CHAPTER e52

Hyperbaric and Diving Medicine

Michael H. Bennett
Simon J. Mitchell

WHAT IS HYPERBARIC AND DIVING MEDICINE?

Hyperbaric medicine is the treatment of health disorders using whole-body exposure to pressures greater than one atmosphere (760 mmHg). In practice, this almost always means the administration of *hyperbaric oxygen therapy* (HBO_2T). The Undersea and Hyperbaric Medical Society (UHMS) defines HBO_2T as: "a treatment in which a patient breathes 100% oxygen . . . while inside a treatment chamber at a pressure higher than sea level pressure (i.e., >1 atmosphere absolute or ATA)." The treatment chamber is an airtight vessel variously called a hyperbaric chamber, recompression chamber, or decompression chamber, depending on the clinical and historical context. Such chambers may be capable of compressing a single patient (a monoplace chamber) or multiple patients and attendants as required (a multiplace chamber) (Figs. e52-1 and e52-2). Historically, these compression chambers were first employed for the treatment of divers and compressed air workers suffering decompression sickness (DCS; "the bends"). While the prevention and treatment of disorders arising after decompression in diving, aviation, and space flight has developed into a specialized field of its own, it remains closely linked to the broader practice of hyperbaric medicine.

Despite an increased understanding of mechanisms and an improving evidence basis, hyperbaric medicine has struggled to achieve widespread recognition as a "legitimate" therapeutic measure. There are several contributing factors, but high among them are a poor grounding in general oxygen physiology and oxygen therapy at medical schools and a continuing tradition of charlatans advocating hyperbaric therapy (often using air) as a panacea. Funding for both basic and clinical research has been difficult in an environment where the pharmacologic agent under study is abundant, cheap, and unpatentable. Recently, however, there are signs of an improved appreciation of the potential importance of HBO_2T with significant National Institutes of Health (NIH) funding for mechanisms research and from the U.S. military for clinical investigation.

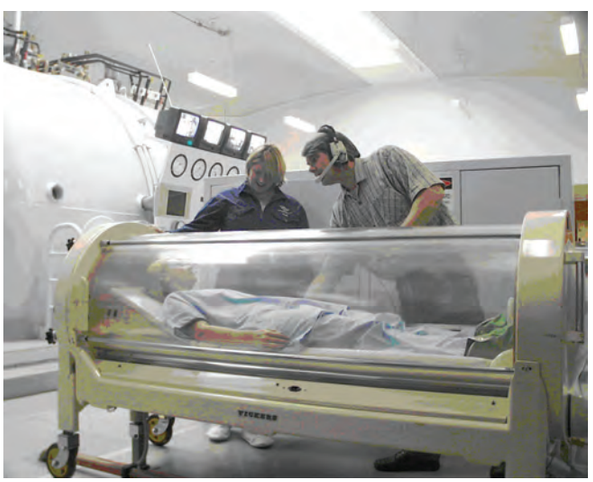

Figure e52-1 A monoplace chamber (Prince of Wales Hospital, Sydney).

Figure e52-2 A chamber designed to treat multiple patients (Karolinska University Hospital).

MECHANISMS OF HYPERBARIC OXYGEN

Increased hydrostatic pressure will reduce the volume of any bubbles present within the body (see "Diving Medicine"), and this is partly responsible for the success of prompt recompression in DCS and arterial gas embolism. Supplemental oxygen breathing has a dose-dependent effect on oxygen transport, ranging from improvement in hemoglobin oxygen saturation when a few liters per minute is delivered by simple mask at 1 ATA to raising the dissolved plasma oxygen sufficiently to sustain life without the need for hemoglobin at all when 100% oxygen is breathed at 3 ATA. Most HBO_2T regimens involve oxygen breathing at between 2 and 2.8 ATA, and the resultant increase in arterial oxygen tensions to greater than 1000 mmHg has widespread physiologic and pharmacologic consequences (Fig. e52-3).

One direct consequence of such high intravascular tension is to greatly increase the effective capillary-tissue diffusion distance for oxygen such that oxygen-dependent cellular processes can resume in hypoxic tissues. Important as this may be, the mechanism of action is not limited to the restoration of oxygenation in hypoxemic tissue. Indeed, there are pharmacologic effects that are profound and long-lasting. While removal from the hyperbaric chamber results in a rapid return of poorly vascularized tissues to their hypoxic state, even a single dose of HBO_2T produces changes in fibroblast, leukocyte, and angiogenic functions and antioxidant defenses that persist many hours after oxygen tensions are returned to pretreatment levels.

It is widely accepted that oxygen in high doses produces adverse effects due to the production of reactive oxygen species (ROS) such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2). It has become increasingly clear over the last decade that both ROS and reactive nitrogen species (RNS) such as nitric oxide (NO) participate in a wide range of intracellular signaling pathways involved in

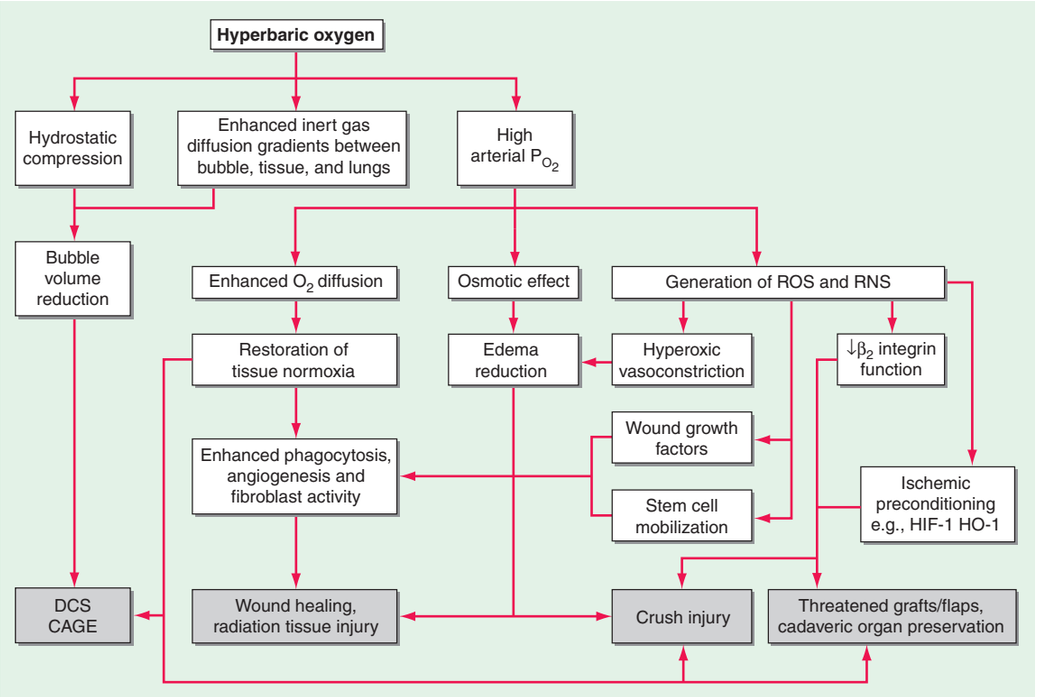

Figure e52-3 Summary of mechanisms of hyperbaric oxygen. There are many consequences of compression and oxygen breathing. The cell-signaling effects of HBO_2T are the least understood but potentially most important. Examples of indications for use are shown in the shaded boxes. CAGE, cerebral arterial gas embolism; DCS, decompression sickness; HIF-1, hypoxia inducible factor-1; HO-1, hemoxygenase 1; RNS, reactive nitrogen species; ROS, reactive oxygen species.

the production of a range of cytokines, growth factors, and other inflammatory and repair modulators. Such mechanisms are complex and at times apparently paradoxical. Taking as an example the treatment of chronic hypoxic wounds, some effects of HBO_2T are to enhance the clearance of cellular debris and bacteria by providing the substrate for macrophage phagocytosis; to stimulate growth factor synthesis by increased production and stabilization of hypoxia-inducible factor 1 (HIF-1); to inhibit leukocyte activation and adherence to damaged endothelium; and, through the induction of nitric oxide synthetase-3 (NOS-3 or eNOS), to mobilize bone marrow stem cells that will enable vasculogenesis. The interactions between these mechanisms remain a very active field of investigation. One exciting development is the concept of *hyperoxic preconditioning* in which a short exposure to HBO_2 can induce tissue protection against future hypoxic/ischemic insult. This has potential applications in several surgical specialties including organ transplantation. One randomized clinical trial has been completed and suggests that HBO_2T prior to coronary artery bypass grafting reduces biochemical markers of ischemic stress and improves neurocognitive outcome.

ADVERSE EFFECTS OF THERAPY

HBO_2T is generally well tolerated and safe in clinical practice. Adverse effects are associated with both alterations in pressure (barotrauma) and the administration of oxygen.

BAROTRAUMA

Barotrauma occurs when any noncompliant gas-filled space within the body does not equalize with environmental pressure during compression or decompression. About 10% of patients complain of some difficulty equalizing middle-ear pressure early in compression, and while most of these problems are minor and can be overcome with training, 2–5% of conscious patients require middle-ear ventilation tubes or formal grommets across the tympanic membrane. Unconscious patients cannot equalize and should have middle-ear ventilation tubes placed prior to compression. Other less common sites for barotrauma of compression include the respiratory sinuses and dental caries. The lungs are potentially vulnerable to barotrauma of decompression as described in the diving medicine section, but the decompression following HBO_2T is so slow that pulmonary gas trapping is extremely rare in the absence of an undrained pneumothorax or lesions such as bullae.

OXYGEN TOXICITY

The practical limit to the dose of oxygen that can be delivered, both in a single treatment session and in a series of daily sessions, is oxygen toxicity. The most common acute manifestation is a seizure, which is often preceded by anxiety and agitation, during which time a switch from oxygen to air breathing may avoid the convulsion. Hyperoxic seizures are typically generalized tonic-clonic seizures followed by a variable postictal period. The cause is an overwhelming of the antioxidant defense systems within the brain. While clearly dose-dependent, onset is very variable both between individuals and within the same individual on different days. In routine clinical hyperbaric practice, the incidence is about 1:1500 to 1:2000 compressions.

Chronic oxygen poisoning most commonly manifests as worsening myopia due to alterations in the refractive index of the lens following oxidative damage to lenticular proteins similar to those associated with senescent cataract formation. Up to 75% of patients show deterioration in visual acuity after a course of 30 treatments at 2 ATA. Almost all return to pretreatment values 3–6 weeks after

cessation of treatment. A more rapid maturation of preexisting cataracts has occasionally been associated with HBO_2T. Although a theoretical problem, the development of pulmonary oxygen toxicity over time does not seem to be problematic in practice—probably due to the intermittent nature of the exposure.

CONTRAINDICATIONS TO HYPERBARIC OXYGEN

There are few absolute contraindications to HBO_2T. The most commonly encountered are an untreated pneumothorax and a history of bleomycin administration. A pneumothorax may expand rapidly on decompression and come under tension. Prior to any compression, patients with a pneumothorax should have a patent chest drain in place. The presence of other obvious risk factors for pulmonary gas trapping such as bullae should trigger a very cautious analysis of the risks of treatment versus the benefit. Bleomycin is associated with a partially dose-dependent pneumonitis in about 20% of people. This subgroup may be at particular risk of subsequent rapid deterioration in ventilatory function on exposure to high oxygen tensions. The relationship between pulmonary oxygen toxicity and bleomycin exposure is not proved, particularly after long periods have elapsed between bleomycin and oxygen exposures. However, any patient with a history of bleomycin administration should be carefully counseled prior to exposure to HBO_2T. For those recently exposed to doses above 200 mg and whose course was complicated by a respiratory reaction to bleomycin, compression should be avoided except in a life-threatening situation.

INDICATIONS FOR HYPERBARIC OXYGEN

The appropriate indications for HBO_2T are controversial and evolving. Practitioners in this area are in a unique position. Unlike most branches of medicine, hyperbaric physicians do not deal with a range of disorders within a defined body system (e.g., cardiology), nor are they masters of a therapy specifically designed for a single group of disorders (e.g., radiotherapy). Inevitably, the encroachment of hyperbaric physicians into other medical fields generates suspicion from specialist practitioners in those fields. At the same time this relatively benign therapy, the prescription and delivery of which requires no medical license, attracts both charlatans and well-motivated proselytizers who tout the benefits of oxygen for a plethora of chronic incurable diseases. This battle on two fronts has meant that mainstream hyperbaric physicians have been careful to claim effectiveness only for those conditions where there is a reasonable body of supporting evidence. In 1977, the UHMS systematically examined the claims for the routine use of HBO_2T in more than 100 disorders and found sufficient evidence to support routine use in only 12. The Hyperbaric Oxygen Therapy Committee of that organization has continued to update this list periodically with an increasingly formalized system of appraisal for new indications and emerging evidence (Table e52-1). Around the world, other relevant medical organizations have generally taken a similar approach, although indications vary considerably—particularly those recommended by hyperbaric medical societies in Russia and China where HBO_2T has gained much wider support than in the United States, Europe, and Australasia. Recently, several Cochrane reviews have examined the randomized trial evidence for many putative indications, and attempts have been made to examine the cost-effectiveness of HBO_2T across a range of conditions. Table e52-2 is a synthesis of these two approaches and lists the estimated cost of attaining health outcomes with the use of HBO_2T. Any savings associated with alternative treatment strategies avoided as a result of HBO_2T have not been taken into account in these estimates (e.g., the avoidance of lower leg amputation in diabetic foot ulcers). Following are short reviews of several important indications that are accepted by the UHMS.

TABLE e52-1 Current List of Indications for Hyperbaric Oxygen Therapy

1. Air or gas embolism (includes diving-related, iatrogenic, and accidental causes)
2. Carbon monoxide poisoning (including poisoning complicated by cyanide poisoning)
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injury, compartment syndrome, and acute traumatic ischemias
5. Decompression sickness
6. Enhancement of healing in selected problem wounds
7. Exceptional blood loss (where transfusion is refused or impossible)
8. Intracranial abscess
9. Necrotizing soft tissue infections (e.g., Fournier's gangrene)
10. Osteomyelitis (refractory to other therapy)
11. Delayed radiation injury (soft-tissue injury and bony necrosis)
12. Skin grafts and flaps (compromised)
13. Thermal burns

Source: The Undersea and Hyperbaric Medical Society (2008).

LATE RADIATION TISSUE INJURY

Radiotherapy is a well-established treatment for suitable malignancies. In the United States alone, approximately 300,000 individuals annually will become long-term survivors of cancer treated by irradiation. Serious radiation-related complications developing months or years after treatment [late radiation tissue injury (LRTI)] will significantly affect between 5 and 15% of those long-term survivors, although incidence varies widely with dose, age, and site. LRTI is most common in the head and neck, chest wall, breast, and pelvis.

Pathology and clinical course

With time, tissues undergo a progressive deterioration characterized by a reduction in the density of small blood vessels (reduced vascularity) and the replacement of normal tissue with dense fibrous tissue (fibrosis). Ultimately, and often triggered by a further physical insult such as surgery or infection, there may be insufficient oxygen to sustain normal function, and the tissue becomes necrotic (radiation necrosis). LRTI may be life-threatening and significantly reduce quality of life. Historically, the management of these injuries has been unsatisfactory. Conservative treatment is usually restricted to symptom management, while definitive treatment traditionally entails surgery to remove the affected part and extensive repair. Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown of a surgical wound, or infection. HBO_2T may act by several mechanisms to improve this situation, including edema reduction, vasculogenesis, and enhancement of macrophage activity (Fig. e52-3). The intermittent application of HBO_2 is the only intervention shown to increase the microvascular density in irradiated tissue.

Clinical evidence

The typical course of HBO_2T consists of 30 once-daily compressions to 2–2.4 ATA for 1.5 to 2 hours each session. This course is often bracketed around surgical intervention if required. While HBO_2T has been used for LRTI since at least 1975, most clinical studies have

TABLE e52-2 Selected Indications for Which There Is Promising Efficacy for the Application of Hyperbaric Oxygen Therapy

Diagnosis	Outcome (number of sessions)	NNT 95% CI	Estimated Cost to Produce One Extra Favorable Outcome 95% CI (USD)	Comments and Recommendations
Radiation tissue injury	**More information is required on the subset of disease severity and affected tissue type that is most likely to benefit, and the time over which benefit may persist.**			
	Resolved proctitis (30)	3 2–11	22,392 14,928–82,104	Large multi-center trial ongoing
	Healed mandible (30)	4 2–8	29,184 14,592–58,368	Based on one poorly reported study
	Mucosal cover in ORN (30)	3 2–4	29,888 14,592–29,184	Based on one poorly reported study
	Bony continuity in ORN (30)	4 2–8	29,184 14,592–58,368	Based on one poorly reported study
	Prevention of ORN after dental extraction (30)	4 2–13	29,184 14,592–94,848	Based on a single study
	Prevention of dehiscence (30)	5 3–8	36,480 21,888–58,368	Based on one poorly reported study
Chronic wounds	**More information is required on the subset of disease severity or classification most likely to benefit, the time over which benefit may persist, and the most appropriate oxygen dose. Economic analysis is required.**			
	Diabetic ulcer healed at 1 year (30)	2 1–5	14,928 7464–37,320	Based on one small study, more research required
	Diabetic ulcer, major amputation avoided (30)	4 3–11	29,856 22,392–82,104	Three small studies. Outcome over a longer time period required
ISSNHL	**No evidence of benefit more than 2 weeks after onset. More research is required to define the role (if any) of HBO_2T in routine therapy.**			
	Improvement of 25% in hearing loss within 2 weeks of onset (15)	5 3–20	18,240 10,944–72,960	Some improvement in hearing, but functional significance unknown
Acute coronary syndrome	**More information is required on the subset of disease severity and timing of therapy most likely to result in benefit. Given the potential of HBO_2T in modifying ischemia-reperfusion injury, attention should be given to the combination of HBO_2T and thrombolysis in early management and in the prevention of restenosis after stent placement.**			
	Episode of MACE (5)	4 3–10	4864 3648–12,160	Based on a single small study; more research required
	Incidence of significant dysrhythmia (5)	6 3–24	7296 3648–29,184	Based on a single moderately powered study in the 1970s
Traumatic brain injury	**Limited evidence that for acute injury HBO_2T reduces mortality but not functional morbidity. Routine use not yet justified.**			
	Mortality (15)	7 4–22	34,104 19,488–58,464	Based on four heterogeneous studies
Enhancement of radiotherapy	**There is some evidence that HBO_2T improves local tumor control and reduces mortality for cancers of the head and neck, as well as reducing the chance of local tumor recurrence in cancers of the head, neck, and uterine cervix.**			
	Head and neck cancer: 5-year mortality (12)	5 3–14	14,592 8755–40,858	Based on trials performed in the 1970s and 1980s. There may be some confounding by radiation fractionation schedule
	Local recurrence 1 year (12)	5 4–8	14,592 11,674–23,347	May no longer be relevant to therapy
	Cancer of uterine cervix: Local recurrence at 2 years (20)	5 4–8	24,320 19,456–38,912	As above
Decompression illness[a]	**Reasonable evidence for reduced number of HBO_2T sessions but similar outcomes when NSAID added.**			
	Reduction of HBO_2T treatment requirement by 1	5 3–18	N/R	Single appropriately powered randomized trial

[a]Tenoxicam used as an adjunct to recompression on oxygen.

Abbreviations: CI, confidence interval; HBO_2T, hyperbaric oxygen therapy; ISSNHL, idiopathic sudden sensorineural hearing loss; MACE, major adverse cardiac events; N/R, not remarkable; NNT, number needed to treat; NSAID, nonsteroidal anti-inflammatory; ORN, osteoradionecrosis; USD, US dollars.

Source: M Bennett: The evidence-basis of diving and hyperbaric medicine—a synthesis of the high level evidence with meta-analysis, *http://unsworks.unsw.edu.au/vital/access/manager/Repository/unsworks:949*.

been limited to small case series or individual case reports. In a recent semi-quantitative review, Feldmeier and Hampson located 71 such reports involving a total of 1193 patients across eight different tissues. There were clinically significant improvements in the majority of patients and only 7 of 71 reports indicated a generally poor response to HBO_2T. A recent Cochrane systematic review with meta-analysis included six randomized trials published since 1985 and drew the following conclusions (see Table e52-2 for numbers needed to treat): HBO_2T improves healing in radiation proctitis [relative risk (RR) of healing with HBO_2T 2.7, 95% confidence interval (CI) 1.2–6] and following hemimandibulectomy and reconstruction of the mandible (RR 1.4, CI 1.1–1.8); HBO_2T improves the probability of achieving mucosal coverage (RR 1.4, CI 1.2–1.6) and the restoration of bony continuity with osteoradionecrosis (ORN) (RR 1.4, CI 1.1–1.8); HBO_2T prevents the development of ORN following tooth extraction from a radiation field (RR 1.4, CI 1.08–1.7); and reduces the risk of wound dehiscence following grafts and flaps in the head and neck (RR 4.2, CI 1.1–16.8). Conversely, there was no evidence of benefit in established radiation brachial plexus lesions or brain injury.

SELECTED PROBLEM WOUNDS

A problem wound is any cutaneous ulceration that requires a prolonged time to heal, does not heal, or recurs. In general, wounds referred to hyperbaric facilities are those where sustained attempts to heal by other means have failed. Problem wounds are common and constitute a significant health problem. It has been estimated that 1% of the population of industrialized countries will experience a leg ulcer at some time. The global cost of chronic wound care may be as high as $25 billion US per year.

Pathology and clinical course

By definition, chronic wounds are indolent or progressive and resistant to the wide array of treatments applied. While there are many contributing factors, most commonly these wounds arise in association with one or more comorbidities such as diabetes, peripheral venous or arterial disease, or prolonged pressure (decubitus ulcers). First-line treatments are aimed at correction of the underlying pathology (e.g., vascular reconstruction, compression bandaging, or normalization of blood glucose level) and HBO_2T is an adjunctive therapy that may be added to good general wound care practice in order to maximize the chance of healing.

For most indolent wounds hypoxia is a major contributor to failure to heal. Many guidelines to patient selection for HBO_2T include the interpretation of transcutaneous oxygen tensions around the wound while breathing air and oxygen at pressure (Fig. e52-4). Wound healing is a complex and incompletely understood process. While it appears that in acute wounds healing is stimulated by the initial hypoxia, low pH, and high lactate concentrations found in freshly injured tissue, some elements of tissue repair are extremely oxygen dependent, for example, collagen elaboration and deposition by fibroblasts, and bacterial killing by macrophages. In this complicated interaction between wound hypoxia and peri-wound oxygenation, successful healing relies on adequate tissue oxygenation in the area surrounding the fresh wound. Certainly, wounds that lie in hypoxic tissue beds are those that most often display poor or absent healing. Some causes of tissue hypoxia will be reversible with HBO_2T, while some will not (e.g., in the presence of severe large vessel disease). When tissue hypoxia can be overcome by a high driving pressure of oxygen in the arterial blood, this can be demonstrated by measuring the tissue partial pressure of oxygen using an implantable oxygen electrode or more commonly, a modified transcutaneous Clarke electrode.

The intermittent presentation of oxygen to those hypoxic tissues facilitates a resumption of healing (Fig. e52-3). As discussed above, these short exposures to high oxygen tensions have long-lasting effects (at least 24 hours) on a wide range of healing processes. The result is a gradual improvement in oxygen tension around the wound that reaches a plateau in experimental studies at about 20 treatments over 4 weeks. Improvements in oxygenation are associated with an eight- to ninefold increase in vascular density over both normobaric oxygen and air-breathing controls.

Clinical evidence

The typical course of HBO_2T consists of 20 to 30 once-daily compressions to 2–2.4 ATA for 1.5 to 2 hours each session, but is highly dependent on the clinical response. There are many case series in the literature supporting the use of HBO_2T for a wide range of

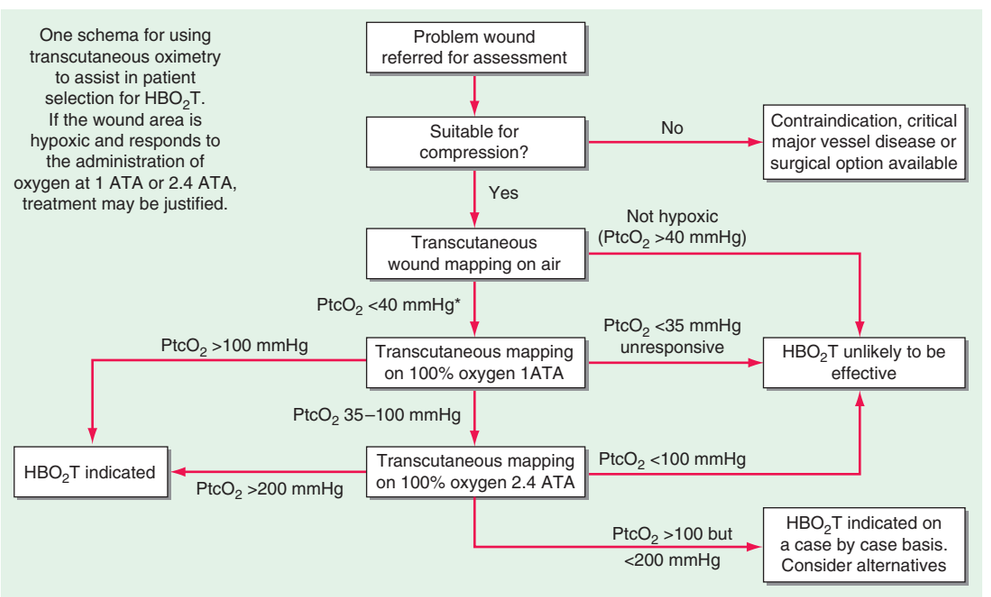

Figure e52-4 **Suitability for hyperbaric oxygen therapy (HBO_2T) guided by transcutaneous oximetry around the wound bed.**
*In diabetic patients <50 mmHg may be more appropriate. $PtcO_2$, transcutaneous oxygen pressure.

problem wounds. Both retrospective and prospective cohort studies suggest that 6 months after a course of therapy about 70% of indolent ulcers will be healed or nearly so. Often the mean period such ulcers have been present is many months or years, suggesting that the application of HBO_2T has a profound effect, either primarily or as a facilitator of other strategies. A Cochrane review included five randomized controlled trials (RCTs) and concluded that HBO_2T reduces the rate of major amputation in people who have chronic foot ulcers as a result of diabetes [the RR of amputation with HBO_2T was 0.31 (95% CI 0.13–0.71) and suggests the number needed to receive HBO_2T to avoid one major amputation is 4 (95% CI 3–11)]. Randomized data on wound healing are notably lacking. Only one small trial reported this outcome and although there was a trend toward better outcomes with HBO_2T, the result is not statistically convincing (78% healed with HBO_2T versus 44% with sham).

CARBON MONOXIDE POISONING

Carbon monoxide (CO) is a colorless, odorless gas formed during incomplete hydrocarbon combustion. While CO is an essential endogenous neurotransmitter linked to NO metabolism and activity, it is also a leading cause of poisoning death and in the United States alone, results in more than 50,000 emergency department visits per year and about 2000 deaths. While there are large variations from country to country, about half of nonlethal exposures are due to self-harm. Accidental poisoning is commonly associated with defective or improperly installed heaters, house fires, and industrial exposures. The motor vehicle is by far the most common source of intentional poisoning.

Pathology and clinical course

The pathophysiology of carbon monoxide exposure is incompletely understood. CO binds to hemoglobin with an affinity more than 200 times that of oxygen, and this not only directly reduces the oxygen-carrying capacity of blood, but further promotes tissue hypoxia by shifting the oxyhemoglobin dissociation curve to the left. CO is also an anesthetic agent that inhibits evoked responses and narcotizes experimental animals in a dose-dependent manner. The associated loss of airway patency together with reduced oxygen carriage in blood may cause death from acute arterial hypoxia in severe poisoning. CO may also cause harm by other mechanisms including direct disruption of cellular oxidative processes, binding to myoglobin and hepatic cytochromes, and peroxidation of brain lipids.

The brain and heart are the most sensitive target organs due to their high blood flow, poor tolerance of hypoxia, and high oxygen requirements. Minor exposure may be asymptomatic or present with vague constitutional symptoms such as headache, lethargy, and nausea, while higher doses may present with poor concentration and cognition, short-term memory loss, confusion, seizures, and loss of consciousness. While carboxyhemoglobin (COHb) levels on admission do not necessarily reflect the severity or the prognosis of CO poisoning, cardiorespiratory arrest carries a very poor prognosis. Over the longer term, surviving patients commonly have neuropsychological sequelae that may present days to months after poisoning. Motor disturbances, peripheral neuropathy, hearing loss, vestibular abnormalities, dementia, and psychosis have all been reported. Risk factors for poor outcome are age >35 years, exposure for >24 hours, acidosis, and loss of consciousness.

Clinical evidence

The typical course of HBO_2T consists of two to three compressions to 2–2.4 ATA for 1.5 to 2 hours each session. It is common for the first two compressions to be delivered within 24 hours of the exposure. CO poisoning is one of the longest-standing indications for HBO_2T—based largely on the obvious connection between exposure, tissue hypoxia, and the ability of HBO_2T rapidly to overcome hypoxemia. CO is eliminated rapidly via the lungs on application of HBO_2T, with a half-life of about 21 minutes at 2.0 ATA versus 5.5 hours breathing air and 71 minutes breathing oxygen at sea level. In practice, however, it seems unlikely that HBO_2T can be delivered in time to prevent either acute hypoxic death or irreversible global cerebral hypoxic injury. If HBO_2T is beneficial in CO poisoning, it must reduce the likelihood of persisting and/or delayed neurocognitive deficit through a mechanism other than the simple reversal of arterial hypoxia due to high levels of COHb. The difficulty in accurately assessing neurocognitive deficit has been one of the primary sources of controversy surrounding the clinical evidence in this area. To date there have been six randomized controlled trials of HBO_2T for CO poisoning, although only four have been reported in full. While a Cochrane review suggested that overall there is insufficient evidence to confirm a beneficial effect of HBO_2T on the chance of persisting neurocognitive deficit following poisoning [34% of patients treated with oxygen at 1 atmosphere versus 29%, of those treated with HBO_2T, odds ratio (OR) 0.78; 95% CI 0.54–1.1], this may have more to do with poor reporting and inadequate follow-up than with evidence that HBO_2T is not effective. The interpretation of the literature has much to do with how one defines neurocognitive deficit. In the most methodologically rigorous of these studies (Weaver et al.), a professionally administered battery of validated neuropsychological tests and a definition based on the deviation of individual subtest scores from the age-adjusted normal values was employed; if the patient complained of memory, attention, or concentration difficulties, the required decrement was decreased. Using this approach, 6 weeks after poisoning, 46% of patients treated with normobaric oxygen alone had cognitive sequelae compared to 25% of those who received HBO_2T [$p = .007$, number needed to treat (NNT) 5, 95% CI 3–16]. At 12 months the difference remained significant (32% versus 18%, $p = .04$, NNT 7, 95% CI 4–124) despite considerable loss to follow-up.

On this basis, HBO_2T remains widely advocated for the routine treatment of patients with moderate to severe poisoning—in particular in those older than 35 years, presenting with a metabolic acidosis on arterial blood-gas analysis, exposed for lengthy periods or with a history of unconsciousness.

DIVING MEDICINE

INTRODUCTION

Underwater diving is both a popular recreational activity and a means of employment in a range of tasks from underwater construction to military operations. It is a complex activity with unique hazards and medical complications arising mainly as a consequence of the dramatic changes in pressure associated with both descent and ascent through the water column. For every 10.13-m increase in depth of seawater, the ambient pressure (P_{amb}) increases by 1 standard atmosphere (101.3 kPa) so that a diver at 20 m depth is exposed to a P_{amb} of approximately 3 atmospheres absolute (ATA): 1 atm due to atmospheric pressure and 2 atm generated by the water column.

BREATHING EQUIPMENT

Most diving is undertaken using a self-contained underwater breathing apparatus (scuba) consisting of one or more cylinders of compressed gas connected to a pressure-reducing regulator and a demand valve activated by inspiratory effort. Alternative sources of compressed gas include "rebreathers" that are closed or semiclosed circle systems with a carbon dioxide scrubber and externally supplied systems (via hoses from the surface), which are common in occupational applications. All of these systems must supply gas to the diver at P_{amb}, otherwise inspiration against the surrounding water pressure would be impossible. For most recreational diving the respired gas is air. Pure oxygen is rarely used because oxygen

may provoke seizures above an inspired P_{O_2} of 1.6 ATA in aquatic environments, limiting the practical safe depth to 6 m. For the same reason, very deep diving requires the use of oxygen fractions <0.21 (at 66 m, air contains 1.6 ATA of oxygen). Deep-diving gas often includes helium instead of nitrogen to reduce both the narcotic effect and high gas density that results from breathing nitrogen at high pressures. As with HBO_2T, therefore, medical problems associated with diving may arise from either changing pressure or the properties of the breathing gas itself. The following discussion is limited to consideration of common or significant barotraumas and DCS, although a range of other problems are relevant including salt-water aspiration, marine envenomation, and the high-pressure neurologic syndrome (HPNS).

BAROTRAUMA (SEE ALSO "ADVERSE EFFECTS OF THERAPY")

Difficulties with equalizing pressure in the middle ear are exaggerated underwater by the rapidity with which pressures can change as a diver descends or ascends. Failure to periodically insufflate the middle-ear spaces via the eustachian tubes during descent results in increasing pain. As the P_{amb} increases, the tympanic membrane (TM) may be bruised or even ruptured as it is pushed inward. Negative pressure in the middle ear results in engorgement of blood vessels in the mucous membranes and leads to effusion or bleeding, which can be associated with a *conductive* hearing loss. Middle-ear barotrauma is much less common during ascent because expanding gas in the middle-ear space tends to open the eustachian tube easily and "automatically." Barotrauma may also affect the respiratory sinuses, although the sinus ostia are usually widely patent and allow automatic pressure equalization without the need for specific maneuvers. If equalization fails, pain usually results in termination of the dive. Difficulty with equalizing ears or sinuses may respond to oral or nasal decongestants.

Much less commonly the inner ear may suffer barotrauma. Several explanations have been proposed, of which the most favored holds that forceful attempts to insufflate the middle-ear space during descent cause sudden transmission of pressure to the perilymph via the cochlear aqueduct and outward rupture of the round window. The clinician should be alerted to possible inner ear barotrauma after diving by a *sensorineural* hearing loss or true vertigo (which is often accompanied by nausea, vomiting, nystagmus, and ataxia). These manifestations can also occur in vestibulocochlear DCS (see below) but should never be attributed to middle-ear barotrauma. Immediate review by an expert diving physician is recommended and urgent referral to an otologist will usually follow.

The lungs are also vulnerable to barotrauma but are at most risk during ascent. If expanding gas becomes trapped in the lungs as P_{amb} falls, this may rupture alveoli and associated vascular tissue. Gas trapping may occur if divers intentionally or involuntarily hold their breath during ascent or if there are bullae. The extent to which asthma predisposes to pulmonary barotrauma is debated, but the presence of active bronchoconstriction must increase risk. Asthmatics who regularly require bronchodilator medications are usually discouraged from diving for this reason. While possible consequences of pulmonary barotrauma include pneumothorax and mediastinal emphysema, the most feared is the introduction of gas into the pulmonary veins leading to cerebral arterial gas embolism (CAGE). Manifestations of CAGE include loss of consciousness, confusion, hemiplegia, and speech and visual disturbances appearing immediately or within minutes after surfacing. The management is the same as that for DCS described below. It is notable that the natural history of CAGE often includes substantial or complete resolution of symptoms early after the event. This is probably the clinical correlate of bubble involution and redistribution with consequent restoration of flow. Patients exhibiting such remissions should still be reviewed at specialist diving medical centers because secondary deterioration or reembolization can occur. Unsurprisingly, these events can be misdiagnosed as strokes or transient ischemic attacks (TIAs) when patients are seen by those unfamiliar with diving medicine. *All patients presenting with neurologic symptoms after diving should have their symptoms discussed with a specialist in diving medicine and be considered for recompression therapy.*

DECOMPRESSION SICKNESS

DCS is caused by the formation of bubbles from dissolved inert gas (usually nitrogen) during or after ascent (decompression) from a compressed gas dive. Bubble formation is also possible following decompression for extravehicular activity during space flight and with ascent to altitude in unpressurized aircraft. DCS in the latter scenarios is probably rare in comparison with diving, where the incidence is approximately 1:10,000 recreational dives.

Breathing at elevated P_{amb} results in increased uptake of inert gas into blood and then into tissues. The rate at which tissue inert gas equilibrates with the inspired inert gas pressure is proportional to tissue blood flow and the blood-tissue partition coefficient for the gas, and inversely proportional to the tissue volume. Similar factors dictate the kinetics of inert gas wash-out during ascent. If the rate of gas wash-out from tissues does not match the rate of decline in P_{amb}, then the sum of dissolved gas pressures in the tissue will exceed P_{amb}, a condition referred to as "supersaturation." This is the prerequisite for bubbles to form during decompression, though other poorly understood factors are involved. Deeper and longer dives result in greater inert gas absorption and greater likelihood of tissue supersaturation during ascent. Divers control their ascent for a given depth and time exposure using algorithms that often include periods where ascent is halted for a prescribed period at different depths to allow time for gas wash-out ("decompression stops"). While a breach of these protocols increases the risk of DCS, adherence does not guarantee against it. DCS should be considered in any diver manifesting symptoms not readily explained by an alternative mechanism.

Bubbles may form within tissues themselves, where they cause symptoms by mechanical distraction of pain-sensitive or functionally important structures. They also appear in the venous circulation as blood drains from supersaturated tissues. Some venous bubbles can be tolerated without symptoms and are efficiently filtered from the circulation in the pulmonary capillaries. In larger numbers these bubbles are capable of inciting inflammatory and coagulation cascades, damaging endothelium, activating formed elements of blood such as platelets, and causing symptomatic pulmonary vascular obstruction. Moreover, if there is a right-to-left shunt [such as through a patent foramen ovale (PFO)], venous bubbles may enter the arterial circulation (25% of adults have a probe-patent PFO). The risk of cerebral, spinal cord, inner ear, and skin manifestations appears higher in the presence of significant shunts, suggesting that these "arterialized" venous bubbles can cause harm, perhaps by disrupting flow in the microcirculation of target organs.

Table e52-3 lists manifestations of DCS grouped according to organ system. The majority of cases present with mild symptoms including musculoskeletal pain, fatigue, and minor neurologic manifestations such as patchy paresthesias. Serious presentations are much less common. Nevertheless, pulmonary and cardiovascular manifestations can be life-threatening, and spinal cord involvement frequently results in permanent disability. Latency is variable. Serious DCS usually has its onset within minutes of surfacing, but mild manifestations may not appear for several hours. Symptoms arising more than 24 hours after diving are very unlikely to be DCS. The presentation may be confusing and nonspecific and there

TABLE e52-3 Manifestations of Decompression Sickness

Organ System	Manifestations
Musculoskeletal	Limb pain
Neurologic	
Cerebral	Confusion
	Visual disturbances
	Speech disturbances
Spinal	Muscular weakness
	Paralysis
	Upper motor neuron signs
	Bladder and sphincter dysfunction
	Dermatomal sensory disturbances
	Abdominal pain
	Girdle pain
Vestibulocochlear	Hearing loss
	Vertigo and ataxia
	Nausea and vomiting
Peripheral	Patchy nondermatomal sensory disturbance
Pulmonary	Cough
	Dyspnea
	Pulmonary edema (rare)
Cardiovascular	Chest pain
	Arrhythmia
	Hemoconcentration
	Coagulopathy
	Hypotension
Cutaneous	Rash, itch
Lymphatic	Soft tissue edema, often relatively localized
Constitutional	Fatigue and malaise

are no useful diagnostic investigations. Diagnosis is based on an integration of findings from examination of the dive profile, the nature and temporal relationship of symptoms, and the clinical examination. Some DCS presentations may be difficult to separate from CAGE following pulmonary barotrauma, but the distinction is unimportant since the first aid and definitive management of both conditions are the same.

TREATMENT Diving Medicine

First aid includes horizontal positioning to reduce the preferential entry of bubbles into the cerebral circulation (especially in suspected CAGE), intravenous fluids if available, and sustained 100% oxygen administration. The latter accelerates inert gas wash-out from tissues and promotes resolution of bubbles. Definitive treatment of DCS or CAGE with recompression and hyperbaric oxygen is justified in most instances, though some very mild or marginal DCS cases may be managed with first aid strategies if evacuation is difficult or hazardous. Evacuations need to avoid further decompression stress and, if over long distance, are usually undertaken using a helicopter flying at low altitude or a fixed-wing air ambulance pressurized to 1 ATA.

Recompression reduces bubble volume in accordance with Boyle's law and increases the inert gas partial pressure difference between bubble and surrounding tissue. At the same time, oxygen administration markedly increases the inert gas partial pressure difference between alveoli and tissue. The combined effect is to significantly increase the rate of inert gas diffusion from the bubble. Hyperbaric oxygen helps oxygenate compromised tissues and appears to ameliorate some of the pro-inflammatory effects of bubbles (Fig. e52-3). It is likely that recompression as early as possible will result in the best outcomes, especially for more serious DCS. Various recompression protocols have been advocated, but there are no data that define the optimum approach. Recompression typically begins with oxygen administered at 2.8 ATA, the maximum pressure at which the risk of oxygen toxicity remains acceptable in a hyperbaric chamber, followed by a stepwise decompression over variable periods adjusted to symptom response. The most widely used algorithm is the US Navy Treatment Table 6, whose shortest format lasts 4 hours and 45 minutes. This is often followed by daily HBO_2T using shorter treatment tables while symptoms persist and appear responsive to treatment. Adjuncts to recompression include intravenous fluids and other supportive care as necessary. Provided recovery is complete, diving can usually be resumed after a stand-down period of at least 1 month. If there are residual symptoms, diving is discouraged. If CAGE secondary to pulmonary barotrauma is suspected, steps must be taken to exclude the presence of an underlying pulmonary predisposition to further events. Investigation for a PFO may be indicated after cerebral, spinal, inner ear, or cutaneous DCS, especially if the event occurred despite clear adherence to dive-planning algorithms. Routine screening of all diving candidates for PFO is not justified given the high prevalence of PFO and the low incidence of significant DCS.

DCS is a variable and potentially confusing condition with many potential pitfalls in diagnosis and management. Clinicians untrained in diving medicine and faced with a patient who is unwell after diving, even with apparently mild symptoms, are strongly advised to contact an appropriate authority for diagnostic and treatment advice at an early stage.

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