disease (decompression sickness) which is caused by a very rapid return from high pressure to normal atmospheric pressure. It is frequently seen in the divers of Okinawa Island. Nowadays instead of performing hyperbaric oxygen (HBO) therapy for CO poisoning, pure oxygen inhalation is used under end-tracheal intubation with mechanical respirator at many emergency medical hospitals [2].

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4.1.2 The Japanese Guidelines for the Management of Stroke

Recommendation C1 for HBO therapy is described in the Japanese guidelines for the management of stroke (2007). C1 means that the use of HBO therapy may be considered but it does not have enough scientific evidence. Kyorin University reviewed patients who underwent the HBO therapy during the past 3 years [3]. The total number of patients underwent HBO therapy was 60. They concluded that 88% of the patients who had HBO therapy were neurological emergency cases. Among them about 70% were reported to have clinical findings improved. However, they believed that large clinical control studies should be done to establish a confirmative effect.

4.1.3 Medical Remuneration Points

As for brain diseases, HBO therapy is objected to help brain cells work actively. It sends oxygen to every corner of the brain in which oxygen became hard to arrive because of narrowed and clogged-up blood vessels. The HBO effect on patients with cerebral infarction in the acute stage does not have enough scientific background. Therefore, it is important to identify the cause of cerebral infarction whether it is originated from cerebral embolism or cerebral thrombosis. Until 2017 FY, the medical insurance covered HBO therapy with 5000 points in the first 7 days from the onset and with 200 points after the eighth day. For the large multi-patient facility, one HBO therapy for cerebral thrombosis patients in the first 7 days was 6000 points and non-first aid HBO therapy was 200 points. Administration of anti-platelet agent Ozagrel sodium or direct thrombin inhibitor Argatroban were frequently combined as drug therapy. But now medical remuneration point of cerebral infarction has become in a single uniform way as 3000 points. In our facility, to enhance medical safety medical passes (MED-PASS) are used for HBO therapy of cerebral infarction. Although the evidence about the efficacy of HBO therapy is not clearly shown in the guidelines for the management of cerebral infarction in Japan, it has been adopted as an adaptation disease for the medical insurance after a long experience. So, there are many hospitals that have an HBO chamber and perform brain surgeries. In those facilities, HBO therapy is used if necessary.

4.1.4 History of HBO Therapy in Hokkaido

Professor Wada in Sapporo Medical University first started using a portable hyperbaric oxygen chamber to treat CO poisoning in 1963. In 1964, it was used to treat victims of gas explosions in coalmines in Yubari, Hokkaido and Chikuho, North Kyushu. A large hyperbaric oxygen operation room was built in 1966, and used for shunt operation of cyanotic heart disease. In 1969, the fourth International Congress on Hyperbaric Medicine was held successfully in Sapporo. In 1975, Sapporo Medical University extended the survival of anoxic heart using a small portable oxygen chamber, a

metabolic inhibitor, and hypothermia. At the university, HBO therapy is presently used to treat the patients with CO poisoning, idiopathic hearing loss, gas gangrene, vision stricture due to retinal artery occlusion, and diver's disease. In the past, doctors operated hyperbaric oxygen chambers, but in compliance with the wishes of the doctors, medical engineers using HBO chambers have gradually increased in number. At Sapporo Medical University, medical engineers started operating the chamber in April, 2000. Nowadays medical engineer stuffs are handling HBO therapies upon request.

In late years, HBO therapy expands its adaptation range depending on various conditions of the patients and shows a curative effect. In our facility, HBO therapy is applied for the purpose of functional recovery after a micro-vessel rebuilding operation. Education on HBO therapy that is necessary for medical students has just commenced at our university. Even in the universities and postgraduate training facilities having HBO medical treatment equipment, the present condition is not enough for education and training because HBO therapies are not routinely done there. Here medical students receive enough education during their attendance at school and they have chances to use the HBO device. It is necessary to gain extensive experience in the HBO facilities, and it is also demanded from the awareness of a university and facilities to recognize what a society pressure is from the very beginning of the duty. To establish HBO specialists, authorized HBO therapy facilities are actively doing their work.

4.1.5 HBO Treatment in the Second Emergency Care Hospitals

Even in the hospitals dealing with neurological disorders, the indication of HBO therapy is different from one another [4–6]. Present conditions of HBO therapy in the hospitals that specialize in cerebrovascular diseases (second emergency care hospitals) in Hokkaido Island were compared. One is Hakodate Shintoshi Hospital that locates in the southern part and the other is Kushiro Kojinkai Memorial Hospital that covers Eastern Hokkaido, both of which have been registered for the training facility authorized by the Japanese Neurosurgical Society. They are equipped with 3.0 Tesla (T) MRI, 1.5 T MRI, multi-detector row CT (64 lines MDCT), and a monoplace hyperbaric chamber for HBO treatment.

Hakodate is a city with a population of 268,617 people as of 2015 which has been continuously declining. Hakodate Shintoshi Hospital serves as a brain surgery-based hospital with 155 beds. The staff includes 18 medical doctors, 2 dentists, 182 nurses, and 82 physical therapists/radiological technologists. Number of HBO treatment were 417 cases in 2011, 626 cases in 2012, 627 cases in 2013, and 630 cases in 2014. Almost all cases were cerebral infarction (cerebral embolism). Treatment effects include fatigue deceleration such as relieving stiff shoulder and alleviating muscle paint.

At the end of December 2015, the population of Kushiro city was 176,576 people. Kushiro Kojinkai Memorial Hospital equips 232 beds with the staff members of 26 medical doctor 26 and 13 biomedical equipment technicians. Number of HBO treatment during the past 3 years were 1616 cases in 2011 were, 915 cases in 2012, and 896 cases in 2013, respectively. Main diseases for the indication of HBO

treatment were cerebrovascular disease such as cerebral thrombosis and cerebral embolism. Other indications include spinal cord injury, arteriosclerosis obliterans (ASO) of lower limbs, acute peripheral vascular disorder, intractable ulcer of lower extremities, spasmodic deafness, ileus, Buerger's disease, carbon monoxide poisoning, caisson disease with various symptoms, etc.

4.1.6 Experimental Study About Liver

HBO therapy has been used for the treatment of clinical conditions such as gas gangrene, carbon monoxide poisoning, refractory osteomyelitis, osteoradionecrosis, decompression sickness, and so on. In addition, experimental and clinical reports have shown that HBO therapy may improve liver function. Dr. Mizuguchi, et al. in Sapporo Medical University published a paper about the liver function that HBO stimulates cell proliferation and normalizes the localization of multidrug resistance protein-2 in primary rat hepatocytes [7]. Although HBO therapy has been used for many disorders including primary liver non-function, the cellular mechanism how HBO treatment ameliorates liver function is not well understood. Therefore, the purpose of their study was to elucidate the cellular mechanism using primary cultured rat hepatocytes in vitro. Hepatocytes were treated with HBO at Day 1 after plating, and morphological and functional characteristics of bile canaliculi formed in the cultured hepatocytes were observed using time-lapse microscopy. The localization of multidrug resistance protein-2 was observed with a confocal laser scanning microscopy. The labeling index of cultured hepatocytes in the HBO therapy group at Day 2 after treatment was significantly higher than that in the control group. The dilatation of bile canaliculi was much significant in the HBO therapy group than in the control group. In the HBO therapy group, multidrug resistance protein-2 was localized at the apical membrane. These results show that HBO therapy stimulates hepatocytes to proliferate and normalize the localization of multidrug resistance-protein-2 to the apical membrane, which did dilate bile canaliculi.

Arikawa et al. described the efficacy of HBO therapy for postoperative hepatic failure. Postoperative hyperbilirubinemia due to infection is a troublesome condition, which can easily develop into multiple organ failure [8]. They concluded that HBO therapy was significantly effective for the alleviation of postoperative hyperbilirubinemia.

Kobayashi et al. investigated the effectiveness of combined treatment of HBO therapy with carboplatin for recurrent high-grade glioma [9]. However, this combination treatment showed minimum activity against recurrent high-grade glioma with low general toxicity profiles. Further study on the treatment protocol including drug selection, the timing of treatment initiation, and optimal target tumor conditions for this treatment strategy is required.

4.1.7 Conclusion

HBO therapy is used in many facilities and hospitals in Japan that deal with neurological disorders, but indications are quite different from one another depending upon their experience. Therefore, randomized controlled trials (RCTs) should be done to see if the HBO therapy is really effective for them.

4.2 Hyperbaric Oxygen Therapy for Ileus

4.2.1 Term Definitions

In Japanese clinical settings, the state of impaired intestinal passage is generally referred to as ileus [10, 11]. Both paralytic and physical blockages are overall defined as ileus. On the other hand, in the literature from Europe and the United States, the two are defined separately [12, 13]. Thus, it appears that the definition of ileus in Japan differs from that in Europe and the United States. The underlying theme for this book is HBO therapy and ileus; therefore, for our manuscript, the term ileus indicates a dynamic ileus as well as mechanical intestinal obstruction.

4.2.2 Ileus Symptoms, Diagnosis, and Treatment

4.2.2.1 Ileus Diagnosis, Treatment, and Management

Textbook descriptions cite various types of management methods for ileus. These include systemic management, conservative management, and surgical treatment.

4.2.2.2 General Treatment Details

Systematic management details are described for ileus treatment [13–15]. Generally, systemic management includes the correction of electrolyte imbalance. However, there is no mention of concurrent HBO therapy in the literature. HBO therapy has been mentioned in Harrison's Principles of Internal Medicine [13], but there is no mention of the indication of HBO therapy for ileus [14]. A Japanese textbook does not address ileus as an indication for HBO therapy [16].

4.2.2.3 Textbooks on Surgery/Review Articles Regarding Surgery

Regarding the indication of surgery for ileus, there is a mention in the Sabiston textbook of preoperative management, but the textbook does not mention the use of HBO therapy [17].

4.2.2.4 English Review Articles

In 2016, the *World Journal of Gastrointestinal Surgery* notes that for the treatment of ileus, if there is no strangulation or peritonitis, the condition should first be managed by conservative treatment. If no improvement is observed, surgical treatment is recommended [18]. In such treatments, the journal notes HBO therapy as one treatment option prior to surgery. Furthermore, the article by Fukami et al. [19] is cited.

4.2.2.5 Mention in the Guidelines

The guidelines for the treatment of ileus have been published. In the guidelines [20, 21], the treatment for adhesive small bowel obstruction (ileus) is summarized. Among which, in the absence of strangulation, systemic management is initiated, and pressure is reduced by fasting and insertion of a nasogastric tube. If the patient's symptoms do not improve, surgery is performed. Although the duration of follow-up observation differs from 48 to 72 h, this difference is thought to be due to differing conditions. In these guidelines, the article by Ambiru et al. is cited [22], which highlights the usefulness of HBO therapy in elderly patients.

4.2.3 Description of the Relationship Between Ileus and HBO Therapy

Article descriptions of ileus mention details common to diagnosis and treatment. Such descriptions address conservative treatment and surgery. The chapter below describes HBO and cites books, reviews, as well as articles.

HBO: considering the relationship with HBO: textbooks and publication

1. Textbooks and publications

   We searched for publications from Europe and the United States on HBO and ileus. In this search, we were able to find several publications, listed below.

   1. Jain KK edited the Textbook of Hyperbaric Medicine [23]: Textbook of Hyperbaric Medicine, fifth edition Jain KK. This book introduces 10 articles that address the application of HBO therapy [24]. In addition, the article by Amburi et al. indicates the usefulness of HBO therapy in adhesive intestinal obstruction [13], and the same publication includes an article by Takahashi K

[25]. In their article, Takahashi et al. explains the situation in Japan and cites paralytic ileus as an indication for HBO therapy.
2. In the publication edited by Mathieu D, Handbook on Hyperbaric Medicine [26], the indication of HBO therapy for ileus is not addressed.
3. In the publication edited by Bakker et al., Hyperbaric Surgery, ileus as an indication of HBO therapy is not addressed [27].
4. In Hyperbaric Medicine Practice, edited by Kindwall EP and Whelan HT [28], HBO is addressed as an item for off-label disorders of the intestine, and the article by Takahashi [29] is mentioned.
5. In the publication edited by Neumann TS and Thom SR, there is no mention of the application of HBO therapy for ileus [30].

4.2.4 Literature Regarding HBO Therapy: Reviews, Articles, Literature Search, Cochrane Review, and Others

4.2.4.1 Reviews of HBO Therapy for Ileus

There have been Japanese reviews conducted on ileus and HBO therapy [10, 11]. Among which, basic research on HBO therapy, early clinical application, and the action mechanism are described. The review by Ambiru [11] mentions articles that even we were not able to gather. In reference to this content, each of the following is listed in this review.

HBO Therapy and Ileus

The commentaries by Kojima [10] and Ambiru [11] explain basic research and clinical research on HBO therapy. In their review, the mechanism by which HBO therapy acts on ileus is also mentioned.

Concerning early clinical application, the authors were unable to obtain original manuscripts and thus could not verify them. However, according to Ambiru et al., Fontaine JA [31] confirmed the effects of HBO therapy and pointed out in their review that it was Fontaine JA who discovered and demonstrated the effect of HBO therapy for ileus. Thereafter, as in subsequent reports, the article describing animal experiments by Cross FS and Wangensteen [32, 33] was presented. The article by Frittelli et al. [34] was also presented, and this noted the usefulness of HBO therapy for ileus.

The action mechanism of HBO therapy is explained in two reviews in the literature. Ambiru et al. reported the action mechanism in their review [11]. They demonstrated the following details:

1. A hyperbaric environment reduces intestinal volume, thereby improving edema by improving intestinal edema (involvement of Boyle's law).

2. Intestinal blood flow improvement as a result of increased blood oxygen partial pressure (increasing dissolved oxygen) helps peristalsis and restores the absorptive ability (involvement of Henry's law).
3. Increased absorption of nitrogen in the intestinal tract due to the increased pressure gradient caused by oxygen inhalation, the inhibitory action of endotoxin, and the inhibition of bacterial translocation [35] are explained.

4.2.4.2 Mentions of HBO Therapy in the Cochrane Review Library

We searched HBO therapy in the Cochrane library. The results of our search are listed below.

1. In the Cochrane review abstracts, there is no mention of the application of HBO therapy for ileus.
2. We searched the Cochrane library with the keyword of "hyperbaric oxygen." Items found to possibly have a relationship to HBO therapy included the management of radiation injury and rectum-related conditions. However, even in these items, there was no mention of the application of HBO therapy for ileus. Upon searching with the terms "hyperbaric oxygen" and "ileus" there were no results.

4.2.4.3 English Articles That Mention HBO Therapy: A Search of the Literature

A literature search was performed excluding the abovementioned reviews. In the English literature, we found five articles involving ileus. Here, articles examining HBO in the treatment of ileus through basic research and clinical application are presented.

1. Fukami Y. Clinical effect of hyperbaric therapy in adhesive postoperative small bowel obstruction. Br J Surg. 2014;101:433–7 [20].

   Fukami conducted a retrospective study on the treatment of patients with adhesive small bowel obstruction between April 2006 and March 2012. For treatment, either decompression therapy by long tube placement or HBO was performed. HBO involved 100% oxygen inhalation at 2 ATA for 60 min once per day. As a result, during the 6-year period, 305 patients received treatment. In the first 3-year period, 142 patients underwent long tube placement at first. In the latter half, 163 patients received HBO therapy at first. A total of 143 patients (87.7%) who received HBO as the first treatment method in the latter half period were able to complete the treatment without long tube placement. Patients who received HBO were capable of earlier oral ingestion and had shorter hospital stays (days) (10.3 vs. 14.1, $P = 0.001$). The rate of surgery needed for treatment was 7.4% in the HBO group and 14.8% in the group that underwent decompression only ($p = 0.037$). In this study, it was concluded that HBO is a safe and effective treatment for ileus.

2. Ambiru S, Furuyama N, Kimura F, Shimizu H, Yoshidime H, Miyazaki M, Ochiai T. Effect of hyperbaric oxygen therapy on patients with adhesive intestinal obstruction associated with abdominal surgery who have failed to respond to more than 7 days of conservative treatment. Hepatogastroenterology. 2008;55:491–5 [23].

   Ambiru et al. examined the effects of HBO therapy. They divided 685 patients out of the 879 study population into multiple groups. Group I underwent decompression within 7 days after the appearance of symptoms, group II had a period of less than 7 days prior to the start of HBO, and group III had a period of 7 days or more. They reported that patients in Group II showed better resolution rates than those in Group I.
3. Prophylactic effect of HBO against the onset of ileus

   With respect to adhesions causing ileus, some articles demonstrate the prophylactic effect of HBO (recurrence preventive effect). Chen et al. [36] reported that HBO effectively prevented adhesions in rat experiments. In clinical patients, Ambiru et al. [37] reported this prophylactic effect of HBO.

4.2.5 Handling by Academic Societies: Indication of HBO for Ileus

The handling of this topic by medical societies worldwide is discussed below.

4.2.5.1 Indications at the Undersea and Hyperbaric Medical Society (UHMS)

The UHMS notes the application of HBO for 14 diseases and conditions. Among these indications, there is no mention of the application of HBO for impaired intestinal passage such as ileus [38].

4.2.5.2 Academic Societies: Japan and Other Countries

In Japan, the Japanese Society of Hyperbaric and Undersea Medicine have described the indications of HBO. The above-mentioned reports describing the usefulness of HBO therapy are introduced in the article [10, 11]. Although the level of evidence is not high, articles showing the usefulness of HBO are introduced. Problems in the lack of randomization are highlighted, but most reports in Japan suggest the effectiveness of HBO. Although further studies are needed, it is argued that attention should be paid to the effectiveness of HBO.

This article simultaneously reports the situation in scientific societies in different countries. In addition to the UHMS noted above, the authors were unable to

check the European Committee for Hyperbaric Medicine and the Australian and New Zealand College of Anaesthetists and Australian and New Zealand Hyperbaric Medicine Group of the South Pacific Underwater Medical Society, but a review [10] presents the judgment that HBO is not an indication for such cases.

4.2.6 Conclusion

As mentioned by Amburi et al. [11], the application of HBO therapy for ileus is not accepted in Europe and the United States. However, many Japanese publications suggest the effectiveness of HBO. Under these conditions, we believe that more study results are needed to prove the effectiveness of HBO.

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Chapter 5
Treatment of Osteomyelitis by Hyperbaric Oxygen Therapy

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5.1 Introduction

Suppurative osteomyelitis is an inflammatory disease of the bone marrow, cortical bone, or periosteum caused by bacterial infection. It is categorized as acute or chronic osteomyelitis according to the duration of infection, as well as traumatic or hematogenous, based on the cause of the infection. Type of osteomyelitis depends on the patients' age. More than half of the acute hematogenous osteomyelitis cases occur in children younger than 5 year old and chronic traumatic osteomyelitis often occurs in adult patients.

Commonly seen on long bones, e.g., femur, tibia, and humerus, but sometimes, also seen on plain and short bones. Pain, swelling, redness, and heat are seen around the focuses and pus discharge from fistulas in serious cases. Before Alexander Fleming discovered penicillin in 1928 5–10% mortality from osteomyelitis was reported. After that mortality decreased remarkably. These days patients scarcely die from osteomyelitis. Morbidity of osteomyelitis has decreased due to the progress of antibiotics and immediate treatment of injuries. Although antibiotics have progressed, the properties of bacteria are changing and are becoming more resistant. Therefore, we sometimes see serious osteomyelitis cases. Commonly, MRSA (*Methicillin-resistant Staphylococcus aureus*), *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis* are detected as pathogenic bacteria from osteomyelitis.

Basic treatment for osteomyelitis is rest, administration of antibiotics, puncture of abscesses, pus drainage in the early period, wound debridement, etc. If abscesses or bone destruction exist, surgical treatment is necessary, viz., curettage of the focus, sequestrum extirpation, and closed irrigation. If a large cavity exists after the curettage and/or skin condition is bad, we perform a pedicle flap supplementary. In

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case of a large bone defect, we perform a vascular pedicle bone graft or a bone graft using an external fixation. Hyperbaric oxygen therapy (HBO) is adjunctively used in addition to the above treatment. Oxygen tension is remarkably low around the osteomyelitis focus. The aim of HBO is recovery from partial hypoxia.

5.2 Rationale

Using HBO for osteomyelitis increases dissolved oxygen into the plasma and other tissues due to 100% oxygen inhalation under high pressure, even when hemoglobin bound oxygen is fully saturated. By increasing dissolved oxygen certain clinical effects arise. Commonly, oxygen tension in osteomyelitic bones is low, rarely exceeding 25 mmHg. Mader [1] and Niinikoski [2] demonstrated that decreased oxygen tension typically associated with bone infections can return to normal or above normal levels while breathing in 100% oxygen in a hyperbaric chamber. Mader showed that oxygen tension in the tibia of rats which have been infected by *Staphylococcus aureus* was 20.9 mmHg and at the normal tibia was 44.7 mmHg before the inhalation of oxygen. During inhalation of 100% oxygen under 2ATA, oxygen dissolved into the plasma increased to 104 mmHg at the infected tibia and 321 mmHg at the normal tibia.

Oxygen directly kills bacteria due to toxic oxygen radicals. Kuo [3] reported that bacteria is effectively destroyed during HBO inhibiting dihydroxyacid dehydratase due to the amino acid composition. Ata [4] showed that *Escherichia coli* and *Staphylococcus aureus* stopped multiplying completely when cultured in 3ATA oxygen. Jain described aerobic bacteria multiplied more between 0.6 and 1.3ATA and stopped at over 1.3ATA. Hohn [5] proved that the amount of radicals are proportionate to oxygen tension. Moor and Williams proved that 2ATA oxygen inhibits the proliferation and growth of *Mycobacterium tuberculosis* or *Staphylococcus epidermidis* in their experiments. Regarding the effect of HBO against aerobic bacteria, Bornside reported that growth of *Escherichia coli* were inhibited at 1.5ATA.

White blood cells necessitate at, at least 30 mmHg oxygen tension for the leukocyte killing action. However, oxygen tension around the infected bone is estimated up to 20 mmHg (normally 30–40 mmHg). Mader [6] proved that ability strengthened by 40% when oxygen tension is increased from 45 to 150 mmHg.

High oxygen tension strengthens the effect of antibiotics. Jain [7] reported HBO combined with Cefazolin treatment was most effective amongst the 3 groups of rats which were experimentally infected: HBO only, Cefazolin only and HBO plus Cefazolin, on the tibia *Staphylococcus aureus* osteomyelitis. Calhoun [8] reported that even VCM which is susceptible to MRSA is therefore ineffective in hypoxic tissues, HBO strengths the effect of sterilization. Active transport of antibiotics across bacterial cell walls do not occur if tissue oxygen tension is below 20–30 mmHg. Gottlieb [9] described some kinds of antibiotics go through the cell walls more effectively with HBO.

Fibroblasts are not composed of collagen fibers neither do they move into focus if oxygen tension is less than 20–30 mmHg. Hunt [10] proved experimentally that HBO promotes the regeneration of collagen fiber. Increasing collagen fiber is an essential factor for wound healing.

Some reports regarding osteogenesis promotion with HBO, regarding bone formation. HBO speeds up osteogenesis, strengthens ossification, and increases the quantity of bone minerals. Strauss [11] reported that the activity of osteoclasts are elevated with the increase of oxygen tension, bone necrosis is absorbed. Penttinen [12] showed that the ossification formation in experimental mice increased with HBO in the tibial bone fracture. Kindwall [13] stated that HBO increases osteoclast activity and hastens the replacement of necrotic bones. The rationale, behind this theory is that HBO is thought to contribute to the treatment of fractures or after osteotomy. Inoue [14] reported that open osteotomy-fixation model using dogs revealed that mineral appositional rate was enhanced by an average 1.75 times with HBO. However, there are very few clinical studies, as its obvious usefulness has still not yet been built up.

5.3 Clinical Application of HBO for Osteomyelitis

To date, no randomized control trials (RCT) measuring the effects of HBO on osteomyelitis exist. Due to the many clinical trials and studies which have been done, the Undersea & Hyperbaric Medical Society (UHMS) advocates using HBO as a standard treatment for osteomyelitis in addition to antibiotics and surgical treatments. Also, UHMS recommends HBO as class II as recommended by the American Heart Association (AHA) for the management of refractory osteomyelitis and the European Committee for Hyperbaric Medicine (ECHM) recommends HBO as type2, level C. (Type 2 is the second grade amongst the 3 grades which their committee of ECHM has defined as Type 2.)

The first report of a clinical study using HBO for osteomyelitis was initiated by Slack et al. [15] in 1965. In this series, 5 patients were treated with antibiotics and HBO at 2ATA, 80% responded with total clearance of the infection. Thereafter, the therapeutic benefits of HBO were reported in either clinical or animal studies [11, 16–34]. Perrince [16] reported the result of 17 out of 24 cases were good which were unsuccessful with sequestrum extirpation, antibiotic administration, and ostomy. Depenbusch [21] reported that 35 out of 50 osteomyelitis patients (70%) whom antibiotics and surgical treatments did not have effect cured with HBO. Davis [24] reported an 89% success rate amongst 38 patients. Morrey [23] described that 85% of refractory osteomyelitis which had a debridement performed at least once, as well as an antibiotic treatment for 2 weeks still continued with the infectious condition for more than 1 month they were then treated with HBO in addition to the debridement and antibiotics, obtained a much more effective result. Chen reported the cure rate was 86.0% amongst the 15 osteomyelitis cases by the end of 17.2 month (average) after having had HBO treatments.

According to those reports, HBO was adjunctively given with surgical treatment or antibiotic administration. Mader [1] reported on *Staphylococcus aureus* osteomyelitis in rabbits which were treated for 28 days and compared either with HBO, antibiotics, or a combination of both or no treatment (control). Positive ratios of bone culture in all 3 groups were significantly lower than the control group, but there was no significant difference amongst the 3 groups. From this it therefore follows that the treatment with HBO is equivalent to an antibiotic treatment.

5.4 HBO Protocol for Osteomyelitis

HBO protocol for osteomyelitis treatment time, pressure, etc. are slightly different in each country or medical societies. The UHMS guideline indicates 2–3 atmosphere absolute (ATA) 20–40 sessions for 90–120 min. Also, according to 20 reports which we found, three-fourth of facilities operate HBO at 2.4–2.5ATA and the others at 2.0ATA [35]. Moor and Ollodart reported bacterial growth is controlled more under 2.0ATA. Mader suggested that HBO twice a day until infection subsides and should be evaluated after 40 sessions. Hamblin compared the therapeutic effect of 3 groups after 21 days amongst some rat regimen groups using HBO. He concluded that the best therapeutic effective group was at 2ATA 3 times a day for 2 h.

Although HBO is useful for osteomyelitis treatment, we hardly treat it with HBO alone. Commonly, HBO is given in collaboration with antibiotics, wound care, and/or surgical treatment. Figure 5.1 shows the treatment strategy in Kawashima orthopaedic hospital. If it is a mild case, conservative treatment is often enough to improve. But, if they are serious cases, surgical treatments are necessitated in addition to the above treatment. In Kawashima orthopaedic hospital, we adopt curettage and closed irrigation therapy as the main surgical treatment. No HBO treatment is done for 2 weeks during closed irrigation therapy, after that HBO is restarted.

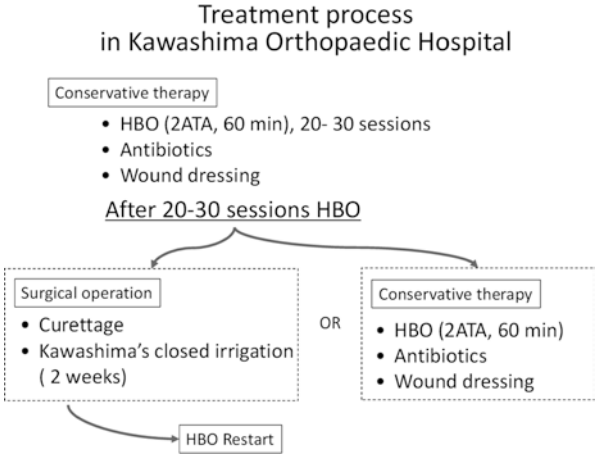


Fig. 5.1 Treatment process of osteomyelitis using HBO

5.5 Closed Irrigation Therapy

The advantage of closed irrigation therapy is: a higher concentration of antibiotics can reach lesions, by filling the cavity with irrigation water, new granulation tends to proliferate.

Figure 5.2 shows the procedure of the surgical operation for closed irrigation therapy. The relevant bone is exposed and a window about 1.5 cm^2 is cut into the cortex to expose the medullary canal. In order to prevent further fractures, the cortical bone should be opened minimally. Then, curettage is performed and the medullary canal is thoroughly washed with water jets. Sequestrum is completely removed. Holes for tube stabilization are made though the bone cortex and then double Salem tubes are inserted. Tubes are infixed to the skin with silicone rubber buttons. The image of the closed irrigation therapy is shown in Fig. 5.3. The lesion is irrigated continuously with irrigation water through a circuit tube for 2 weeks. Generally, 1000–3000 mL per day saline mixed with sensitive antibiotics or povidone-iodine is used as the irrigation water. Recently, we started using "ozone nano-bubble water"

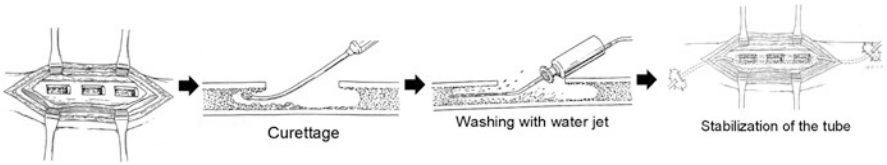
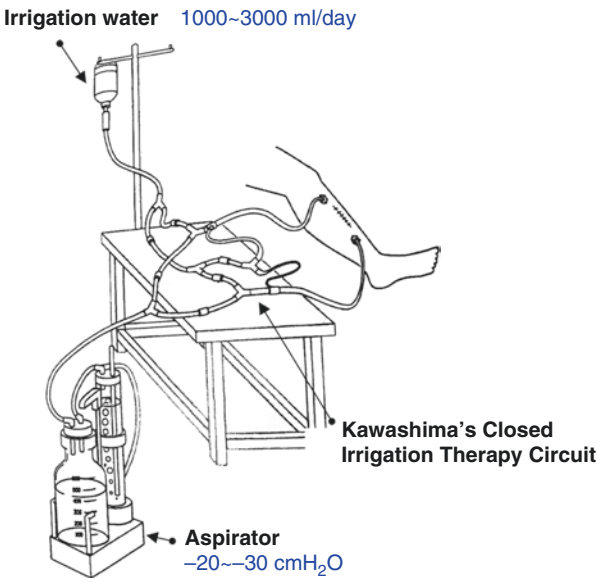


Fig. 5.2 Curettage and setting of irrigation tube

Fig. 5.3 Closed irrigation therapy



as the irrigation water. The drain side is negatively pressurized about 20–30 cmH_2O with an aspirator. By filling the cavities with irrigation, water, bacteria, necrotic tissue, or exudate are washed out.

A common problem with this treatment is obstruction in the tubes due to discharge matter from the lesions. By curetting and washing well, the treatment progresses smoothly. However, it is impossible that obstruction in the tubes does not occur at all. We use an original irrigation circuit system to avoid this trouble. The circuit tube has 3 channels to reverse the flow when any tube is blocked. There are also clamps on the tubes. These clamps are separately marked with three colors: blue, green, or red. Usually, all the blue clamps are closed. When obstruction occurs, we close all the green clamps and open the blue clamps to change the flow. If the tube again becomes blocked, we close the red clamps and open the green clamps (Figs. 5.4 and 5.5). By repeating this operation, we can easily continue with the closed irrigation therapy during the planned period.

If patients have anemia, hypoproteinemia, or diabetes mellitus, condition must first be improved before closed irrigation therapy can begin. Antibiotics are administrated before an operation to prevent sepsis after a local debridement.

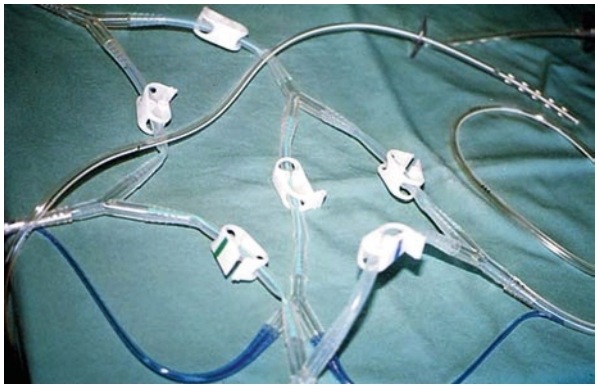


Fig. 5.4 Kawashima's irrigation circuit system to avoid obstruction in the tubes

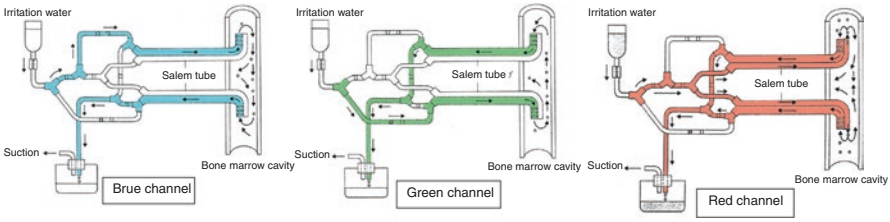


Fig. 5.5 Kawashima's closed irrigation therapy

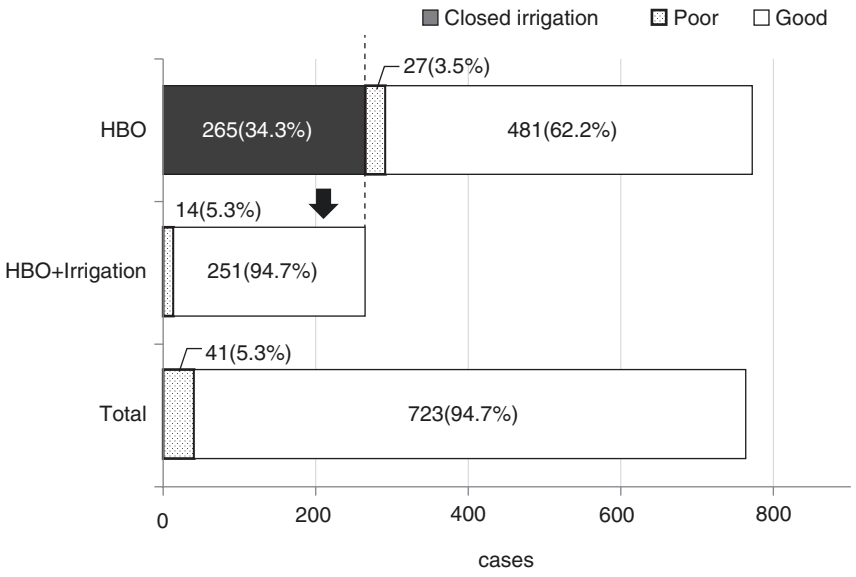


Fig. 5.6 Result of treatment with HBO for osteomyelitis

5.6 Actual Treatment for Osteomyelitis

We treated 773 osteomyelitis cases (Fig. 5.6). 508 of them (65.7%) were treated conservatively and the other 265 cases (34.3%) were treated surgically in addition to having HBO. 481 cases (94.7%) from the conservatively treated group did not have recurring symptoms. 251 cases (94.7%) treated with irrigation therapy did not have recurring symptoms, too. Insufficient concentration of medication reaches the focus area as the blood flow is prevented due to scar tissue and/or hard bones. If there is much sequestrum or tissue, it is important to surgically remove it without prolonged conservative therapy.

5.6.1 Case 1

A 75-year-old male, with right femur osteomyelitis (Fig. 5.7).

This case was treated for osteomyelitis on his right femur in another hospital for 24 years. The symptom subsided due to a drainage incision and/or skin graft. 10 months ago he relapsed. He was treated with antibiotics, drainage incision, and HBO in the previous hospital. However, his symptoms repeatedly worsened and pus discharge continued. It was suggested that he should to go Kawashima orthopaedic hospital. Pus discharge was recognized at 2 fistulas on his right femur. An angiography showed that the fistulas had come through the bone marrow to the skin surface. The CT scan showed the cortical bone was thick and hard. *Pseudomonas aeruginosa*

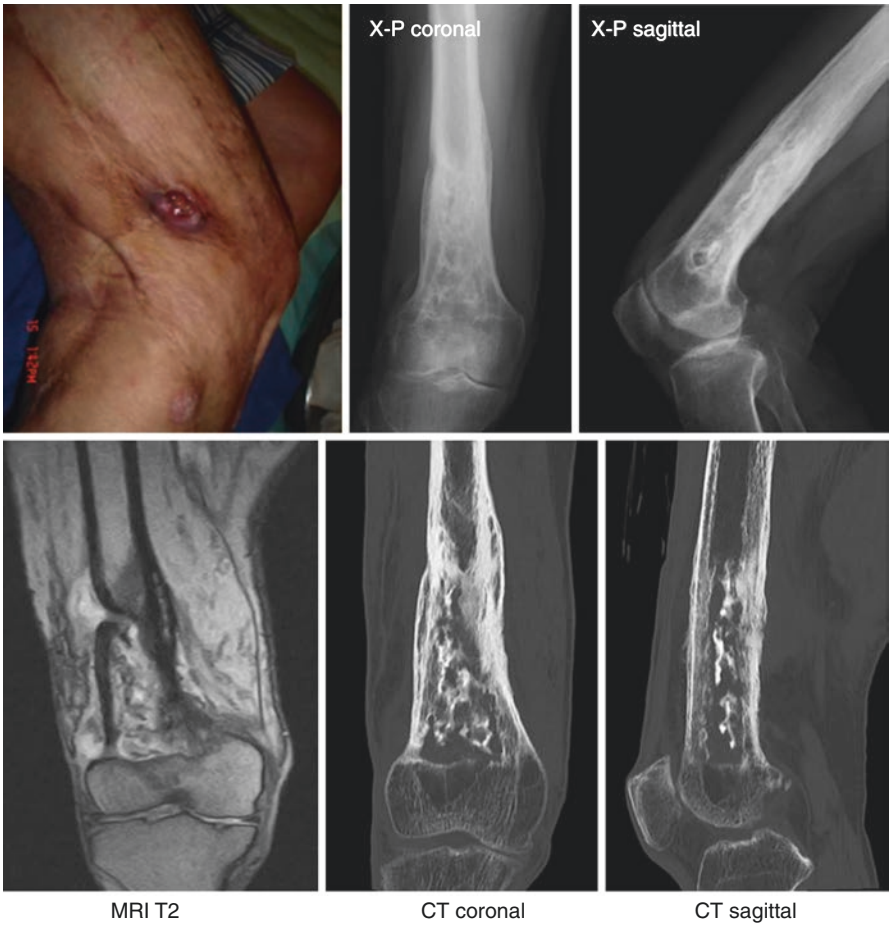


Fig. 5.7 Case 1 (75 yr. old male, with right femur osteomyelitis)

was detected in a bacterial culture of pus. Daily HBO at 2 ATA for 80 min and wound dressing were started after admission. In addition, a carbapenem infusion for 5 days was performed. Oral administration of broad spectrum antibiotics were administered for 20 days. On the 15th day, the wound gradually improved and on the 18th day discharge had stopped. The patient left the hospital on the 39th day, HBO was performed a total of 36 times. Symptoms never reoccurred after being discharged.

5.6.2 Case 2

A 75-year-old male, with pelvic osteomyelitis (Fig. 5.8).

This patient had fractured his pelvis after falling from a ladder 7 years ago. He previously received osteosynthesis. Necrosis and infection occurred on the skin and

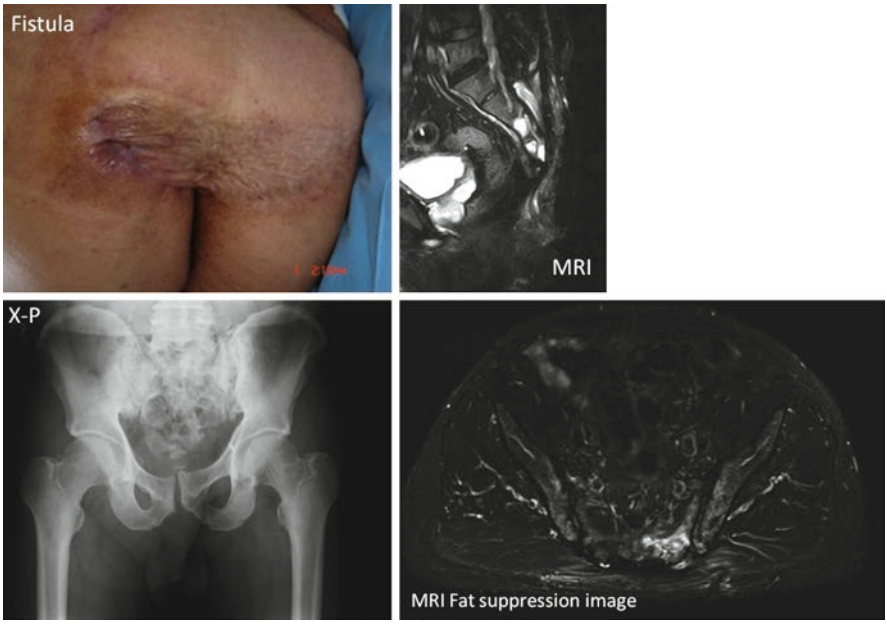


Fig. 5.8 Case 2 (75 yr. old male, with Pelvis osteomyelitis)

muscles of the hip afterwards. In spite of this, he received a negative pressure wound therapy (NPWT) plus a musculocutaneous flap surgery. Bone necrosis occurred and pus discharge from the fistula started. This condition continued for 6 years. He then came to Kawashima orthopaedic hospital for a second opinion. After being admitted, HBO at 2ATA for 80 min, wound washing with "ozone nano-bubble water" and a carbapenem infusion were started. From the sixth day, antibiotics were changed to oral administration of cephem antibiotics. On the seventh day, pus discharge stopped. He was discharged on the 20th day after having had 32 sessions of HBO therapy.

5.6.3 Case 3

A 40-year-old female, with left femur osteomyelitis (Fig. 5.9). When she was 19 years old, SLE occurred; pyogenic arthritis occurred in her left knee after injections at hospital A. Although she received closed irrigation therapy twice at hospital B, inflammation did not subside and turned into osteomyelitis. Pus discharge from her thigh and lower leg continued for 20 years. Symptoms worsened, she then received a surgical curettage at hospital C. Although her wounds closed temporarily 1 month after surgery with HBO, pus discharge restarted 1 week later. She was then referred to Kawashima orthopaedic hospital. After admission, antibiotics and 30

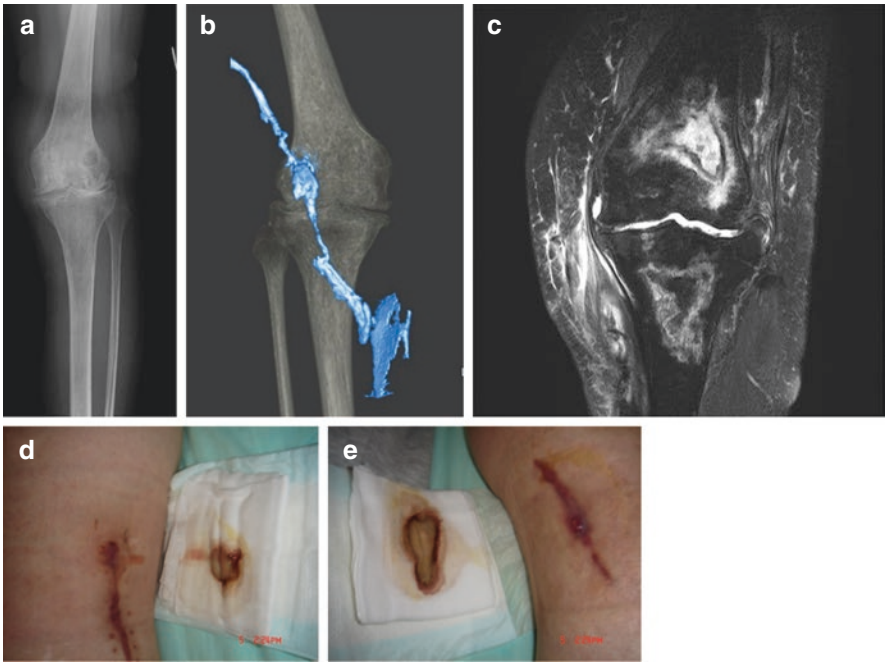


Fig. 5.9 Case 3-1 (40 yr. old female, with left femur osteomyelitis)

sessions of HBO were administered. However, pus discharge still continued. Curettage and closed irrigation therapy using ozone nano-bubble water were performed. Closed irrigation continued for 2 weeks, pus subsided 1 week later (Fig. 5.10). There has been no recurrence for more than 2 years.

5.7 Application of HBO to Other Bone/Joint Infectious Diseases

As noted in the chapter of Rationale, HBO is effective for bacterial infectious diseases. HBO is used for diseases such as pyogenic arthritis, infectious pseudoarthrosis, or pyogenic spondylitis. Treatment of infectious pseudoarthrosis is difficult for reasons, viz., bacterial infection and pseudoarthrosis exist at the same time. HBO is an advantageous treatment for both conditions as it kills bacteria and repairs bone. Treatment results of 33 cases of infectious pseudoarthrosis at Kawashima orthopaedic hospital, 28 patients were healed, pus discharge diminished in 3 patients, 1 case had to have below the knee amputation, and the other was moved to another hospital.

Pyogenic spondylitis is a bacterial infectious disease of the spine. The most common treatment is antibiotics and rest. A few serious cases received surgical treatment. Eighteen pyogenic spondylitis cases were treated with HBO at Kawashima

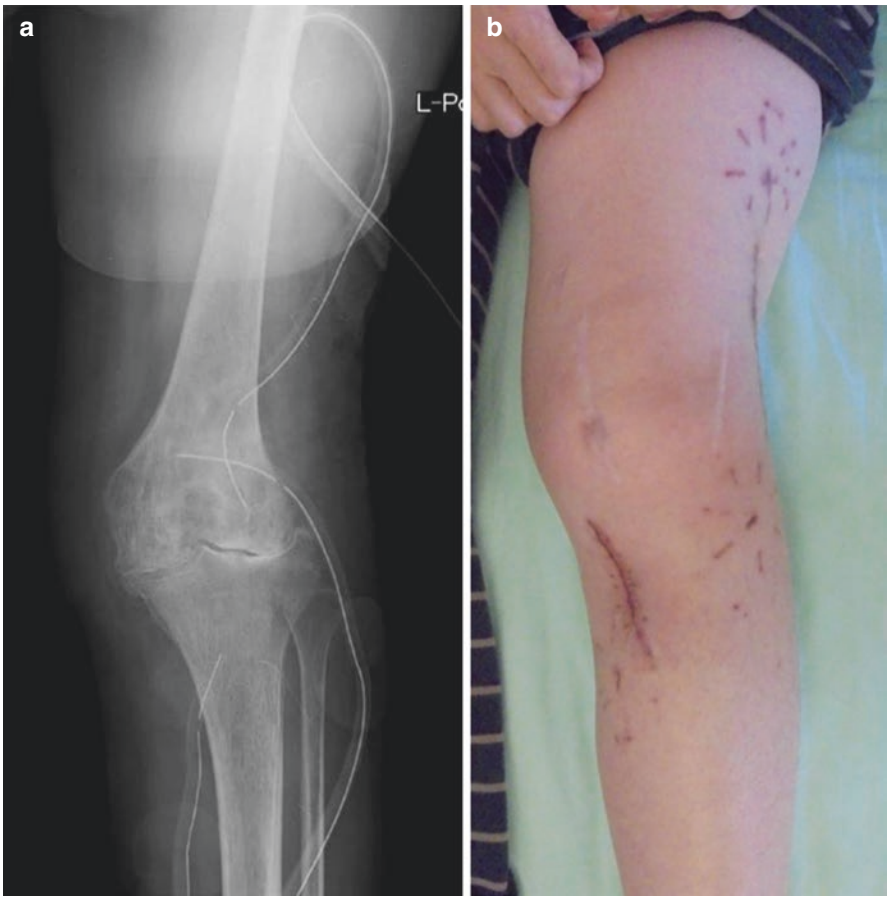


Fig. 5.10 Case 3-2 (40 yr. old female, with left femur osteomyelitis)

orthopaedic hospital. The mean duration of healing was 39.2 days. Two cases which necessitated a surgical debridement were observed in both cases during follow-up symptoms reoccurred. Finally, both cases were treated successfully.

5.7.1 Case 4

A 61-year-old man, with left tibia infectious pseudoarthrosis (Fig. 5.11).

This patient sustained a closed fracture of the left tibia and fibula 7 months before admission to Kawashima orthopaedic hospital. During that time, he received 6 operations. Finally, his tibia stabilized using an external fixation device. Infection and ununited fracture of the tibia persisted after admission to Kawashima orthopaedic hospital. A 10 cm area of the tibia was exposed and MRSA was detected in bacterial

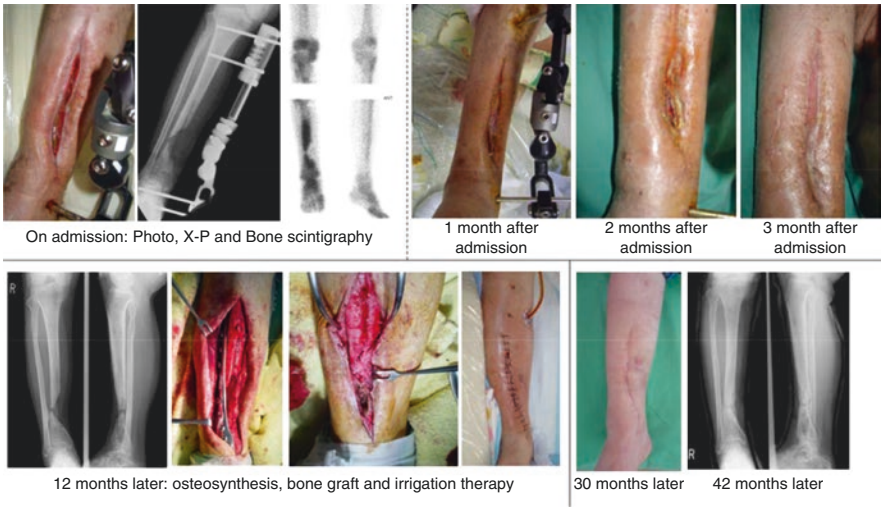


Fig. 5.11 Case 4 (61 yr. old man, with left tibia infectious pseudoarthrosis)

culture of pus. After 60 HBO treatments, the wound completely healed. Osteosynthesis and autogenous bone grafting were performed at the same time as closed suction irrigation was carried out. Fourteen months after surgery, bone union were achieved and reccurence of infection has not be appeared.

In conclusion, HBO has an oxidative, leukocyte killing and an antibiotic effective strength due to the improvement of hypoxia with HBO. Also, HBO helps reform bone marrow. Even today with various kinds of antibiotics developed, bone/joint infection is still a common disease due to the bacteria's resistance as well as in diabetes mellitus patients. HBO is a useful adjunctive therapy for these diseases and is an advantageous noninvasive therapy. We hope HBO spreads more further afield as it shortens the duration of treatment and decreases medical costs. However, the number of hyperbaric chambers tends to have decreased in Japan due to medical insurance problems, viz., payment from the public medical insurance is much too low compared to other countries. We strongly hope it will be evaluated more fully, plus clinicians should accumulate more HBO data on osteomyelitis cases to ensure HBO's usefulness.

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Chapter 6
Hyperbaric Oxygen Therapy in the Management of Severe Soft Tissue Injuries

Noriaki Yamada, Izumi Toyoda, and Shinji Ogura

Abbreviations

RNS Reactive nitrogen species
ROS Reactive oxygen species

6.1 Introduction

In recent decades, clinical practices, procedures, and therapeutic strategies for the management of trauma and wounds have improved remarkably. This "therapeutic bundle" for trauma, severe soft tissue injuries including crush injuries, and open fractures has also improved. However, managing severe soft tissue injuries such as severe open fractures is still challenging in clinical and critical settings because these injuries are associated with a high risk of complications and physical or functional limb loss. A previous study showed that compound open fractures involving bone and soft tissue result in high complication and amputation rates, which can reach 10–50%, mostly according to ischemia and infection [1]. Higher severity (Table 6.1; Gustilo Classification) [2] is associated with higher complication rates because severe injuries damage deep functional structures (e.g., blood vessels, nerves, bones, tendons, and joints) and the microcirculation.

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Table 6.1 Gustilo Classification

Grade	Criteria
I	Minimal contamination, comminution and soft tissue damage, wound <1 cm inside-out perforation
II	Wound laceration >1 cm, moderate contamination, comminution, and soft tissue damage
III	Extensive contamination, comminution and soft tissue damage, exposed bone marked fracture instability due to comminution/segmental defects
IIIA	Adequate soft tissue coverage of the fractured bone despite the extensive soft tissue laceration or flaps, or high energy trauma irrespective of the size of the wound
IIIB	Extensive soft tissue injury loss with periosteal stripping and bone exposure
IIIC	Associated with an arterial injury requiring vascular repair

Serious tissue and structural destruction cause tissue hypoperfusion and hypoxia, which can inhibit wound healing processes and interfere with the host defense system. In the worst clinical course it can result in serious complications and physical and functional limb loss. In addition, once complications occur, there are additional costs from the viewpoint of the patient's activity, as well as human and products medical resources, and economics. Therefore, it is important to prevent complications with these injuries. Indeed, Schenker et al. [3] stated that these injuries are associated with significant health care expenditures. The lifetime per-patient cost of the most severe injuries has been reported to be as high as $509,275.4. The cost of infection associated with open fractures has not been specifically calculated; however, the overall individual and socioeconomic burden of musculoskeletal infection is significant.

The pathophysiology of crush injuries has two important clinical aspects. One is the "problem" wound, it means the un-healing properly and another is "infection." Infection does not develop in the primary phase, but we usually deal with these wounds as infected wounds because wounds are contaminated in most cases.

Hyperbaric oxygen therapy (HBO_2 therapy), which has been used to treat wounds, especially unhealed "problem" wounds and infectious diseases such as necrotizing fasciitis and gas gangrene, has improved prognosis. On the basis of these findings, HBO_2 therapy can be effective in treating crush injuries and severe soft tissue injuries. Some studies suggest that HBO_2 therapy can improve the clinical situation.

In this chapter, we describe the pathophysiology of crush injuries, as well as the mechanism and present status of HBO_2 therapy for crush injuries in clinical settings.

6.2 Wound Healing Process

In order to understand pathophysiology of crush injuries and severe soft tissue injuries, we need to understand the normal wound healing process and the role of oxygen in wound healing. Therefore, in the following section we describe the wound healing process and the role of oxygen.

6.2.1 Normal Wound Healing: Outline

The normal wound healing process has several phases. Each phase overlap and there is no clear distinction between phases. In addition, each phase interacts with other processes. Figure 6.1 also explains the process of wound healing [4].

6.2.1.1 Stop Bleeding and Sealing

Just after invasion of the skin, tissue, or vessels, clot formation starts immediately to stop bleeding and seal the defect. Invasion initiates platelet plug and blood clot formation, resulting in a temporary surface covering the wound. It provides a first barrier against bacterial invasion and serves as a provisional matrix that invades the wound from the circulation or the wound edges.

6.2.1.2 Inflammatory Phase

These processes also initiate chemokine secretion to induce inflammatory cell migration to the wound site. Inflammatory cells migrate to the wound and debride the site to prevent infection. Inflammatory cells such as leucocytes, monocytes, and macrophages play important roles in this process. These inflammatory cells are also important sources of growth factors and cytokines, which initiate the next phase of wound repair, the proliferative phase, by secreting various kinds of cytokines.

6.2.1.3 Tissue Formation Phase

Following the inflammatory phase, cells for tissue re-construction such as fibroblasts, keratinocytes, and endothelial cells migrate to the wound and initiate the tissue repair phase. These cells proliferate and differentiate in the wound and develop granulation tissue around the wound edges.

New tissue formation starts with the migration of keratinocytes from the injured epidermis, followed by the proliferation of these cells at the wound edge. In parallel, fibroblasts migrate and proliferate, producing large amounts of extracellular matrix. In addition, some wound fibroblasts transform into myofibroblasts that are responsible for wound contraction. Endothelial cells promote angiogenesis, which leads to the formation of new vessels in the microcirculation. This wound connective tissue with numerous capillaries is called granulation tissue because of its granular appearance.

This series of processes is regulated by large amounts of cytokines and other chemical mediators. We will explain in greater detail in the following paragraph.

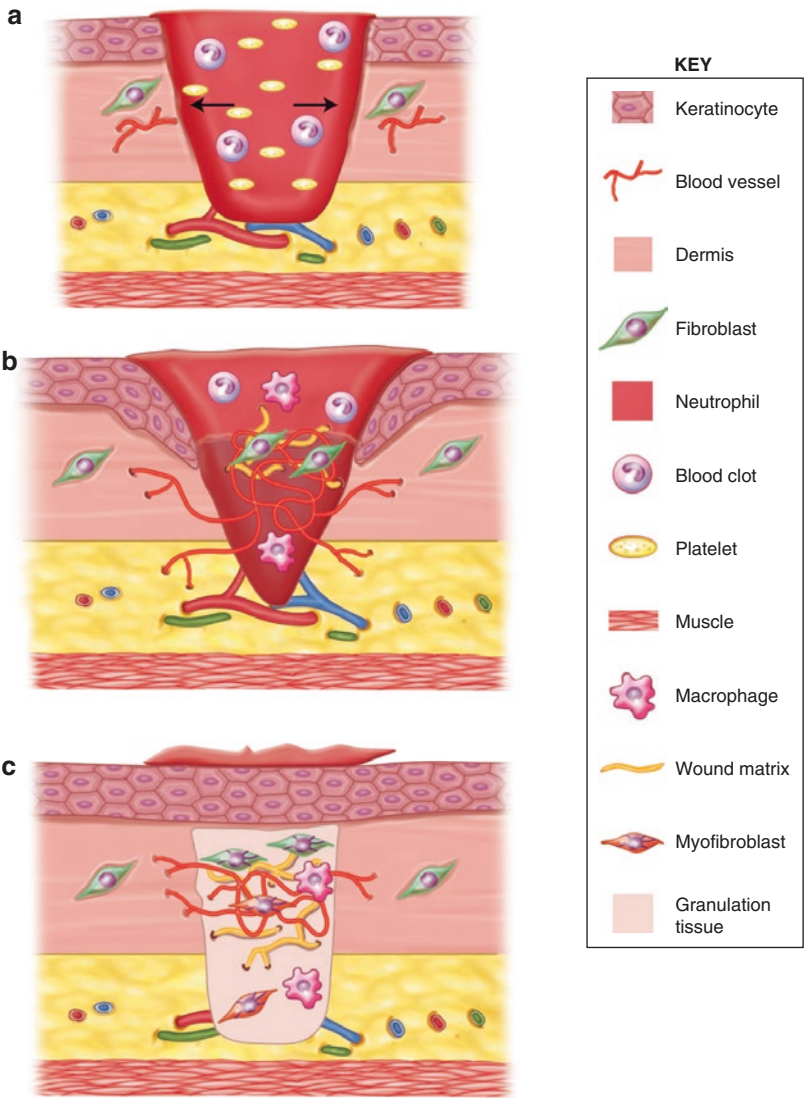

Fig. 6.1 Schematic representation of different stages of wound repair. (**a**) 12–24 h after injury the wounded area is filled with a blood clot. Then neutrophils invade into the clot. (**b**) At days 3–7 after injury, the majority of neutrophils undergo apoptosis. Instead, macrophages are abundant in the wound tissue at this stage of repair. Endothelial cells migrate into the clot; they proliferate and form new blood vessels. Fibroblasts migrate into the wound tissue, where they proliferate and deposit extracellular matrix. New tissue undergoing tissue recovery is called granulation tissue. Keratinocytes proliferate at the wound edge and migrate down the injured dermis and above the provisional matrix. (**c**) 1–2 weeks after injury the wound is completely filled with granulation tissue. Fibroblasts transform into myofibroblasts, leading to wound contraction and collagen deposition. The wound is completely covered with a neoepidermis. *[This figure and figure legend is cited from; Wermer S.,* et al. *Regulation of wound healing by growth factors and cytokines. Physiol. Rev. 2003 Jul; 83:835–70. under permission. © 2003 the American Physiological Society]*

6.2.1.4 Tissue Remodelling

In this phase, tissue tensile strength increases through collagen conversion via extracellular matrix degradation and re-construction. When remodelling of the extracellular matrix occurs, Type III collagen, which is characteristic of granulation tissue, is continuously replaced by type I collagen. Maturation of the latter subsequently occurs through enhanced intermolecular cross-linking. This increases wound breaking strength although the original strength of the normal dermis is never fully restored.

6.2.2 Role of Oxygen in the Wound Healing Process

In the wound healing process, initial tissue hypoxia caused by external damage and invasion is an important primary step for tissue repairing. Hypoxia triggers the wound healing and inflammatory process. However, if tissue hypoxia is prolonged, there can be serious damage to cell function and the wound healing process. Oxygen tension in tissue fluid greater than 30 mmHg is required for vital processes to adequate wound healing and cellular function. Therefore, if oxygen deficiency continues, the subsequent restricted availability of ATP would inhibit effective synthesis or repair of essential cell components, resulting in cell death and tissue necrosis. Consequently, adequate oxygen is needed during the normal healing process. In addition, since inflammatory cells that migrate at the wound site need large amounts of oxygen, the wound environment tends to be "energy-poor" environment. Maintaining adequate oxygen tension is important for wound healing and prevention of infections.

As we described above, the normal wound healing process has several important steps. During all the steps, oxygen is essential for progression to the next step without problems. We describe in detail the relationship between oxygen and wound healing in the following section.

6.2.2.1 Inflammatory Phase

As we described, inflammatory cells such as leucocytes, monocytes, and macrophages migrate to the wound site in order to debride the wound site. They play a role in preventing infection by killing microorganisms during the inflammation phase; these functions depend on high amounts of oxidants. The rate of production of toxic radicals is directly promotional to local oxygen tension. Hypoxia is known to impair phagocytosis by polymorphonuclear leukocytes.

On the enzymatic level, when the leukocyte kills microorganisms, they produce reactive oxygen species (ROS). ROS production depends on oxygen tension. NADPH is a key co-enzyme for oxygenize in ROS production. For NADPH to func-

tion at 50% of the maximum enzymatic speed, the enzyme requires oxygen tensions between 40 and 80 mmHg. To work at 90%, oxygen tension above 400 mmHg may be required. If hypoxia is present, enzyme speed will slow down [5].

6.2.2.2 Re-epithelialization/Proliferation Phase

There are three major aspects of tissue proliferation and differentiation: collagen synthesis, re-epithelialization, and angiogenesis. Fibroblasts need oxygen as an essential element for their proliferative activity [6]. Fibroblasts need oxygen tensions of 30–40 mmHg for proliferation. The amount of deposited collagen is directly proportional to the measured tissue oxygen tension.

On the enzymatic level, prolyl-hydroxylase, the enzyme responsible for hydroxylation of proline and lysine in procollagen, needs 20 mmHg to work at 50% of its maximum speed and more than 150 mmHg to work at 90% of its maximum speed. If it does not work well, protein structures fail to form [7]. For this reason, continuous tissue hypoxia decreases the rate of collagen synthesis.

As we describe in the following section, oxygen increases ROS production. It also stimulates the function of growth factors, keratinocyte differentiation and migration, and fibroblast and endothelial cell production. In addition, oxygen enhances wound contraction by triggering myofibroblast differentiation. Epithelial growth factor is also oxygen dependent; there is decreased epithelialization in a hypoxic environment.

6.2.3 The Wound Healing Process: Viewpoint Form the Mediator

The wound healing process is supported and regulated by a large variety of growth factors, cytokines, and hormones. In order to explain the mechanism of HBO_2 therapy for severe soft tissue injury, we describe their role in normal wound healing, using the following outline from reports by Werner et al. [4] and Schäfer et al. [5]. We would like to refer the reader to these review articles to understand the details about each factor and mediator. [*Most of the following descriptions are cited from these reviews, with permission from the American Physiological Society © 2003].*

PDGF (platelet-derived growth factor) family

1. Cells migration into the healing skin wound (i.e., neutrophils, monocyte)
2. Enhancement proliferation of fibroblasts
3. Production of extracellular matrix
4. Stimulate fibroblasts to contract collagen matrix

FGFs (fibroblast growth factors) family

1. Stimulate migration and proliferation of mesodermal, ectodermal, and also endodermal origin cells
2. Being cytoprotective and to support cell survival under stress conditions
3. Stimulate angiogenesis

EGFs (epidermal growth factors) family

- Regulate re-epithelialization of skin wounds

VEGF (vascular endothelial growth factor)

- Regulates vasculogenesis, angiogenesis, and lymphangiogenesis in the phase of not only during development but also during cutaneous wound repair

Angiopoietin

1. Angiopoietin-1 is responsible for the stabilization of blood vessels.
2. Whereas angiopoietin-2 causes vessel destabilization and remodelling. As a result, stabilize angiogenesis.
3. Unlike VEGF, do not regulate endothelial cells.

IGFs (insulin-like growth factors)

- IGF-I and IGF-II are potent stimulators of mitogenesis and survival of the cell dealing with wound repair.

Scatter Factors (SF)/plasminogen-related growth factor (PRGF)

- HGF; hepatocyte growth factor (one member of the SF/PRGF); stimulator of dissociation of epithelial cells. Stimulates migration, proliferation, and matrix metalloproteinase production of keratinocytes.
- MSP (macrophage stimulating protein) regulates proliferation and differentiation of macrophages and keratinocytes.

NGF (nerve growth factor)

1. Plays a key role in the initiation and maintenance of inflammation.
2. NGF stimulates proliferation and inhibits apoptosis of keratinocytes.

TGFs (transforming growth factors)

- TGF-βs are very potent stimulators of the expression of extracellular matrix proteins and integrins.
- TGF-β was shown to stimulate keratinocyte migration and wound re-epithelialization, angiogenesis, fibroblast proliferation, myofibroblast differentiation, and matrix deposition.
- Activins regulate various aspects of cell growth and differentiation.

Bone morphogenetic proteins

- The sites of expression of these proteins in wounded skin and their roles in wound repair have not yet been determined.

Connective tissue growth factor (CTGF)/Cysteine-rich 61/Nephroblastoma overexpressed (CNN) family

1. CTGF stimulates proliferation and chemotaxis of fibroblasts directly.
2. CTGF is a potent inducer of extracellular matrix proteins, such as collagen type I and fibronectin and their integrin receptors.
3. Cyr61 was shown to promote chemotaxis of fibroblasts and to enhance the mitogenic effect of other growth factors for these cells.

Chemokines

1. Stimulate chemotaxis and extravasation of leukocytes
2. Playing an important role for recruitment inflammatory cells to wound site
3. Regulate re-epithelization, tissue re-modelling, and angiogenesis

Pro-inflammatory cytokines

- Stimulate keratinocyte and fibroblast proliferation, synthesis and breakdown of extracellular matrix proteins, fibroblast chemotaxis, and regulation of the immune response

Granulocyte macrophage colony stimulating factor (GM-CSF)

1. Mitogen for keratinocytes
2. Stimulate migration and proliferation of endothelial cells

6.2.4 Wound Healing and Reactive Oxygen Species (ROS)

As we described in the previous paragraph, ROS play an important integrated role in the wound healing process, which involves cytokine action, angiogenesis, cell motility, and extracellular matrix formation. We focus on ROS in this paragraph.

It is important to note the positive influence that low ROS levels can have on wound healing. Dunnill et al. summarized the role of ROS in their paper [8]. (Please see also Fig. 6.2) According to their explanation, the roles of ROS are:

- Pathogen defense
- Initial protection
- Leukocyte recruitment
- Tissue repair

6.2.4.1 Pathogen Defense

Killing microorganisms with ROS-driven phagocytosis and bactericidal ROS release by platelets and neutrophils.

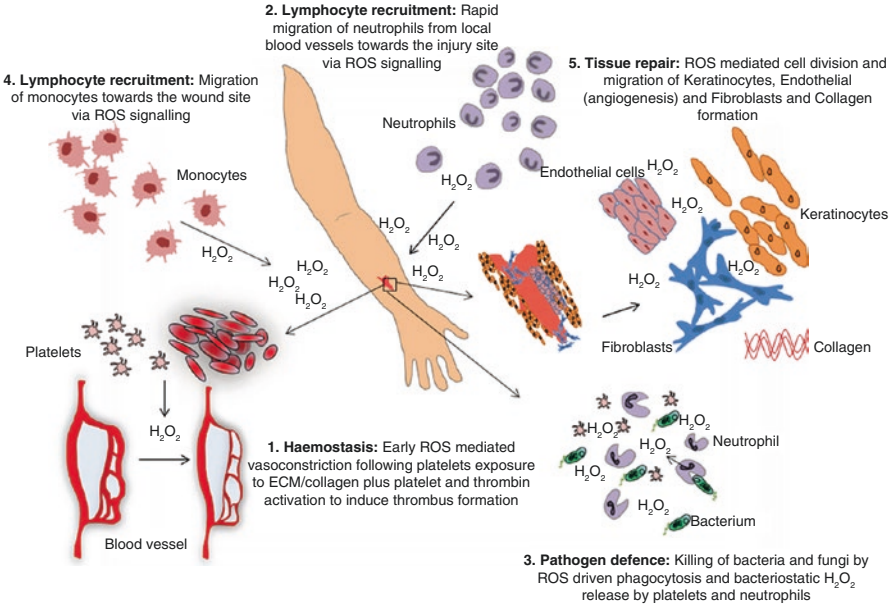

Fig. 6.2 Reactive oxygen species (ROS) and its role in wound healing. The schematic diagram depicts the multiple roles of ROS during acute wound healing (note that this refers to homeostatic, not excessive, levels of ROS). (i) ROS are important in initial wound protection by reducing blood flow and local cell signalling for thrombus formation; (ii) Local ROS release attracts blood vessel-bound local neutrophils to the wound site for bacterial protection; (iii) Phagocytosis releases ROS to stunt bacterial growth and provide further signals supporting the wound response; (iv) Other immunocytes, including monocytes, migrate towards the wound site to help attack invading pathogens; (v) Wound edge and general release of ROS stimulates endothelial cell division and migration for blood vessel reformation, fibroblast division and migration for new ECM formation (including collagen synthesis), and promote keratinocyte proliferation and migration. [*This figure and figure legend is cited from;. Dunnill C,* et al. *Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. Int Wound J. 2015 Dec 21. doi:* https://doi.org/10.1111/iwj.12557. *under permission. © 2015 Medicalhelplines.com Inc and John Wiley & Sons Ltd*]

6.2.4.2 Initial Protection

In the first wound repair phase, ROS-mediated vasoconstriction reduces blood flow to the wound and stimulates platelet and thrombin activation to create a thrombus for primary protection of the wound.

6.2.4.3 Leukocyte Recruitment

Local ROS release attracts immunocytes such as vessel bounded neutrophils and monocytes to the wound to debride microorganisms and debris.

6.2.4.4 Tissue Repair

Local ROS release and generation ROS stimulate cell differentiation and the proliferation and migration of keratinocytes, endothelial cells, and fibroblasts. These roles of ROS in the wound healing process can be divided into major two types: host defense (e.g., phagocytosis by neutrophils and macrophages using their reactive and destructive properties) and chemical mediator.

a) Host Defense
Phagocytes such as neutrophils and macrophages destroy microorganisms in their phagosomes. These cells use ROS in this cyto-killing process. These cells can take microorganisms into phagosomes, and cytosolic NADPH oxidase subunits act in concert with a membrane subunit. An intense uptake of oxygen, known as the respiratory burst, occurs whereby NADPH reduces molecular oxygen in the phagosome to either $\bullet O_2^-$ or H_2O_2. This creates lethal levels of ROS that can destroy pathogens within the phagosome.

b) Chemical Mediator
ROS are the main secondary messengers in the wound healing response. ROS levels are regulated at the wound edge by local antioxidants. Previous studies have shown that ROS act as mediators in the wound healing process. For example, Cho et al. [9] have demonstrated that 100 μM of H_2O_2 stimulates angiogenesis via vascular endothelial growth factor (VEGF) signalling. Low levels of H_2O_2 promote keratinocyte cell migration and formation.

ROS generation, and thus ROS-mediated responses, depends on the presence of oxygen. Low partial pressures of blood O_2 reduces the rate of mitochondrial energy production and makes many endogenous enzymes that utilize O_2 reduce ROS from these cell components. The resulting wound hypoxia typifies poor wound healing.

6.3 Pathophysiology of Crush Injuries

The key points of crush injuries are summarized below in Fig. 6.3.

1. Proper blood supply/microcirculation deserted.
2. Tissues lose their oxygen supply.
3. Tissue hypoxia.
4. Cellular function and enzyme activity for wound repair are inhibited.
5. Consequently, infection and inhibited wound repair occurs.

Macroscopically, crush injuries make large and complex defects in the essential component of the injured tissue or organ, and destroy deep functional structures such as bones, blood vessels, tendons, joints, and nerves. Crush injuries also destroy the micro-

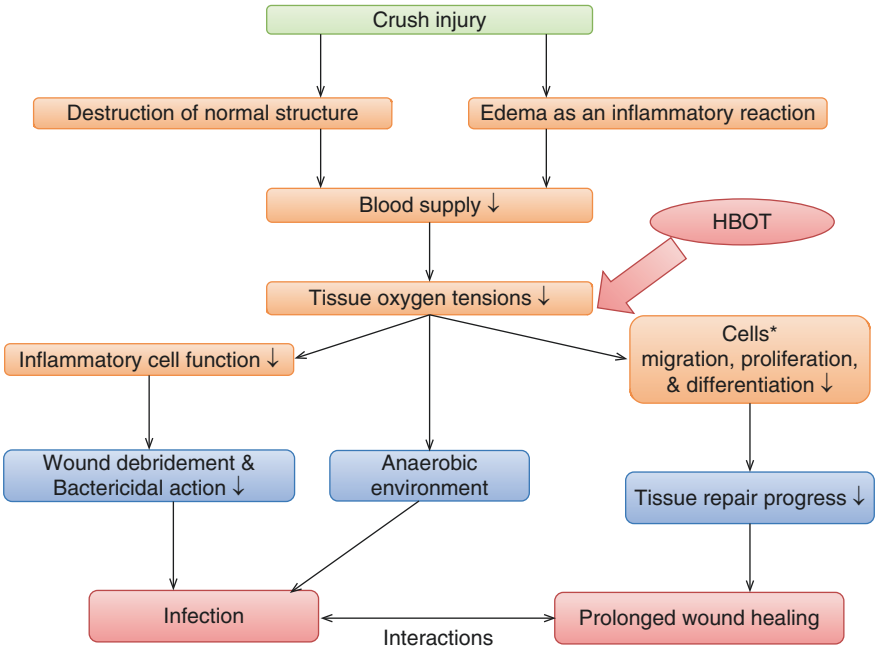

Fig. 6.3 Pathophysiology of crush injuries and target point HBO_2 therapy as a therapeutic intervention. A decrease in blood supply and following low tissue oxygen tensions are the main pathophysiology of crush injuries. HBO_2 therapy can resolve this key point. ∗Cells here include fibroblast, keratinocyte, endothelial, etc. that contribute to tissue repairing

circulation. Indirect external compression of a vessel wall are caused swelling in the wound as a result of inflammation. It inhibits adequate blood supply to the wound site, resulting in inadequate oxygen delivery to the tissue or organ. As a result, organ, tissue, and cell hypoxia occurs. As described previously, primary hypoxia is an essential process of the wound healing, but if it is prolonged, it harms the wound healing process. In particular, it leads to prolonged wound healing and can be high risk of infection. What is worse, these problems interact, leading to a "negative spiral." In this process, an important point is tissue hypoxia. If oxygen tension is kept at an adequate level, we will be able to solve these problems. Therefore, HBO_2 therapy plays an important role.

6.4 Hyperbaric Oxygen Therapy and Crush Injuries

6.4.1 How to Resolve the Problem of Hypoxia

Normally, tissue oxygen delivery depends on the local blood supply volume, NOT blood flow, and arterial and capillary oxygen tension because oxygen delivery to the wound site occurs mainly through diffusion. The oxygen-carrying capacity of hemoglobin is not rate limiting adequate tissue oxygenation until hemoglobin levels

fall to substantially low values. Indeed, a previous study showed that in healthy human volunteers tissue oxygen tension levels did not decrease if adequate circulation is maintained, even at hemoglobin values of 5 mg/dL [10]. Therefore, the best way to maintain oxygen tension is to increase arterial and capillary oxygen tension. The physiology of HBO_2 therapy focuses on these points.

From this perspective, we have to increase the amount of oxygen in the blood to increase oxygen tension in tissue. However, the range is limited in a normobaric environment. In a normobaric environment, the partial pressure and tension of oxygen in blood cannot be over 760 mmHg (atmospheric pressure) because the total pressure of a mixture of gases is equal to the sum of individual partial pressures according to Dalton's law, so the partial pressure of oxygen in blood should be below the environment pressure. However, under hyperbaric conditions, we expand the range of environment gas pressures because the dissolvable amount of gas is proportional to pressure (Henry's law). Therefore, oxygen tension and partial oxygen tension dissolved in blood can increase.

In this situation, if a human inhales 100% oxygen, the maximum oxygen tension will increase to approximately 1433 mmHg under 2 ATA, assuming saturation vapor pressure of 47 mmHg and $PaCO_2$ of 25 mmHg. Of course, if we increase the pressure of the environment, oxygen tension can be higher. For example, if we set the pressure at 3 ATA, the calculated maximum oxygen tension can be 2193 mmHg. It will allow oxygen to diffuse further and deeper than in the normobaric environment because diffusion distance is proportion to the oxygen tension in blood. Indeed, a previous study showed that the diffusion distance for effective tissue oxygen delivery increases from 64 μm at 100 mmHg to 246 μm at 2000 mmHg oxygen tension [11]. In hyperbaric conditions, tissue oxygen tension should be up to 500 mmHg [12]. As a result, oxygen tension can be maintained at higher levels in peripheral tissues and organs.

6.4.2 Effect of Hyperbaric Oxygen Therapy on Wound Healing

We discussed how HBO_2 therapy can elevate tissue oxygen tension in the previous section. How does this affect the wound healing process? As Broussard [13] also summarize, HBO_2 therapy has the following effects on the wound healing process. We describe the points in detail in the following section.

[Beneficial effects of HBO_2 therapy on wound healing]

- Decrease local tissue edema
- Improvement of local cellular energy metabolism
- Improvement of local tissue oxygenation
- Improvement of leukocyte killing ability
- Increase effectiveness of antibiotics
- Directly/indirectly bacteriostatic and bactericidal effects
- Enhance osteogenesis
- Enhance the uptake of platelet-derived growth factor

- Promotion of collagen deposition
- Promotion of neo-angiogenesis
- Promotion of epithelial migration
- Promotion of epithelial neogenesis

[Decrease local tissue edema]

- Tissue hyperoxia leads to vasoconstriction. Vasoconstriction induced by hyperoxia with HBO_2 therapy reduces blood flow to distal tissue by 20% [14]. Since inflow is decreased while outflow is maintained this leads to a reduction in edema.

[Improvement of local tissue oxygenation]

- As we described previously, HBO_2 therapy can increase oxygen tension in blood and the peripheral wound site. Judging from the standard HBO_2 therapeutic table modified oxygen levels are adequate to maintain cellular function.

[Improvement of local cellular energy metabolism]

- Generally, cellular and organ metabolism depends on oxygen tension because cells need oxygen to produce ATP for proper function. As we described previously, HBO_2 therapy can deliver oxygen deeper and further because it increases the diffusion distance. Finally, it can increase peripheral tissue oxygen tension. It keeps the suitable situation for the proper cell metabolize.

[Improvement of leukocyte killing ability]

- A previous study showed that leukocyte killing is likely maximized at a PO_2 of 250 mmHg [15]. HBO_2 therapy can make this situation. In addition, ROS plays an important role in the killing of microorganisms by leukocytes. HBO_2 therapy promotes the production of ROS by providing adequate levels of oxygen.

[Increase effectiveness of antibiotics]

- Several studies have shown that HBO_2 therapy improves the effectiveness of antibiotics. Verklin et al. showed HBO_2 therapy augments the transport of certain antibiotics across bacterial cell walls [16] and work synergistically. Mendel et al. reported that the combination of cefazolin and HBO_2 therapy produced a 100-fold reduction in bacterial counts than antibiotic alone [17]. Almzaiel et al. also showed that exposure to HBO_2 therapy increases respiratory burst activity of neutrophil-like cells and increases the phagocytosis of *Staphylococcus aureus* [18].

[Directly/indirectly bacteriostatic and bactericidal effects of HBO_2 therapy]

- Hyperoxia has direct bactericidal effects on anaerobic microorganisms. Since aerobic microorganisms do not have scavenger enzymes, they are sensitive to sign concentration in oxygen-free radicals.

[Enhancement osteogenesis]

- Previous studies have shown that HBO_2 therapy enhances osteogenesis. Animal data suggest that bone mineralization and healing can be accelerated by intermittent exposures to HBO_2 therapy [19–21]. It can support bone fracture healing.

[Effect of HBO_2 therapy on cytokine and growth factor secretion]

- HBO_2 therapy does not affect circulating levels of insulin-like growth factors or pro-inflammatory cytokines [i.e., tumor necrosis factor-α (TNF-α) interleukin (IL)-6 and IL-8] in healthy humans [22, 23]. On the other hand, HBO_2 therapy increases the synthesis of VFGF in animal models [24] and significantly enhances the secretion of bFGF and TGF-β1 [25]. It also enhances the expression of angiopoietin-2 [26] and up-regulates platelet-derived growth factor (PDGF) receptor expression in wounds [27].

[Promotion of collagen deposition]

- As we described in the section of normal wound healing, keeping on the adequate tissue oxygen tension is needed for collagen synthesis. Hopf et al. reported that increased oxygen concentration might also satisfy other requirements for angiogenesis such as hydroxylation and export of collagen [7]. In addition, fibroblast proliferation increases in a dose-dependent manner between 1.0 and 2.5 ATA. Raising oxygen tension above normal physiologic levels enhances collagen synthesis and tensile strength [28–30] and can increase the level of collagen organization [31]. The rate of collagen deposition has been shown to increase proportionally with oxygen levels greater than 250 mmHg [32].

[Promotion of angiogenesis]

- The rate of angiogenesis is directly proportional to oxygen levels in injured tissues [32]. Extracellular matrix formation is closely linked to neo-vascularization and is an oxygen-dependent process.

[Enhanced epithelial migration and neogenesis]

- Previous study has shown that HBO_2 therapy increases endothelial cell proliferation thereby aiding granulation tissue and wound contraction [33]. HBO_2 therapy increases keratinocyte differentiation and migration in a human skin model.

[Other]

- Hyperoxic conditions under HBO_2 therapy stimulate endothelial progenitor cell (EPC) mobilization via eNOS activation [34].

[From the viewpoint of gene expression]

- As described above, HBO_2 therapy affects the wound healing process. Many studies have reported these mechanisms although some details on the molecular level still remain unclear. However, some studies show effects of HBO_2 therapy on the genetic or molecular level. We describe these studies in this section.
- Although their study was performed on chronic wounds, Kendell et al. [35] studied the effects of HBO_2 therapy on the expression of genes associated with inflammation and wound healing. This study shows that HBO_2 therapy appears to promote angiogenin expression and eNOS activity, which correlates with a decrease in endothelial IL-8 mRNA and protein during the early phase (5 h). However, at 22.5 h after HBO_2 therapy, IL-8 levels begin to recover and a number of genes that regulate

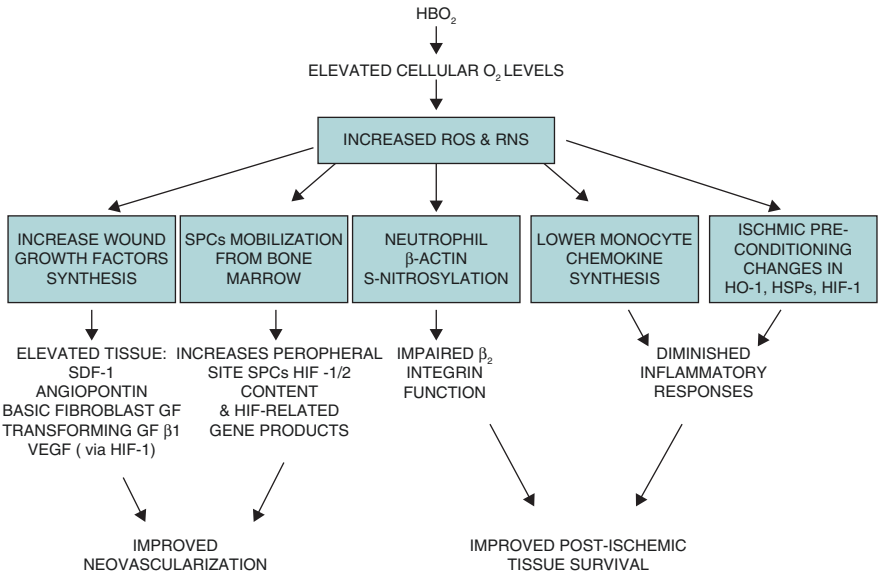

Fig. 6.4 Overview on therapeutic mechanisms of HBO_2 related to elevations of tissue oxygen tensions. The figure outlines initial effects (denoted by boxes) that occur due to increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their consequences. Other abbreviations: *GF* growth factor, *VEGF* vascular endothelial growth factor, *HIF* hypoxia inducible factor, *SPCs* stem/progenitor cells, *HO-1* heme oxygenase-1, *HSPs* heat shock proteins. *[This figure and figure legend is cited from; Thom SR, Hyperbaric oxygen: its mechanisms and efficacy. Plast Reconstr Surg. 2011 Jan; 127 Suppl. 1:131S–141S. under permission. ©2011 American Society of Plastic Surgeons]*

endothelial cell survival and angiogenesis are activated. Zhang et al. studied the effect of HBO_2 therapy on ischemic flap wounds. They suggest that HBO_2 therapy improves ischemic wound healing by down-regulating HIF-1α and subsequent target gene expression with attenuation of cell apoptosis and reduction of inflammation [36]. In addition, Goldman et al. studied the effect of HBO_2 therapy using human microvascular endothelial cells. They suggested that increased expression of immediate early and cytoprotective genes corresponds with an HBO_2 therapy-induced increase in cell proliferation and oxidative stress resistance. In addition, HBO_2 therapy enhances endothelial tube formation on matrigel plates, with particularly dramatic effects observed following twice-daily HBO_2 therapy [37].

[Relationship between HBO_2 and ROS]

- As described previously, ROS play an important role in the wound healing process. HBO_2 therapy can increase cellular oxygen tension and promote ROS and RNS (reactive nitrogen species) production. As a result, HBO_2 therapy can promote the role of ROS. Figure 6.4 (cited from the paper published by Thom [38]) explains the mechanism in detail.

6.5 Clinical Experience in the Management of Crush Injuries

6.5.1 Present Status of HBO_2 Therapy in the Wound Management

6.5.1.1 From the Viewpoint of Wound Management

1. Wound management

   Generally, HBO_2 therapy is not stated as a therapeutic option in the management of unproblematic wounds. As Gottrup pointed out [39], HBO_2 therapy has little effect on the healing of normal, uncomplicated wounds. However, when health care providers manage and treat problem wounds, they have to perform "intensive" wound care to promote healing of problem wounds. Some position statements and studies recommend the use of HBO_2 therapy as an adjuvant therapy and as a part of intensive wound management strategy. In particular, HBO_2 therapy has been recommended for problem wounds associated with arterial insufficiencies such as diabetic foot because it can improve the oxygen supply to wound. Indeed, many studies dealing with HBO_2 therapy for problem wounds have been performed. They recommend HBO_2 therapy as part of the treatment strategy.
2. Management of open limb fractures and crush injuries

   There are some updated clinical practice guidelines, clinical and principal statements, and papers on the management of severe soft tissue injuries such as open fractures and crush injuries. In these updated guidelines, statements, and papers, some novel therapeutic procedures, such as negative pressure wound therapy, are included. However, there is little description of HBO_2 therapy as a therapeutic option for crush injuries. Judging from the situation, HBO_2 therapy to crush injury is not a common therapeutic option in present consensus for crush injuries. For example, we cannot find a description of HBO_2 therapy for open limb fractures in the AO Foundation statement and national guidelines in the UK. We only found a description in one position statement [1]. The guideline published by the Wound Healing Society in 2006 stressed that keeping adequate oxygenation is important for good control, but it did not specify how to do so [40].

6.5.1.2 Position Statements and Guidelines in the Field of Hyperbaric Medicine

Guidelines and position statements published by the Undersea and Hyperbaric Medical Society (UHMS), European Committee for Hyperbaric Medicine (ECHM), Japanese Society of Hyperbaric and Undersea Medicine (JSHUM) [41] include crush injuries and severe soft tissue injures as indications for HBO_2 therapy. HBO_2 therapy is not an exceptional therapeutic option according to these organizations.

On the other hand, experts have pointed out their concern that HBO_2 therapy is not a common therapy in clinical settings and that it has not been used effectively in clinical situations [42]. This may be due to the problem that only few HBO_2 therapeutic strategies can be available for crush injuries, as we describe in the following paragraph.

6.5.1.3 Clinical Position

Basically, in critical and acute care settings HBO_2 therapy, if we performed, is an important adjuvant therapy. However, standard treatments, such as controlling the general status and adequate surgical intervention, are more important than attempting HBO_2 therapy. We should try to perform HBO_2 therapy only when the patient's status is stable and suitable for HBO_2 therapy. However we must not interfere with standard therapeutic strategies.

6.5.2 Clinical Experience in the Literature

There are few studies on HBO_2 therapy for crush injuries. Previously, some researchers have performed literature reviews, but many reviews include studies of compromised flaps, limb or finger replantation, and skeletal muscle-compartment syndrome. These explanations might have been confusing the readers. In this section, we focus on the literature dealing with "crush injuries," "traumatic limb injuries associated with fractures," "severe vascular trauma associated with fractures," and severe limb injuries associated with fractures, which is summarized in Table 6.2. This review refers to MEDLINE, UHMS archives, the JSHUM committee report [41], a review by Garcia-Covarrubias et al. [43], and a review in a textbook chapter [44] written by Strauss et al.

As described in Table 6.2, many previous studies were case series [45–53]. Only two well-designed studies have been published. Boueachor et al. conducted a small-randomized controlled study. They divided patients with crush injuries into two groups: HBO_2 group vs. placebo. In that trial, complete wound healing was achieved in 17 patients (94%) treated with HBO_2 versus 10 patients (56%) ($p < 0.01$) treated with placebo. Additional surgery was required in 1 patient (5.5%) treated with HBO_2 versus 6 patients (33%) treated with placebo ($p < 0.05$). It showed a statistically significant difference in favor of HBO_2 therapy. On the other hand, no significant differences were found in the length of hospital stay and number of wound dressings needed. Roje et al. performed a retrospective cohort study related to the war in Bosnia and Herzegovina. They included 388 patients in the analysis, 99 of whom received HBO_2 therapy. Deep soft tissue infections developed in 196 (68%) patients who did not receive HBO_2 therapy and in only 35 (35%) of those who did. Osteomyelitis developed in 214 (74%) patients who did not receive HBO_2 therapy and in 62 (63%) who did. They concluded that HBO_2 therapy is associated with a lower incidence of infectious complications. In addition,

Table 6.2 HBO for crush injuries

Author/published by	Study design	Patients	Outcome	HBO protocol	Benefit
Szèkely [45]	Case series	16 cases with severe injury to limbs[a]	12 cases are effective, 4 were ineffective	2 ATA Variable duration	Unclear
Monies-Chass [46]	Case series	7 patients with severe vascular trauma and associated fractures to lower extremities	Disappearance of ischemia were shown in 6 patients, dry gangrene of toes was shown in 1 patient	2 h at 2.8 ATA every 4 h Mean 9.5 treatments	Yes
Shupak [47]	Case series	13 patients with traumatic injuries to lower limbs	Complete limb salvage in 8 (61.5%) patients	2.4 ATA 90 min twice a day Mean 5 treatments	Yes
Radnic [48]	Retrospective Case series	13 patients with crural arteries injury 10 with fractures. (Under war, Combat injuries)	Function was very good 2, good 3, fair 7	7–21sessions of 60–120 min at 220 kPa	Yes
Bouachor [49]	RCT	36 patients with typeII or III injury.(18 patients; HBO, 18 patients placebo)	Complete wound healing without necrosis requiring excision in 17/18 patients (HBO_2) vs. 10/18 patients (placebo). ($p < 0.01$). Repeat surgical procedure needed 33% in placebo vs. 5.6% in HBO ($p < 0.05$)	After surgery 2.5 ATA 2 treatments/day for 6 days	Yes
Matos [50]	Case series	23 patients with type III crush injuries	20 had preservation of the threatened limbs	2.36 ATA for 90 min, 2 treatments/day Average; of 12 treatments	Yes
Roje [51]	Retrospective Cohort	388 patients undergoing re-constructive surgery Gustilo type III 99 patients treated by HBO (Under war situation)	Deep soft tissue infection; 196 patients (68%) in non-HBO vs. 35 patients (35%) received HBO ($P < 0.001$). Skin graft lysis; 151 (52%) non-HBO vs. in 23 (23%) received HBO. ($P < 0.001$) Flap necrosis; 147 (51%) non-HBO vs. 15 (15%) who received it ($P < 0.001$). Median time to granulation formation was 9 (5–57) in HBO therapy, and 12 (1–12) non-HBO	2.2 bar(7 patients was under 2.8 bar) The number of HBO depends on clinical situations	Yes

Takao [52]	Case series	169 patients with crush injury	2 patients need toe amputation, but all other patients (167 patients; 98.8%) recoveredcompletely	2ATA 60 min 1 treatment/day 30 sessions/1 course, if ulcer remain at the end of first course, 1 course was added	Yes
Yamada [53]	Retrospective Cohort	29 patients with type III. 16 patients received HBO treatment	Infection; 6/16 patients 46% (control) vs. no patients 0/13% (HBO) repeat surgical procedure 5/16 patients (38%) vs. no patients	2ATA for 60 min, 1 treatment/day Average; 6 sessions	Yes

This table shows the clinical experience being reported in previous literature. We reviewed using Medline, and UHMS archives, Japanese committee report, and previous review. Type means Gustilo classifications. Unit of pressure was described in difference, it is because we directly cited each literature
In addition, if the study was performed under war, we stated in the table because these circumstances are different from ordinary times. For example, medical supply was limited, sterilized might insufficiency etc
HBO hyperbaric oxygen therapy, *ATA* atmosphere absolute, *RCT* randomized control trial
[a]This case review includes 19 patients, 7 subjects with severe limb injuries, 4 with ruptured vessels or ischemic complications, 5 with extensive skin loss, 2 with anaerobic infections, and 1 with a finger re-implantation. However, the patients' status, such as Gustilo type, was unclear, therefore we only include the presented cases

skin graft lysis occurred in 151 (52%) patients who did not receive HBO_2 therapy and in 23 (23%) who did. Similarly, flap necrosis occurred in 147 (51%) patients who did not receive HBO_2 therapy and in 15 (15%) who did. These results suggest that HBO_2 therapy helps accelerate tissue repair. Although the patient population differed from our own, those results show a similar pattern in terms of a lower rate of complications.

However, we still have only a few studies. In 2013, Eskes et al. [54] performed a Cochrane Database Systematic Review in which they concluded that there is a lack of high-quality valid research evidence regarding the effects of HBO_2 therapy on wound healing. Further evaluation by means of high-quality randomized control trials is needed.

One international multi-center study entitled Hyperbaric Oxygen therapy in Lower Limb Trauma (HOLLT) is ongoing [55]. This study is a prospective, single-blinded, randomized controlled trial organized by Monash University in Australia. Results of this study have not been published as of the end of June 2016, but when the results of this study are published, they will provide important suggestions to our clinical question whether this result is positive or negative.

6.6 Future Challenges

Many experimental and clinical studies support the role of HBO_2 therapy in the management of crush injuries, from the viewpoint of its effects on wound healing and infections. However, when investigating these studies in detail, we found that protocols differed from each other. Almost all studies are different from other studies in regard to therapeutic pressure, treatment frequency, treatment duration, etc. These points have not been investigated well in this field. As a result, we do not have a standard protocol for this therapeutic procedure. In addition, we also do not have adequate indication criteria for determining right patients for HBO_2 therapy. Strauss et al. [56] suggest therapeutic criteria for indications and therapeutic tables, but it has not been commonly used in recent years.

Since HBO_2 therapy is an “extraordinary” environmental treatment method that is invasive, we need to minimize the risks of treatment. The latest guidelines on indications also point out these problems. Therefore, we need to conduct further research about best practices, such as therapeutic pressure, treatment frequency, and treatment duration, to establish a standard protocol.

In addition, we still have a “modality” problem. HBO_2 therapy can be performed in both monoplace and multiplace chambers. Monoplace chambers are widely used in the world because their placement and maintenance are not difficult. However, we sometimes cannot attempt HBO_2 therapy in a monoplace chamber due to patient status (e.g., requires artificial support, patient status, and external fixture size). By using multiplace chambers, we can overcome those problems and perform HBO_2 therapy smoothly. However, multiplace facilities are limited, and it is also difficult to maintain such facilities. Recently, we have seen “mini” multiplace chambers, which can treat 3 to 4 persons in one session. This is one solution for the “modality” problem.

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Author contributions:

N. Y.: Writing the main text, reviewing previous studies

I. T.: Reviewing previous studies and supervising

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Chapter 7
Evaluation of Hyperbaric Oxygen Therapy as a First-Line Treatment for Carbon Monoxide Poisoning

Kenji Taki and Shogo Goda

7.1 Introduction

Carbon monoxide (CO) is a colorless, tasteless, odorless, dangerous gas, which exists anywhere people live, and it is slightly lighter than air. The prognosis of CO poisoning varies depending on the exposure situation of CO gas, and some suffer from disorientation, urinary incontinence, energy loss, or even death after a full recovery from CO poisoning. The pathogenesis of acute CO poisoning has not been clearly identified, and the treatment protocol has also not been established.

CO goes through the lungs [1] to combine with hemoglobin (Hb) in a high affinity (200–250 times stronger than oxygen), [2] to shift Hb oxygen dissociation curve to left, and [3] to be coupled with the cytochrome c in mitochondria, and cause breathing difficulties of organ, which induces organ failure by low oxygen transport (hypoxia). When CO-Hb level goes up to more than 20%, it increases the impact on the brain and heart [1], to make big damage on the brain, which consumes oxygen the most, followed by cardiac muscle, and skeletal muscle [2, 3]. And, after fully recovering from the consciousness disorders once in an acute phase, psychoneurotic symptoms may be caused sometimes (delayed neuropsychological sequelae; DNS). Therefore, the treatment is important for eliminating CO from the body as soon as possible.

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7.2 Implementation Criteria in Each Hospital and Institute

The criteria for implementation of hyperbaric oxygen therapy (HBOT) for acute CO poisoning differ according to hospitals and institutes. So far, the criteria for implementation (Table 7.1) by Colignon and Lamy (1986) [4] is the only one published as the world standards. However, HBOT has been performed for severe cases and normobaric oxygen therapy (NBOT) for the mild cases, which clearly suggests that the method of treatment varies depending on the severity of the cases. Therefore, the severity of the cases should be equal when comparing the therapeutic effects between HBOT and NBOT. Kusuba et al. [5] classified the implementing facilities into three ranks; facility where HBOT is rarely performed (A rank), the intermediate facilities (B rank), and facility where HBOT is frequently performed (C rank), respectively (Table 7.2). According to this classification, the therapeutic effect was compared considering the severity, and a new interpretation has been added to the application of HBOT and NBOT [5].

Table 7.1 Hyperbaric oxygen (HBO) versus normobaric oxygen (NBO) (Colignon & Lamy 1986) [22]

Hyperbaric facilities available	COHb>25% COHb<25%	HBO HBO if symptoms, NBO if none
No hyperbaric facilities	COHb>40% COHb<40% no symptoms COHb<40% with symptoms	Immediate referral to HBO center NBO Referral to HBO center

Table 7.2 Grouping of institutions regarding criteria for HBOT [5]

Items Groups	CO-Hb value	Symptom	Clinical laboratory data	Clinical exam findings	Clinical history	Number of items in criteria for HBOT
A	>40%	Loss of consciousness	Showing organ failure	Abnormal	>1 h	Abnormal findings in 0–1 item
B	>25%	Any symptom	Abnormal	Abnormal	>30 min	Abnormal findings in 2–3 items
C	>5%	Any symptom	Abnormal	Abnormal	>A few min	Abnormal findings in >4 items

Symptoms: impaired consciousness, headache
Clinical laboratory data: CO-Hb, CPK, lactate, GOT/LDH, white blood cell
Clinical examination: ECG, cardiac echo, CT, MRI, EEG
Clinical history: exposure to CO gas

7.3 Pathophysiology of CO Poisoning

As oxygen delivery is controlled by inhaled oxygen concentration, Hb level, and blood flow volume, CO gas reduces the amount of Hb that can transport oxygen as anemia by combining with Hb at the high affinity (left shift of the oxygen dissociation curve). If the oxygen consumption is not remediated instantly, hypoxia continues for long term to induce tissue acidosis, and the patient lapses in delayed neuropsychological sequelae (DNS) of CO poisoning.

In CO poisoning, myelin basic protein (MBP), acetaldehyde, and malondialdehyde (MDA) are produced as antigens [6], which has been thought to cause DNS of CO poisoning as a result of immunological reactions [7]. Therefore, treatment against immune response has started to be used as the treatment of DNS of CO poisoning.

7.3.1 CO-NO-O_2 Competitive Coupling

7.3.1.1 Hemoglobin (Hb)

Since carbon monoxide competitively binds to Hb in red blood cells with 200–250 times higher affinity than oxygen [8], it has been said that CO-Hb indicates the severity of CO poisoning.

However, CO-Hb level can be easily dropped down by O_2 inhalation, thus oxygen inhalation is considered to be a possible effective treatment (both NBO and HBO). Carbon monoxide diffuses from the alveoli in the body; CO-Hb level can change due to various factors related with CO uptake and release impacts (Table 7.3), and a small amount of CO is directly oxidized into CO_2. Due to the factors affecting the Hb level in the body, the average half-life ($t_{1/2}$) of CO-Hb varies widely between 27 and 464 min (Table 7.4) [9–11]. NBOT is similar to HBOT in that it can reduce the level of CO-Hb, but the difference in the therapeutic effect between the two treatments is being questioned. Some think NBOT is sufficient for CO poisoning and it can improve oxygen transport capacity in the blood. If CO gas remains in peripheral tissues, however, hypoxic state continues there, which suggests that HBOT would be better indicated in severe CO poisoning.

CO is taken in from the outside of the body. Also, when heme is degraded by heme oxygenase into Fe and biliverdin, CO is produced in the body. Although CO directly up-regulates the activity of nitric oxide synthase (NOS) enzymes, NO radicals (•NO) compete with CO in the active site at the cellular level. Thus, CO inhibits NO from binding to heme protein, which increases the NO concentration both inside and outside of platelets and also in endothelial cells [12–14].

Table 7.3 Laboratory diagnosis of CO poisoning [22]

Various laboratory procedures that may be used in the diagnosis of CO poisoning are as follows:
1. Determination of CO in the blood
Direct measurement of the CO-Hb levels
Measurement of CO exhaled from the blood
Measurement of CO content of the exhaled air
2. Arterial blood gases and lactic acid levels
3. Screening tests for drug intoxication and alcohol intoxication
4. Biochemistry
Enzymes:creatine kinase, lactate dehydrogenase, SGOT, SGPT
Serum glucose
5. Complete blood count
6. Electroencephalogram
7. Electrocardiogram
8. Computed tomography (CT) scan
9. Magnetic resonance imaging (MRI)
10. Neuropsychological testing

Table 7.4 Factors influencing CO release and intake [32]

1. Relation of CO concentration with the partial pressure of O_2, CO_2, and N_2O in respiratory gas
2. Concentration of respiratory mixed gas
3. Temperature and humidity of inhaled gas
4. Alveolar ventilation
5. Concentration gradient of CO in alveola and lungs
6. Cardiac output
7. Diffusion volume of CO in lungs
8. Reaction speed of Hb with CO
9. Blood volume and flow in the lung capillary
10. Hb and Ht
11. Production rate of endogenous CO
12. Consumption of metabolic CO
13. Excretion rate of CO

7.3.1.2 Cytochrome c oxidase (CCO)

Cytochrome c oxidase (CCO) is the final enzyme in a mitochondrial electron transport chain. CO incorporated into the tissues competitively binds with various intracellular proteins that use O_2, CO, or •NO gases as ligands. CO inhibits mitochondrial respiration once it binds to CCO. In the cascade of electron transport for producing ATP (Fig. 7.1), CO inhibits CCO in the final stage (site III) and stops the

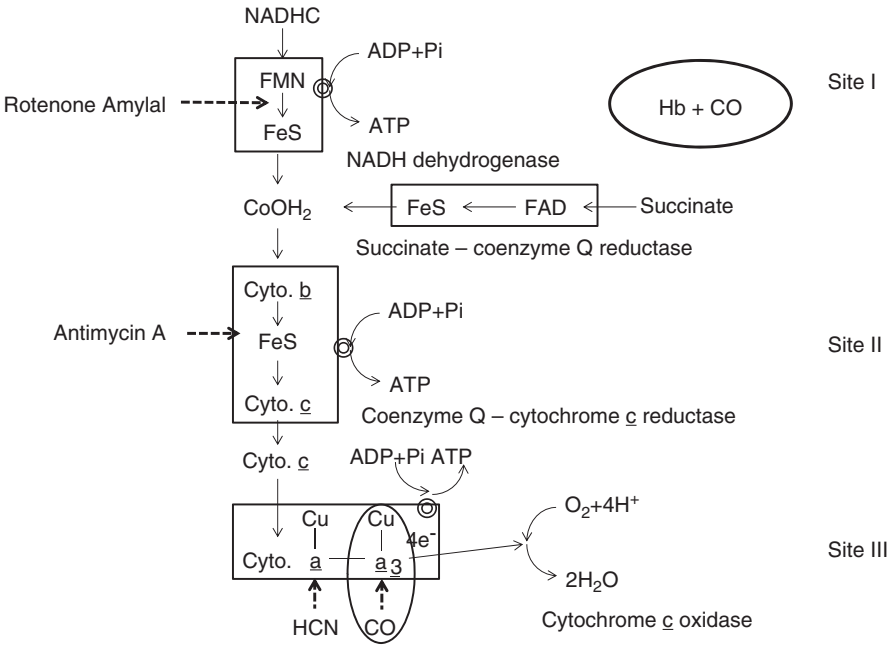
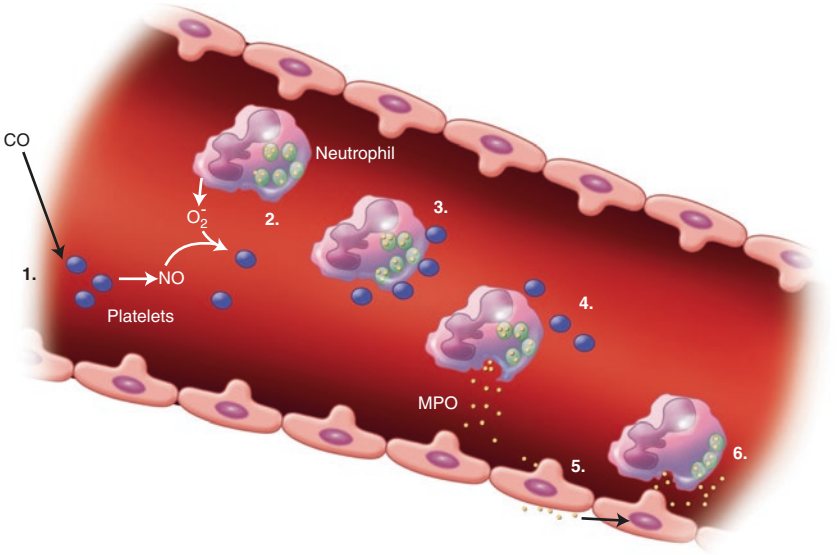


Fig. 7.1 Respiratory chain in mitochondria [22]. The mitochondrial respiratory chain indicating sequence of electron transport, three sites of energy coupling (oxidative phosphorylation), and location of acting CO

cells from functioning [15, 16]. Although the binding capacity of CO to CCO is not as strong as to O_2 or •NO, it has great significance when the cells go into the low oxygen status. Synthesized endogenous CO reduces cellular respiration by 30% [17]. When CO-Hb level reaches 20%, the injuries due to shock, postoperative ileus, organ transplantation, and ischemia reperfusion have been reported to be prevented [18–20]. However, exogenous CO combines with CCO and inhibits mitochondrial respiration [21], which might selectively induce apoptosis in brain nerve cells [22, 23]. The inflammatory and apoptotic effects of CO occur as a result of the synthesis of stress-dependent protein [24, 25]. Free radicals produced from mitochondria that are exposed to CO are key stressers to induce necrosis or apoptosis of nerve cells [26, 27]. On the other hand, stabilization and activation of hypoxia-inducible factor-lα regulates genes involved in cell proliferation, differentiation, and survival [28], and reduces the organ response to the injury, which is considered to be "protective" [24].

Since CO gas binds tightly with CCO in the mitochondria, it cannot be easily released from the peripheral tissues. It disrupts the electron transport chain at the cellular level, which leads to an excessive production of reactive oxygen species with disturbance of adenosine triphosphate (ATP) synthesis. Thus, CO stops oxygen metabolism in the mitochondria [22, 29]. Treatment with HBO assists to inhibit

lipid peroxidation caused by CO exposure [30] and prevents white blood cells from adhering to small blood vessels (microvasculature) [31], then helps prevent the injury of central nervous system. If the treatment is inadequate and residual CO gas continues to remain with the state of low oxygen in peripheral tissues, it results in an increased permeability of blood vessels and may cause pulmonary and cerebral edema. Long-term hypoxia may cause an impairment of consciousness and induce a vicious cycle that worsens the condition after CO exposure. CO also induces neutrophil-platelet aggregation/activation to deteriorate tissue injuries and may lead to an intermittent type CO poisoning which is characterized by the dysfunction of critical organs (Fig. 7.2) [32].



1. CO combines with heme protein to prompt ·NO-release from platelets competitively.
2. Platelet primed with ·NO reacts with neutrophil primed with ·O2- to create the chemical reaction mediator which can activate platelets.
3. As a consequence, platelet-neutrophil aggregation is produced.
4. Reaction between platelets and neutrophils produces an aggregation with molecular adhesion, and prompt degranulation from neutrophil to release myeloperoxidase (MPO) into the blood.
5. MPO releasing from neutrophil remains along the vascular wall, and some of MPO imigrates into substance under the endothelial cell.
6. Productions by reacted with MPO activate endothelial cells, and prompt adhesion of neutrophils on the vascular wall to degranulate from neutrophils.

Fig. 7.2 Mechanism of perivascular injury by CO [32]. *nNOS* neuronal nitric oxide synthase, *NO* nitric oxide, NO_2 nitrogen dioxide, HNO_2 nitrite

7.3.2 *Priming of Blood and Perivascular Injury*

After entering the blood vessels through the lungs, CO acts on red blood cells, platelets, and neutrophils. It forms nitrotyrosine around the blood vessels and promotes a chain of activation and degranulation of polymorphonuclear neutrophils (PMNs) as shown in Fig. 7.3 [33]. Accordingly as the walls of blood vessels are injured, capillary leakage may occur around the aorta, lungs, skeletal muscles, and brain [13]. The injury of blood vessel walls can cause tissue edema, circulatory disorders, and an insufficiency of coagulation system [31]. Infiltrated neutrophils promote a rapid activation of the synthesis of reactive oxygen species as well as •NO-generating substances. Oxidative stress has a critical role in neurological injuries [7, 34, 35]. On the other hand, CO has a beneficial role to healthy human bodies because of its complex functions in metabolism and inflammatory reactions. The physiological role of CO is becoming more and more clearly [22], thus how to treat CO poisoning has been reconsidered.

Heart and brain injuries caused by CO are considered as a result from the combination of hypoxic/ischemic stress, damage around the blood vessels, and excitotoxicity. By acting on the platelets, PMNs, and Hb in the blood, CO gas stimulates

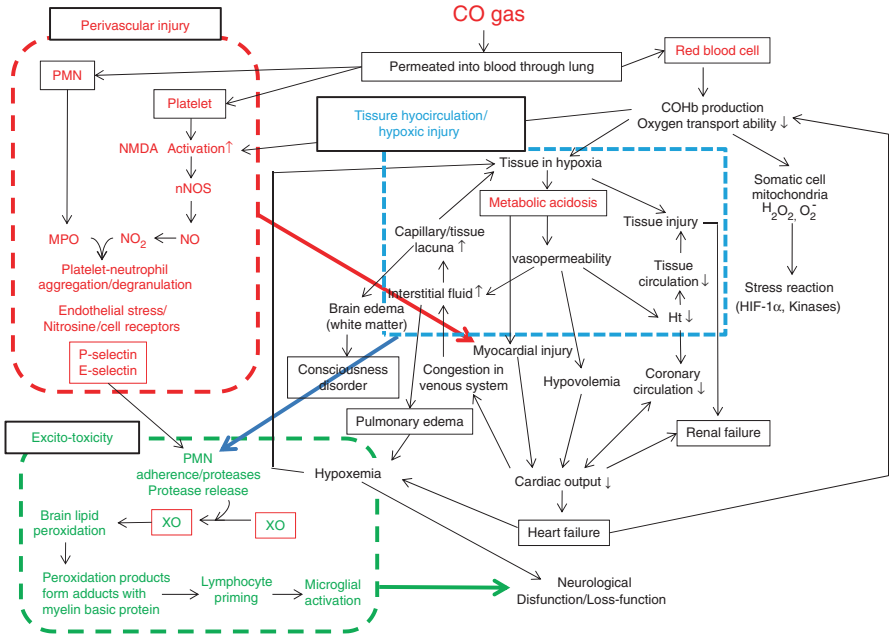


Fig. 7.3 Cascade of the functional disturbance induced by CO

N-methyl-D-aspartate (NMDA) excitatory neurons in the brain and activates neural nitric oxide synthase (nNOS) to increase the concentration of brain nitrite [36–38]. Dysfunction of mitochondria and excessive perivascular oxidative stress caused by CO inhibit the reuptake of glutamate. Arachidonic acid release in the neurophysiological pathway is also inhibited by CO. Hypoxic/ischemic stress followed by an increase of reactive oxygen species can cause nervous activation and present its effect on neurons due to an exacerbation of excitotoxicity [39].

Activation of platelets by CO induces the aggregation of PMNs and stimulates a degranulation to release myeloperoxidase (MPO) into the blood plasma. After the degranulation, MPO deposits on the blood vessel walls and increases the amount of nitrite production, where the expression of adhesion molecules on the endothelial cells is enhanced and PMN adhesion is thus increased. Adhered PMNs activate the production of xanthine oxidase, thereby increasing the amount of oxidants to cause brain lipid peroxidation. Products of lipid peroxidation reaction and myelin basic protein together form additives, denaturing the myelin basic protein into immunological substances, and consequently lymphocytes are primed to start the immune response in the brain. As a result, survivors from CO gas intoxication suffer from learning disabilities because of the brain damage.

CO combines with much of heme proteins (hemoglobin; Hb) with 250-times higher affinity than oxygen, shifts the oxygen dissociation curve to the left, and disturbs oxygen supply to the peripheral tissues [8, 40, 41]. CO also combines with myoglobin in the muscle; however, it is unknown whether its interaction with cellular proteins does any harm in the physiological pathway [42].

7.3.3 Relation with Blood Flow

CO gas permeated into the tissues promotes NO production and increases microcirculation of the blood flow by dilatation of blood vessels in the peripheral tissues. It is recognized as a partial compensation for the hypoxic stress [43]. This vasodilatation breaks the balance of blood flow distribution in the peripheral tissues, causing a steal phenomenon, which decreases blood flow in an area to induce another hypoxia. Therefore, aerobic metabolism is hindered, and metabolic acidosis occurs in this area. In each chemical reaction of the pathological cascade, injuries of nervous system or dysfunction of various organs occur as a manifestation of the cytotoxic effects of CO as shown in Fig. 7.2 [32], which is considered to cause late-onset brain injuries. When the CO-Hb level increases to about 9%, vasodilatation of retina and choroidal vessels occurs [44] along with the systemic adverse effects, such as tissue hypoxia, kidney failure, heart failure, coma, and pulmonary edema. Also, the organs which require oxygen the most, i.e., the brain and heart, fall into dysfunction first and foremost. CO injures the tissue or nerve surrounding blood vessels, which causes neurological dysfunction or loss of function in the end (Fig. 7.3).

7.3.4 Neurotransmitter and Excitotoxicity

CO poisoning increases the activity of NMDA neurons and nNOS. Neurologic sequelae have been confirmed by using animal models in two processes (blood vessels around MPO deposition and excitotoxicity) [45].

7.3.4.1 Neurotransmitter

Upon, activated heme oxygenase-2 (HO-2) increases endogenous CO synthesis from heme, and the CO thus produced plays a neurotransmitter role as mediates nerve signal transduction by activating guanylate cyclase [46]. It has not been determined, however, whether exogenous CO, one of the sources of environmental pollution, affects the neurotransmitting function in a similar manner. HO-2/CO coordinates the secretory stimulation of vasopressin in hypothalamus, which plays a role on long-term potentiation action of the upper cervical ganglia and hippocampus [47].

7.3.4.2 Excitotoxicity

In CO poisoning, the excitatory neurotransmitter increases in the brain, and the receptor is activated by the excitatory amino acid such as NMDA, metabotropic, D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainic acid [48]. In particular, the activation of NMDA receptor causes nervous injuries due to the excitotoxicity [46]. Then, NMDA receptor antagonism reduces the degeneration of neurons due to CO in the hippocampus and the lack of memory. The activation of NMDA induces calcium influx and stimulates nNOS (type I), which means NMDA-induced excessive NO production causes neuronal damages [45, 49]. Therefore, Ca channel blocker (nimodipine) is considered to be a treatment candidate drug for preventing nerve cell death, learning disabilities, and hippocampal pathology [50].

7.3.5 Cardiac Damage

The tissue with high O_2 consumption has a steep oxygen gradient inside the cells, which facilitates CO reuptake into mitochondria [51]. In the most O_2-sensitive tissues such as the heart, vasoconstriction is a typical disorder easily affected by an increase of CO-Hb levels. For example, coronary arterial reflux to the systemic circulation is an important factor for heart failure in addition to hypoxia [42, 52]. In the cases of severe CO poisoning, arrhythmia, cardiomyopathy, myocardial infarction, and sudden cardiac arrest may occur. Accordingly, CO poisoning could be the cause of acute cardiac death [53–55].

The decrease in neutrophil MPO index (MPO/cell) which is the proof of platelet–neutrophil interaction and the simultaneous increase in intravascular MPO levels is a high-risk factor for an acute coronary syndrome among the patients with moderate to severe CO poisoning [3, 56]. The patients who have suffered from an acute myocardial injury in CO poisoning carry the high risk of cardiovascular death for 10 years after exposure. To control the myocardial risks, ECG and myocardial marker in the blood plasma are useful monitors. Chest X-ray examination can be used for the evaluation of myocardial function in the case of emergency. It enables the evaluation of pulmonary injury by smoke inhalation or pulmonary congestion/alveolar infiltration due to myocardial injury [53]. Since HBOT improves the hypoxia of myocardial cells in CO poisoning, it is performed not only for the purpose of the treatment of consciousness disorder but also for the improvement of cardiac contractility.

7.4 Symptoms of CO Poisoning

Symptoms of CO poisoning include redness or cherry-red color of the skin, which is not specific to the disease, and some various cold-like symptoms, such as slight fever, tachycardia, tachypnea, mild headache, nausea, and coma (Table 7.5). Without knowing the fact of CO exposure, differentiating a disturbance of consciousness from other diseases such as cerebrovascular disease, diabetic coma, or drug poisoning is difficult. It may cause considerable delay in identifying the source of CO contamination or correctly diagnosing for treatment [23], which means status hearing is crucial.

Although correlation between clinical symptoms and CO-Hb levels (2–10%) is well known (Table 7.6), CO-Hb levels do not always match with the severity due to various factors including oxygen insufflations during transportation, duration of exposure, or medications which the victims take [10, 11]. Even CO exposure at 5–10% or lower CO-Hb level may cause some subtle changes in visual or auditory function, level of consciousness, occupational or learning ability [57, 58], and there may be some abnormality identified in higher brain functions by objective test such as auditory evoked potentials. These nonspecific initial symptoms appear in the course of time after the CO exposure, and as the CO-Hb level increases, it leads to respiratory insufficiency or consciousness disturbance, and finally to a circulatory collapse followed by death. Patients exposed suddenly with high concentration of CO, however, lose the consciousness immediately.

Table 7.5 Clinical features of CO poisoning

Headache	Collapse convulsion
Visual disturbance	Changes in electrocardiogram
Mental confusion	Comatose
Anxiety	Angina
Dyspnea/Tachypnea	Psychological deficit symptoms

Table 7.6 Severity of CO poisoning, CO-Hb levels, and clinical features [22]

Severity	CO-Hb level	Clinical features
Occult	>5%	No apparent symptoms Psychological deficits on testing
	5–10%	Decreased exercise tolerance in patients with chronic obstructive pulmonary disease Decreased threshold for angina and claudication in patients with atherosclerosis Increased threshold for visual stimuli
Mild	10–20%	Dyspnea on vigorous exertion Headaches, dizziness Impairment of higher cerebral function Decreased visual acuity
Moderate	20–30%	Severe headache, irritability, impaired judgment Visual disturbances, nausea, dizziness Increased respiratory rate
	30–40%	Cardiac disturbances, muscle weakness Vomiting, reduced awareness
Severe	40–50%	Fainting on exertion Mental confusion
	50–60%	Collapse convulsions Paralysis
Very severe	60–70%	Coma, frequently fatal within a few minutes
	Over 70%	Immediately fatal Respiratory and cardiac arrest

The patients with coronary artery disease may decrease exercise capacity and have early myocardial contraction frequency and symptoms of myocardial ischemia at the low CO-Hb level of 2–6% [55, 59]. In addition, exercise tolerance decreases in patients with chronic obstructive pulmonary disease [60], and complications such as angina, pulmonary edema, gastrointestinal bleeding, and acute renal failure may occur.

7.5 Laboratory Test of CO Poisoning

Measurement of blood CO-Hb level is a standard diagnostic test, but due to the similar optical absorption characteristics among O_2-Hb, CO-Hb, and fetal hemoglobin (HbF), CO exposure cannot be identified by pulse oximetry [61, 62]. In recent years, it became possible, however, to diagnose CO poisoning before arriving the hospital using new models which can detect CO-Hb. On the other hand, metabolic acidosis and lactic acidosis, which reflects the decrease in oxygen transportation capacity, are indicators to evaluate the severity. Especially in the case of consciousness disturbance, metabolic acidosis with wide anion gap, or unexplainable lactic acidosis, it is important to suspect CO poisoning regardless of the CO-Hb levels.

In the case of acute myocardial injury showing circulatory depression due to CO exposure, both the ECG which reflects myocardial ischemia and cardiac marker levels (troponin and creatine kinase: CK-MB fraction) which reflect organ ischemia are good monitoring tools (Table 7.7). In addition, the echocardiography which is able to sensitively detect myocardial wall motions is also a useful examination tool for diagnosing myocardial injury in CO poisoning. Chest X-ray can be one of the best examinations to urgently evaluate pulmonary edema or alveolar infiltration due to smoke inhalation or myocardial injury [53].

The degree of brain damage is determined by how much a victim has been exposed to the CO gas. And consciousness disturbance or abnormal findings in CT or MRI results are considered due to the following two situations; "an initial brain injury on exposure"; and "a late-onset brain injury caused by CO residues in the tissues (delayed neuropsychological sequelae (DNS) of CO poisoning)." In brain CT (computed tomography) and MRI (magnetic resonance imaging), abnormalities of low density or high intensity are found in the wide area including the globus pallidus, putamen, thalamus, the caudate nuclei, substantia nigra, fornix, hippocampus, corpus callosum, and cortex [63–65]. These clinical symptoms do not always reflect abnormal findings on the images, and the nerve injuries by CO are not much completely with anatomic areas. However, since these changes are observed in the regions where oxygen required in the brain blood stream and the nerves in CO poisoning [66, 67], the neurotoxicity of CO can be assumed to coincide with the pathophysiology around the surrounding blood vessels. It is a fact that symptoms and radiographic findings disappear by the repeated HBOT. It is interesting that the prognosis is bad in a case with identified abnormality in acute CO poisoning. But, it is not clear whether HBOT is necessary until they disappear.

From research using EEG, it is said that EEG is also deeply related to the course of the CO poisoning, and EEG is a test to detect the characteristic findings of ischemic lesions in cerebral basal ganglia. As EEG test is a good prognostic indicator [3, 68], it is suggested that consciousness disturbance and the duration of CO gas exposure must be emphasized as the criteria of severity and selecting treatment methods.

Table 7.7 ECG abnormalities due to CO poisoning [22]

1. Arrhythmias, extrasystoles, atrial fibrillation
2. Low voltage
3. Depression of S-T segment
4. Prolongation of ventricular complex, particularly the Q-T interval
5. Conduction defects
• Increased P-R interval
• A-V block
• Branch bundle block

7.6 Diagnosis of CO Poisoning

As the symptoms of CO poisoning are similar to that of a cold, CO poisoning is sometimes overlooked from unawareness of the exposure to CO gas [23]. Thus, emergency doctors should always bear the possibility of CO poisoning in their minds, and it is important to obtain the information necessary to grasp the situations such as "the family in the same house had a headache at the same time," "the car was idling in a small garage," or "to inhale the smoke at the fire scene" for the diagnosis. To diagnose CO poisoning, the situation of the scene will be the most important basis in addition to the CO-Hb levels and clinical signs. The classical cherry-red findings on the face and trunk are never specific, and in the case of consciousness disturbance, it is necessary to differentiate it from cerebrovascular disease, diabetic coma, or drug poisoning.

Although clinical symptoms of headache and dizziness have a constant relationship with CO-Hb levels (2–10%), it is important to keep in mind that its relationship is different in reality. Because the blood CO-Hb level declines in the course of time or due to oxygen insufflations during transportation, the case of CO-Hb levels less than 10% on arrival could be a severe CO poisoning case [69].

Since a CO-Hb level in the arterial blood is almost same as that of the venous blood, the CO-Hb level should not necessarily tested with the arterial blood. When an increase in oxygen partial pressure of venous blood is confirmed, it is expected that respiratory enzyme is inhibited due to CO poisoning. It is important to make note in the outbreak situations and the clinical symptoms. In the case of fire, it may be complicated with the symptoms of hydrogen cyanide [22], and there are more cases of mixed gas poisoning accompanying chemical choking by other gas such as hydrogen cyanide, carbon dioxide, or hydrogen sulfide. Therefore, the blood measurement of CO-Hb is important in the diagnosis.

Brain CT (computed tomography)/MRI (magnetic resonance imaging)/SPECT (the single photon emission computed tomography) have been reported in wide areas of lesions [63, 65], which is evidence in those tests (Table 7.8). CT can't capture the changes of cerebral blood flow, but it is to detect abnormalities like edema of the basal ganglia and white matter. While MRI can detect those abnormalities in

Table 7.8 Comparative value of brain imaging studies in CO poisoning [22]

	CT	MRI	SPECT
Basal ganglia lesions	+	++	
White matter lesions	+	+++	
Both white and gray matter	+	++	+++
Cerebral edema	+	++	
Cerebral perfusion			+++
Predicting late sequelae	+	++	++
Assessing response to HBOT	+	++	+++

more sensitive than CT, SPECT is more sensitive to changes in white/gray matter and detection of delayed change, and better in cerebral blood flow than CT or MRI. The effect of HBOT can be assessed, with increasing sensitivity, by using CT, MRI, SPECT, respectively [22]. However, these CO-associated findings do not reflect nerve injuries and anatomical area [64]. These findings are suggested to match with pathophysiology of the blood vessels surrounding.

7.7 Treatment for CO Poisoning

Treatment for CO poisoning is based on general management of poisoning and is special to CO poisoning.

7.7.1 General Management of CO Poisoning

7.7.1.1 Primary Treatment for CO Poisoning

As to direct treatment for CO poisoning, pure oxygen insufflations, artificial respiration, and HBOT are used to: [1] prevent its invasion; (2) eliminate from the body; and (3) antagonize the toxins absorbed (Table 7.9). The oxygen insufflations are basic treatment, and the methods are separated into atmospheric pressure and high pressure. CO poisoning is one of the most common indications for HBOT, HBOT quickly increases the oxygenation in tissues and at the same time rapidly isolates CO from the hemoglobin, which is the most theoretical treatment.

7.7.1.2 Intensive Care for Life Support

As the CO poisoning complicate various diseases, in severe CO poisoning cases, the treatment includes improving or preventing cerebral edema and activating cerebral metabolism. In addition, the multimodal treatment is required to address DIC

Table 7.9 Guidelines for the management of CO poisoning [22]

1. Remove patient from the site of exposure
2. Immediately administer oxygen, if possible after taking a blood sample for CO-Hb
3. ndotracheal intubation in comatose patients to facilitate ventilation
4. Removal of patient to HBO facility when indicated
5. General supportive treatment; for cerebral edema, acid-base imbalance, etc
6. Keep patient calm and avoid physical exertion by the patient

or circulation failure, and so on. HBOT improves cardiovascular diseases, reduces the mortality rate, and prevents autoimmune neurological sequela [70]. It is said to reduce the mortality rate further when using hypothermia therapy together with HBO after CO exposure, however, it is unlikely that HBOT helps to improve the prognosis when the brain has been injured by hypoxia [27].

7.7.2 Treatment by HBO

Since HBOT has the two effective points: (1) high oxygen partial pressure promoting the exclusion of CO from the body, and (2) high dissolved oxygen increasing oxygen supply. HBOT is used for recovery from CO poisoning and prevent intermittent-CO poisoning. HBOT or NBOT is selected according to the triage criteria by Colignon and Lamy (1986) [4], and for patients presenting with any symptoms, HBOT is performed instantly. Even if the consciousness is recovered or the electroencephalogram (EEG) are normalized, it is recommended to continue every day for 1–2 weeks to prevent late-onset of brain damage [22, 71] (Table 7.1). The therapeutic effects of HBOT have been discussed for many years; the combined treatment of HBO with thyrotropin-releasing hormone (TRH) or Ca channel blocker (Nimodipine) inhibits neuronal degeneration, learning disabilities, and hippocampal neuronal cell death caused by CO, and is meaningful as a method for treatment of acute CO poisoning [51, 72, 73]. However, there are reports that both confirm and deny the HBOT from the standpoint of evidence-based medicine.

7.7.2.1 Effects of HBOT

In a retrospective multicenter comparison study of HBOT and NBOT, it is difficult to unify (1) background of the patient, (2) evaluation of patient, and (3) management of HBOT (pressure, duration, and times). Effectiveness of HBOT is not determined in acute CO poisoning because evaluation criteria for therapeutic effect is unequal between each center (Fig. 7.4) [74–76]. As evaluation of the treatment effects differ according to the HBOT practices and implementation criteria, comparative research is never an ideal method. The prognosis and treatment of acute CO poisoning cases in Japan was surveyed by Kusuba et al., and the institutions were divided into three groups: FULL RECOVERY (where symptoms or abnormal findings disappeared completely); IMPROVED (where symptoms or abnormal findings were improved; and UNCHANGED (where any changes in symptoms or abnormal findings were confirmed), by using their own HBOT implementation criteria for acute CO poisoning. Consequently, it is concluded that HBOT is more effective than NBOT [5] (Fig. 7.5). Interestingly, it is reported that there was no difference in ratio of effective to ineffective between each rank (group) in HBOT cases, however in NBOT cases, the ratio of ineffective cases was higher than that of HBOT cases [5] (Fig. 7.6). This report minimized the difference between the comparison groups

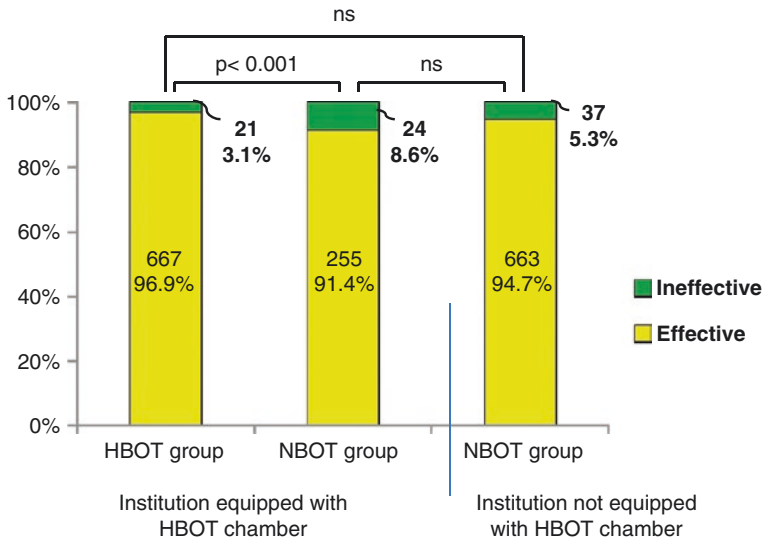


Fig. 7.4 Comparison of prognosis between types of treatment administered among institutions with and without an HBOT chamber [5]. (Pearson's Chi-Square Test, $n = 1667$)

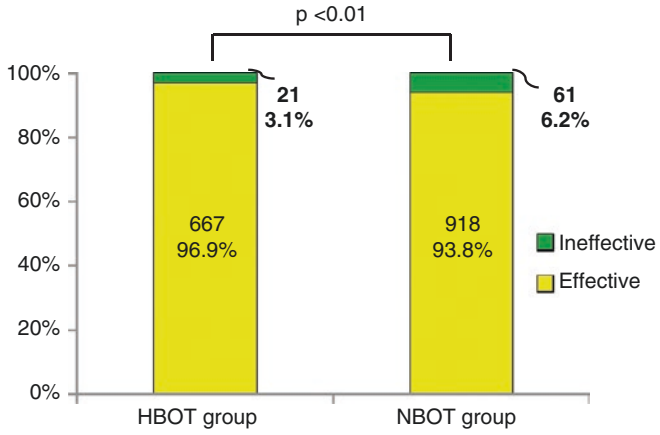


Fig. 7.5 Prognosis of cases included in the study [5]. (Pearson's Chi-Square Test, $n = 1667$)

by simplifying the evaluation criteria and comparing within the same institutions, which makes it the large retrospective comparison test (RCT) with the highest reliability in the world. Hyperbaric oxygen administration has been proven to relieve the symptoms of poisoning in animal experiments [77], and it was reported that oxygen administration, brain anti-edema therapy, and brain activation therapy for recovery of consciousness were the therapeutic effects of HBOT [22, 73, 78, 79],

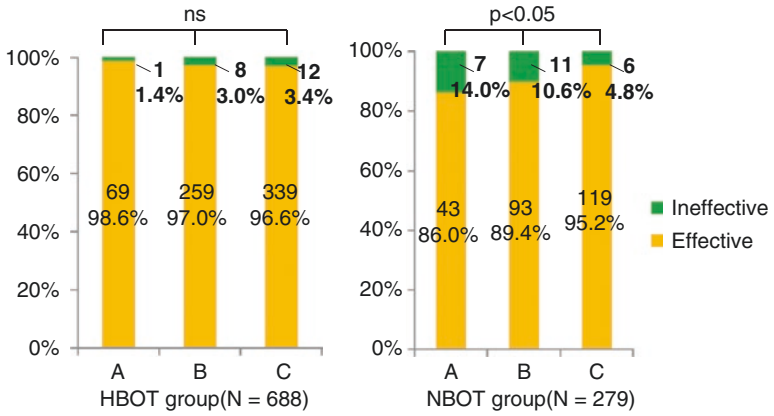


Fig. 7.6 Comparison of prognosis between groups A, B, and C among institutions equipped with HBOT chambers [5]. (Cochram-Armitage test, $n = 967$)

whose active implementation was discussed. From these things, it needs to be promoted that HBOT should be prioritized over NBOT in treating severe acute CO poisoning.

HBOT reduces the acute mortality and decreases the occurrence of neurological sequelae and the neurological injuries due to immunity; however, it does not reduce the injuries caused by hypoxia [27, 70]. Therefore, there is another idea that HBOT is effective in the patients with CO poisoning who fall under one of the following categories: with consciousness disturbance; with the CO-Hb level of more than 25%; or more than 36 years old. Considering the mechanism of hypoxia in tissue, just because the CO-Hb level decreases does not mean that it has been cured. Since a small amount of residue of the CO gas in the tissue can cause a various injuries, HBOT is considered to be a reasonable choice for severe CO poisoning.

7.7.2.2 Prognosis in the NBOT Group

As described in the implementation criteria for HBOT by Colingnon and Lamy [79], HBOT group is more severe than NBOT group. It is suggested that the patients with mild acute CO poisoning tend to be transported to the facilities without a HBOT instrument, and the patients with any severity, severe to mild, to the facilities with a HBOT system. Therefore, the installation of HBOT equipment makes difference in the patients' severity. Also, according to the Cochrane review, the implementation of HBO to an acute CO poisoning only shorten the half-life of CO and is not recommended as a routine treatment [80]. Even the clinical policy of American College of Emergency Physicians, HBOT has no high-quality evidence but is just one of the choices [81]. HBOT was believed to have the same therapeutic effect as NBOT [9–11]; however, Kusuba et al. [5] observed the difference in the percentage of non- effectiveness by NBOT among the facilities (Fig. 7.6). To be assessed, on

the other hand, no differences in both therapeutic effects of HBOT and NBOT group cannot negate the effect of HBOT therapy, which can show the prognosis of severe and mild acute CO poisoning patients could be the same. Consequently, it means the marked therapeutic effects of HBOT.

7.7.3 Historical Transition of HBOT

7.7.3.1 Efficacy of HBOT

Many clinical experiences were reported about effectiveness of HBO for CO poisoning [82–84]. In 1895, Ha1dane showed preventive effect of HBO for CO poisoning in animal experiments [32]. Since Smith reported the effective results of HBO in 1962 [85], HBOT became to be used for acute CO poisoning. Although HBO was recognized then as only and absolute treatment by this poisoning case, tissue damage due to CO poisoning had not fully elucidated yet, and HBOT was not generalized as an effective treatment. The HBOT triage criteria (Table 7.1) for CO poisoning was first published by Colignon and Lamy (1986) [4], which has generalized HBOT as a treatment for CO poisoning. In 1995, Ducasse et al. [74] and Thom et al. [86] reported in their two RCTs that HBO was more effective treatment than NBO in mild cases. Although one RCT was reported in 1999 [72] which denied the effect of HBO for acute CO poisoning, it had the problems that there was no consideration for the involvement of alcohol and medication and that the duration of oxygen administration was short as 60 min, even at 2.8 ATA [32]. In 2002, Weaver et al. [73] reported that HBO suppressed DNS of CO poisoning and improved its neurological prognosis better than NBOT, and reported in the RCT that HBOT has positive treatment effects for higher order functions.

After these reports, there were a report recommending HBOT [87], and other studies were conducted to compare the neuropsychological functions between the HBO groups (which received HBO treatment three times within 24 h from the discovery) and the NBO groups (which received NBO two times for 125 min as control). Compared to the NBO, it was found that HBO inhibited the intermittent-CO poisoning and improved the neurological prognosis, which has changed the understanding of the treatment in Japan, and the idea has become popular that HBOT is an effective treatment for an acute CO poisoning. This RCT was internationally valued as the most designed clinical trial in acute CO poisoning, and Sheridan et al. [88] stated that HBOT could be a prospective treatment for severe CO poisoning. However, at this time, it suggests that it is important to let experienced specialists make the judgment of effect and to accumulate the results of clinical treatment to determine the effectiveness of HBOT. The high CO-Hb level and the sustained cerebral ischemia in the early stage of acute CO poisoning may induce a delayed neuronal apoptosis, and thus it might be possible to determine the early transition to an intermittent-CO poisoning.

7.7.3.2 Unnecessary-Theory of HBOT

The randomized comparative test (RCT) in 1989 by Raphae1 et al. [89] was the very first relevant trial report. However, in the patients without consciousness disturbance there was no difference found between the NBO group (with 6-h pure oxygen inhalation) and the HBO group (1-h treatment under 2 ATA) in the outcome of the neurological function one month after treatment. And, in the patients with consciousness disturbance, there was no difference shown in its therapeutic effect between the patients who received the HBO treatment once and twice. In addition, Scheinkestel et al. [90] reported that about half of the CO poisoning patients who had been treated with HBOT received an additional treatment, and they considered that HBOT was not necessary but NBOT was sufficient. According to these argument which designated HBOT unnecessary, it was considered that "there is no evidence that HBO is more effective than NBO groups (22) in CO poisoning," and also in Japan, the theory designating HBOT unnecessary became the majority. However, in the discussion about HBOT, it was shown that treatment procedures of each individual were so different that the randomized controlled trial was difficult. As HBOT was performed in only once or twice, which means the severity of patients was mild in this RCT, it seemed to be difficult to estimate the effect of HBOT [89]. According to the reports, those articles which question the evaluation of the effect of HBOT could not be the conclusion [79, 91, 92].

7.7.4 HBOT Procedure

Weaver et al. (2002) [73] reported that three times of HBOT within 24 h (3 ATA for 60 min at the first time, and 2 ATA for 100 min at second and third times) could suppress the incidence of neuropsychological (cognitive) failure, and had recommended the implementation of HBOT. However, it is still unknown which procedure of HBOT is the most effective for acute CO poisoning, which is one of the causes making it questionable for the effectiveness of HBOT. As a result by Weaver et al. [73], the Pan-European Committee in 2004 had put out the treatment guideline for CO poisoning. If a patient has a history of neurological symptoms or impaired consciousness, HBO (at 2.5 ATA for 90 min) treatment should be carried out for 1 to 3 times as soon as possible. If a patient is a pregnant woman or a child, also HBO is recommended even in a mild case, otherwise NBO for more than 12 h is recommended. In addition, the treatment pressure of 2.5–3.0 ATA is recommended also in the United States. In Japan, HBO for 60 min at 2 ATA is a standard HBOT procedure, which was introduced by Raphael et al. as mentioned earlier (1989) [89]. In contrast, Weaver et al. [73] insisted that it is important to perform long-running HBO with high pressure multiple times within 24 h in the early phase. This points the characteristics of their treatment procedure.

HBOT procedures for acute CO poisoning vary in Japan [55, 57–59], and even the combination of the therapeutic pressure and duration of HBO is not

standardized internationally. In the first 24 h on the first day of arrival to hospital, HBOT is performed 1–3 times at 2.5–3.0 ATA for 60 min, and for the following days it is continuously performed at 2.0 ATA for 60 min for 7–14 times referring to clinical symptoms (Fig. 7.7). As the prognosis becomes worse, the frequency of HBOT increases. HBOT had no significant effect even when the frequency increased over 14 times. In contrast, as the frequency of HBOT of cases with complete recovery (full recovery) is as low as seven times, the rationale for HBOT frequency for acute CO poisoning is 7–14 times (Table 7.10). To address the sequelae from CO poisoning after the acute phase, patients have been followed up including high-order neurofunctional evaluation by the multidisciplinary team formed with the department of Neurosurgery, Neurology, and Rehabilitation.

7.7.5 Investigating Issues in the Treatment

HBO treatment method has some investigating issues. As HBOT is often performed for 7–14 times in Japan, there is expectation that the ongoing HBO might suppress the occurrence of DNS of CO poisoning. In the treatment of acute CO poisoning, HBOT has still many issues right now. It is worthy of attention as to whether HBOT can prevent DNS of CO poisoning, what can be the procedure criteria, based on

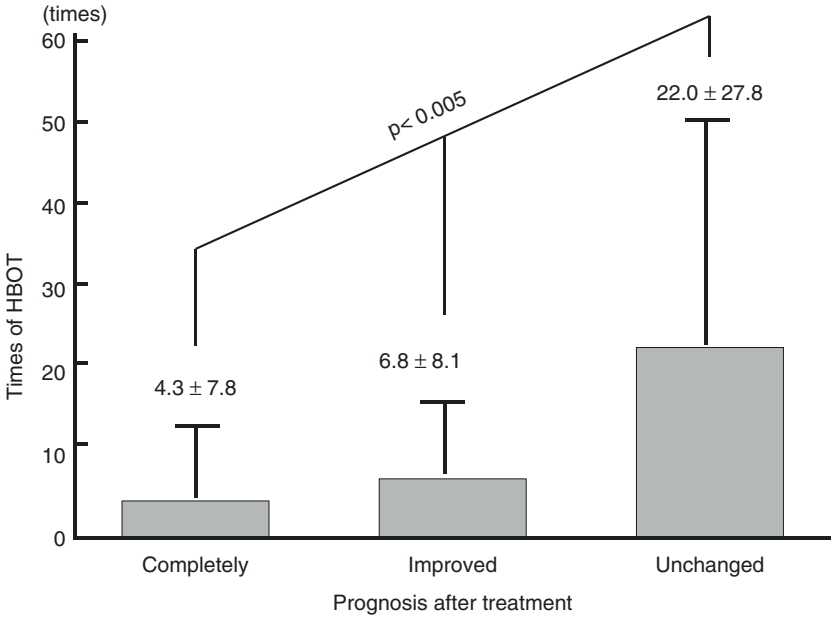


Fig. 7.7 Prognosis and proceeding time by HBOT. (Multiple comparison test, $n = 407$)

Table 7.10 Summary of the management for acute CO poisoning in Japan

1. Proceeding protocol of HBOT
Removal of patient to HBO within 24 h after CO exposure
• First: One man hyperbaric chamber…2.0 ATA for 60 min
(Multiplace hyperbaric chamber…2.8 ATA for 60 min)
• Second: 2.0 ATA for 60 min within 24 h
• Third: 2.0 ATA for 60 min within 24 h after second
• Total frequency is 7–8 times of HBOT basically (on some day, 2 times/day)
• After 7–8 times of HBOT, HBOT must be proceeded continuously until the abnormal signs disappear fast (HBOT is discontinued after 10 times if signs disappear)
2. Indication for HBOT
(a) HBOT if one of them observed
• CO-Hb >10%
• or some symptoms
• or some abnormalities in the laboratory tests
(b) CT/MRI before/after HBOT
• Before HBOT procedure
• At the discharge
• At 2–3 weeks after CO exposure

Table 7.11 Remarkable signs expecting the worse prognosis

• Metabolic acidosis or deep coma at arriving…severe
• Complication of lung or/and kidney in a early phase…poor prognosis with neuropsychological symptom
• Disturbance of consciousness
If recovered in 2–4 h…sequela may be almost disappeared
If recovered after 72 h…neuropsychological symptom may be appeared
• Conscious level after first HBOT…it could reflect the prognosis
• If wide low density area (LDA) in the globus pallidus or/and white matter appears in CT at the early stage, it will be poor prognosis
• If brain blood flow decreases in SPECT at the early stage, it will be poor prognosis

what criteria the treatment can be terminated, whether the half-life of CO-Hb level or improvement of the results of CT/MRI can be the criteria, or whether NBO is inadequate as a treatment. Also, it is still unknown whether neurological sequelae can occur even if a patient is without consciousness disturbance in acute poisoning, even if the patient receives a rapid and appropriate emergency treatment [73, 86], or whether the pathological apoptosis similar to a late-onset neurological necrosis can occur by an transient cerebral ischemia [78]. As the expectations of HBOT involve the evaluation of the acute poisoning, clinical findings to guess the prognosis by many clinicians have been known empirically (Table 7.11). In the accumulation of evidence, the issues would be solved scientifically in the near future.

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Chapter 8
Recompression Therapy for Decompression Sickness and Arterial Gas Embolism

Fumitaka Ikomi

8.1 Introduction

Air, oxygen, and mixed gases are widely used for pneumatic construction work, diving, and hyperbaric oxygen therapy (HBOT). Atmospheric air consists of nitrogen (79%), oxygen (21%) and very small quantity of other gases. The mixed gases for these uses usually consist of several combinations of oxygen, nitrogen, and helium [1]. Nitrogen and helium are metabolically inactive gases, the so-called inert gases, and accumulated in the body fluid under pressure according to Henry's law. During and/or after decompression, i.e., reduction in environmental pressure, these inert gases occasionally form small bubbles in blood and tissues. These bubbles of inert gases are considered to be the direct cause of decompression sickness (DCS), which is characterized by various symptoms including joint pain, skin rashes, paralysis, and other neurological disorders [2]. On the other hand, inhaled oxygen is used for tissue respiration and metabolized into carbon dioxide and water. Since carbon dioxide has high solubility in water, inhaled oxygen does not highly contribute to form in situ bubbles contrary to inert gases [3].

In addition to DCS, decompression process may induce expansion of trapped gases and lead to injuries of gas-contained tissues in the human body, which is called barotrauma. For example, pneumothorax [4], pneumoperitoneum [5], and pneumocephalus [6] can be caused by intolerable expansion of trapped gases in the lung, intestine, and paranasal sinuses, respectively. Rupture of the lung also causes alveolar gas entry from alveolar space into arterial circulation via pulmonary vein, resulting arterial gas embolism (AGE) [7, 8]. Because the symptoms as well as the causes of DCS and AGE are often overlapped and difficult to be clinically distinguished to each other, they are collectively called decompression illness (DCI) [9, 10].

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To enhance exhaustion of the inert gases accumulated in the body, administration of 100% oxygen is the first-aid treatment for DCI [8, 10]. HBOT specifically designed for the treatment of DCI is called recompression therapy, and U.S. Navy treatment tables for this purpose are widely used [11, 12]. In this chapter, basic biomechanical mechanisms as well as molecular basis of recompression therapy, criteria of selecting the tables, and our recent experience for the treatment of severe DCI cases are described.

8.2 Decompression-Induced Disorders in Human Body

Bubble formation and expansion of trapped gases in the human body are the two major etiologies of decompression-induced disorders. While the cause of DCS is highly related to accumulation of bubbles formed in the body during the decompression process, AGE is exclusively induced by the pulmonary barotrauma [10]. During decompression, inert gases dissolved in the body fluid at high ambient pressure would be supersaturated and begin to form small babbles. These bubbles formed in the tissues sometimes destroy surrounding tissues, and press the nearby nerves and blood vessels, thereby causing neuronal disorders and circulatory failure. Accumulation of bubbles in the spinal venous system has also been suspected to be one of the main causes of spinal ischemia and edema [13, 14]. MRI pictures of some DCS patient are compatible with the mechanisms [15]. On the other hand, the intravascular bubbles activate blood coagulation system [16], complements cascade, platelet aggregation [16, 17], neutrophil adhesion [18], and permeation of the small vessel walls [19]. Thus, both direct biophysical effects and indirect biochemical effects are important for the pathophysiological mechanisms of DCS. However these bubbles are strongly related to trigger DCS, not all of the bubbles lead DCS and the harmless bubbles are called silent bubbles [20]. Arterial bubbles in DCS patients may induce infarctions in some tissues if the bubbles are aggregated large enough but clinical implications of these bubbles are controversial [9].

If there is a certain amount of gas trapped in the closed space of the body at a certain depth, the volume of the gas will increase and apply compression to the surrounding tissues according as ascent from the depth. When dive in the seawater, ambient pressure decreases by 0.1 MPa (1 atm, 10 mps (meters of seawater)) for every 10 m ascending. Pressure–volume relationship of the gas follows Boyle's law, which demonstrates that the product of volume and absolute pressure of a given mass of a gas is always equal at a constant temperature. For example, ambient pressures are 0.2 MPa (2 ATA) at 10 m deep in seawater and 0.1 MPa (1 ATA) at the sea surface, thus, the gas volume at the sea surface is twice as large as that at 10 m deep. Rapid expansion of the gas leads to the unbalance between the space and volume and may cause decompression-induced barotrauma [21]. Decompression-induced barotrauma in nasal sinuses, middle ear, and teeth are called block or reverse squeeze [22]. In a similar fashion, intestinal gas may cause abdominal pain during decompression [23, 24].

8.2.1 Risks of Occurring Decompression Sickness

Not all of decompressions cause DCS even if oversaturation of inert gases occurs in the body fluid. In 1908, Boycott, Damant, and Haldane [25] demonstrated that, when goats were breathing air, they did not suffer from DCS after decompressions that were limited to one-half of the saturation depth. Thus, decompression stop to eliminate supersaturated gases from the body was proved effective for the prevention of DCS, and it depends to a large extent on the time and depth of the diving. Actually, DCS tends to occur when decompression stop is too shallow and/or short to washout enough inert gases from the tissue.

Diving conditions are listed as the risk of DCS, which include immersion (vs. dry) [26, 27], long diving, deep diving, repetitive diving [28], warm environment during the bottom time, cold environment during decompression, rest at decompression stops, and strenuous exercise after diving [9, 10]. Most of these conditions apparently enhance blood circulation and inert gas uptake during the bottom time. Conversely, cold and resting conditions during the decompression period suppress inert gas elimination from the circulation [9, 10]. Strenuous exercise immediately after surfacing induces bubble formation in the tissue fluid supersaturated with inert gases [9, 10]. Increasing age and large body mass index (BMI) are also the risk of DCS [28].

DCS is observed in pneumatic caisson workers, pressurized tunnel workers, self-contained underwater breathing apparatus (SCUBA) divers, surface supplied divers, personnel transfer capsule (PTC) divers, and saturation divers. Even in breath-hold divers, deep and repetitive dives are known to cause DCS [29, 30]. Decreasing ambient pressure from 0.1 MPa (1 ATA) also causes DCS that is called aviation DCS or altitude DCS. Aviation DCS results from ascent to altitude in an unpressurized aircraft and extravehicular activity during spaceflight [31, 32].

8.2.2 Types of Decompression Sickness

DCS, which is strongly related to intravascular and extravascular bubbles, is a systemic disease and manifests a wide variety of symptoms. Typical symptoms of DCS include joint pain, skin rashes, headache, vertigo, nausea, cough, hemosputum, chest pain, stomachache, lumbago, and neurological symptoms, such as reduced level of consciousness, convulsion, numbness, hyposthenia, paresthesia, paralysis, bladder dysfunction, and rectal disturbance [9, 10]. Cases of DCS are classified based on the severity of the disease and on the organs mainly cause the symptoms. When no symptom other than itching, burning, local edema, rash, and pain in the muscle and joint of the extremities is observed, the case of DCS is clarified into Type I DCS. Type I DCS is neither severe nor life threatening [10, 33].

On the contrary to Type I DCS, Type II DCS is serious and sometimes life threatening [33]. Type II DCS has some sub-categories, such as of the so-called

cerebral DCS, spinal DCS (spinal cord DCS), pulmonary DCS, inner ear DCS, and decompression-induced shock [34]. Cerebral DCS shows symptoms predominantly associated with brain damages, such as focal signs, reduced level of consciousness and convulsion. Bubbles formed inside the brain or those occluding cerebral artery that come through the pulmonary circulation or a cardiac right to left shunt may be the etiology of this type [35, 36]. Spinal DCS commonly commences with gait disturbance and then it is followed by sensory and motor deficits which progress to an ascending level [15]. Also, bladder dysfunction and rectal disturbance are occasionally observed in spinal DCS. Bubbles formed in the spinal cord and those occluding spinal veins are thought to induce neuronal damage, bleeding, edema, and compression of the spinal cord [9]. Pulmonary DCS, inner ear DCS, and decompression-induced shock are considered to be caused as a result of accumulated bubbles in the pulmonary circulation [37], bubbles formed in the inner ear [38], and dehydration induced by increased permeability in the systemic microcirculation [19], respectively [9].

8.2.3 Pulmonary Barotrauma and Arterial Gas Embolism

During decompression, volume of the gases expands according to Boyle's law. If the airway is occluded or breath is held under that situation, expanded gases may break alveoli and consequent interstitial emphysema, pneumothorax, mediastinal emphysema, aerodermectasia, and AGE occur. These situations are resulted from pulmonary barotrauma and called pulmonary overinflation syndrome (POIS) [39]. Different from DCS, POIS tends to take place in a shallow diving because the volume of the alveolar gas changes larger at shallower place per certain pressure change [40]. Even at the decompression from 1 meter of seawater, alveolar rupture has been observed [41].

After alveolar gases enter pulmonary vein through the ruptured alveolar walls, they are carried into systemic circulation via the heart. The arterial gases spread all organs and tissues of the body along the arterial tree and make gas embolisms. Especially, cerebral and cardiac AGE are life threatening. Gases coming from pulmonary vein along the blood stream tend to make embolisms in cerebral circulation [42]. Thus, pulmonary barotrauma-induced AGE patients usually show early onset after decompression and similar symptoms to cerebral infarction [9]. Representative symptoms of AGE are extreme fatigue, nausea, vomiting, vertigo, difficulty in thinking, unconsciousness, convulsions, vision abnormalities, numbness, paresthesias in large areas, weakness, paralysis, and loss of coordination. Cerebral DCS has similar latency, progress, and neurologic manifestations to AGE. Thus, clinically, it is difficult to differentiate these two conditions [43].

8.2.4 Treatment for Decompression Illness

A first-aid treatment for a diver with no pulse or respiration, regardless of the origin, is cardiovascular resuscitation. For DCI patient with pulse and respirations, immediate administration of 100% oxygen on sight is highly recommended. If HBOT chamber is available, recompression therapy should be applied to DCI patients. As described below, U.S. Navy treatment tables are widely adopted for recompression therapy (see Sect. 8.4) [10, 12].

In addition to recompression therapy, oral or intravenous administration of electrolyte solution is recommended for DCS, except for pulmonary DCS, patients [44]. In the treatment of AGE, but not DCS, intravenous or intramuscular administration of lidocaine is shown to be useful for recovery of brain functions [45]. For the patients of DCI-induced inability to walk, low molecular weight heparin is used to prevent deep venous thrombosis and pulmonary thrombosis. Other anticoagulants, non-steroidal anti-inflammatory drugs, and steroids are no longer recommended for the treatment of DCI [44].

8.2.5 Evacuation of Patients Suffering Decompression Illness

It is necessary for DCI patients to be evacuated to a hospital, a clinic, or another appropriate facility where the patients can receive recompression therapy. During the evacuation, to continue administration of 100% oxygen and not to decrease environmental pressure are both important for stabilizing the patients' condition [10, 46]. These behaviors prevent development and expansion of bubbles in blood and tissues of DCI patients.

Up to about 2000 m of an altitude, atmospheric pressure decreases almost 1.0 kPa (0.01 atm = 1/100 atm) every 100 m increase in height [47]. Thus, DCI patients should not move to higher place to prevent a decrease in the ambient pressure. If aircraft is used for transporting the patient, the cabin should be kept 0.1 MPa (1 ATA). On an empirical basis, unpressurized aircraft is preferred to fly less than 300 m for the use of transporting the patients [10, 46]. It should be noted that even if an aircraft has pressurized cabin, usually cabin altitude is not kept lower than 300 m during cruise but is kept about 1500~2400 m [48].

In addition to altitude, weather is also important for ambient pressure. For example, central pressure of the strongest typhoon (Tip 1979) ever observed is 87.0 kPa (0.87 ATA) [49]. This pressure is 1400 m of equivalent altitude above mean sea level. This amount of reduction in ambient pressure may worse symptoms of DCI patients. During evacuation of DCI patients, altitude and weather along the route to a hospital should be carefully considered [50].

8.3 Mechanisms of Recompression Therapy

Recompression therapy, except for using air compression tables, is a kind of HBOT that is used for DCS patients. Purpose of the therapy is as follows: (1) To reduce volume of the bubbles in the body. (2) To increase absorption of the bubbles into the body fluid and exhalation of inert gases from the lung. (3) To increase oxygen supply via plasma to the cells in peripheral tissues [51]. By recompression therapy, bubble-induced occlusions of the blood vessels will recover, pressure of the tissues will be released and highly oxygenated blood will perfuse the tissues. In addition to these effects, recompression therapy is also expected to reveal anti-inflammatory [52, 53], anti-infectious [54] and wound healing effects [55].

Unfortunately, recompression therapy has some adverse effects, such as cerebral oxygen toxicity, pulmonary oxygen toxicity, and barotrauma [56]. Oxygen toxicities are resulted from high oxygen partial pressure and/or longer exposure to oxygen. Air breaks, i.e., air breathing period, are put among oxygen-breathing periods during recompression therapy to attenuate the oxygen toxicities [34, 57].

8.3.1 Volume Reduction of Bubbles in the Blood Vessels and the Tissues

Size of individual bubbles decreases in accordance with increasing ambient pressure. If the pressure increases from 0.1 MPa (1.0 ATA) to 0.2 MPa (2.0 ATA), volume of the bubbles decreases to 50%. Thus, the size of the sphere shape bubbles decreases to 79% in diameter. In case of AGE, intraarterial gases occlude the blood stream and make ischemic regions in the downstream tissues. When recompression therapy is applied to the patient, size of the intraarterial gases, gas emboli, is decreased and the gases are expected to flow down to more peripheral arteries. Smaller gases may pass through the capillaries. Consequently, blood can perfuse wider areas and ischemic lesions may decrease [34].

In case of spinal DCS, intra-spinal venous bubbles that occlude venous circulation might be reduced in size during recompression therapy. This compression is expected to recover the venous circulation and release spinal edema via decreasing microcirculatory pressure in upstream of the vein [58]. Compression of extravascular bubbles in the spinal cord may reduce solid tissue pressure. This reduction of the solid tissue pressure is expected to prevent development of tissue damage, improve ischemia of the tissue, and recover conduction of the nerves.

In pulmonary circulation, compressed bubbles may pass through the pulmonary capillaries and release respiratory failure [59]. The bubbles would be recompressed in the systemic arteries because pressures in the systemic arteries are much higher than those in the pulmonary arteries. This kind of arterial bubbles, however,

may grow according to an increase in oxygen partial pressure (vs. venous blood) (see Sects. 8.3.3 and 8.3.4) [60].

8.3.2 Increased Absorption of Bubbles in the Blood Vessels and the Tissues

Partial pressures of the dissolved gases are not altered by changes of the ambient pressure per se. Gas pressure of bubbles, however, increases in accordance with increasing ambient pressure. Following Henry's law, the amount of dissolved gas in a certain volume of fluid is proportional to its partial pressure. Thus, increased bubble pressure enhances to dissolve the gas into the surrounding fluid. Even though the pressure gradient increases, decreased surface area of the bubble tends to slow down the absorption rate [61]. By recompression therapy, bubbles in DCI patients' body reduce not only in volume but also in mass of the gas through dissolving into the body fluid [61].

Enhanced dissolution of gases from the bubbles consequently increases partial pressure of the gases in the body fluid. Thus, partial pressure of each inert gas in plasma in DCI patient increases by recompression therapy. As breathing gas is 100% oxygen instead of air during the therapy, concentration of nitrogen and other inert gases in the lung decreases. Thus, pressure gradient of the inert gases between the alveolar wall much increases by oxygen breathing in addition to increase ambient pressure. This increment in the pressure gradient promotes diffusion of the inert gases into alveolar spaces. As a result, recompression therapy enhances exhaust of bubble-forming gases from the body through the lung [51].

8.3.3 Non-Inert Gases

Not only inert gases but also oxygen, carbon dioxide, and water vapor are members of the gases that made partial pressures in a bubble. Water vapor at body temperature of 37 °C is 47 mmHg (0.006 MPa, 0.06 atm). This is much smaller than atmospheric pressure of 760 mmHg (0.1 MPa, 1 ATA). On the other hand, carbon dioxide usually shows partial pressures of 20 mmHg (0.003 MPa, 0.026 atm) and 40 mmHg (0.005 MPa, 0.053 atm) in arterial blood and venous blood, respectively. Thus, partial pressure of water vapor and carbon dioxide play only a small role in total pressure of the bubble gas [3]. In aviation DCS, however, these gases are simulated to play appreciable role in expanding the bubble [3].

In each tissue of the body, inhaled oxygen is metabolized into carbon dioxide and water. Because carbon dioxide has much higher solubility in water than oxygen, total pressure of venous gases does not exceed arterial gases. For this reason, except for aeronautical DCS, oxygen is not thought to contribute to enhance development of bubbles in the body, especially in venous bubbles [3, 62].

8.3.4 Oxygen Window Effect

Regarding partial pressure of oxygen in the body, arterial blood shows higher value than venous one (100 mmHg (0.013 MPa, 0.132 atm) vs. 40 mmHg (0.005 MPa, 0.053 atm)). Partial pressure of inert gas and water vapor are similar between arterial and venous blood. Thus, changes in amounts of oxygen and carbon dioxide mainly affect change in total pressure between arterial and venous blood (100 (PaO_2) − 40 (PvO_2) + 20 ($PaCO_2$) − 40 ($PvCO_2$) = 80 mmHg). Arterial gases are almost equilibrated to the alveolar gases [63]. Thus, total pressure of arterial gases is almost equal to the ambient pressure but that of venous gases is much lower than the ambient pressure. Similar discrepancy of total pressure of dissolved gases occurs between arterial blood and tissue fluid. These discrepancies of the total pressures [60] or difference in partial pressure of inert gas between the inside and outside of decompression bubbles [62] are called oxygen window. This oxygen window, reduction in the total pressure of dissolved gases, prevents formation of bubbles in venous blood and the tissues.

In bubbles and bubble nuclei of the vein, gases might be rapidly equilibrated to the surrounding blood. When oxygen is pulled out from the bubbles into the blood, size of the bubbles decreases and concentration of inert gases in the bubbles increases. The concentrated inert gases show higher partial pressures than before. Higher partial pressure enhances to dissolve the gases into surrounding blood. Finally, the dissolved gases are exhausted from the lung.

Under hyperbaric oxygenation, much higher value of the partial pressure in arterial blood should be appeared. In the pulmonary circulation, after hemoglobin was saturated with oxygen, newly dissolved oxygen into the blood totally follows Henry's law and solubility of oxygen in plasma is relatively low [63]. This means, when hemoglobin is saturated, an amount of oxygen dissolved in plasma shows small alteration for comparatively large change in the oxygen partial pressure. Thus, difference of oxygen partial pressure between arterial and venous blood, oxygen window, are much larger under breathing hyperbaric oxygen, even in normobaric oxygen, compared with air [62].

8.3.5 Increased Supply of Oxygen Dissolved in Plasma

In physiological conditions, more than 95% of oxygen is supplied to the tissues by carrying with hemoglobin [63]. Under hyperbaric oxygenation, however, much more oxygen can dissolve in plasma [64]. Actually, previous study demonstrated that severe anemic porcine survived at 0.3 MPa (3 ATA) breathing with 100% oxygen [64]. This result supports the fact that recompression therapy enhances blood and tissue oxygenation.

Embolization of arterial gas and accumulation of venous bubbles cause tissue ischemia. Perfusion in the tissues with highly oxygenated blood improves by recompression therapy. Therefore, recompression therapy is efficient for oxygenation of the ischemic tissues. In these situations, increasing supply of oxygen dis-

solved in plasma plays an important role. This therapy may also be efficient for the temporal hypoxia which is caused by diving-related lung damages [65].

8.3.6 Additional Effects of Recompression Therapy

In addition to reduce bubble size, to promote bubble absorption and to enhance blood and tissue oxygenation, recompression therapy has some more potential effects. HBOT is known to inhibit leukocyte adhesion to vascular endothelium [53], reduce edema formation, improve wound healing [55], and suggested to increase anti-bacterial function of leukocyte [66, 67]. These anti-inflammatory, wound healing and anti-infectious effects of HBOT might be a benefit for DCI patient.

Hyperbaric oxygenation is reported to induce expression of physiologically active substances and structural components. These molecules are several growth factors, such as angiogenin [68], VEGF [52, 69], PlGF [70], and bFGF [71], and other molecules, such as SDF-1α [72], iNOS [53], MMP-9, TIMP-1 [73], and collagen [74]. On the other hand, pro-inflammatory cytokines of TNF-α and IL-6 show down-regulation by hyperbaric oxygenation [75]. Down-regulation of TGF-β_1 [74], IL-10 [75], COX-2 [52], and endothelins [52] might also be involved in the anti-inflammatory effect.

Under hyperbaric-hyperoxic conditions, some plasma proteins, such as transthyretin, alpha-1-acid glycoprotein 1, and haptoglobin were observed to be upregulated in saturation divers [76]. These proteins are abundant proteins in human plasma, which have an antioxidant effect [77–79]. These proteins are suggested to activate a defense mechanism to counteract the effects of hyperbaric-hyperoxic conditions during saturation diving.

8.3.7 Adverse Effects of Recompression Therapy

Cerebral and pulmonary oxygen toxicities are two main adverse effects of recompression therapy. Typical symptoms of cerebral oxygen toxicity are twitching of the lip, tinnitus, vertigo, tunnel vision, consciousness loss, and convulsion [34, 80]. Cerebral oxygen toxicity tends to happen under breathing a gas which partial pressure of oxygen is more than 0.3 MPa (3 atm). Prolonged oxygen exposure tends to bring the symptoms even if the partial pressure is relatively low. Enormous variations in sensitivity of cerebral oxygen toxicity, however, are known between individuals and from day to day [81, 82]. Some reports suggest that the cause of cerebral oxygen toxicity are involved in increment of reactive oxygen species in the central nervous system but detailed mechanisms still remain to be clarified [83, 84].

Pulmonary oxygen toxicity is caused by oxygen partial pressure of more than 0.04–0.05 MPa (0.4–0.5 atm) [85]. Typical symptoms of pulmonary oxygen toxicity are dyspnea, chest pain, and cough [34, 80]. Prolonged exposure and/or increased partial pressure of oxygen worsen the symptoms [80]. This kind of hyperbaric oxygen decreases in vital capacity, diffusing capacity and compliance of the lung [86].

Damage of the lung induced by hyperbaric oxygen can be estimated using unit pulmonary toxic dose (UPTD) [60, 80]. UPTD is defined as the following equation:

$$\mathrm{UPTD} = t\left(2P_{O_2} - 1\right)^{0.83}$$

where t is the exposure time in minute and P_{O_2} is the oxygen partial pressure in atm in the breathing gas. It is recommended to keep UPTD under 400/day and 2000/week for patients received recompression therapy [87].

During treatment of DCI, the patients sometimes show worsening of their symptoms, such as joint and muscle pains. Most of these worsening may not be the adverse effects of the hyperbaric oxygen but results of the effects of the treatment. These worsening are thought to be results of recovery of sensory nervous functions induced by increasing oxygen supply and decreasing solid tissue pressure. Ischemia-reperfusion injury may also occur as a result of recovery of blood flow and tissue oxygenation [88, 89].

8.4 Protocols of Recompression Therapy

As mentioned above, extra- and intravascular bubbles of inert gases are strongly suggested to lead DCS [2]. Thus, DCI patients are anticipated to recover by recompression because the bubbles may collapse. Then, gradual decompression following appropriate table would be necessary for the patients not to create new bubbles. Decompression table was originally reported by Boycott, Damant, and Haldane (1908) [25], which has been studied to prevent DCS of caisson workers. This table was created depending on a principle that no subject suffered DCS when assent up to one-half of the saturation depth.

Main concepts of recompression therapy are to decrease the bubble size and increase washout of the inert gases. Accumulation of experience of treatment for DCI patients gradually improves efficiency and safety of recompression therapy. Many protocols of recompression therapy have been presented previously [51]. In this session, we will focus on the tables described in U.S. Navy Diving Manual [12]. These tables are provided for mild-to-severe DCI and adopted worldwide for the treatments [11, 90].

8.4.1 U.S. Navy Treatment Table 5

U.S. Navy Treatment Table 5 (TT5) is mainly used for Type I DCS, except for cutis marmorata, and follow-up treatment for DCI [90]. Protocol of TT5 is shown in Fig. 8.1. This table can be extended up to two oxygen-breathing periods at the 30-foot stop if it is considered to be necessary. It takes 2 h 15 min to complete the

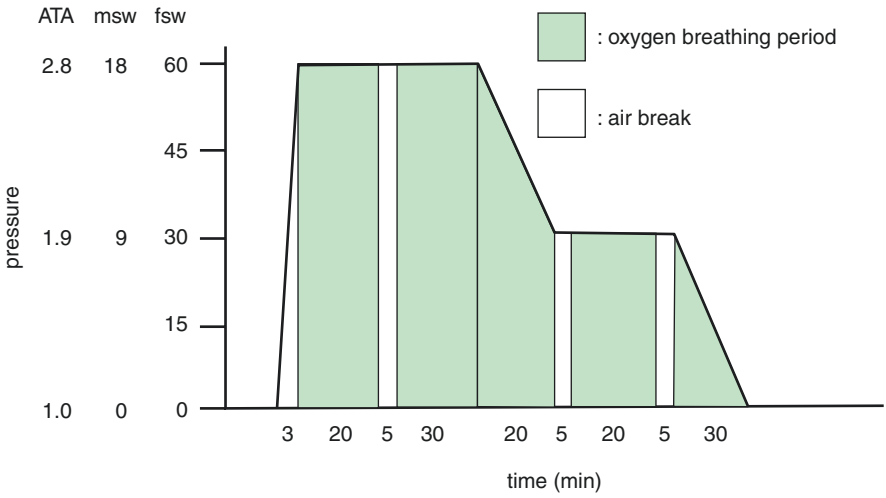

Fig. 8.1 U.S. Navy Treatment Table 5

table when the protocol is not extended and 3 h when the protocol is fully extended. UPTD of TT5 is about 340 when the protocol is not extended and about 430 when the protocol is fully extended.

If symptoms of Type I DCS are not completely relieved within the first 10 min at 60-foot stop of TT5, the table should be converted to U.S. Navy Treatment Table 6 (TT6) (see Sect. 8.4.2). In addition to the first recompression therapy, repetitive recompression therapies are usually required for DCI patients to improve residual symptoms. U.S. Navy Treatment Table 9 (TT9) (see Sect. 8.4.5) as well as TT5 can also be adopted for the residual symptoms.

8.4.2 U.S. Navy Treatment Table 6 and 6A

TT6 is mainly used for cutis marmorata of Type I DCS, Type II DCS, and AGE [90]. Protocol of TT6 is shown in Fig. 8.2a. This table can be extended up to two oxygen-breathing periods at the 60-foot stop and up to two oxygen-breathing periods at the 30-foot stop if it is considered to be necessary. It takes 4 h 45 min to complete the table when the protocol is not extended and 8 h 5 min when the protocol is fully extended. UPTD of TT6 is about 650 when the protocol is not extended and about 1080 when the protocol is fully extended.

If severe symptoms of DCI remain unchanged or worsen within the first 20 min at 60-foot stop of TT6, the table should be converted to U.S. Navy Treatment Table 6A (TT6A) (Fig. 8.2b) [90]. After reaching a depth of relief, the DCI patient stays 30 min at the depth. If no significant relief is observed at the maximum depth of 165-foot within 30 min, the table may be converted to U.S. Navy Treatment

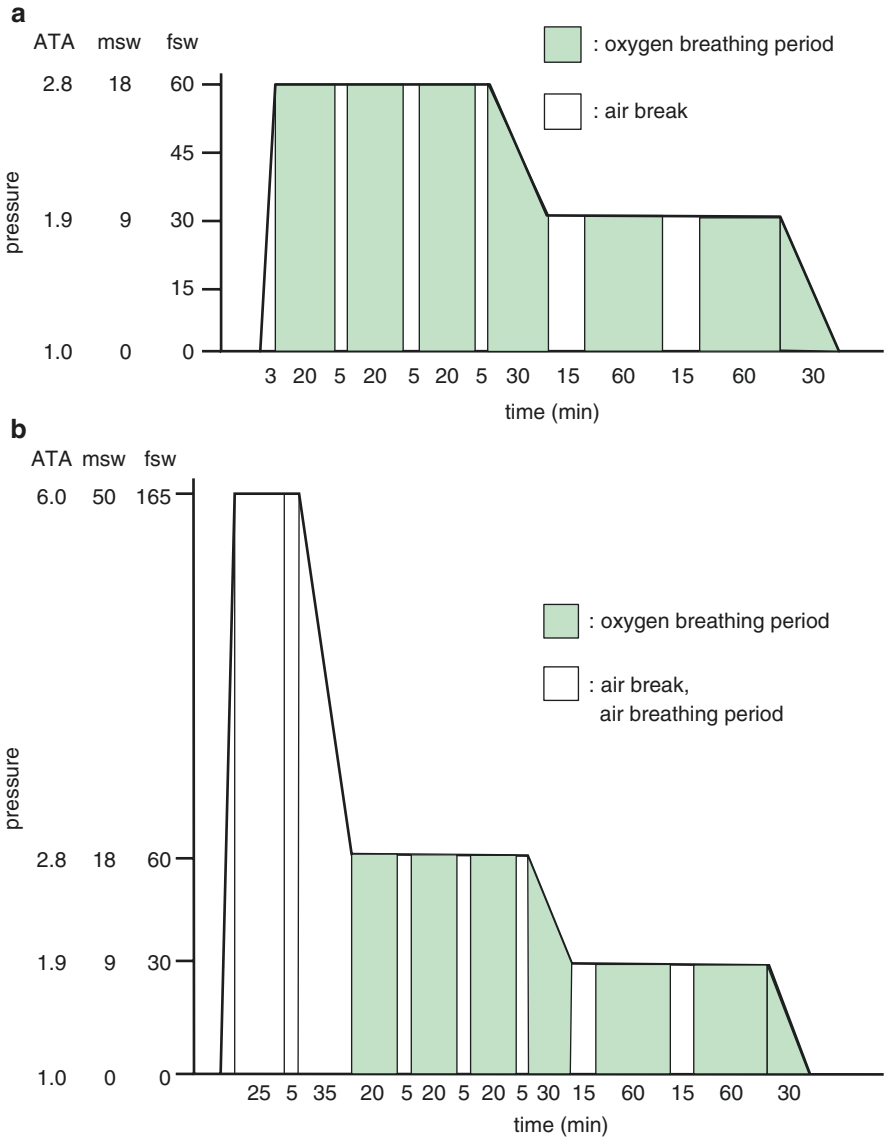

Fig. 8.2 (**a**) U.S. Navy Treatment Table 6. (**b**) U.S. Navy Treatment Table 6A

Table 4 (TT4) (see Sect. 8.4.3) under recommendation of diving medical officer (DMO). If life-threatening DCI is observed at 60-foot of TT6, 6A or 4, the table may be converted to U.S. Navy Treatment Table 7 (TT7) (see Sect. 8.4.4) under recommendation of DMO. TT6A can also be extended same as TT6. It takes 5 h 50 min to complete the table when the protocol is not extended and 9 h 10 min when the protocol is fully extended. UPTD of TT6A is about 720 when the protocol is not extended and about 1160 when the protocol is fully extended.

8.4.3 U.S. Navy Treatment Table 4

TT4 is used for extending TT6A when the DCI patient is expected to receive additional benefit at 60- to 165-foot stop [90]. Depending on the patient's response, the depth should be kept between 30 and 120 min. Protocol of TT4 is shown in Fig. 8.3. TT4 may shift to TT7 for life-threatening DCI. It should be mentioned that TT4 spends 39 h 6 min to 40 h 36 min and the UPTD exceeds the unit of about 1360.

8.4.4 U.S. Navy Treatment Table 7

TT7 is used for extending 60-foot stop of TT6, 6A or 4 to treat life-threatening DCI [90]. Protocol of TT7 is shown in Fig. 8.4. The first 60-foot stop of TT7 needs to continue at least 12 h, which includes 60-foot stop of preceding TT6, 6A or 4. It should be mentioned that TT7 spends more than 48 h and the UPTD exceeds the unit of about 2000.

However TT7 takes long period and exposes high value of UTPD to the patient, some reports were published regarding treatment of DCI patients by using TT7. In MSDF Undersea Medical Center, three cases of severe spinal DCS happened after

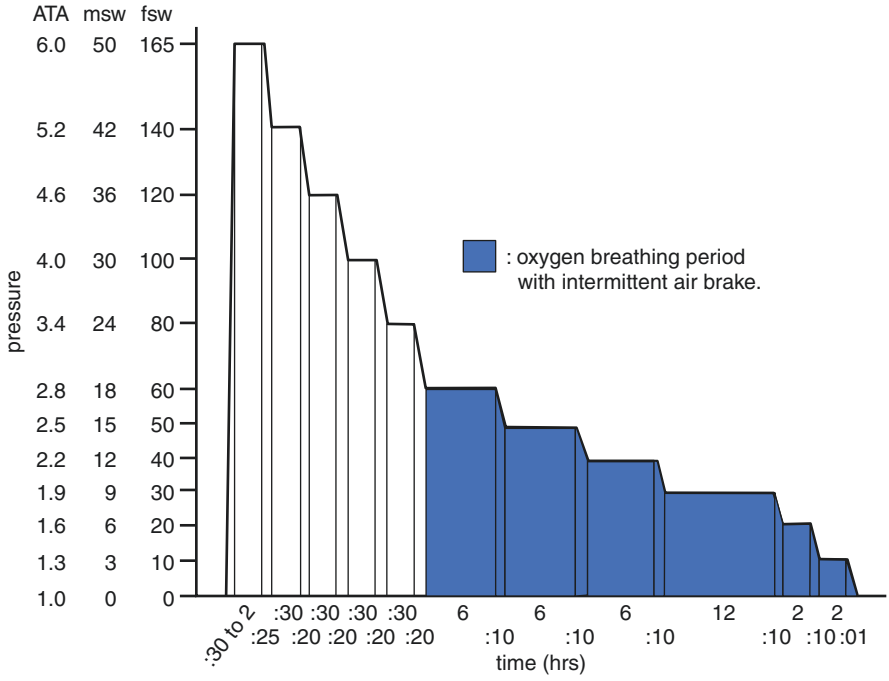

Fig. 8.3 U.S. Navy Treatment Table 4. After reaching 60 fsw, 25 min of 100% oxygen breathing followed by 5 min of air break should be started as soon as possible

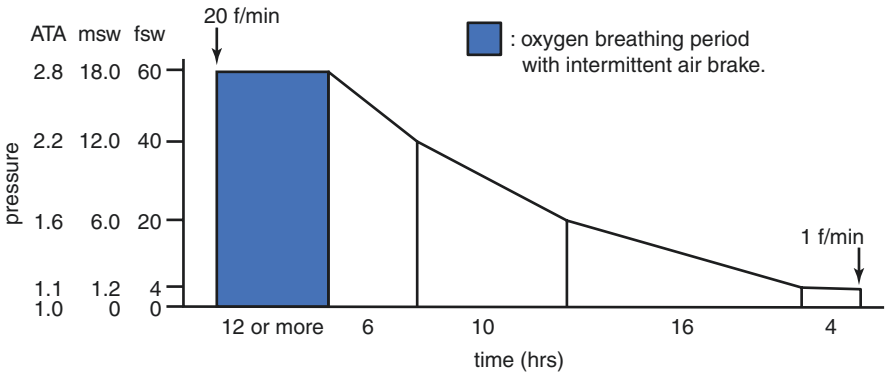

Fig. 8.4 U.S. Navy Treatment Table 7. At 60 fsw, 25 min of 100% oxygen breathing followed by 5 min of air break should be started as soon as possible. Four oxygen-breathing periods are alternated with 2 h of continuous air break. The oxygen-breathing periods should be continued as long as improvement is noted or the oxygen is tolerated by the patient

SCUBA diving and three cases of slight DCS happened in saturation diving have been treated by TT7 [91]. All of these six patients would completely recovered and returned to their daily life without severe oxygen toxicity (Table 8.1) [92].

8.4.5 U.S. Navy Treatment Table 9

TT9 is mainly used for follow-up treatment for residual symptoms remaining after initial treatment of DCI [90]. This table can also be used for severely injured patient who is not considered to tolerate longer table. Protocol of TT9 is shown in Fig. 8.5. It takes 1 h 45 min to complete this table. UPTD of this table is about 270.

If patient cannot breath 100% oxygen at 45-foot stop, the maximum depth of this table can be changed to 30 feet. In this case, oxygen-breathing time can be varied from 1 h 30 min to 4 h. Air brakes for 5 min are necessary in each 30 min of oxygen breathing. It takes 1 h 43 min to complete the modified TT9 when the protocol is not extended and 4 h 41 min when the protocol is fully extended. UPTD of the modified TT9 is about 220 when the protocol is not extended and about 570 when the protocol is fully extended.

8.5 Instruments for Recompression Therapy

Many types of treatment chambers are used to perform recompression therapy [93–95]. In hospitals and clinics, typically, a rigid shelled pressure vessel with acrylic windows for multiple patients, a multiplace chamber, are operated (Fig. 8.6a). Deep diving system for saturation and non-saturation dive training, which is placed

Table 8.1 Effects of recompression treatment using U.S. Navy treatment Table 7 on 6 cases treated in MSDF Undersea Medical Center

Case				Main symptoms	Type of DCS	Other tables used	Additional treatment	Outcome
1.	38 yo.	M	SAT	Right knee dull pain	Type I	Not applied	Not applied	Completely recovered
2.	43 yo.	M	SAT	Bilateral knee pain	Type I	Not applied	Hydrocortisone (dose unknown)	Completely recovered
3	48 yo.	M	SAT	Left knee pain	Type I	Not applied	Not applied	Completely recovered
4.	28 yo.	M	SCUBA	Paresthesia below Th6, gait disturbance, bladder dysfunction	Type II Spinal cord DCs	TT6 × 3 (before TT7) An additional recompression therapy was administered in the transferred hospital	Methylprednisolone pulse therapy (first day 1000 mg, second day 500 mg, third day 125 mg iv.) (before TT7), rehabilitation (after TT7)	Completely recovered
5.	55 yo.	M	SCUBA	Numbness on rt. below Th9, bladder and rectal disturbance	Type II Spinal cord DCs	TT6 × 2 (before TT7) TT6 × 2 (after TT7)	Hydrocortisone 1000 mg iv. × 2 (during each TT6 applied before TT7), PSS (detail unknown) + hydrocortisone 1000 mg div. (during TT7)	Completely recovered
6.	45 yo.	M	SCUBA	Numbness on rt. at Th8–Th11, numbness in both the legs, gait disturbance, bladder dysfunction	Type II Spinal cord DCs	TT6 × 1 (before TT7) TT6 × 10 (after TT7)	Dextran 40 (10% in PSS) 500 mL + hydrocortisone 1000 mg + solcoseryl 4 mL + ascorbic acid 500 mg div. (before TT7), saline 500 mL + hydrocortisone 1000 mg div. (during TT7)	Completely recovered

M male; *SAT* saturation diver; *SCUBA* self-contained underwater breathing apparatus diver; *rt.* the right side of the body; *DCS* decompression sickness; *TT* U.S. Navy treatment table; *PSS* physiological saline solution

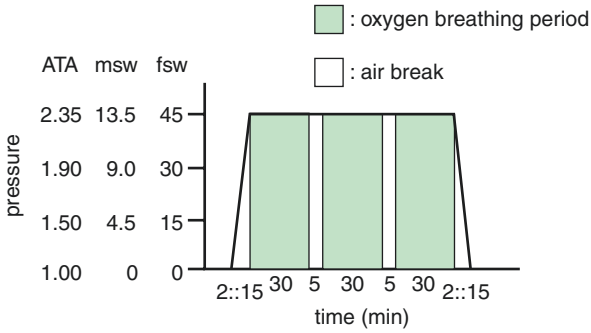

Fig. 8.5 U.S. Navy Treatment Table 9

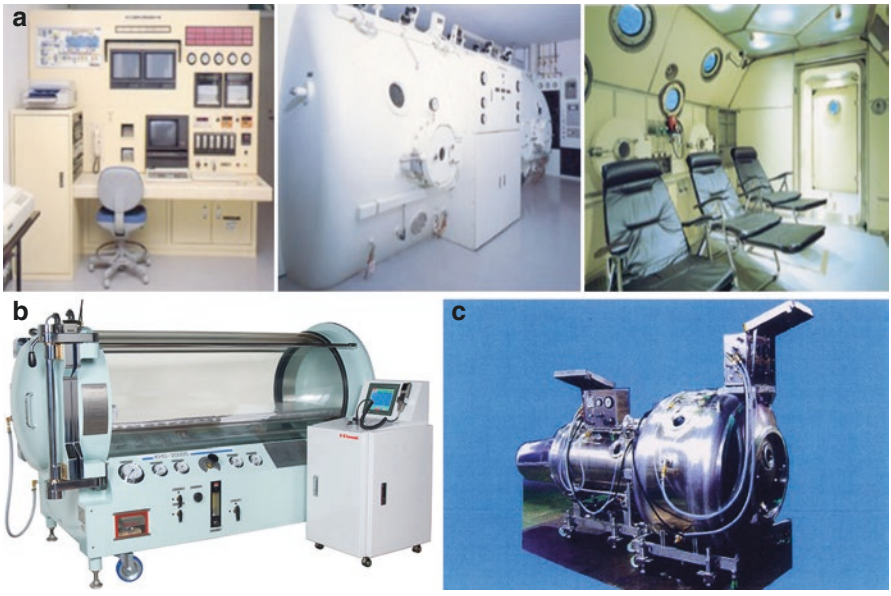

Fig. 8.6 (**a**) A multiplace chamber, "P-1100" (Barotec Hanyuda Co., Ltd., Tokyo). Left picture: Control panel. Middle picture: Outer view. Right picture: Inside view. (**b**) A monoplace chamber, "KHO-2000S" (Kawasaki Engineering Co., Ltd., Kobe). (**c**) Two-men portable recompression chamber, "Shiosai-II" (Barotec Hanyuda Co., Ltd., Tokyo)

specific facilities and ships, can also be used as multiplace chamber. In this type of the chamber, pressure is taken with air and oxygen hoods or masks are provided to the patients for breathing 100% oxygen. A medical staff, tender, may attend the patients in the chamber.

Monoplace chambers designed for treating 1 patient at a time are also adopted in hospitals and clinics (Fig. 8.6b). This type of the chamber consists of a clear plastic tube and other accessory parts. In the monoplace chamber, pressure is taken with air or 100% oxygen. If the chamber is pressurized with air, a mask is provided to the patient for breathing 100% oxygen. On the other hand, in some cases, a chamber is

pressurized with 100% oxygen during the treatment and air-breathing periods were provided by a demand regulator to perform U.S. Navy treatment tables [11].

Portable recompression chambers can be operated on-scene and used for evacuation [94]. This type of the chambers enables DCI patients to receive earlier recompression therapy, to move through high altitude place, and to be carried by an aircraft without pressurized cabin. Some types of one-man and two-men chambers are operated for these purposes. Two-men portable recompression chamber, such as "Shiosai-II" (Barotec Hanyuda Co., Ltd., Tokyo) (Fig. 8.6c), consists of patient room and tender room. In this chamber, a patient breathes 100% oxygen through a mask and tender can treat the patient under pressure.

8.6 A Case of Spinal DCS

MSDF Undersea medical center has offered recompression therapy to several cases of spinal DCS. Here present one of the cases briefly [50]:

A 52-year-old male with mild chronic obstructive pulmonary disease (COPD) was diving near Iwo Jima, which places about 1200 km south of Tokyo metropolitan area. Open-circuit SCUBA with compressed air was used in the diving. The first dive was to a maximum depth of 15 m for a bottom time of 6 min. After a surface interval of 8 h, he carried out a second dive to a maximum depth of 15 m for a bottom time of 5 min. After a surface interval of 3 h, he carried out a third dive to a maximum depth of 17 m for a bottom time of 27 min. These diving were within the non-decompression limits. No trouble happened to him during the diving and at the surface.

At 1 a.m. on the following day, seven and half hours after finishing the last dive, he felt numbness and paresthesia in the bilateral feet. At 5 a.m. he developed bilateral leg weakness with bilateral hand and leg numbness. Then, immediately transferred to a ship of minesweeper tender by a diving tender boat. Treated with recompression therapy on the deck using fully extended TT6 on the same day and plane TT6 on the second day of the onset. After the first recompression therapy, he recovered to be able to walk with assistance and completely recovered from bladder dysfunction that was observed during the therapy.

He was evacuated to Iwo Jima by MH53-E type helicopter by flying less than 300 m of altitude under breathing 100% oxygen. Then, to Atsugi Air Base by US-2 type STOL search and rescue amphibian, in which he was contained in a one-man portable recompression chamber to maintain the ambient pressure of 0.1 MPa (1 ATA) and continued to breath 100% oxygen through a mask. From Atsugi Air Base to the hospital in Yokosuka, breathing of 100% oxygen was continued in an ambulance.

On admission, examination demonstrated bilateral symmetrical hypalgesia and hypesthesia lower than Th12 level, slight muscle weakness in bilateral leg and bilateral positive Babinski reflex. These symptoms have been gradually improved by repetitive recompression therapy by using TT6 (1 time), TT5 (3 times), and TT9 (5

times) at the hospital. Slight paresthesia in the left leg remained at his discharge, which has not changed any more by the recompression therapies.

In this session, a case of spinal DCS patient who was required long range evacuation was presented. It is strongly suggested to benefit the patient that recompression therapy was performed rapidly, 100% oxygen was administered continuously through the evacuation, ambient pressure was kept almost 0.1 MPa (1 ATA) in the aircrafts, and sufficient recompression therapies were repeated.

8.7 Conclusions

Recompression therapy for DCI patients by 100% oxygen breathing is a kind of HBOT. Main purposes of recompression therapy are (1) to shrink bubbles in the body, (2) to increase elimination of inert gases from the body, and (3) to oxygenize ischemic tissues in the body. Other beneficial effects of recompression therapy, such as anti-inflammatory, wound healing, and anti-infectious effects, are also known.

Treatment tables for DCI patients have gradually improved efficiency and safety of the therapy. According to U.S. Navy diving manual revision 7, for Type I DCS, except for cutis marmorata, TT5 is recommended for use. For cutis marmorata, Type II DCS and AGE, TT6, or 6A is recommended for use. TT6A can be extended to TT4 depending on a patient's condition and TT4, 6, and 6A can be extended to TT7 to treat life-threatening DCI. It is important for all physicians who are possible to treat DCI patients to be versed in mechanisms of recompression therapy and handling the treatment tables.

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