

## **ACUTE THERMAL BURN INJURY**

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### **Rationale**

Severe thermal injury is one of the most devastating physical and psychological injuries a person can suffer. Over 2 million burn injuries are brought to medical attention in the United States per year. Of these, there are 14,000 deaths and approximately 20,000 sustain injuries requiring admission to a specialized burn unit.<sup>(1)</sup> About 75,000 patients require hospitalization each year, and 25,000 of those remain hospitalized for more than 2 months.<sup>(2)</sup> The most common mechanisms of burn injury are flame and scalding, and the upper extremity, head and neck are the most common body areas involved.<sup>(3)</sup>

Goals of burn treatment include survival of the patient with rapid wound healing, minimal scarring and abnormal pigmentation, and cost-effectiveness. The optimal outcome is restoration, as nearly as possible, to the pre-burn quality of health and psychological well being.<sup>(4)</sup>

Physiologic responses to a major burn include a fall in arterial pressure, tachycardia, and a progressive decrease in cardiac output and stroke volume. Metabolic responses are complex and include metabolic acidosis and hyperventilation. Cellular adenosine triphosphate levels fall, resting cell membrane potential decreases, and intracellular accumulation of sodium, calcium and water is paralleled by a loss of cellular potassium. Immunologic responses include alteration of macrophage function, and cellular and humoral immunity.<sup>(1)</sup>

The burn wound is a complex and dynamic injury characterized by a central zone of coagulation, surrounded by an area of stasis, and bordered by an area of erythema. The zone of coagulation or complete capillary occlusion may progress by a factor of 10 during the first 48 hours after injury; local microcirculation is compromised to the worst extent 12-24 hours post-burn. Burns are in this dynamic state of change for up to 72 hours after injury.<sup>(1)</sup> Ischemic necrosis quickly follows. Hematologic changes, including platelet microthrombi and hemoconcentration, occur in the postcapillary venules. Edema formation is rapid in the area of the injury; factors include increased capillary permeability, decreased plasma oncotic pressure, increased interstitial oncotic pressure, changes in interstitial space compliance, and lymphatic damage.<sup>(5)</sup> Edema is most prominent in directly involved burned tissues, but also develops in distant, uninjured tissue, including muscle, intestine and lung.

Changes occur in the distant microvasculature including red cell aggregation, white cell adhesion to venular walls, and platelet thromboemboli.<sup>(6)</sup> Inflammatory mediators are elaborated locally in part from activated platelets, macrophages, and leukocytes, contribute to local and systemic hyperpermeability of the microcirculation and appear histologically as gaps in the venular and capillary endothelium.<sup>(7)</sup> This progressive process may extend damage dramatically during the early days after injury.<sup>(8)</sup> The ongoing tissue damage in thermal injury is due to multiple factors including the failure of the surrounding tissue to supply borderline cells with oxygen and nutrients necessary to sustain viability,<sup>(9)</sup> capillary or microvascular occlusion in deeper burns leading to decreased perfusion of the burned tissue, and destruction of lymphatics resulting in

impaired absorption. The impediment of circulation below the injury leads to desiccation of the wound, as fluid cannot be supplied via the thrombosed or obstructed capillaries. Topical agents and dressings may reduce, but cannot prevent, desiccation of the burn wound and the inexorable progression to deeper layers. Altered permeability is not caused by heat injury alone. Oxidants and other mediators (prostaglandins, kinins and histamine) also contribute to vascular permeability. Neutrophils are a major source of oxidants and injury in the ischemia-reperfusion mechanism. This complex process may be favorably effected by several interventions.

A decrease in edema formation has a marked positive proactive impact, especially on the early hemodynamic instability, as well as the later wound conversion from partial to full thickness injury,<sup>(2)</sup> defining a role for the use of adjunctive hyperbaric oxygen therapy as a modulator of inflammation.

### **Infection**

Infection remains the leading overall cause of death from burns. Susceptibility to infection is greatly increased due to the loss of the integumentary barrier to bacterial invasion, the ideal substrate present in the burn wound, and the compromised or obstructed microvasculature that prevents humoral and cellular elements from reaching the injured tissue. Additionally, the immune system is seriously affected, demonstrating decreased levels of immunoglobulins and serious perturbations of polymorphonuclear leukocyte (PMNL) function including a reduction in chemotaxis, phagocytosis and diminished killing ability,<sup>(10)</sup> resulting in increased morbidity and mortality. Patients with specific polymorphisms in the tumor necrosis factor and bacterial recognition genes have a higher incidence of sepsis than the burn injury alone would predict.<sup>(11)</sup>

Regeneration cannot take place until equilibrium is reached; hence, healing is retarded. Prolongation of the healing process may lead to excessive scarring. Hypertrophic scars are seen in only 4% of cases requiring 10 days to heal, but up to 40% of cases requiring longer than 21 days to heal.<sup>(12)</sup> Therapy of burns, therefore, must be directed toward minimizing edema, preserving marginally viable tissue, protecting the microvasculature, enhancing host defenses, and promoting wound closure.

Adjunctive HBO<sub>2</sub> therapy can benefit each of these problems directly, and shows promise in the treatment of inhalation injury.

### **Experimental data**

The efficacy of HBO<sub>2</sub> in the treatment of thermal injury is supported by animal studies and human clinical data. Edema reduction with HBO<sub>2</sub> therapy has been demonstrated in burned rabbits,<sup>(13)</sup> rats,<sup>(14)</sup> mice<sup>(15)</sup> and guinea pigs.<sup>(16,17)</sup> Improvement in healing time has been reported in burned rabbits<sup>(18)</sup> and rats<sup>(19,20)</sup> and decreased infection rates were noted in these models.<sup>(18,19)</sup> In 1970 Gruber demonstrated in a rat model that the area subjacent to a third-degree burn was hypoxic when compared to normal skin and that the tissue oxygen tension could be raised only by oxygen administered at pressure.<sup>(21)</sup> In 1974, Hartwig reported similar findings and additionally noted less inflammatory response.<sup>(14)</sup> Those authors suggested hyperbaric oxygen might be a useful adjunct to the technique of early debridement. Wells and Hilton, in a carefully

designed and controlled experiment, reported a marked decrease (35%) in extravasation of fluid in 40% flame-burned dogs.<sup>(22)</sup> The effect was clearly related to oxygen, and not simply increased pressure. A reduction in hemoconcentration and improved cardiac output were also noted.

Kaiser observed progression of the full thickness burn wound in control guinea pigs, but a decrease in wound size in the HBO<sub>2</sub>-treated animals.<sup>(16,17)</sup> Stewart found similar findings in a burned rat model, confirmed by biopsy.<sup>(23,24)</sup> Germonpre showed decreased extension of burn injury with HBO<sub>2</sub>.<sup>(25)</sup> HBO<sub>2</sub> dramatically improved the microvasculature of burned rats,<sup>(14,19)</sup> and in guinea pigs, earlier return of capillary patency ( $p < 0.05$ ) was demonstrated using an India ink technique.<sup>(26)</sup> Korn also demonstrated faster re-epithelialization ( $p < 0.001$ ) from these regenerative sites in guinea pigs treated with HBO<sub>2</sub> vs. controls. The observed decrease in wound desiccation was felt to be due to preservation of capillary integrity in the HBO<sub>2</sub>-treated animals. Saunders similarly reported improved dermal circulation, preservation of dermal elements, and less collagen denaturation with HBO<sub>2</sub> treatments.<sup>(27)</sup> There was no observed modification of progressive tissue destruction in a pig scald injury treated with HBO<sub>2</sub>.<sup>(28)</sup> One report concluded that HBO<sub>2</sub> provided no advantage over topical antibiotic therapy in controlling bacterial counts in a rat model, but significantly reduced the time to complete epithelial coverage in a partial thickness burn injury.<sup>(20)</sup> The author proposed that HBO<sub>2</sub> alone acted as a mild antiseptic.

The pathophysiologic changes within the burn wound show a striking similarity to those noted in the ischemia reperfusion injury, i.e., depletion of ATP, production of xanthine oxidase, lipid peroxidation, activation of polymorphonuclear cells with subsequent endothelial adherence, and generation of reactive oxygen species (ROS).<sup>(29-32)</sup>

HBO<sub>2</sub> cardiac pre-conditioning (inducing cellular tolerance and protection from ischemia) and adaptive responses resulting in cardio-protection and attenuation of ischemia-reperfusion injury are mediated by HBO<sub>2</sub>-induced ROS (eg., superoxide and hydrogen peroxide), that stimulate the production of nitric oxide. HBO<sub>2</sub>-induced ROS are known to initiate gene expression, reduce neutrophil adhesion (via a decrease in CD11a/18 function, P-selectin, and down-regulation of intracellular adhesion molecule-1), decrease lipid peroxidation, stimulate neovascularization, and increase antioxidants, all resulting in cardioprotection.<sup>(33)</sup> Elucidation of these mechanisms for cardio-protection provides another step toward understanding the mechanisms of benefit with HBO<sub>2</sub> in acute thermal injury.

Data from Zamboni suggest that hyperbaric oxygen is a potent blocker of white cell adherence to endothelial cell walls in skeletal muscle, interrupting the cascade that causes vascular damage.<sup>(34)</sup> The mechanism is felt to be an inhibitory effect on the CD18 locus.<sup>(35)</sup> Germonpre's data support this observation and may explain the beneficial effect of hyperbaric oxygen therapy on the microcirculation previously observed.<sup>(14,23-25,27)</sup>

Stewart and colleagues have shown preservation of or increased levels of ATP in tissue subjacent to partial thickness injury.<sup>(23,24)</sup> These studies may relate directly to the preservation of energy sources for the sodium pump. Failure of the sodium pump is felt to be a major factor in the ballooning of the endothelial cells that occurs after burn injury and subsequent massive fluid losses.<sup>(36)</sup> Shoshani reported no benefit of HBO<sub>2</sub> in a rat burn model where all animals received standard sulfadiazene treatment.<sup>(37)</sup> There was no difference in burn wound size, re-

epithelialization rate, doppler blood flow or healing. In this report, the author stated that this was the first study utilizing standard burn care (topical agents). The findings contradict the study by Stewart's group who utilized silvadene dressings and confirmed preservation of dermal elements.<sup>(23,24)</sup> Bleser and Benichoux, in a very large controlled study in a rat model with 30% BSA burns, reported reduced burn shock and increased survival (fourfold) in HBO<sub>2</sub> treated animals vs. controls.<sup>(38)</sup> Tenenhaus and colleagues showed reduction in mesenteric bacterial colonization ( $p < 0.005$ ) in an HBO<sub>2</sub>-treated burned mouse model.<sup>(39)</sup> Bacterial translocation was felt to be a major source of burn wound infection.

Magnotti, et al, in 2005 proposed an evolution from bacterial translocation to gut ischemia-reperfusion injury after burn injury as the pathogenesis of multiple organ dysfunction syndrome. Systemic inflammation, acute lung injury, and multiple organ failure after a major thermal injury are relatively common causes of morbidity and mortality. In the normal host, the intestinal mucosa functions as a major local defense barrier, a component of multiple defense mechanisms, that helps prevent bacteria that colonize the gut, as well as their products, from crossing the mucosal barrier. After a major thermal injury, and in other clinical and experimental situations, this intestinal barrier function becomes overwhelmed or impaired, resulting in the movement of bacteria and / or endotoxin to the mesenteric lymph nodes and systemic tissues, defined as bacterial translocation. The importance of this intestinal barrier function becomes clear when considering that the distal small bowel and colon contain 10<sup>10</sup> concentrations of anaerobes and 10<sup>5</sup> to 10<sup>8</sup> each of Gram-positive and Gram-negative aerobic and facultative microorganisms per gram of tissue, and enough endotoxin to kill the host thousands of times over.<sup>(40)</sup> Loss of gut barrier function and a resultant gut inflammatory response- lead to the production of proinflammatory factors causing a septic state leading to distant organ failure. Splanchnic hypoperfusion leading to gut ischemia-reperfusion injury appears to be the dominant hemodynamic event triggering the release of biologically active factors into the mesenteric lymphatics. The benefits of the early use of hyperbaric oxygen in burn victims may in part be mediated through amelioration of gut reperfusion injury. The beneficial effects of HBO<sub>2</sub> in ischemic-reperfused tissues have been demonstrated in intestine,<sup>(41)</sup> skeletal muscle,<sup>(34,42)</sup> brain,<sup>(43-45)</sup> and testicular tissue,<sup>(46)</sup> and myocardium.<sup>(47-50)</sup> In a study of severely burned humans (> 30% TBSA), HBO<sub>2</sub>-treated patients compared to controls had increased levels of serum soluble interleukin 2 receptor ( $p < 0.05$ ) and decreased plasma fibronectin ( $p < 0.01$ ), resulting clinically in a lower incidence of sepsis ( $p < 0.05$ ).<sup>(51)</sup>

Total enteral nutrition, starting as early as possible after thermal injury, is recommended for burn patients. It results in decreased morbidity and mortality, and supports intestinal structure and function. Studies of intestinal barrier function biology, pathophysiology and consequences of gut barrier failure demonstrate that the ischemic and / or stressed gut can become a proinflammatory organ<sup>(52)</sup> and gut-derived factors liberated after periods of splanchnic hypoperfusion can lead to acute distant organ, cellular dysfunction, and activation of neutrophils and other proinflammatory cells.<sup>(53)</sup>

Reduction of PMNL killing ability in hypoxic tissue has been well documented.<sup>(54)</sup> The ability of hyperbaric oxygen to elevate tissue oxygen tension and the enhancement of PMNL killing in an O<sub>2</sub>-enriched animal model as demonstrated by Mader<sup>(55)</sup> suggest that this may be an additional benefit of HBO<sub>2</sub>. Hussman et al. have shown no evidence of HBO<sub>2</sub>-induced immunosuppression

in a carefully controlled animal model.<sup>(56)</sup>

In a 2005 randomized controlled study to evaluate effects of HBO<sub>2</sub> on burn wound healing, standard, deep 2<sup>nd</sup> degree burns were produced in male Wistar rats treated with silver sulfadiazine then randomly assigned to either a normoxic, placebo gas or to 2.5 ata HBO<sub>2</sub> for 60 minutes for a total of 21 sessions. HBO<sub>2</sub> had a beneficial effect on post-burn edema (p=0.022), neoangiogenesis (p=0.009), number of regenerative active follicles (p=0.009), and time to epithelial regeneration (p=0.048). There were no significant differences in necrosis staging or margination of leukocytes. The authors conclude that the data support earlier conclusions that HBO<sub>2</sub> is beneficial in the healing of burn wounds.<sup>(57)</sup>

The overwhelming evidence in a large number of controlled animal studies suggests that hyperbaric oxygen reduces edema, prevents conversion of partial to full thickness injury, preserves the microcirculation, preserves ATP and, perhaps secondarily, the sodium pump, improves survival, and may enhance PMNL killing.

### **Clinical Experience**

Beginning in 1965, Wada demonstrated improved healing of burns in carbon monoxide-poisoned coal miners treated with HBO<sub>2</sub>, and continuing with Ikeda, Wada, Lamy, Tabor and Grossman, reports of clinical series began to accumulate.<sup>(13,58-63)</sup> These case series evaluating the use of HBO<sub>2</sub> in wound healing show improved healing,<sup>(58)</sup> decreased length of hospital stay,<sup>(63)</sup> decreased mortality,<sup>(63,64)</sup> decreased overall cost of care,<sup>(63,65)</sup> improved morbidity,<sup>(63)</sup> decreased fluid requirements (30-35%),<sup>(64)</sup> and decreased number of surgeries (p < 0.041).<sup>(65)</sup> Niu reported a large clinical series showing a statistically significant reduction in mortality (p = 0.028) in 266 seriously burned patients who received HBO<sub>2</sub> when compared to 609 control patients.<sup>(64)</sup> He also observed a lower incidence of infection and stated that HBO<sub>2</sub> allowed the burn surgeon more time to more accurately define the extent of injury. Cianci has shown a significant reduction in length of hospital stay in burns up to 39% TBSA.<sup>(66)</sup> Additionally, a reduction in the need for surgery, including grafting, in a series of patients with 40-80% burns when compared to non-HBO<sub>2</sub> treated controls was noted. HBO<sub>2</sub>-treated patients showed an average savings of \$107,000 (36%) per case.<sup>(65,67)</sup>

Hart reported a controlled randomized series showing reduced fluid requirements, mean healing time (p < 0.005), and mortality and morbidity in 10-50% TBSA burn patients treated with HBO<sub>2</sub> when compared to controls and to United States National Burn Information Exchange Standards (68). In a retrospective paired, controlled series of burn patients treated with HBO<sub>2</sub>, Waibren reported increased sepsis, reduced renal function, and decreased circulating white blood cells in control patients, with no effect on mortality.<sup>(69)</sup> However, he noted a 75% reduced need for grafting (p < 0.01) in the HBO<sub>2</sub> group. In a randomized, controlled study of 37 partial thickness burn patients treated with HBO<sub>2</sub> versus 37 controls, Merola reported increased granulation, faster healing and decreased scarring.<sup>(70)</sup> Cianci observed similar results in a series of patients averaging 28% TBSA burns.<sup>(71)</sup> In a small, blinded review, Cianci's group reported a 25% reduction in resuscitative fluid requirements (p < 0.07), and maximum (and percent) weight gain (p < 0.012) in seriously burned (40-80% TBSA) patients treated with adjunctive HBO<sub>2</sub> vs. controls at a regional burn center.<sup>(65,67)</sup> In a small controlled pilot series, Maxwell reported

reduced surgery, resuscitative weight gain, intensive care days, total hospitalization time, wound sepsis, and cost of hospitalization in the HBO<sub>2</sub> group.<sup>(72)</sup> Cianci demonstrated reduced surgeries ( $p < 0.03$ ), length of hospital stay (53%) and cost of care (49%) in 40-80% TBSA burns.<sup>(73)</sup> Hammarlund and colleagues showed reduced edema and wound exudation in a controlled series of human volunteers with UV-irradiated blister wounds.<sup>(74)</sup> In a subsequent similar study, Niezgodá demonstrated reduced wound size ( $p < 0.03$ ), laser doppler-measured hyperemia ( $p < 0.05$ ), and wound exudate ( $p < 0.04$ ) in the HBO<sub>2</sub>-treated group. This study was the first prospective, randomized, controlled, double-blinded trial comparing HBO<sub>2</sub> with sham controls in a human burn model.<sup>(75)</sup>

A 2004 Cochrane Database Systematic Review of the efficacy of HBO<sub>2</sub> for thermal burns<sup>(76)</sup> found that only 2 of 4 identified randomized controlled trials met their inclusion criteria. In the first trial, Brannan reported no differences in length of stay, mortality or number of surgeries between the control and HBO<sub>2</sub>-treated groups.<sup>(77)</sup> In this trial, the failure to demonstrate any reduction in surgical procedures is expected since both groups had early and aggressive excision, thus invalidating not only this study outcome parameter, but also potentially prolonging length of stay. In the post-article discussion section, the authors state that the HBO<sub>2</sub>-treated patients definitely had less fluid loss, were drier, and they appeared to heal earlier. This would support the unreported reduction in overall cost of care in the group treated with HBO<sub>2</sub>. The other trial reported shorter mean healing times in HBO<sub>2</sub> patients (19.7 vs. 43.8 days).<sup>(68)</sup> The reviewers stated that the trials were of poor methodological quality, making it difficult to have confidence in the individual results, and data pooling inappropriate. They concluded that there is insufficient evidence to support or refute the effectiveness of HBO<sub>2</sub> for the management of thermal burns, and called for further research to better define a role for HBO<sub>2</sub>.<sup>(76)</sup>

### **Inhalation injury**

Considerable attention has been given to the use of HBO<sub>2</sub> in inhalation injury due in part to fear that HBO<sub>2</sub> may cause worsening of pulmonary damage, particularly in those patients maintained on high levels of inspired oxygen. The more extensive the burn injury, the higher the incidence of an inhalation injury,<sup>(78)</sup> and pulmonary injury caused by smoke inhalation is the primary cause of fire-related deaths.<sup>(79)</sup> The airway injury can be worsened by a variety of chemical pyrolysis products, depending on the material burned.<sup>(80)</sup> Grim studied products of lipid peroxidation in the exhaled gases in HBO<sub>2</sub>-treated burn patients and found no indication of oxidative stress.<sup>(81)</sup> In comparison with a comparable size burn alone, the combination of a body burn and smoke inhalation injury results in a marked increase in mortality and morbidity, in hemodynamic instability, in burn wound edema, a 30-50% increase in initial fluid requirements, and an accentuation of the degree of lung dysfunction. Ray analyzed high acuity patients being treated for concurrent inhalation injury, thermal injury, and adult respiratory distress syndrome.<sup>(82)</sup> She noted no deleterious effect of HBO<sub>2</sub>, even in those patients on continuous high levels of inspired oxygen. More rapid weaning from mechanical ventilation was possible in the HBO<sub>2</sub>-treated group (5.3 days vs. 26 days,  $p < 0.05$ ). There was a significant reduction in cost of care per case (\$60,000) in the HBO<sub>2</sub>-treated patients ( $p < 0.05$ ). There is no current evidence to controvert these studies.

## **Patient Selection Criteria**

Hyperbaric oxygen therapy is recommended to treat serious burns, i.e., greater than 20% total body surface area and/or with involvement of the hands, face, feet or perineum, that are deep partial or full thickness injury. Patients with superficial burns or those not expected to survive are not accepted for therapy. Transfer of patients for HBO<sub>2</sub> treatment should be considered carefully and should only be to a facility that has both a hyperbaric chamber and a burn unit.

Burns related to methamphetamine manufacture can present to burn units in large numbers, typically involve the face and hands, and are associated with a vague history of explosion. About half experience withdrawal (agitation) followed by hypersomnolence. Some may exhibit hemodynamic instability during HBO<sub>2</sub> treatments (authors' personal observation). Costs for management of these patients are high, imposing significant financial burdens on burn unit hospitals.<sup>(83)</sup>

## **Clinical Management**

**Surgical Perspectives:** Over the past 20 years, the pendulum has swung to an aggressive surgical management of the burn wound, i.e., early tangential or sequential excision and grafting of the deep second-degree and probable third-degree burns, especially to functionally important parts of the body.<sup>(84-85)</sup> Hyperbaric oxygen, as an adjunctive therapy, has allowed the surgeon yet another modality of treatment for these deep second-degree burns, especially including those to the hands and fingers, face and ears, and other areas where the surgical technique of excision is often imprecise and coverage is sometimes difficult. These wounds, not obvious third degree, are then best treated with topical antimicrobial agents, bedside and enzymatic debridement, wound care, and adjunctive hyperbaric oxygen therapy, allowing the surgeon more time for healing to take place and for definition of the extent and depth of injury. Adjunctive hyperbaric oxygen therapy has drastically reduced the healing time in the major burn injury, especially if the wounds are deep second degree.<sup>(64-66,71)</sup>

There is theoretical benefit of HBO<sub>2</sub> therapy for obviously less well-defined third-degree burns.<sup>(17)</sup> Fourth-degree burns, most commonly seen in high voltage electrical injuries, are benefited by reduction in fascial compartment pressures as injured muscle swelling is lessened by preservation of aerobic glycolysis and, later, by a reduction of anaerobic infection.

Finally, reconstruction utilizing flaps, full-thickness skin and composite grafts, i.e., ear to nose grafts, has been greatly facilitated using adjunctive HBO<sub>2</sub>.<sup>(86)</sup> Often the decision to use HBO<sub>2</sub> therapy has been made intraoperatively when a surgeon is concerned about a compromised cutaneous or myocutaneous flap. Patients are, in many instances, prepared preoperatively about the possibility of receiving adjunctive HBO<sub>2</sub> therapy immediately postoperatively. Units planning treatment of burn patients should be experienced in management of critical care patients in the hyperbaric setting and to specific problems of burn patients prior to initiation of a therapy program. Preferably personnel should be certified in burn care and hyperbaric oxygen therapy. The hyperbaric department should function as an extension of the burn unit and part of the "team approach" to burn management.

## **Hyperbaric Oxygen**

Hyperbaric oxygen therapy is begun as soon as possible after injury, often during initial resuscitation. Treatments are attempted 3 times within the first 24 hours and twice daily thereafter on a regimen of 90 minutes of 100% oxygen delivery at 2.0-2.4 atmospheres absolute (atm abs). Early experience in treating children recommended 45 minutes twice daily,<sup>(63)</sup> but more recent extensive clinical use of HBO<sub>2</sub> in children demonstrates that adult protocols are safe. Patients are monitored during initial treatment and as necessary thereafter. Blood pressure can be monitored via transducers or noninvasively using blood pressure cuffs designed for use in monoplace chambers. Patients can be maintained on ventilator support during treatment, which is frequently the case in larger burns with concurrent inhalation injury.

Careful attention to fluid management is mandatory. Initial requirements may be several liters per hour, and pumps capable of this delivery at pressure must be utilized in order to maintain appropriate fluid replacement in the hyperbaric chamber. In larger burn injuries, adequate fluid and electrolyte resuscitation during the first 24 hours can be problematic. Certain patients can develop hypotension shortly after exiting the chamber. Careful volume replacement and assessment of fluid status is mandatory prior to, during, and immediately after HBO<sub>2</sub> treatment. Increasing fluids during ascent may help compensate for any hypovolemia unmasked by the hyperbaric oxygen exposure.

Maintenance of a comfortable, ambient temperature must be accomplished. Thermal instability may be a problem within 1-2 hours of burn wound cleansing and dressing change (depending on the methods used), especially in large TBSA burns. These patients should be carefully assessed prior to an HBO<sub>2</sub> exposure. Febrile patients must be closely monitored and fever controlled as O<sub>2</sub> toxicity is reported to be more common in this group.

In large burns of 40% or greater, treatment is rendered for 10-14 days in close consultation with the burn surgeon. Many partial thickness burns will heal without surgery during this time frame and obviate the need for grafting. Treatment beyond 20-30 sessions is usually utilized to optimize graft take. While there is no absolute limit to the total number of hyperbaric treatments, it is rare to exceed 40-50 sessions, and utilization review is recommended. Concern has been expressed about the use of the carbonic anhydrase inhibitor mafenide (Sulfamylon), and its removal recommended prior to HBO<sub>2</sub> treatment based on the potential for CO<sub>2</sub> build-up leading to vasodilatation.<sup>(87)</sup> Sulfamylon is very seldom utilized in burn centers and at our facility except in select cases (small TBSA, associated infection and/or contraindication to silver sulfadiazene). Its limited use in this setting has not resulted in any observed untoward effects.<sup>(88)</sup> Silver sulfadiazine is the most widely used topical therapy for routine prophylaxis because of its relatively low toxicity and ease of use.<sup>(7)</sup>

In larger TBSA burns, especially of the head and neck, barotrauma may be a problem, and careful attention should be given to this potential complication. The HBO<sub>2</sub> team should make use of early ENT consultation when indicated.

Patients may be treated in a multiplace or monoplace configuration. Movement over long distances is not recommended, and patients should not be transported to a hyperbaric chamber



that is not within the same facility as the burn center.<sup>(89)</sup>

### **Summary**

Future prospects for ideal burn therapy will promote rapid healing while acting as an anti-scarring therapy, enhance “positive” growth hormones and cytokines, and suppress “negative” factors through molecular or genetic manipulation. A logical therapeutic approach would be to block the immediate triggering of the inflammatory cascades that lead to prolonged metabolic imbalances and thereby enhance wound healing. HBO<sub>2</sub> has recently been shown to mobilize stem/progenitor cells in both humans and mice, by stimulation of nitric oxide synthesis causing the release of stem cell factor. Findings suggest that some of the cells mobilized from the bone marrow by HBO<sub>2</sub> may function as de novo endothelial progenitor cells, contributing to wound vasculogenesis, a complement to local angiogenesis. These findings provide new insight into possible mechanisms for the known clinical benefits of hyperbaric oxygen in burn injury.<sup>(90,91)</sup>

Current data show that hyperbaric oxygen therapy, when used as an adjunct in a comprehensive program of burn care, can significantly improve morbidity and mortality, reduce length of hospital stay, and lessen the need for surgery. It has been demonstrated to be safe in the hands of those thoroughly trained in rendering hyperbaric oxygen therapy in the critical care setting and with appropriate monitoring precautions. Careful patient selection and screening is mandatory.

### **Evidence-Based Review**

Twenty experimental animal studies cited in this report support the benefits of HBO<sub>2</sub> treatments in acute thermal injury. Mechanisms of action include edema reduction, amelioration or reduction in ischemia-reperfusion injury, enhancement of leukocyte killing, preservation of ATP, angiogenesis and maintenance of the microcirculation, and epithelial regeneration.

Twenty-two clinical series in this report meet AHA Criteria, 20 demonstrating benefit with the use of HBO<sub>2</sub> in thermal injury. Reported benefits include improved healing, and reductions in hospital stay, morbidity, mortality and hospital-related complications. HBO<sub>2</sub> therapy has been shown to be safe in these reports.

The American Heart Association (AHA) Criteria classifies clinical studies according to the level of evidence.

Level	American Heart Association
1	Randomized, controlled trial, statistically significant
2	Randomized, controlled trial, statistically insignificant
3	Prospective, controlled, non-randomized
4	Historic, non-randomized cohort or case-controlled
5	Human case series

#### **American Heart Association Criteria**

Seven human case series (AHA Level 5) show improved healing of burns, decreased hospital

length of stay, mortality, overall costs in improved morbidity.

One of 2 studies that meet AHA Level 4 criteria noted statistically significant reductions in renal function, circulating leukocytes, and an increase in positive blood cultures in the HBO<sub>2</sub> group. However, there was a 75% decrease in the need for grafting in the HBO<sub>2</sub> group. The other, a small pilot study, reported reduced number of surgeries, resuscitative weight gain, intensive care unit days, total hospitalization time, wound sepsis, and cost of hospitalization in the HBO<sub>2</sub> group.

Eight AHA Level 3 studies show statistically significant benefits with HBO<sub>2</sub> that include decreased mortality, lower incidence of infection, reduction in length of hospital stay, number of surgeries, wound size, wound exudation, resuscitative fluid requirements, and maximum and percent weight gain. Costs savings were also demonstrated. In patients with inhalation injury, HBO<sub>2</sub> did not cause oxidative lung injury as measured by arterial plasma and exhaled gases.

The 2 studies that meet AHA Level 2 criteria show benefit with HBO<sub>2</sub>.<sup>(70,51)</sup> For patients treated with HBO<sub>2</sub>, findings include faster healing and a probable decreased incidence of sepsis ( $p < 0.05$ ) attributed to increased interleukin 2 receptor ( $p < 0.05$ ) and decreased plasma fibronectin ( $p < 0.01$ ) compared to controls.

Three studies meet AHA Level 1 criteria. A 1974, prospective, randomized, controlled, double-blind series of 4 groups of patients stratified by percent TBSA burn showed reduced healing time ( $p < 0.005$ ) and reduced fluid requirements and mortality when the HBO<sub>2</sub>-treated patients were compared to controls and to United States National Burn Information Exchange Standards.<sup>(68)</sup> A 1997 prospective, randomized, controlled, double-blinded trial compared HBO<sub>2</sub> with sham controls in a human burn model. The HBO<sub>2</sub> group was treated at 2.4 ata (100% O<sub>2</sub>) twice daily for 3 days, while the control group received a normoxic gas mix (8.75% oxygen) at 2.4 ata on the same schedule. Day 2 study outcome measurements revealed reduced wound hyperemia ( $p = 0.05$ ), wound size ( $p = 0.02$ ), and wound exudation ( $p = 0.04$ ), in the HBO<sub>2</sub>-treated group. While wound hyperemia and size were not significantly different in the 2 groups by day 6, wound exudation in the HBO<sub>2</sub> group remained lower than controls throughout the duration of the study.<sup>(75)</sup> In a prospective, randomized clinical trial of HBO<sub>2</sub> in a referral burn center of 125 burn patients, the primary outcome variable of the study was length of stay, with secondary outcome measures of mortality and number of surgeries. The authors failed to show any reduction in length of stay, number of surgical procedures or mortality in the HBO<sub>2</sub> treatment group. These results were not unexpected as both groups underwent very early and aggressive excision, thus invalidating not only this important study outcome parameter, but also potentially effecting length of stay. The authors state that they were very impressed when they began to use HBO<sub>2</sub> noting that these patients definitely had less fluid loss, were drier, and appeared to heal earlier. These observations support the unreported reduction in overall cost of care in the group treated with HBO<sub>2</sub>.<sup>(77)</sup>

Of the 22 clinical studies cited in this report, 20 show benefit of the use of HBO<sub>2</sub> for acute thermal injury. The AHA therapeutic intervention classification for thermal injury merits a designation as a "Class IIa" indication for HBO<sub>2</sub>.

## Utilization Review

Utilization review is recommended after 30 hyperbaric oxygen sessions.

## Cost Impact

Burn care is expensive. During 1997-98, in a northern California regional burn center, hospital costs for 20 burn patients averaged \$253,000 (range \$1,100 to \$1.5 million) per patient.<sup>(92)</sup> This includes the cost of hyperbaric oxygen that averaged \$6,360 (range \$1,000 to \$27,500) per patient.

Cost data from the Executive Director of the American Burn Association indicate that for patients who survive 60% total body surface area (TBSA) burns, charges average \$400,000 (in 2003 U.S. dollars) for the hospital stay alone. This does not include operating room time, surgeon's bills, artificial skin, rehabilitation, and other costs that can reach \$500,000 for burns over 80% TBSA.<sup>(93)</sup>

Although not calculated, cost savings as a result of the use of HBO<sub>2</sub> in acute thermal injury are implied in all of the 22 clinical studies in this report by demonstrating reductions in healing time, hospital length-of-stay, and numbers of surgeries including grafting. In 6 of the studies, the authors specifically analyzed costs of care in thermal injury with and without adjunctive HBO<sub>2</sub>, and estimates of average savings in patients treated with HBO<sub>2</sub> range from \$60,000 to \$107,000 per case.

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