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Hyperbaric Oxygen Treatment and Therapy

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Editor's Note—*Hyperbaric oxygen therapy (HBOT), first described in the medical literature more than 120 years ago,[1] is the administration of 100% inspired oxygen while in a chamber at pressures greater than sea level. This increases the amount of dissolved oxygen in plasma, which is the basis behind treatment. Treatments take place in a single- or multiperson chamber. A single- or mono-place chamber, as it is commonly called, can hold only 1 person with no inside attendant. The chamber itself is pressurized with 100% oxygen, and when the patient inspires they are always breathing pressurized oxygen. A multiplace chamber can hold more than 1 person and has capability to hold a trained medical attendant, which gives greater treatment capability, especially with critically ill patients. The multiplace chamber is not pressurized with oxygen-only air, and the patient breaths oxygen via a hood or aviator mask. Today hyperbaric medicine has evolved into a specialty with board certifications offered through either the boards of Emergency Medicine or Preventative Medicine. Through the efforts of the Undersea and Hyperbaric Medicine Society, evidence-based medicine research has validated 13 approved indications for HBOT* (see Table 1). *The field of hyperbaric medicine is an evolving specialty, and the scope and practice is fluid with new research. This article will give an explanation into the various approved indications, the basic science rationale, and the pathophysiolgy of why hyperbaric medicine works.*

Decompression Sickness

Introduction

Decompression sickness (DCS), also known as "the bends," was first observed around 1840 in divers with the British Royal Engineers.[2] The condition later became known as Caisson's disease, as described by Paul Bert in 1878,[3] who also correctly diagnosed the pathology as it related to nitrogen in the tissues secondary to supersaturation. His discovery led to the use of repressurization chambers during the construction of the subway tunnel under the Hudson River. In the scuba diving model, as a person descends, they must breathe gases at higher pressures to sustain respiration thereby increasing the concentration of oxygen and nitrogen in the blood. Higher partial pressures, both of nitrogen and oxygen, can be detrimental in a relatively short time. The dissolved nitrogen in the blood diffuses into fatty tissue and accumulates in a time-dependent fashion. When the diver ascends, the nitrogen does not immediately release from the tissues and it is this lag in

nitrogen release that is thought to represent the initiating factor in decompression sickness. If the person ascends too quickly, the nitrogen changes from dissolved form into gaseous bubbles, setting off a chain of pathological events.

Clinical Features

Historically, DCS was categorized into types I and II. Type I was considered "pain only" symptoms, whereas type II involved multiple organ systems. The distinction between the 2 types was often blurred, and it is unusual to find a patient with only pain symptoms. Presently, the diagnosis is described based on the patient's presentation and disease manifestations, of which 6 are typically described. In the cutaneous form of DCS, the patient may present with a marbling of the skin, described as "cutis marmorata," which may be pruritic. Ear manifestations may include nystagmus, inner ear hemorrhage, and hearing loss. The musculoskeletal symptoms of DCS are commonly described as "the bends," as patients are known to double over with pain. The pain of the bends is diffusely distributed and commonly observed. Constitutional manifestations are typically nonspecific and include fatigue, malaise, and anorexia. Neurological manifestations can involve either the brain or the spinal cord. Spinal cord symptoms tend to dominate in DCS associated with diving, whereas altitude-related DCS more commonly causes brain symptoms. The symptoms of spinal DCS include low back and abdominal pain, as well as weakness, paralysis, and paresthesias of the limbs. Symptoms in the limbs begin with paresthesias progressing distally to proximally, subsequently followed by sensory and/or motor loss. These patients may also develop symptoms consistent with cord injury, such as fecal incontinence, urinary retention, and priapism. Cerebral symptoms are vague and may include headache, blurred vision, diplopia, dysarthria, fatigue, and inappropriate behavior.[3] Neurological symptoms can range from mild memory loss, to patchy paresthesias, to paralysis. Cardiopulmonary manifestations, although rare, are mostly related to rapid decompression, leading to pulmonary hypertension, CHF, and shock. Symptoms may include ischemic chest pain.

Table 1. Approved Indications for Hyperbaric Oxygen Therapy

1. Decompression sickness
2. Gas embolism
3. Carbon monoxide
4. Enhancement of nonhealing wounds
5. Gas gangrene (myonecrosis) and clostridial myositis
6. Necrotizing soft-tissue infections
7. Ischemic crush injuries, compartment syndromes, and other acute traumatic peripheral injuries
8. Refractory osteomyelitis
9. Delayed radiation injury
10. Compromised skin grafts and flaps
11. Thermal burns
12. Exceptional blood loss anemia
13. Intracranial abscess

Therapy

Treatment for DCS is hyperbaric oxygen therapy with additional supportive measures—fluids, airway control, and maintenance of blood pressure. There is an inverse relationship between the delay to HBOT and complete resolution of symptoms, thus transfer to a hyperbaric facility should occur as soon as possible. Tomassoni suggests that if treatment is delayed up to 5 hours, mortality is 10% and morbidity is nearly 50%.[4] HBOT treats decompression sickness with pressure and high oxygen concentrations by reducing the bubble volume, increasing the gas diffusion gradients to allow the transfer of gases into the blood and tissues, facilitating oxygenation, and reducing edema. It is proposed that HBOT reduces neutrophil adhesion to the capillary endothelium, disrupting the inflammatory cascade described previously.[5] While the majority of patients respond well to a single hyperbaric treatment, patients with recurrent symptoms may require additional recompression until improvement is no longer noted. The US Navy has the most experience with the treatment of DCS and has developed tables to guide therapy depending upon the clinical presentation and diving history of the patient. Most DCS patients are routinely treated by naval treatment table 6. The Navy's other treatment tables are used for more advanced and serious cases but are rarely required in the sport diving community.

Air Gas Embolism (AGE)

Introduction

Brauer first described the symptom complex of air

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embolism in 1913,[6] though experiments by Boyle in 1670 were the first to demonstrate pathology related to an acute gas embolus.[7] While up to 30% of diving-related deaths[7] are attributable to AGE, surgical causes are probably more prevalent. Whitby suggested that air embolism is the most common cause of death in any surgery-involving invasion of the vasculature.[9] Air embolism is reported in nonvascular surgery as well, including burr hole placement, arthroplasty, arthroscopy, endoscopy, and bronchoscopy. AGE is associated with intra-aortic balloon pump use, as well as with various diagnostic modalities involving the use of cannulae and/or needles. Other nonsurgical interventions such as mechanical ventilation have also been associated with AGE. Finally, traumatic injuries, including head and chest trauma, are particularly prone to AGE as well.

Four gas laws (Boyle, Dalton, Henry, and Charles) help clarify the pathophysiology involved in both decompression sickness and air gas embolism. The pathology of an air embolus includes the vasoocclusive/obstructive aspects of organ damage with the resultant ischemia distal to the obstruction. In addition, the blood/embolus interface may cause endothelial damage with the associated platelet deposition, plasma transudate, loss of intravascular volume, and late deterioration of blood flow.[10]

Clinical Features

AGE symptoms tend to present within 10 minutes of resurfacing, whereas the symptoms of DCS typically present later, although more then half tend to present within the first hour. Clinically, AGE is presumed in any compressed-air-breathing diver who is unconscious on resurfacing or loses consciousness within 10 minutes of resurfacing.

Bubbles tend to favor the middle and anterior cerebral arteries, and CNS involvement may resemble an acute stroke. Dick and Massey note that loss of consciousness in DCS is rare, in contrast to AGE.[11] Physical and lab findings in these patients reveal cyanosis, hypotension, evidence of right-sided strain on ECG, and decreased end-tidal CO_2 levels. Untreated, this condition will lead to respiratory arrest and death. Of note, Bove suggests divers with a patent foramen ovale (PFO) may have up to 2.5 times the risk of decompression sickness.[12] Strauss and Borer suggest echocardiogram work-up for hemodynamically significant PFO in divers with a history of unexplained AGE or DCS type II.[13] It is suggested that the dysrhythmias seen are indirectly caused by cerebral gas emboli and resultant autonomic dysfunction.[14]

Treatment

As with DCS, hyperbaric oxygen is the primary treatment. The change here is if clinical judgment and short time to a recompression chamber, higher depth of treatment may be required. The initial approach is the same with DCS as far as stabilization of the patient, including IV fluids, oxygen, and close monitoring of vital signs.

Carbon Monoxide Poisoning

Introduction

Between the years 1979 and 1988, carbon monoxide (CO) killed more than 5000 people per year,[15] making it the leading cause of poisoning deaths in the United States. This odorless, nonirritating, colorless gas is a combustion by-product of nearly all organic fuels, has a density nearly the same as air, and equilibrates quickly to indoor air spaces. Human exposures most commonly occur from natural gas combustion, kerosene heaters, and cigarettes. Automobile exhaust accounts for nearly one-half of all unintentional CO-related deaths. Toxicity may also occur from exposure to methylene chloride vapors, a common chemical used in degreasers, paint removers, and other solvents. The liver will metabolize up to one-third of this inhaled volatile chemical into CO. However, direct exposure is more common and as discussed below, all physicians must be highly suspicious of CO toxicity in patients during the wintertime who complain of flu-like symptoms.

CO causes its toxicity by affecting oxygen delivery and use at the cellular level. It reversibly binds hemoglobin with an affinity more than 200 times greater than oxygen, forming carboxyhemoglobin (HbCO). In doing so, a relative anemia ensues. HbCO formation causes an increased binding of oxygen to hemoglobin at its remaining sites, shifting the oxygen-dissociation curve to the left. This worsens the relative anemia as even less oxygen is available for delivery to the tissues. CO also binds to cardiac myoglobin and cytochrome oxidase. This combination of carboxymyoglobin-causing dysrhythmias and ischemia, plus the effect of decreased cellular respiration via impaired cytochrome oxidase (a mechanism similar to cyanide toxicity), worsens the already hypoxic tissues.

In addition to immediate tissue hypoxia, there are well-known delayed neurologic sequelae that occur with CO poisoning. The exact mechanism remains unknown, but researchers speculate that the hallmark syncopal episode is likely caused by hypotension related to vasodilation. This vasodilation is thought to occur secondary to nitric oxide release from platelets, carboxymyoglobin-related cardiac depression, and activation of cyclic guanosine monophosphate.[16] Formation of oxygen-free radicals and lipid peroxidation is likely the end point of the ischemic brain injury.

CO is cleared through the lungs. Normal half-life at room temperatures is 3-4 hours. Placing the patient on 100% oxygen reduces the half-life to 30-90 minutes, and hyperbaric 100% oxygen at 2.5 atmospheres reduces it further to 23 minutes—potentially a 16-fold reduction.

Clinical Features

Diagnosis may be difficult—a detailed history and physical exam, as well as having a high index for suspicion, is important in making the diagnosis. Patients may present with vague symptoms such as headache, dizziness, and nausea, and symptoms do not correlate well with the measured carboxyhemoglobin levels. As the severity of the exposure increases, the signs and symptoms may be predominantly cardiac and neurologic systems. These signs can include vomiting, ataxia, confusion, syncope, coma, seizures, cardiac dysrhythmias, tachypnea, and myocardial ischemia. Patients may complain of symptoms of weakness, dyspnea, chest pain, and visual changes. With severe exposure, patients may have an identical presentation to cyanide poisoning including all of the symptoms above, plus markedly abnormal vital signs with hypotension, cardiac arrest, and metabolic acidosis. Of note, the lack of cherry-red skin discoloration should not discourage the diagnosis of CO toxicity, as it is usually a postmortem finding.

In contrast, patients with chronic exposure may present differently, and often, not to the emergency department. Their symptoms typically include neuropsychiatric disorders involving memory, depression, and cognitive skills. Physical signs may include seizures and Parkinson-like symptoms.

Prognosis is generally poorer for patients with underlying cardiac illness, age older than 60 years, and those who have suffered an episode of unconsciousness related to their CO exposure. As previously mentioned, the severity of illness does not always correlate with HbCO level. Brief, but high concentration, exposure can result in higher HbCO levels without evident pathology, and low concentration long-term exposure may reveal a lower HbCO level with significant illness. Despite this, some generalizations regarding the HbCO level are usually made. Around a level of 10%, patients may present with headache. Seizure, coma, and death may occur with levels in the range of 50-70%. Additional diagnostic strategies involve the measurement of arterial blood gases. It is noted, however, that the presence of CO does not change serum oxygen concentration, thus the ABG, apart from indicating metabolic acidosis in severe cases, may be otherwise normal. Pulse oximetry is also an inadequate test as commercial oximeters measure oxy- vs de-oxyhemoglobin and will incorrectly characterize carboxyhemoglobin as the oxygenated form.[17]

Treatment

Though oversimplified, oxygen and supportive care are the mainstays of therapy for CO poisoning. As noted above, the concentration of carboxyhemoglobin is decreased in the face of increased PaO_2. Additionally, the increased oxygen concentration decreases the pathological hypoxia. In the face of mild toxicity, some guidelines suggest normobaric 100% oxygen until symptoms resolve or the carboxyhemoglobin levels diminish to less than 10%. Controversy surrounds the use of HBOT in this setting. The first prospective clinical trial published only 14 years ago showed no statistically significant benefit comparing 2 atm of hyperbaric to normobaric 100% oxygen.[18] Clinicians point out that this study may have been limited by treatment delay in half of the patients. Though at present there remains no consensus on what truly constitutes delay, hyperbaricists generally recommend therapy within 6 hours of exposure if possible. Later studies have also shown significant benefit when higher pressures of oxygen (typically 2.5-2.8 atm) were used.[19,20]

The larger challenge is to determine which patients are most likely to benefit from the addition of HBOT to their treatment plan. Though no precise definition for severe poisoning yet exists, patients who present with signs of serious toxicity (syncope, cardiovascular dysfunction, neurologic symptoms) should receive HBOT regardless of their carboxyhemoglobin level.

Treatment for CO poisoning typically consists of 90-120 minutes of 100% oxygen at 2.5-3.0 atm and may include single or multiple episodes depending on the clinical circumstances. Multiple treatments, though controversial, are generally performed for those with persistent neurological deficits until there is no further demonstrable improvement in cognitive function.

Enhancement of Nonhealing Wounds

Introduction

A large portion of annual health care dollars is spent on the management of lower extremity ulcers. Physicians who care for these patients should develop a comprehensive plan including care of the wound and management of other comorbidities that may delay the healing process (*see Table 2*). There are 4 main ulcers that predominate as problem, nonhealing wounds. These include ulcers from pressure, venous stasis, arterial insufficiency, and the diabetic lower extremity. Most lower extremity ulcers can be managed with standard medical and surgical care. Venous stasis ulcers need proper compression to control edema. The same is true for pressure ulcers, most of which will respond to routine wound care, proper nutrition, and pressure reduction. While most ulcers will heal with standard therapy, some may require skin grafting or flap advancement. Hyperbaric therapy may be indicated for a compromised skin graft or flap, but to date there are no controlled studies demonstrating efficacy for use in venous insufficiency or pressure ulcers.

Arterial insufficiency warrants special consideration, as revascularization, either by surgery or angioplasty, is necessary for proper healing. However, HBOT may benefit patients who, despite attempts to improve blood flow, have persistent ulcers.

Diabetic lower extremity ulcers have demonstrated the most benefit from hyperbaric therapy. In April 2003, the Centers for Medicare and Medicaid Services (CMC) announced approval of HBOT for diabetic lower extremity ulcers that meet the following criteria: 1) Patient has type I or II diabetes and has a lower extremity wound that is due to diabetes; 2) Patient has a wound classified as Wagner grade III or higher; and 3) the patient has failed an adequate course of standard wound therapy.[21]

Pathophysiology

Hyperbaric oxygen is reserved for compromised wounds that suffer from poor perfusion. The wound healing process is very dependent on oxygen as a central catalyst in the healing process, and hyperbarics lends itself to the role of wound healing from 3 general mechanisms. Hyperbarics is used to help re-establish wound metabolism by enhancement of fibroblast replication, collagen synthesis, angiogenesis, and epithelialization.

The host immune response destroys bacteria via a direct and indirect cytokine mediated effect on leukocytes. The stimulus of nitric oxide production leads to leukocyte and endothelial adhesion, inhibition of platelet aggregation, and the production of oxygen-free radicals.[22]

Wound hypoxia is measured by transcutaneous oximetry that provides a quantitative assessment of oxygen availability to wounds.[23] This approach is well documented but can be a

Table 2. Comorbidities That Could Delay Healing Process

- Blood sugar management
- Nutrition
- Smoking
- Renal failure
- Peripheral vascular perfusion

limiting assessment due to varying factors that can influence data collection.

Therapy

Treatment protocols vary but are typically daily at a depth of 2.0-2.4 ATA for 90-220 minutes. Wounds must demonstrate improvement on reassessment every 30 days to justify continued therapy.

Gas Gangrene (Myonecrosis) and Clostridial Myositis

Introduction

Myonecrosis and clostridial myositis are acute infections hallmarked by rapid progression, extensive edema, and a clinical picture of sepsis. Notably, these infections are nonpyogenic, and as the name suggests, are associated with gas production. *Clostridium* species, most commonly *C perfringens*, are the causative agents. These infections may occur from endogenous sources, but typically they are exogenous from trauma or recent surgical wounds.[24] Though much less frequent, endogenous infections found in diabetics and other immunocompromised usually involve *C septicum* and are associated with much higher mortality. Fortunately, *Clostridial* infections are relatively rare; Reenstra-Buras quotes a figure of only 900-1000 US cases in 1975.[25]

Clostridia species are encapsulated Gram-positive, spore-forming anaerobes commonly found in soil and the human intestine. More than 150 species have been identified, but the majority of human infections are caused by *C perfringens* alone or in combination with *C septicum* and *C novyi*.[26] Despite its anaerobe label, *C perfringens* can exist in oxygen concentrations up to 30-70 mm Hg. It has multiple exotoxins primarily causing its pathology—the most prevalent is lecithinase-C, an alpha-toxin that is oxygen stable. This alpha-toxin, along with others, causes hemolysis, hemoglobinuria, tissue necrosis, renal failure, and cardiotoxicity. Tissue destruction occurs when toxin production is high enough to overwhelm local host defenses. Continued tissue destruction promotes additional anaerobic areas, promoting further bacterial growth. Products of the tissue destruction, including potassium and creatine phosphokinase, contribute to the secondary toxicity. Although the human immune system can develop antitoxin against alpha-toxin, its continuous production in infection kills the patient before significant immunity can occur. Interestingly, a genetically engineered vaccine against alpha-toxin has been shown effective in experimental infection in the murine model.[27]

Hyperbaric oxygen is thought to act against the alpha-toxin by stopping the production of the alpha-toxin at high oxygen tensions and the degradation of oxygen-free radicals. Riseman suggests that HBOT may inhibit anaerobe growth by decreasing edema via hyperoxic vasoconstriction, enhancing phagocytosis, and by improving angiogenesis.[28]

Clinical Features

As previously mentioned, most cases of gas gangrene are caused by exogenous *Clostridium* as a result of trauma or recent surgery. However, immunocompromised patients, alcoholics, drug abusers, chemotherapy patients, and particularly diabetics with peripheral vascular disease are at risk for these infections. Infected individuals present with a rapid onset of symptoms and will commonly have pain out of proportion to their examination. Systemic findings may include low-grade fever, tachycardia disproportionate to their fever, and altered level of consciousness. At the site of infection, signs may include crepitans, brown or bronze skin discoloration, massive brawny edema, and occasionally a foul- or sweet-smelling wound discharge. The involved muscle tissue may appear dark red, black, or green and will not bleed when cut. Incredibly, these infections can spread up to 6 inches per hour, thus progression to shock and/or death may be extremely rapid.

Diagnosis is made on these clinical grounds and is supported by demonstration of Gram-positive rods from the site with the general absence of pus. The presence of white blood cells generally indicates a mixed infection in this setting. Radiographs of the area may reveal gas in the tissue, though CT may be needed to demonstrate the extent of tissue involvement. Additional laboratory work-up should include: CBC to evaluate for significant hemolysis, coagulation studies for possible coagulopathy and thrombocytopenia, a chemistry panel to rule-out hyperkalemia and renal failure, ABG for metabolic acidosis, LFTs for hyperbilirubinemia and liver toxicity, and a serum myoglobin level and urinalysis to evaluate myoglobinemia and myoglobinuria.

Treatment

Although HBOT and intravenous antibiotics play a large role, rapid surgical debridement remains the mainstay of treatment and should not be delayed. Stabilization, including fluids, oxygen, and antibiotics, must occur as rapidly as possible. Most authors suggest avoidance of vasoconstrictors as a resuscitative adjunct unless absolutely necessary as they may worsen peripheral hypoxia.

Hyperbaric oxygen at 3.0 atm has been shown to create tissue oxygen concentrations to 300 mm Hg.[29] Van Unnik in his 1965 article demonstrated that an oxygen tension of 250 mm Hg is necessary to stop alpha-toxin production by *Clostridia*.[30] Several studies have demonstrated the additional benefit HBOT provides to the care of these patients in reducing morbidity and decreasing the extent of amputations and tissue debridement.[31] Presently, the current recommended protocol is hyperbaric 100% oxygen as soon as possible at 3.0 atm for 90 minutes 3 times in the first 24 hours, followed by therapy twice daily over the next 4-5 days.

Ischemic Crush Injuries, Compartment Syndromes, and Other Acute Traumatic Peripheral Injuries

Introduction

Hyperbaric oxygen is an adjunct to standard therapies in the case of acute traumatic injury. Standard of care still remains advanced trauma life support, revascularization, fasciotomy, and surgical debridement. Its main role is in the preservation of tissue in the face of profound tissue hypoxia, arterial vasospasm, and edema. The rationale for using hyperbaric oxygen is to increase tissue oxygen levels, maintain cellular function, and to help prevent cellular-related injury. When tissue oxygen ten-

sions fall below 30 mm Hg, the body's host response to infection and wound healing becomes compromised.[32] When tissues become injured, subsequent vasogenic edema occurs; tissue-swelling leads to cellular collapse because of osmotic loss of intracellular water. When there is tissue reperfusion, there is an increase in circulating oxygen-free radicals. Hyperbaric oxygen helps to antagonize lipid peroxidation of the cell wall membranes, preventing oxygen-free radical injury.[33]

Clinical Features

There are no controlled studies into the use of hyperbaric medicine in acute traumatic injuries. A review done by Strauss summarized 700 case reports, which described the benefit of hyperbaric oxygen, but no clinical scientific evidence was reported.[34] The goal of hyperbaric therapy is to enhance oxygen tissue levels to help reduce tissue edema and eventual muscle necrosis. The decision to use hyperbarics is based on clinical judgment and the body's ability to respond to stress. The more compromised the host, the more beneficial the use of hyperbarics may be. The other main point to consider: if there is a decision to use hyperbarics, it should be made early in the decision process, and one should not wait until tissue edemas and ischemia develop.

Treatment

Treatment schedules vary, but within the first 24-48 hours patients may require 2-3 1½ hour treatment schedules until either reperfusion is obtained or edema reduction is achieved.

Refractory Osteomyelitis

Introduction

Osteomyelitis is generally divided into acute and chronic forms. As a review, acute osteomyelitis is further divided into hematogenous vs direct, or contiguous inoculation, form. Hematogenous osteomyelitis is most often found in children and typically attacks the growing bony metaphysis. In newborns, these infections are usually caused by *S aureus*, group A and B *Streptococcus*, and *Enterobacter* species. Children up to 4 years of age include the same species as newborns but also include *Haemophilus influenzae*, and children beyond 4 years predominate with *S aureus* species. Adults generally carry the same infecting organisms with the exception of *Salmonella* species in patients with sickle cell disease.

Patients with the direct form of acute osteomyelitis typically receive their infections as a result of trauma or surgery. Their manifestations generally are more localized and may present rapidly. The infecting organisms are similar but tend to be polymicrobial, with *S aureus*, *Pseudomonas*, and *Enterobacter* species predominating.

Refractory osteomyelitis is chronic or acute osteomyelitis that has failed to respond to standard therapies. Systemic comorbidities, including diabetes, malignancy, tobacco abuse, malnutrition, renal failure, and liver failure often complicate the healing process and must be considered in the management of this condition. Refractory osteomyelitis is more difficult to define, as presently little consensus exists on what marks cure or true treatment failure.

Much of the pathophysiology, as it relates to hyperbaric oxygen therapy, is based on animal studies. These studies have demonstrated positive effects in 4 areas: angiogenesis, leukocyte function, antibiotic function, and osteoclastic activity.

In the rabbit model, hyperbaric oxygen has been demonstrated to increase the normally low oxygen tension in infected bone to normal or supernormal levels.[35] It is believed that the increased oxygen levels promote fibroblastic collagen production, and subsequent angiogenesis.[36] Additionally, neutrophils use an oxidative process that requires oxygen tensions of 30-40 mm Hg to destroy bacteria. It has been shown that increasing the oxygen tension above this range further facilitates this bacteriostatic function.[37] As mentioned in the section on gas gangrene, elevated oxygen tensions have a direct killing effect on anaerobic bacteria. In chronic direct osteomyelitis, approximately 15% of infecting organisms are anaerobic, thus HBOT may be of benefit.

Antibiotic efficacy of aminoglycosides is diminished in hypoxic environments. At least 1 study suggests transport across the bacterial cell wall is oxygen dependent and subsequently may be enhanced in an oxygen-rich environment.[38] Finally, osteoclastic and osteoblastic activity, studied in rabbit and rat models, increases in an oxygen-enriched environment.

Clinical Features

At the time these patients present to a hyperbaricist, the diagnosis has been made and treatment has been initiated; however, a brief review of relevant signs and symptoms is appropriate. Direct osteomyelitis generally is an easier diagnosis with signs and symptoms localized to the site of infection, usually with obvious preceding traumatic injury or surgery. The presentation of the hematogenous form may be subtle. Symptoms include insidious onset of fever, malaise, and fatigue. These patients may also complain of pain, swelling, and erythema at the site. Signs include fluctuance, tenderness to palpation, and evidence of sinus tract infection in the chronic osteomyelitic.

Treatment

HBOT recommendations follow the Cierny-Mader classification of stage 3B and 4B refractory osteomyelitis. The staging number is based on anatomical site—stage 3 and 4 are localized and diffuse respectively. The "B" classification refers to any systemic or local factors that can affect host immunity, including diabetes, malnutrition, advanced age, venous stasis, and underlying malignancy (*see Table 3*).

When the appropriate patients are chosen, treatment frequency and duration depend on the severity of illness. Typically, treatments occur at 2.0-2.5 atm and will last 90-120 minutes. If the patient has undergone recent extensive debridement surgery, recommendations are for daily therapy. Therapy is continued until no further improvement is noted. The mainstay of treatment is still aggressive surgical debridement and antibiotics. If standard treatment fails, there then may be a role for hyperbaric medicine based on a clinical assessment of the patient.

Delayed Radiation Injury

Introduction

The use of HBOT for treatment of delayed radiation injury

Table 3. Cierny and Mader Classification System[39]

Anatomic site	
Stage 1	Medullary osteomyelitis
Stage 2	Superficial osteomyelitis
Stage 3	Localized osteomyelitis
Stage 4	Diffuse osteomyelitis
Physiologic change	
A Host	Normal host
B Host	Systemic compromise (BS)
Local compromise (BL)	
C Host	Treatment worse than disease

is best studied in osteoradionecrosis of the mandible—an unfortunate condition that commonly follows head and neck tumor irradiation. Following success here, researchers began to investigate the use of HBOT in other organs with radiation damage. In addition to osteonecrosis of the mandible, chest wall, and pelvic bones, hyperbaric medicine has been used to treat soft-tissue radiation injuries in the larynx, bladder, intestine, vaginal vault, and CNS.

Cancer statistics in 1998 showed an incidence of more than 40,000[40] cases of head and neck lesions; of those who receive radiation therapy, estimates suggest 5% of patients could succumb to osteoradionecrosis. HBOT fills a needed void in the treatment of these patients.

Elements of the pathophysiology of osteonecrosis are related to cellular destruction and damage of the vasculature.[41] In contrast to osteomyelitis, bacterial infection does not appear to have any causative effects in this setting.

The mechanisms by which HBOT aids in this setting are similar to those discussed above in osteomyelitis. Promotion of fibroblast growth and angiogenesis seem to be the primary benefits of hyperbaric therapy.

Therapy

Research is positive and ongoing in this field. As with refractory osteomyelitis, appropriate patient selection is paramount. As an example, patients with osteoradionecrosis and exposed mandible, for 6 months or more, are started on a 90-minute regimen of 2.4 atm HBOT for up to 30 treatments. If no improvement or worsening is noted, the patient undergoes local surgical debridement and an additional 10 treatments. Again, if no improvement is seen, the patient will likely undergo mandibular reconstruction with cadaveric bone and an additional 20 hyperbaric treatments.

Interestingly, there has been research toward using HBOT as a prophylactic in prevention of radiation injuries. Again, this has been best studied in the mandible. In 1985, Marx and colleagues showed a reduction in the incidence of osteoradionecrosis from 29.9% to 5.4% when HBOT was used in conjunction with dental extractions in irradiated mandibles.[42] Additional studies in pelvis and neck soft-tissue necrosis have also shown promising results.

One concern expressed by many is the possibility of HBOT enhancing the growth of tumor cells via its effects on angiogenesis or other means. This has been studied, and to date no increased likelihood of tumor recurrence or development has been shown.[43] Feldmeier and associates suggested, after review of 24 papers related to this topic, that the majority of authors found no increase in growth of primary or metastatic lesions.[44]

Compromised Skin Grafts and Flaps

Introduction

HBOT has not found a role in the treatment of normal healing uncompromised skin grafts and flaps. However, it has been studied extensively in tissue compromised by hypoxia or radiation injury, both in the experimental and clinical setting, and has shown significant efficacy.

Most of the experimental studies involve rat tissue. Grafts and flaps studied in a variety of settings, from infection, radiation injury, and hypoxia have shown significant improvement. Proposed mechanisms of improvement are similar to those previously mentioned and appear to include improvement of tissue oxygen tension, reduction of bacterial growth, and increases in angiogenesis. One study proposed the reduction of venular neutrophilic endothelial adherence. This study also suggested that the neutrophil involvement in association with decreased arteriolar vasoconstriction might reduce the risk of tissue death following reperfusion. This was a surprise finding as the authors had considered that HBOT could have, in fact, worsened reperfusion injuries.[45,46]

Case reports and controlled clinical trials have also shown promise in human studies. Greenwood and Gilchrist found improved healing in laryngectomy patients following radiation therapy.[47] Additionally, free flaps and grafts, even those compromised by primary and secondary ischemia, have shown improved survival following hyperbaric therapy. These studies propose similar mechanisms of improvement via enhancement of fibroblast function and neovascularization.

Clinical Features

Surgeons select these patients based on clinical appearance and lack of improvement. No specific clinical criteria exist other than that of the judgment of the treating physician.

Treatments are usually given at a pressure of 2.0-2.5 atm for 90-120 minutes with a recommendation of initial twice-daily therapy until some improvement is seen. Once improvement is noted, therapy is changed to once daily until no further improvement is seen.

Thermal burns

Introduction

Presently, HBOT exists as an adjunctive treatment for patients carefully selected and screened. As burn therapy has changed somewhat dramatically over the past 2 decades, hyperbaric oxygen continues to find its place among the other therapeutic modalities. As discussed with skin grafts and

refractory osteomyelitis, both animal experimental and human clinical trials show promise. Presently, HBOT is recommended for serious second- and third-degree burns.

The pathophysiology of a burn, particularly regarding HBOT, is similar to that of skin grafts and flaps, discussed in the previous section. Hyperbaric oxygen seems to promote healing through the previously mentioned areas of neovascularization, fibroblast and collagen formation, decreased leukocyte adherence to endothelium, and improved tissue oxygenation. In addition, in the animal model, reduction of edema,[48] and preservation of ATP levels have been demonstrated,[49] both of which seemed to speed healing time. As discussed in the section on osteomyelitis, HBOT has shown benefit in reducing existing bacterial infection, and in the case of thermal burns, may in fact be a prophylactic against infection.[50]

Human studies began in 1965, and most have demonstrated decreased hospital stays, improved wound-healing time, and decreased need for surgical grafting. Human studies are often tied to inhalational injuries and both carbon monoxide and cyanide poisoning. In fact, some of these studies have been initiated over concerns of potential pulmonary injury from barotraumas and oxygen toxicity. This study showed no increase in pulmonary disease and indeed demonstrated improved mechanical ventilation weaning, potentially saving up to $60,000 per patient.[51]

This therapy is generally reserved for those patients suffering extensive burns of second or third degree, especially if there is additional concern regarding inhalational injuries. The treating surgeon is often the physician who decides whether to embark on this course of therapy. Often the decision is made intra-operatively if concern is noted regarding the viability of a cutaneous flap or graft.

Treatment

Ideally, treatment is initiated as soon as possible after the injury. Current recommendations include 3 treatments in the first 24 hours of care, followed by twice-daily therapy of 90-120 minutes at 2.0-2.4 atm. There is no upper limit for treatments, but more than 40-50 would be unusual.

Note that ventilators can be used in HBOT patients with some advance preparation as discussed below. Finally, Grube and associates recommended that long transportation to an outside hyperbaric center should be avoided in this population.[52]

Complications, Side Effects, Pearls

Side Effects

Though it is the most common side effect of HBOT, middle ear barotraumas has an incidence reported at only about 2%.[534] In intubated patients, myringotomy or tympanostomy tubes are necessary prior to therapy. It can be prevented in most patients through teaching of ear-clearing techniques and may be assisted with the use of pseudoephedrine.

Sinus squeeze is the second most common HBOT complication and is more often seen in patients who have a concurrent upper respiratory infection or allergic rhinitis. Nasal decongestant sprays, nasal steroids, and antihistamines may aid in prevention.

Patients who undergo repeated daily treatments are at risk of progressive myopia. Fortunately, this is not a permanent effect, and most patients will rapidly restore their normal vision in weeks. One study looked at 26 patients undergoing HBOT for longer than 1 month. Eighteen of the 26 developed myopia ranging from 0.5 to 5.5 diopters. Most patients had rapid reversal within the first few weeks, but some took up to a year to return to normal vision. Of note, no other ocular effects were noted.[54]

A feared but uncommon complication is the development of tension pneumothorax from an existing pneumothorax. This is easily avoided by placement of a chest tube prior to initiation of HBOT.

Another concern patients and physicians express is that of oxygen toxicity. Generally, pulmonary oxygen toxicity will not occur, even in daily exposures, at up to 2.0-2.4 atm over 2.0 or 1.5 hours, respectively. Patients who have airway obstructions are at increased risk for barotraumas during decompression, but otherwise, this is an uncommon occurrence. Neurologic oxygen toxicity manifests as seizures, which again is fairly uncommon. One study of 900 patients receiving HBOT for carbon monoxide exposure showed an incidence of 1.8%.[55] Studies suggest that when seizures do occur, there are no long-term effects. Seizure treatment includes removal of the oxygen mask in a multi-person chamber or decompression in a single-person chamber. Care must be taken to not decompress during the tonic phase of the seizure to avoid pulmonary barotrauma from breath holding.

Summary

Already a well-known primary and adjunctive therapy for a variety of medical and surgical conditions, hyperbarics continues to find new roles. Research, both case controls and randomized, controlled trials, is ongoing and promising. Ongoing research related to HBOT is published quarterly in the journal *Undersea & Hyperbaric Medicine*. The web site for the Undersea and Hyperbaric Medical Society (UHMS) is http://www.uhms.org.

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CME Questions

4. Concerning the onset of symptoms of DCS and AGE, which of the following is true?
   a. DCS typically manifests itself before AGE.
   b. A total of 99% of DCS cases present within the first hour.
   c. Almost half of AGE cases present within 6 hours of surfacing.
   d. More than half the cases of DCS cases present within the first hour after surfacing.

5. The most common side effect of hyperbaric oxygen treatment is:
   a. pulmonary oxygen toxicity.
   b. CNS oxygen toxicity.
   c. middle-ear barotrauma.
   d. progressive myopathy.

6. Concerning carbon monoxide poisoning, which of the following statements is true?
   a. The half-life of CO under hyperbaric conditions is reduced to 23 minutes.
   b. The symptoms of CO poisoning are very specific.
   c. All patients with CO poisoning require hyperbarics.
   d. Pulse oximetry correlates with the severity of CO poisoning.

7. Hyperbaric oxygen's role in wound healing is:
   a. enhancement of leukocyte killing of bacteria.
   b. collagen synthesis.
   c. elimination of oxygen-free radicals.
   e. stimulus of nitric oxide.
   d. All of the above

Answers: 4.(d); 5.(c); 6.(a); 7.(d)

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