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Uses of hyperbaric oxygen therapy in the 1990s

ERIC P. KINDWALL, MD

■ Hyperbaric oxygen can produce a variety of effects in addition to reducing air and gas embolism. It increases the killing ability of leukocytes and is lethal to certain anaerobic bacteria. It inhibits toxin formation by certain anaerobes, increases the flexibility of red cells, reduces tissue edema, preserves intracellular adenosine triphosphate, maintains tissue oxygenation in the absence of hemoglobin. In addition, it stimulates fibroblast growth, increases collagen formation, promotes more rapid growth of capillaries, and terminates lipid peroxidation. These actions of hyperbaric oxygen are useful in treating anaerobic infections that result in gas gangrene, as well as severe aerobic infections such as necrotizing fasciitis, malignant external otitis, and chronic refractory osteomyelitis. Hyperbaric oxygen can help preserve ischemic tissues and facilitates the rapid spread and arborization of new capillaries. It promotes healing in certain problem wounds. Adjunctive hyperbaric oxygen treatment is a new approach to the management of radionecrosis. Hyperbaric oxygen treatment reduces morbidity and mortality resulting from carbon monoxide poisoning. Protocols for hyperbaric oxygen therapy are at present mostly empirical; much additional research is needed to better define therapeutic indications.

YPERBARIC OXYGEN (HBO) is useful in a number of clinical situations, especially in treating carbon monoxide (CO) poisoning, crush injuries, necrotizing fasciitis, and gas gangrene. Unfortunately, due to limited human data and a general unfamiliarity with this mode of therapy in the medical community, the precise indications for HBO therapy are still not well understood by many physicians, and its use continues to be largely empirical. This article examines current indications

and future directions for HBO therapy in the light of research data and clinical experience to date.

BACKGROUND

Clinical use of HBO therapy involving intermittent inhalation of 100% oxygen under pressure had its beginnings in 1939 when Albert Behnke of the US Navy reported success treating decompression sickness with oxygen at 2.8 atmospheres absolute (ATA), after an initial excursion to 6 ATA breathing air in an attempt to immediately suppress bubbles. At the time, this method was not adopted Navy-wide because of concern over the fire hazard. In 1967, HBO treatment of the bends was officially accepted, and the failure rate

From the Department of Plastic and Reconstructive Surgery, Medical College of Wisconsin, Milwaukee.

Address reprint requests to E.P.K., Froedtert Memorial Lutheran Hospital, 9200 West Wisconson Avenue, Milwaukee, WI 53226.

of initial recompression dropped from 47.1% to 3.6%.¹ HBO treatment for the bends has since become a standard worldwide.

Some of the first systematic studies on the physiological effects of HBO, primarily in relation to diving, were conducted at Harvard University in the early 1930s. This work was much amplified during World War II when safe limits for oxygen breathing had to be determined for frogmen and other clandestine divers. The closed-circuit breathing gear used by these men differed from the familiar self-contained underwater breathing apparatus, or scuba, in that it left no telltale bubbles and required the use of pure oxygen, not air.

Oxygen under pressure is much more toxic than when breathed at 1 atmosphere. In continuous breathing of oxygen at 2 ATA, pulmonary oxygen toxicity manifests within about 6 hours. After breathing oxygen at 3 ATA for about 3 hours, most people will suffer a grand mal seizure. This is termed the Bert effect, having been first described by Bert in 1878.² Only because of extensive military experimentation with oxygen under pressure do we know the safe time and pressure limits for clinical patients.

HBO FOR NON-DIVING DISEASES

HBO therapy was first used for non-diving diseases in 1956, when Boerema, a Dutch cardiovascular surgeon, used a large pressurized operating room to carry out procedures requiring the interruption of circulation to the brain and other vital organs.³ Operations that would have been impossible without heart-lung bypass machines were successfully carried out in adults and children. Similar pressurized surgical chambers were soon built in the United Kingdom, the United States, and elsewhere. In time, however, effective cardiopulmonary bypass equipment became available and intraoperative use of the chamber was no longer necessary. Most of the surgeons using HBO abandoned it and a number of the large chambers were closed by 1975, with the use of HBO in surgery reaching a nadir bv 1977.

During this time, some hyperbaric enthusiasts began treating a wide variety of conditions, frequently without scientific foundation. Their claims were not based on carefully controlled experiments and often represented wishful thinking or, more ominously, a desire to secure a source of revenue. Self-styled HBO "clinics," frequently sponsored by nonphysicians, advertised hyperbaric cures for skin wrinkles, impotence, arthritis, baldness, and many other (usually chronic) maladies.

The struggle for reimbursement

These events alarmed the legitimate, academic HBO community to the extent that the Undersea Medical Society (UMS) set up the Committee on Hyperbaric Oxygenation to investigate the field of clinical HBO. The UMS was an organization made up primarily of academic and military physicians and researchers interested in the physiology of deep- sea diving. As the committee's chairman from 1976 to 1980, this author established liaison with Blue Cross/Blue Shield and the Health Care Financing Administration to determine the needs of insurers. The committee found little scientific basis for HBO chamber treatment of many of the 64 different disorders it investigated, and it concluded that HBO treatment was a very limited tool. However, for a number of disorders, animal experiments and clinical series showed that HBO treatment was beneficial. This evidence was at least as convincing as that for other treatments for which reimbursement is routinely made, so the committee determined that HBO treatment for these disorders should be eligible for reimbursement by third-party payers.

In 1977, the UMS produced a report that was accepted as a source document by Blue Cross/Blue Shield for determining third-party payment. The report has been updated every 2 to 3 years; currently, the committee recognizes 12 disorders to be reimbursable for HBO treatment (*Table*).⁴

The UMS report helped to stabilize the field of HBO therapy, with a scientific organization assuming responsibility for controlling its use. A group of persistent researchers continued to investigate the clinical uses of the chamber in wound healing, infections, and other conditions where hypoxia plays a central role. From these turbulent beginnings, a body of knowledge based on thousands of published experiments and clinical trials has grown that delineates the physiological parameters of HBO treatment. Safe time and pressure limits for high-dose oxygen breathing are now recognized. Both therapeutic and toxic effects that have been described in the literature result from two features of HBO: the physiologic effects of hyperoxia or elevated partial pressure of oxygen in tissues, and the mechanical effects of increased pressure.

In 1977, only 37 clinical hyperbaric chambers were operating in the United States. Today, the UMS, which in 1986 changed its name to the Undersea and Hyperbaric Medical Society (UHMS), reports that nearly 300 chambers are operating nationwide. Worldwide use of HBO treatment is apparent from increasing UHMS membership in a score of countries, as well as the formation of European, South Pacific, Russian, and Japanese hyperbaric treatment societies.

CHAMBER TYPES AND INDICATIONS FOR USE

Hyperbaric chambers are of two general types: a larger "multiplace" or walk-in chamber, and a smaller "monoplace" or one-man chamber. Multiplace chambers are filled with compressed air, and the patient breathes oxygen by mask, head tent, or endotracheal tube. The monoplace chamber is filled with 100% oxygen, usually from the standard hospital wall source, obviating the need for a mask. Apneic, ventilator-dependent patients who require complete monitoring and continuous intravenous infusions can be treated in either type of chamber.

HBO has been often misunderstood as being an exotic or even parascientific treatment. Actually, it consists only of the delivery of oxygen to body tissues at a greater dose than can be given at normal barometric pressure. The late Jefferson C. Davis, Chief of the United States Air Force Hyperbaric program for many years, suggested that the clinician ask the following questions when considering the use of HBO⁵:

1. Does experimental and clinical experience indicate that breathing oxygen at any dose is of value in the patient's disorder?

2. Is hypoxia present?

3. Can breathing oxygen at ground-level pressure provide adequate PO_2 to the tissue in question?

4. Does HBO significantly elevate PO_2 in the target tissue?

5. Will intermittent elevation of tissue PO_2 be of value?

6. Is there experimental and clinical evidence of efficacy?

7. Can HBO be administered safely?

With these points in mind, we shall now consider in detail some of the disorders approved for HBO treatment by the UHMS Committee on Hyperbaric Oxygenation (*Table*).

MECHANISMS OF ACTION

The most familiar action of HBO treatment is mechanical compression to reduce the size of gas bubbles that result from diving accidents and surgically
 TABLE
 DISORDERS APPROVED FOR HYPERBARIC OXYGEN
 THERAPY

Clostridial myonecrosis Necrotizing soft-tissue infections Osteomyelitis (refractory)
Acute traumatic ischemias (eg, crush injury, compartment syndrome) Skin grafts and flaps (compromised) Selected problem wounds Radiation tissue damage
Carbon monoxide poisoning and smoke inhalation Air or gas embolism Thermal burns
Decompression sickness Anemia due to excessive blood loss

induced air embolism. Aside from this, the most important component of HBO therapy is increasing the amount of oxygen dissolved in the plasma and tissues. Placing a patient in the hyperbaric chamber has no other known physiologic effect.

However, the body's reactions to increased pressures of oxygen are multiple, and the effects of high-pressure oxygen resemble those of a drug (eg, it can block lipid peroxidation or induce neovascularization). Under specific circumstances, HBO has been shown to increase the killing ability of leukocytes; to cause vasoconstriction in normal vessels; to kill certain anaerobic bacteria; to inhibit toxin formation by certain anaerobes; to increase the flexibility of red cells and white cells; to reduce tissue edema; to preserve intracellular adenosine triphosphate (ATP); to maintain tissue oxygenation in the absence of hemoglobin; to stimulate fibroblast growth; to increase collagen formation; to promote more rapid growth of capillaries; and to terminate lipid peroxidation. These mechanisms will be discussed in more detail below.

INFECTIOUS DISEASE

Gas gangrene

In 1960, Brummelkamp successfully treated gas gangrene in two patients who were moribund at the onset of treatment.⁶ HBO was considered because *Clostridium perfringens*, which causes gas gangrene, is anaerobic; it was thought that high doses of molecular oxygen could in some way inhibit this organism. A number of clinical series have since demonstrated the value of HBO when used early in the course of the disease and before performing ablative surgery.⁷⁻⁹

Clinical evidence of HBO's efficacy was established before its mechanism of action was thoroughly understood. Oxygen at a pressure of 1,400 mm Hg kills the

organism. At 3 ATA, arterial partial pressures of oxygen of approximately 1,800 mm Hg are achieved. Thus, the circulating blood is sterilized by HBO. However, this factor is probably not important, since it is in the tissues that the organisms are rapidly multiplying and producing alpha-toxin. Alpha-toxin is a lecithinase which can liquify muscle on contact, lyse red cells, and cause necrosis of kidney tubules. It attacks every organ in the body, and it belongs to the same class of compounds as meat tenderizers used in cooking. In the infected tissues, oxygen tensions considerably less than 1,000 mm Hg are achieved during HBO treatment, and the organism is not killed by direct contact with oxygen. However, alpha-toxin production appears to be severely inhibited by HBO treatment, and it is probably through this mechanism that the victim receives the principle benefit.^{13,14}

Hyperbaric treatment for gas gangrene should be instituted before surgery to get the patient out of shock, stop the hemolytic process, and provide a good demarcation between viable and necrotic tissue. In a series of 54 patients treated by the United States Air Force, Heimbach showed that 75% of patients with truncal gangrene survived if they were treated within 24 hours of diagnosis. In patients treated later than 24 hours, the survival rate was 18%. The survival rate was 100% for patients with gas gangrene of the limb treated within 24 hours, compared with a 9% mortality for those treated later than 24 hours, even with amputation. Overall, the mortality was 6% in all patients treated within 24 hours of the time of diagnosis.¹¹ Thus, early use of HBO makes a profound difference in mortality, regardless of what other treatment is given-be it immediate and high amputation, or massive antibiotics. If HBO treatment is delayed, survival decreases.

In a study by DeMello in dogs,¹² the combination of surgery, antibiotics, and HBO resulted in a 5% mortality rate. When HBO was eliminated from the regimen, mortality rose significantly.

It is important to remember that HBO should be used before the patient is given general anesthesia for surgery: the combination of septic shock, induction of anesthesia, and surgical trauma makes it very difficult to later resuscitate the patient in the recovery room. It is much better to control the infection through HBO first, and to operate to remove devitalized tissue later. The patient is then at much less risk from surgery, and the surgery can almost be carried out on an elective basis.

Before HBO was available, the only rational method

to preserve the life of a patient with gas gangrene was immediate surgical intervention. In Altemeier's experience, the best that could be achieved without HBO treatment was 14.8% mortality, with high and immediate amputation and disfiguring "commando" debridement.¹⁰

Aerobic and mixed soft-tissue infections

HBO seemed appropriate for treating anaerobic infections, but its use in aerobic infections was for a long time discounted, overlooked, or even felt to be harmful. The reason was that, in vitro, oxygen at pressures up to 1.3 atmospheres had been found to stimulate the growth of most bacterial species.¹⁵ Only at this point did increasing the pressure begin to inhibit aerobes; but even at high pressures, it is not lethal. It is impossible to achieve pressures of 1.3 atmospheres of dissolved oxygen in tissues; thus, aerobic infections would be expected to get worse with hyperbaric treatment.

Subsequent research by Hohn, Mader, and others demonstrated that this was not true, but rather the converse.^{16,17} In vivo, white cell function dominates in controlling the growth of bacteria. Leukocytes kill bacteria by an oxidative process, the "respiratory burst." The PO₂ in normal tissue is usually between 30 and 40 mm Hg.¹⁶ White blood cells cannot aerobically kill bacteria until the tissue PO₂ reaches a threshold of 30 mm Hg. It has been shown that when more oxygen than this is available, the killing action of the leukocytes becomes increasingly efficient up to pressures of at least 150 mm Hg.¹⁷ This has been demonstrated in the laboratory to be true for both *Staphylococcus* and *Pseudomonas*. Clinically, other organisms have been found to be similarly affected.

Because of the ability of HBO to enhance leukocytes' killing activity, it has been increasingly used in recent years in the treatment of severely infected diabetic feet, where ischemia plays a major role. It has also been used successfully for necrotizing fasciitis. Riseman et al¹⁸ recently reported on 29 patients with necrotizing fasciitis, 12 of whom received surgical debridement and antibiotics only, while the remaining 17 received adjunctive HBO in addition to debridement, surgery, and antibiotics. Both groups were similar with respect to wound bacteriology, antibiotic regimen, age, race, and sex distribution. Of the hyperbaric group, 53% had perineal involvement, compared with 12% of the control group. In addition, 29% of the hyperbaric group were in shock, as opposed to 8% of the control group. Only 33% of the control group were diabetic, compared with 47% of the hyperbaric group.

Nevertheless, mortality was 23% in the hyperbaric group vs 66% in the control group (P<.02). The need for surgery was much reduced in the HBO group, with an average of only 1.2 debridements to achieve wound control vs 3.3 debridements in the control group (P<.03). As a result of this study, Riseman et al recommend the routine use of adjunctive HBO in treating necrotizing fasciitis. However, this study spanned an 8-year period and was retrospective, not prospective. The controls and hyperbaric patients were not randomized for treatment, but were treated successively.

Because HBO can enhance the bactericidal effects of leukocytes, it has also been used successfully in the treatment of malignant external otitis, where three patients with intracranial, or stage 3 disease, have survived.¹⁹ Before the HBO treatment was available, no survival of stage 3 malignant otitis was reported. HBO has also been used experimentally to treat cerebral abscesses. One recent German series had no mortality in 11 consecutive cases (Lampl LA, personal communication, 1991). No published series of cerebral abscess patients has achieved 100% survival.

Osteomyelitis

Among infections that are primarily aerobic, HBO was first used with success in chronic bone infections. In 1965, Perrins et al reported on 24 cases of osteomyelitis treated with HBO.²⁰ The patients had been infected for an average of 14.5 years, with duration of infection ranging from 5 months to 49 years. Of the 24 patients, 17 healed (of whom 4 relapsed) and the discharge diminished in 4 others. In only 3 cases was the draining sinus apparently unaffected. Since the Perrins study, numerous other reports have shown a beneficial effect of HBO on chronic refractory osteomyelitis. In a rabbit model, Mader²¹ found HBO to be as effective as cephalothin in terms of therapeutic effect. Regrettably, there have been no useful, double-blind, controlled, prospective studies of any form of therapy for chronic refractory osteomyelitis. Esterhai et al²² reported a controlled study of osteomyelitis treated with HBO; however, the patients were not randomized, and 93% of the controls achieved remission, effectively invalidating the study.

Davis et al^{23,24} reported on 38 patients followed for 2 to 10.5 years. The patients received an average of 48 hyperbaric treatments with a 90% success rate. Many of these patients had bone grafts and 4 had muscle flaps. There were no complications among the patients receiving bone grafts, which all healed.

It is important to note, however, that HBO is never

used alone in treating osteomyelitis, but is part of a comprehensive regimen consisting of adequate debridement, sequestrectomy, bone grafting when necessary, muscle grafting, and antibiotics. Because most patients in all of the above-mentioned series reportedly received excellent surgical care, it is difficult to distinguish the effects of HBO from those of optimal management with conventional methods. Nevertheless, based on evidence from animal experimentation and clinical experience, HBO should be considered in any case of osteomyelitis which has defied at least 6 weeks of antibiotic therapy and surgery designed for cure. Chronic refractory osteomyelitis carries a very high treatment cost over the years, and the addition of HBO as an adjunct can be extremely costeffective despite its expense. Furthermore, in bone infections involving the sternum and skull, immediate HBO may be indicated before the infection is classified as refractory because of the high morbidity and mortality associated with infection at these sites.

WOUND HEALING

Traumatic crush injury

In traumatic crush injury, a number of factors contribute to tissue death and loss of function (typically of an extremity). Torn large vessels can be repaired surgically, but the surgeon is helpless to do anything about microvasculature which may have been crushed or may be suffering from the "no-reflow" phenomenon. In evulsions and crush injury, edema formation immediately worsens the microcirculation by increasing both the tissue pressure and the distance oxygen must diffuse from functioning capillaries. As tissue cells become ischemic, the tissue PO₂ drops and ATP is not replenished.²⁵ This causes the cells to lose the ability to control their osmolarity, and further edema develops. Compartment syndrome can worsen an already bad situation.

In cases of traumatic crush injury, if the major arteries are intact or are quickly repaired, adjunctive HBO can oxygenate greater volumes of tissue, preserving ATP in postischemic muscle and reducing edema by about 50%.²⁶

Strauss et al found HBO of value with impending compartment syndrome.²⁷ In a dog model in which compartment syndrome was created in the hind limb musculature by infusing plasma under pressure, necrosis did not occur in those animals treated with HBO until compartment pressures reached 60 mm Hg. At pressures of 100 mm Hg, muscle necrosis in HBO-

treated animals was only 36% of that seen in the control group, as measured by technetium 99 uptake. If applied early, HBO can control compartment syndrome and often can obviate the need for fasciotomy. If fasciotomy can be avoided through the use of HBO treatment, the cost of treatment is reduced by 75%.²⁸

A major logistical problem is getting patients with traumatic crush injury to a hyperbaric chamber early. Typically, the patient will arrive in an emergency room and, after stabilization and evaluation, will go directly to the operating room. Surgery to reconstruct critical tendons, nerves, and blood vessels often takes many hours. Thus, the patient may not be presented to the hyperbaric chamber until 12 to 24 hours after the injury. Optimal results can be achieved if the patient is treated within 8 hours after injury. If it is known that surgery will be delayed for 2 or 3 hours, the patient should be put into the hyperbaric chamber initially, before surgical correction is carried out. While this will not effectively oxygenate all of the tissues where major arteries have been disrupted, it will enhance the viability of tissues which have some blood supply.

Tissue flaps and grafts

Most tissue flaps, including flaps swung in situ and free tissue transfer flaps, will heal readily without the use of HBO. However, when a flap becomes compromised due to ischemia, adjunctive HBO therapy can often maintain the flap until adequate revascularization is accomplished. The chamber must be used before the graft becomes unsalvageable; however, this requires early recognition and prompt referral. There is no value in treating a flap that has become black from total stagnation of circulation. If a problem is anticipated while the patient is in the operating room, HBO should be used immediately following surgery. Under these circumstances, a twice-a-day regimen of HBO is optimal.

Numerous animal studies have demonstrated the utility of adjunctive HBO in preserving graft tissue. Jurell and Kaijser²⁹ found that, in rats with pedicle flaps, HBO treatment resulted in significantly greater flap survival compared with controls (P<.001). The surviving area was approximately twice that seen in the control group. However, when HBO was delayed for 24 hours, the surviving area was smaller, even though the amount of tissue saved was significant (P<.01). ATP was shown to be preserved in small blood vessels in pedicle flaps of guinea pigs, using histochemical staining. In guinea pigs, histochemical

staining showed that HBO preserved ATP in small blood vessels in pedicle flaps. Manson et al³⁰ showed that hyperbarically treated animals had three times more distal growth of capillaries than did controls. Nemiroff and Lungu³¹ found that the number and size of blood vessels in microvasculature was significantly greater in animal skin flaps treated with HBO when compared with controls (P>.01). They concluded that graft survival was enhanced by increasing or maintaining the number and possibly the size of vessels within the microvasculature.

In a clinical study, Perrins and Cantab³² noted complete survival of grafts in 64% of HBO-treated patients as opposed to only 17% of the controls (P=.01). Overall, there was a 28% increase in graft take in the hyperbarically treated patients. In another study, Perrins³³ created a full-thickness skin defect in pigs. The defects then underwent a split-thickness graft. Half of the animals were treated in the hyperbaric chamber at 2 ATA for 2 hours bid; the rest of the animals served as controls. Punch biopsies taken through the grafts were then submitted to a pathologist with instructions to attempt to identify the hyperbarically treated animals. The pathologist successfully identified the hyperbarically treated animals from biopsies taken during the first 3 days. After that, there was no difference. For this reason, the clinical protocol for the treatment of splitthickness grafts is twice-daily treatment for 3 days immediately following surgery, after which treatment is discontinued. Treatment pressure is at 2 ATA for 2 hours in the usual case, or 2.4 atmospheres for 90 minutes, if the multiplace chamber is used.

Diabetic ulcers of the leg and foot

The mechanisms responsible for healing in previously intractable diabetic lesions of the lower extremities are probably increased capillary ingrowth, better control of infections through enhanced killing of bacteria by leukocytes, and decreased rigidity of the red cells.

Collagen formation is severely impaired at PO_2 concentrations below 30 mm Hg. When tissue PO_2 reaches 30 mm Hg, fibroblasts can produce collagen. When sufficient collagen has been formed, the capillary buds then invade the collagenous matrix, facilitating rapid capillary ingrowth. Without this collagenous support, capillary growth is retarded. This is the mechanism for the increase in capillary growth seen with hyperbaric treatment.

In conjunction with increased capillary growth, Manson et al³⁰ measured increased glucose and

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decreased lactose concentrations in ischemic flaps, and Mathieu³⁴ has shown that after 15 HBO treatments at 2.5 ATA for 90 minutes, red blood cells double their flexibility, as measured by their ability to pass through a $3-\mu m$ filter.

Diabetic ulcers of the leg and foot are extremely common, and these patients are often referred for hyperbaric treatment. However, a careful workup is required to determine whether a patient will benefit: the appearance of the wound is not prognostic. Doppler studies or angiography are necessary to determine whether the diabetic patient's large vessels are sufficiently patent.

If the ankle-to-brachial blood pressure ratio (ischemic index) is less than 0.45, or if the Doppler ankle pressure is less than 75 mm Hg, there is little chance of healing even with HBO. Before accepting such a patient for HBO treatment, angioplasty or bypass grafting will be required.

Transcutaneous PO_2 (TCPO₂) measurements can be useful in working up these patients.³⁵ However, TCPO₂ does not actually reflect arterial PO_2 or even tissue PO_2 , because of artifact introduced by passage through the dermis and epidermis. The heated electrode used in this apparatus may also cause varying amounts of vasodilatation from patient to patient. Unfortunately, there are very few studies to guide the clinician in determining the meaning of transcutaneous PO_2 levels. Nevertheless, when the TCPO₂ is less than 30 mm Hg when breathing air at 1 atmosphere, the patient will usually not do well. However, if the TCPO₂ trends upward with HBO treatment, this is presumably evidence that the microvasculature is improving.^{36,37}

Radionecrosis

Ionizing radiation in proper dosage can kill tumor cells. However, even with the best modern techniques the normal tissues overlying and adjacent to the tumor can be damaged considerably by radiation therapy. Within 6 to 18 months following radiation, progressive sclerosis of the vessels in the radiated area begins to gradually render the affected tissue ischemic. This progression does not abate, but continues for the rest of the patient's life. Recurrent tumor, intercurrent illness, trauma of surgery, and other factors can hasten its progression. Due to hypovascularization, the irradiated area becomes hypoxic and hypocellular; any new lesion occasioned by trauma or further surgery may thus be incapable of healing.

Classically, the only treatment for radionecrosis has been to surgically replace the radiated tissue with fresh vascularized tissue in the form of flaps or free tissue transfers. However, this may be difficult or impossible if vital structures such as major arteries or the mandible are involved. Statistics from the University of Miami clinics indicate that before the advent of HBO treatment the cure rate for radionecrosis of the mandible was only 8%. ³⁸

Adjunctive HBO treatment represents a new approach to the management of radionecrosis in that the radiated tissue itself is the target of treatment.³⁹ Tissue PO_2 is raised during intermittent HBO therapy, stimulating collagen production by the fibroblasts. This in turn facilitates the rapid spread and arborization of new capillaries. Studies carried out at the hyperbaric unit at the U.S. Air Force School of Aerospace Medicine⁴⁰ demonstrate that the PO₂ in the radiated area will rise to approximately 80% of normal after 18 to 30 treatments. It plateaus at this level, but this is sufficient to make surgery and even grafting in the radiated area possible. These tissues can often go on to heal spontaneously.

Surgical approaches in patients with significant previous radiation must take advantage of adjunctive hyperbaric treatment. If surgery is planned in an area that has had significant radiation, at least 30 HBO treatments should be given preoperatively. Following surgery, additional treatments may be given to ensure complete healing.³⁹ The comprehensive protocols developed by Marx³⁹ for the use of HBO in managing radionecrosis appear to produce the best results. Cure rates in radionecrosis of the mandible are now over 90% with adjunctive HBO. These results are obtained only when HBO is used before surgery and when the described surgical techniques and grafting procedures are followed closely.

Extraction of teeth in the previously radiated jaw accounts for 89% of all trauma-induced cases of mandibular radionecrosis. When teeth must be extracted due to radiation caries, subsequent mandibular radionecrosis can be avoided in 92% of cases by giving 20 treatments in the hyperbaric chamber before surgery, followed by 10 treatments after tooth extraction. These data are borne out by a prospective, randomized, controlled study which showed fivefold greater incidence of radionecrosis in patients who received only perioperative antibiotics.⁴¹

CARBON MONOXIDE POISONING

Our understanding of the pathophysiology of CO poisoning has changed markedly since 1975. Formerly,

it was thought that CO inhalation produced carboxyhemoglobin (COHgb), blocking oxygen transport by the red cells and causing subsequent tissue hypoxia. However, when CO is tightly bound to hemoglobin, it is not easily released to enter tissues and cause further damage. In dog studies, Goldbaum et al replaced 68% of the normal circulating blood with packed donor cells containing 80% COHgb. They found no adverse effect with circulating COHgb levels up to 64%.⁴²

The COHgb level is no longer used as an index of the severity of CO poisoning. In 100 consecutive cases of CO poisoning treated at Lutheran General Hospital in Park Ridge, Illinois (Olskey and Wood, unpublished data, 1983), found no correlation between the COHgb level on admission and eventual outcome. (However, arterial pH correlated with severity.) Today, COHgb is used primarily to confirm CO exposure.

The pathophysiology of CO poisoning seems to involve a different mechanism. When the victim inhales CO, some of it goes directly into the tissues, where it alters proteins. It may or may not attach to cytochrome P450, cytochrome A₃ oxidase, or other iron-containing proteins. CO will not cause intracellular toxicity unless the tissues are first rendered hypoxic.^{43,44} This occurs as the COHgb level increases.

The mechanism of action of CO within the cell is still not completely understood. However, recent research shows that lipid peroxidation occurs, attacking the lipoprotein bilayer of cell membranes and the membranes of the organelles within the cells. Thom⁴⁵ showed that 100% oxygen given at a pressure of 1 atmosphere does not control lipid peroxidation, but at pressures greater than 2 atmospheres terminates lipid peroxidation. This may be the mechanism by which HBO exerts its greatest benefit in the treatment of CO poisoning.

Goulon⁴⁶ studied 200 patients with severe CO poisoning who were treated with HBO after having received oxygen at 1 atmosphere. Patients treated with HBO within 6 hours of removal from the toxic environment (n=147) had a mortality of 13.5%, whereas those treated later than 6 hours (n=53) had a mortality of 30.19% (P=.01). If HBO offered no advantage over oxygen at one atmosphere, there should have been no difference. When death is the end point, the validity of the unit of measure is undeniable.

Raphael et al studied 629 patients with CO poisoning and asserted that HBO treatment had little or no effect.⁴⁷ However, the study was severely flawed. Only 18 of 629 patients were admitted unconscious, indicating that for the majority the degree of poisoning was not severe, and some of the most severely poisoned were not treated in the hyperbaric chamber because they could not be placed on ventilation. The most serious defect of the study was that the patients were randomized to the treatment and control groups at times averaging 5.68 hours after admission. Thus, the mean time to hyperbaric treatment was almost exactly 6 hours. Since all patients were admitted within 12 hours of poisoning, it appears that about half were treated later than 6 hours after CO exposure. The data from the study do not allow us to separate these patients from those treated earlier. Thus, the effect of early treatment, which Goulon showed to be effective, cannot be deduced from the study.

In our own experience of 266 cases of severe CO poisoning treated with HBO at 3 atmospheres, only 3 patients (1.1%) developed delayed evidence of dementia ("late syndrome"). This is in sharp contrast to other series which report incidence of sequelae between 10% and 40% following survival of acute CO poisoning.^{48,49}

The best gauge of whether HBO should be used is the patient's mental status, including orientation, short-term memory, attention and calculation (eg, serial 7s, repeating phone numbers backwards), and a history of unconsciousness. Treatment is normally carried out at pressures of 2.5 ATA to 3 ATA. Treatment in the monoplace chamber consists of 90 minutes at 2.5 ATA, which may be followed by repeated treatment if the patient does not return to a normal neurological status. In the walk-in chamber, treatment is often for 46 minutes at 3 ATA followed by continued treatment at 2 ATA. Often, the US Navy regimen (US Navy Treatment Table 6) for the treatment of decompression sickness is used. This table provides a regimen of 4 hours of oxygen breathing at pressures starting at 2.8 ATA.⁵⁰ There is no question that in cases of CO poisoning morbidity is much diminished when HBO is used, and that mortality in severe cases can also be reduced.

AIR EMBOLISM

The hyperbaric chamber has been used to treat air embolism in divers for more than 50 years. Now, with HBO becoming available in hospitals, iatrogenic air embolism can also be effectively managed.

Air may enter the vascular tree as a venous or arterial embolism. An embolism that begins on the venous side but later crosses over to the arterial side through an atrial septal defect or through arteriovenous shunts in the lungs, is termed a paradoxi-

cal embolism. Common causes of embolism are accidents with cardiopulmonary bypass,⁵¹ cardiac catheterization, neurosurgery in the sitting position, renal dialysis, percutaneous lung biopsy,⁵² disconnection of central lines, and gynecologic procedures, particularly with the gravid uterus. Outside the hospital, it is seen in patients who have escaped from submerged vehicles while holding their breath, and also as a consequence of blowing air into the vagina during pregnancy as part of sexual foreplay.⁵³

Massive venous air embolism can cause death through embolization of the lung with respiratory embarrassment and reflex cardiac arrhythmia. However, it is much more liable to produce a lethal effect by migrating to the arterial side and there producing a cerebral air embolism and, possibly, embolism of the coronary arteries. Tiny amounts of gas (as little as 0.5 mL) on the arterial side can be fatal. Ilyin, quoted by VanAllen et al,⁵⁴ reported injecting up to 2 L of air intravenously in the dog at the rate of 30 cc per minute without causing symptoms. However, a large bolus of intravenous air suddenly arriving at the lung will raise the pulmonary arterial pressure and, consequently, the pressure in the right side of the heart. This may open a probe-patent atrial septal defect and force gas from the right atrium into the left atrium. After passing through the left ventricle, the embolism is usually pumped directly into the brain. Alternatively, a large bolus of air arriving at the lung may overwhelm the pulmonary vasculature and force some of the air through the arteriovenous shunts within the lung, resulting in arterial gas embolism.

Diagnosis of arterial embolism is usually made on observing abrupt onset of cerebral signs or loss of consciousness. The patient may appear to have had a stroke. In fatal cases, arrhythmia results in cardiac arrest. Examination of the tongue may reveal mottling (Liebermeister's sign) caused by blockage of nutrient arterioles by air. If the patient survives the initial few minutes, there is usually time for transportation to the hyperbaric chamber.

Classically, HBO treatment for embolism has involved taking the patient to 6 ATA in the chamber, followed by gradual decompression.⁵⁵ This compresses the gas bubbles to one sixth of their original volume, reestablishing circulation. However, in recent years, HBO treatment has been given in monoplace chambers at pressures no greater than 2.8 or 3 atmospheres with excellent results. Kindwall and Johnson,⁵⁶ treating 32 cases of air embolism at 6 ATA, achieved a survival rate of 84%. This was no better than a similar

number of patients treated by Hart⁵⁷ at 2.8 to 3 atmospheres with HBO. Animal experiments by Leitch et al have also confirmed that there is no advantage in using a treatment pressure of 6 ATA.⁵⁸ Moreover, when air was breathed at 6 ATA, embolization of the spinal cord, presumably with nitrogen emboli, followed. In our series, we used a helium-oxygen mixture or a 50/50 nitrogen-oxygen breathing medium. It is my strong feeling that compressed air should never be breathed by the embolism patient at 6 ATA.

The sooner the embolism patient is treated in the chamber the better: if the patient can be brought to a monoplace chamber with a 3-atmosphere capability more rapidly than to a chamber with a 6-atmosphere capability, it is advisable to use the monoplace facility. In my experience with cases stemming from scuba diving, the average delay before treatment was 2.4 hours, and the longest delay was 6 hours.⁵⁶ In the 6-hour delay group, all survived, and there were no residual adverse effects. Survivors among all cases averaged 3.7 hours to treatment, whereas those who died averaged 9.1 hours. Nevertheless, two patients were treated successfully at 14 and 24 hours, with no sequelae. Surgeons and others who carry out procedures that carry air embolism as a risk should acquaint themselves with local hyperbaric facilities and know how to reach them. Helicopter transport may be necessary in some cases.

THERMAL BURNS

Attention was drawn to the possibility of hyperbaric treatment of burns in 1968, when Japanese coal miners suffering from burns following a coal mine explosion were treated for CO poisoning in a hyperbaric chamber.59 Their burns seemed to heal more rapidly, and their physicians attributed this to HBO. Since that time, there has been a great deal of animal research into the HBO treatment of burns, but only recently have clinical series been reported. Not until 1988 did the UHMS Committee on Hyperbaric Oxygenation feel that enough data were available to remove thermal burn from a category of "special considerations" and to recommend that it be reimbursed by third-party carriers. However, the UHMS requires that the burn patient be treated in a recognized burn care facility according to a strict protocol.⁴ Treatment is usually given at 2 ATA for 90 minutes twice a day, a schedule that was derived empirically. HBO treatment is continued until grafting is complete.

The rationale for using HBO in burn injuries is that

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it helps maintain microvascular integrity and minimize edema.⁶⁰ It provides the oxygen necessary to maintain the viability of marginally vascularized tissue. By preserving ATP in the cell membrane, HBO enables the cell to control its osmolarity and stops the exuberant edema formation normally seen in burns.⁶¹⁻⁶³ Moreover, increased levels of hydroxyproline, a precursor to collagen, have been seen in the healing tissues of HBO-treated burned animals.⁶⁴

Edema progressively causes capillary occlusion that may spread from the initial zone of coagulation. This has been known to increase by a factor of 10 during the first 48 hours following injury.⁶⁵ Burn toxins also cause edema in uninjured tissue remote from the area of burn.

HBO appears to decrease the inflammatory response while improving the microvasculature. Controlled animal studies have shown a 30% reduction in the extravasation of fluid in the first 24 hours. Similar findings have been noted in humans. Generalized edema is also reduced. Animal studies have shown progression of second-degree burn to full-thickness injury compared with controls, on biopsy. Animals treated with HBO show greater preservation of the dermal elements and more capillary patency than do controls. HBO does not change the bacterial flora of the burn site, but there is some evidence to suggest that *Candida* and *Streptococcus* are inhibited and are less likely to cause clinically significant infection.⁶⁶

Niu et al, at a large naval hospital in Taiwan, reported that in severely burned patients with burns over 35% to 75% of the total body surface, 6.8% of 117 patients treated with HBO died, vs 14.8% of the 169 controls (P=.028).⁶⁷ Mortality rates were not significantly different in less severely burned patients. The average number of hospital days in the hyperbarically treated high-risk group was 47 days, vs 59 days for the controls (however, this was not statistically significant). Hart et al did a small controlled study in humans, matching patients with similar burns.⁶⁶ Using a two-way (air vs oxygen/percent burn) factorial analysis of variance, the mean healing time in the controls was 43.8 days, whereas it was 19.7 days in a hyperbarically treated group (P>.005).

Cost factors

Cianci et al investigated the economic costs of burn treatment with adjunctive HBO.⁶⁸ They found that, in patients with burns over 18% to 39% of total body surface, reduction in the mean length of hospitalization from 33 to 20.8 days (P=.012) reduced the total

cost per case by \$10,850. However, this study comprised only 16 patients. Cianci et al also studied the effect of HBO on grafting.⁶⁹ In severely burned patients with burns over 40% to 80% of total body surface, matched for age, percentage, and thickness of burn, the number of surgeries for grafting fell from 8 to 3.7 when the HBO chamber was used (P=.041). Waisbren et al found that although HBO failed to influence mortality in severe burns, grafting was reduced 75% in the hyperbarically treated group (P>.01).⁷⁰

CONCLUSIONS

HBO is a useful tool for surgeons and emergency room physicians. When properly used, it can help preserve ischemic tissue, suppress production of alphatoxin in anaerobic infections, and inhibit aerobic infections. It promotes healing in certain problem wounds and is useful in the management of radionecrosis. In CO poisoning, morbidity is much diminished when HBO is used, and mortality in severe cases can also be reduced. In acute situations such as crush injury, necrotizing fasciitis and gas gangrene, HBO must be used early to be effective.

Adjunctive HBO is not inexpensive; however, if used properly it has been reported to save money overall or to be an effective stop-loss procedure for the institution. In the few well-documented economic analyses, HBO appears to be cost-effective. In gaping or ischemic wounds, the curbing of infection or preservation of a graft or flap with HBO treatment can vastly shorten hospitalization or the need for reoperation. Moreover, the ability of HBO to help establish granulation in indolent wounds can spell the difference between successful and failed treatment.

Despite favorable data from animal studies and successful human series, the use of HBO in many situations is not yet considered the standard of care. There are several reasons for this: the number of chambers is limited; many surgeons are unacquainted with HBO therapy or have little training or experience with it; and well-controlled human studies are lacking. At present, HBO treatment protocols are mostly empirical, and a great deal of additional research is required before these protocols can be optimized and the therapeutic indications more accurately defined. In addition, surgeons need more experience with HBO in order to learn when it is useful and when it is a waste of time. In short, HBO will not heal normal wounds more rapidly, but under certain circumstances it may induce problem wounds to heal more like normal ones.

ADDENDUM

To locate a hyperbaric chamber in your area, nationwide information can be obtained from the Diver's Alert Network at Duke University. Information about

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