

ADJUNCTIVE HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF THERMAL BURNS AND FROSTBITE

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INTRODUCTION

The use of hyperbaric oxygen therapy as an adjunct in the treatment of thermal injury remains a subject of considerable controversy. It is frequently condemned as being too dangerous and/or too expensive for routine use. A comprehensive review of the world literature fails to support these conclusions. Indeed, a significant body of data suggests it is of great benefit. Any therapy should pass scrutiny based on its merits; that is, can it favorably affect the pathology? Will it improve currently accepted results? Is it safe? Is it cost effective? This chapter will explore the specific application of hyperbaric oxygen therapy in the treatment of thermal injury, its relation to the pathophysiology, how it can favorably affect outcome, discuss relevant side effects and complications, and demonstrate its cost effectiveness when utilized as part of a comprehensive program of burn care.

The use of hyperbaric oxygen therapy in the treatment of thermal burns began in 1965 when Ikeda and Wada noted more rapid healing of second-degree burns in a group of coal miners being treated for carbon monoxide poisoning.(51) They followed this serendipitous observation with a series of experiments that demonstrated a reduction of edema and improved healing in animal studies.(26) The Japanese experience (25-27,50,51) stimulated interest in other countries, and there followed a series of reports of uncontrolled clinical experience with favorable results.(32,48) In 1970 Gruber, (18) (Figure 1) working at the U.S. Army biophysics laboratory at the Edgewood Arsenal in Maryland, devised a series of experiments placing rats in a hyperbaric chamber breathing 100% oxygen at sea level and at 2 and 3 atmospheres, respectively. He demonstrated that the area subjacent to a third-degree burn was hypoxic when compared to normal skin and that the tissue oxygen tension could only be raised by oxygen administered at pressure. This important study suggested that hyperbaric oxygen therapy could have a direct effect on the pathophysiology of the burn wound.

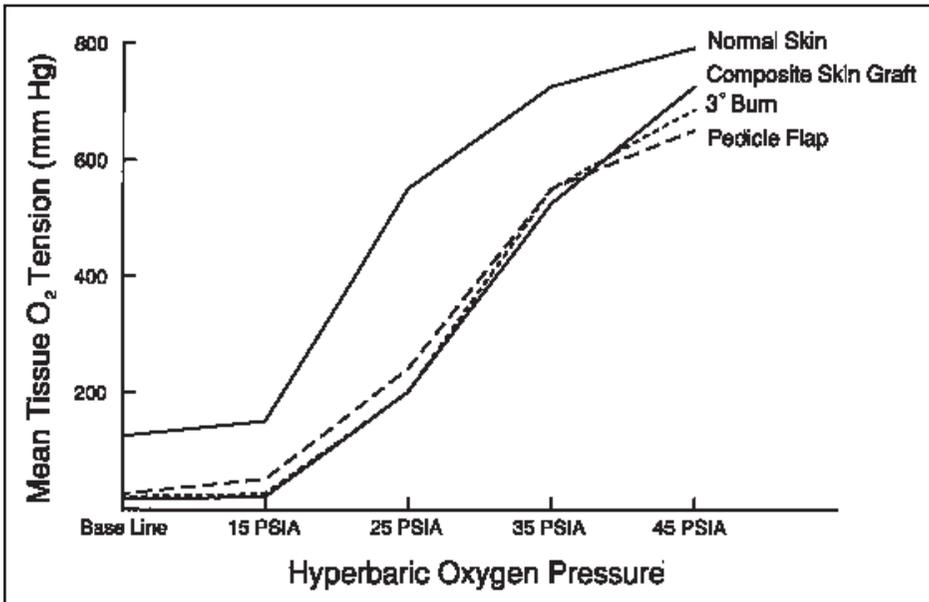


Figure 1. Tissue Oxygen Tension

Mean oxygen tension of normal skin and various hypoxic tissues as a function of hyperbaric oxygen pressure. Note: Oxygen tension rises in burned skin only with increasing pressure.

PATHOPHYSIOLOGY

In order to understand the rationale for therapy, it is necessary to review the physiology of the thermal injury. 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. 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 but also develops in distant, uninjured tissue. There are also changes occurring in the distal microvasculature where red cell aggregation, white cell adhesion to venular walls, and platelet thrombo-emboli occur.(6) "This progressive ischemic process, when set in motion, may extend damage dramatically during the early days after injury."(22) The ongoing tissue damage seen in thermal injury is due to the failure of surrounding tissue to supply borderline cells with oxygen and nutrients necessary to sustain viability.(4) 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.

INFECTION

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 which 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, (1,2,15,50) including disorders of chemotaxis, phagocytosis, and diminished killing ability. These functions greatly increase morbidity and mortality; infection remains the leading cause of death from burns.

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 about 4% of cases taking 10 days to heal, in 14% of cases taking 14 days or less, in 28% of cases taking 21 days, and up to 40% of cases taking longer than 21 days to heal.(12) Therapy of burns, then, is directed towards minimizing edema, preserving marginally viable tissue, protecting the microvasculature, enhancing host defenses, and providing the essential substrate necessary to sustain viability.

EXPERIMENTAL EVIDENCE

A significant body of animal data support the efficacy of hyperbaric oxygen in the treatment of thermal injury. Ikeda noted a reduction of edema in burned rabbits.(26) Ketchum in 1967 reported an improvement in healing time and reduced infection in an animal model.(30) He later demonstrated dramatic improvement in the microvasculature of burned rats treated with hyperbaric oxygen therapy.(29) In 1974 Hartwig (21) working in Germany reported similar findings and additionally noted less inflammatory response in those animals that had been treated with hyperbaric oxygen. He suggested at that time that hyperbaric oxygen might be a useful adjunct to the technique of early debridement. Wells and Hilton, (53) in a carefully designed and controlled experiment, reported a marked decrease in extravasation of fluid in a series of dogs with 40% flame burns. The effect was clearly related to oxygen and not simply increased pressure (Figure 2). They additionally reported a reduction in hemoconcentration and improved cardiac output in oxygen-treated dogs. Nylander (39) in a well-accepted animal model showed that hyperbaric oxygen therapy reduced the generalized edema associated with burn injury (Figure 3).

Kaiser (28) showed that hyperbaric oxygen treatment resulted in shrinkage of third-degree (full thickness) injury in a rabbit model. Untreated animals demonstrated the expected increase in wound size during the first 48 hours. Treated animals showed shrinkage of their wounds. At all times treated animal wounds remained smaller than those of the controls (Figure 4).

Korn and colleagues (31) in 1977 showed an early return of capillary patency in the hyperbaric-treated animals using an India ink technique. He also demonstrated survival of the dermal elements and more rapid epithelialization from these regenerative sites. He suggested the decreased desiccation of the wound he observed was a function of subjacent capillary integrity

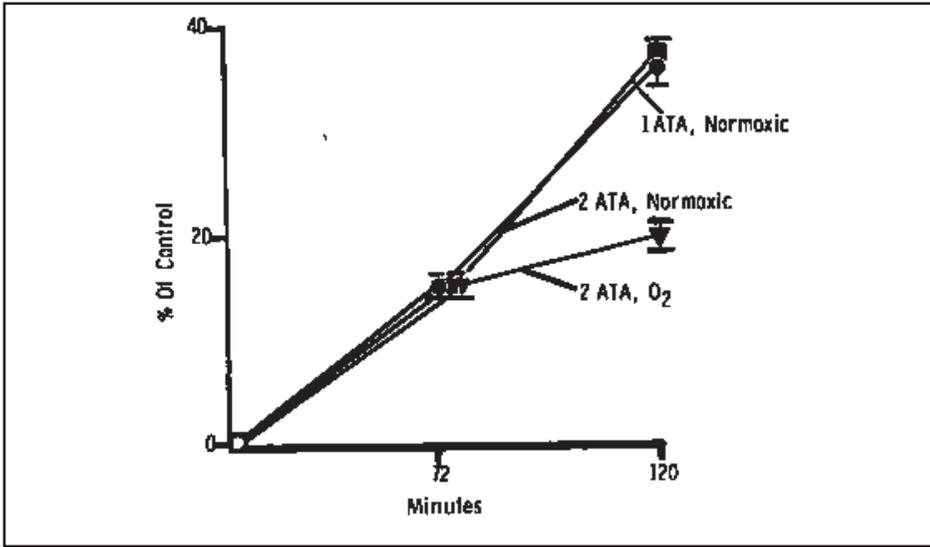


Figure 2. Plasma Volume Losses

Plasma volume losses after burn in untreated animals (1 ATA, normoxic), animals exposed to hyperbaric oxygen (2 ATA O₂) and to pressure alone (2 ATA, normoxic).

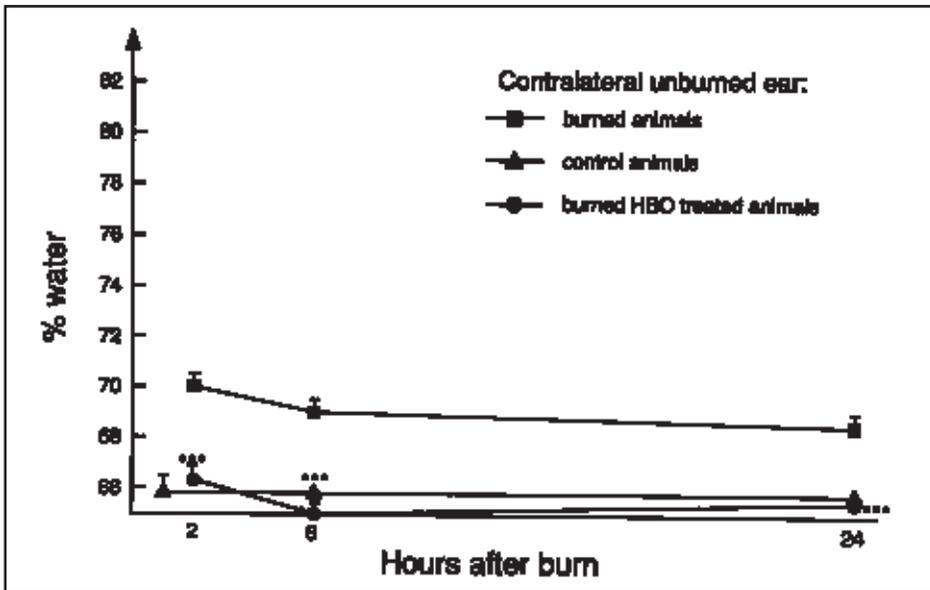


Figure 3. Water Content of the Contralateral Unburned Ear

Water content (\pm SEM) of the contralateral unburned ear in burned animals with and without HBO treatment.

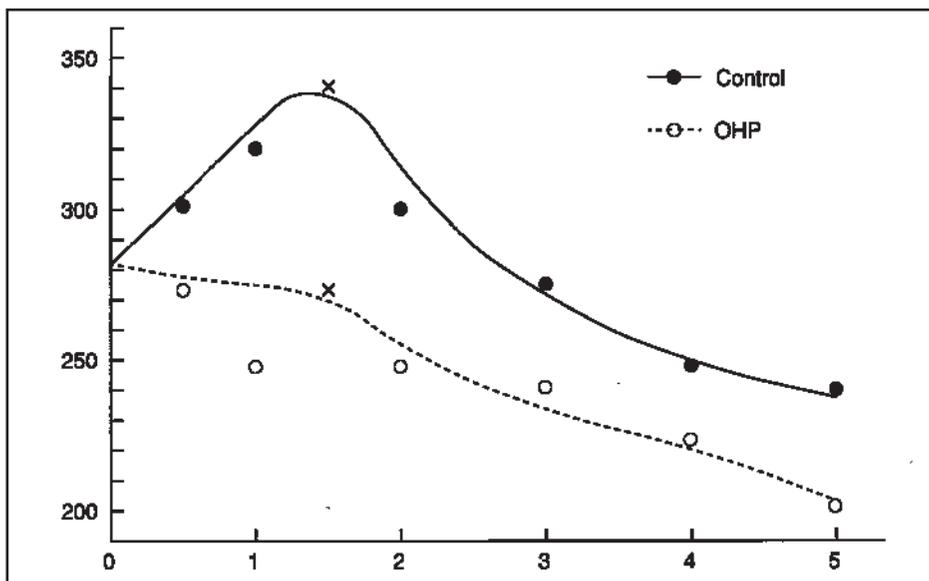


Figure 4.

Kaiser demonstrated in a full thickness animal model a significant reduction of wound size in the hyperbaric-treated animals vs. an increase in the control group, which remained larger at all times measured. (28)

noted in the HBO-treated animals. Saunders (44) and colleagues have shown similar results. They have also reported an improvement in collagen synthesis in HBO-treated animals. Perrins failed to show a beneficial effect in a small scald wound in a pig model treated with HBO.(41) Niccole (36) in 1977 reported that HBO offered no advantage over topical agents in controlling wound bacterial counts. He proposed that HBO acted as a mild antiseptic. His data, however, supported the observation of improved healing of partial thickness injury noted by earlier investigators. Stewart (46,47) and colleagues subjected rats to a controlled burn wound resulting in a deep partial thickness injury. Both experimental groups were treated with topical agents. The hyperbaric oxygen treated group showed preservation of dermal elements, no conversion of partial to full thickness injury, and preservation of adenosine triphosphate (ATP) levels; whereas, the untreated animals demonstrated marked diminution in ATP levels and conversion of partial to full thickness injury (Figures 5, 6).

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.(3) Bleser (5) in 1973 in a very large controlled series reported reduction of burn shock and a fourfold increased survival in 30% burned animals vs. controls. Reduction of PMNL killing ability in hypoxic tissue has been well documented by Hohn et al.(23) The ability of hyperbaric oxygen to elevate tissue oxygen tension and the

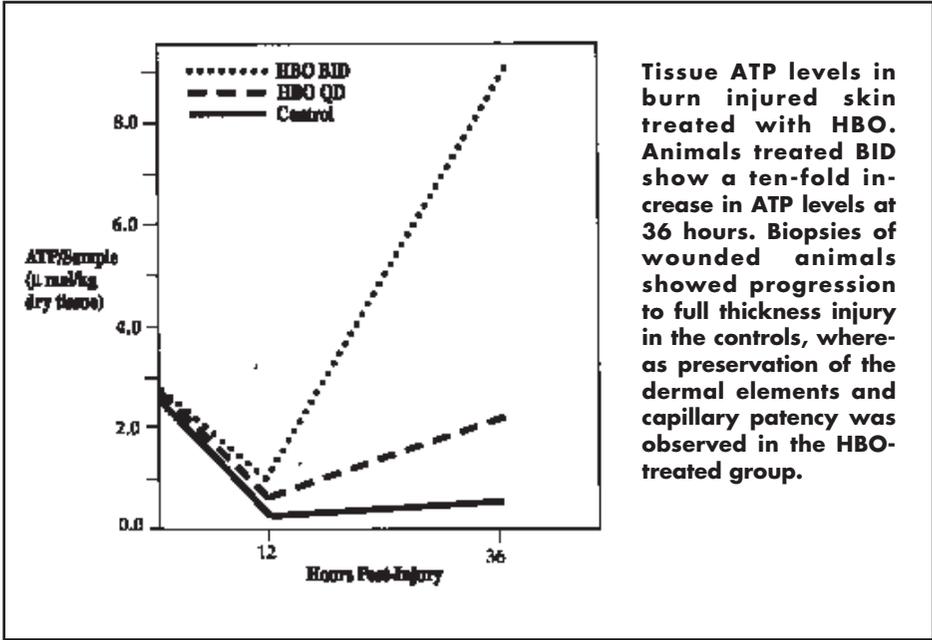
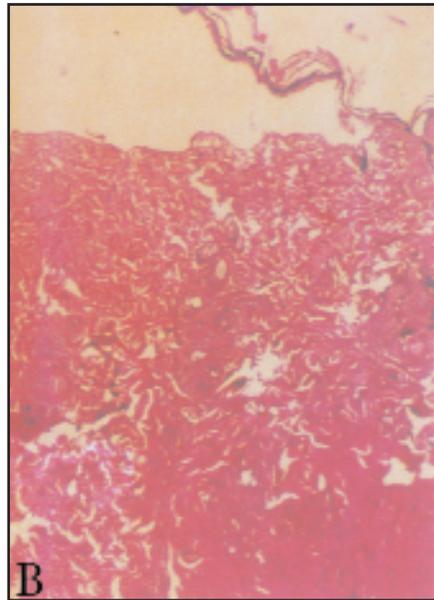
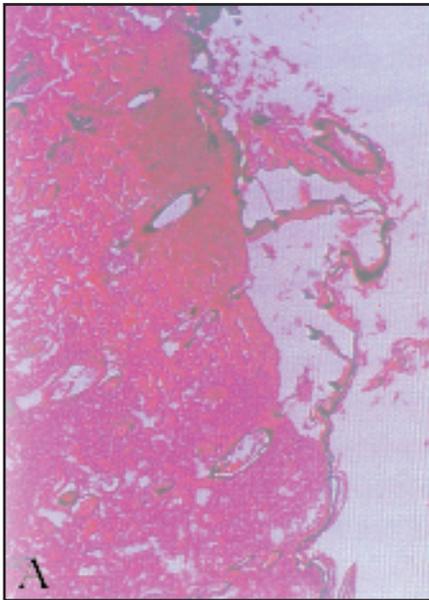


Figure 5. Rats: Burn with Silvadene Dressing



Figures 6A and 6B. Partial Thickness Burns

Biopsy of experimental partial thickness burns at five days.
(A) HBO-treated animals show preservation of the dermal elements.
(B) Nontreated animals show coagulation necrosis.

enhancement of PMNL killing in an O₂ enriched animal model as demonstrated by Mader (33) suggests that this may be an additional benefit of HBO. Recent data from Zamboni (55) suggest that hyperbaric oxygen is a potent blocker of white cell adherence to endothelial cell walls, interrupting the cascade which causes vascular damage. The mechanism is felt to be an inhibitory effect on the CD18 locus.(56) Germonpre's data tends to bear out this observation and may explain the beneficial effect of hyperbaric oxygen therapy on the microcirculation previously observed. (13,21,44,46,47) Shoshani reported no benefit of HBO in a rat model where all animals received standard sulfadiazene treatment.(45) There was no improvement reported in Doppler studies of blood flow, epithelialization, or wound contraction. All groups were treated with topical agents. The authors postulated that hyperbaric oxygen added little to the topical therapy. These data are not in agreement with the report by Stewart, who also treated all animals with topical burn therapy. Hussman et al. have shown no evidence of immunosuppression in a carefully controlled animal model.(24) Tenenhaus and colleagues showed reduction in mesenteric bacterial colonization in a hyperbaric oxygen treated mouse model.(49) Intestinal villus damage was also minimized in the hyperbaric oxygen group. Bacterial translocation the gut is felt to be a major source of infection in burn sepsis. Thus, 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, though not yet proven, may enhance PMNL killing.

CLINICAL EXPERIENCE

Beginning with the reports of Wada in 1965 and continuing with Ikeda, (25-27,50,51) Lamy, (32) and Tabor, (48) reports of clinical series began to accumulate. In 1974 Hart (20) reported a controlled, randomized series showing a reduction of fluid requirements, faster healing, and reduced mortality when his patients were compared to controls and to U.S. National Burn Information Exchange standards. Waisbren (52) in 1982 reported a reduction in renal function, a decrease in circulating WBCs, and an increase in positive blood cultures in a retrospective series of patients who had received hyperbaric oxygen therapy. He stated he could demonstrate neither a salutary nor deleterious effect; however, his data showed a 75% decrease in the need for grafting in the hyperbaric treated group. Grossman and colleagues (16,17,54) have reported a very large clinical series showing improved healing, reduced hospital stay, and reduced mortality. Merola (35) in 1978 in a randomized study reported faster healing of partial thickness burns in 37 patients treated with HBO vs. 37 untreated controls. Niu and his associates (38) from the naval burn center in Taiwan have reported a very large clinical series showing a statistically significant reduction in mortality in 266 seriously burned patients who received adjunctive hyperbaric oxygen when compared to 609 control patients who did not receive this additional modality of therapy. Hammarlund and colleagues (19) have reported a reduction of edema and wound exudation in a carefully controlled series of human volunteers with ultraviolet irradiated blister wounds (Figure 7).

The author has shown a significant reduction in length of hospital stay in burns of up to 39% total body surface area (Table 1).(9) Additionally, a reduction in the need for surgery, including grafting, in a series of patients with up to 80% burns was noted when they were compared to non-HBO treated controls (Table 2).

HBO-treated patients in this study experienced an average savings of \$95,000 per case.(7) In a series of patients with burns of up to 50% TBSA averaging 28% total body surface area injury, similar results were obtained.(11) In a retrospective, blinded review, this same group examined resuscitative fluid requirements in a group of severely burned patients. A 25% reduction in resuscitative fluid administration and a statistically significant reduction in maximum weight gain and percent weight gain was noted in the hyperbaric oxygen-treated group vs. the controls.(8) Maxwell and colleagues in 1991 reported a small controlled series showing a reduction of surgery, resuscitative weight gain, intensive care days, total hospitalization time, wound sepsis, and cost of hospitalization in the hyperbaric oxygen-treated group.(34) Data from our facility demonstrate continuing improvement in outcome of large burns with a reduction of surgeries of 86% ($p < 0.03$). (10) Niezgoda and colleagues have demonstrated a similar reduction of wound exudate and wound size in a randomized, blinded human study utilizing normoxic controls (Figure 8).(37)

Considerable attention has been given to the use of hyperbaric oxygen in inhalation injury. There is fear that it may cause worsening of pulmonary damage, particularly in those patients maintained on high levels of

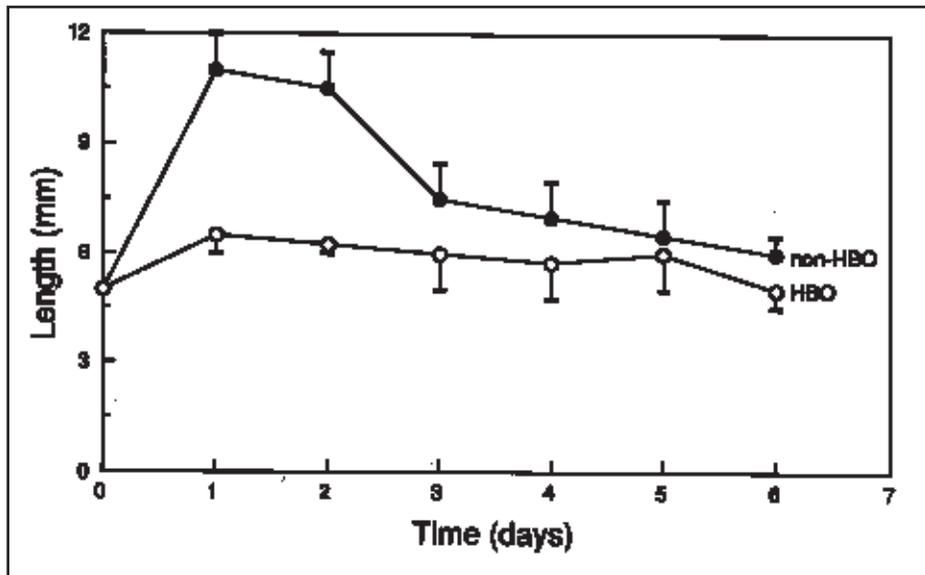


Figure 7. Maximum Length Including Edema

Maximum length (including edema adjacent to the wound) (mean \pm s.d.) of u.v.-irradiated (\bullet) and HBO-treated U.V.-irradiated (\circ) blister wounds as a function of time. The value on day 0 is approximately the diameter of the suction cup used to create the blister. ($p < 0.05$)

inspired O₂. Grim et al., (14) have studied products of lipid peroxidation in the exhaled gases in HBO-treated burn patients and found no indication of oxidative stress. Ray et al., (42) have analyzed serious burns being treated for concurrent inhalation injury, thermal injury, and adult respiratory distress syndrome. She noted no deleterious effect, even in those patients on continuously high inspired oxygen. More rapid weaning from mechanical ventilation was possible in the HBO-treated group (5.3 days vs. 26 days, $p < 0.05$). A significant saving in cost of care per case (\$60,000) was effected in the HBO-treated patients ($p < 0.05$). There is presently no evidence to controvert these studies.

TABLE 1. COMPARISON OF FACTORS IN HBO AND NON-HBO GROUPS IN PATIENTS WITH 18-39% TBSA

VARIABLE	HBO (N=8)	CONTROL (N=12)	
Age			
Average	29.5	30.9	
Range	16-47	18-42	$p < 0.57$ NS
Standard Deviation	9.6	8.5	
Total Body Surface Burn (%)			
Average	24.0	25.8	
Range	20-33	18-39	$p < 0.91$ NS
Standard Deviation	4.3	7.6	
Full Thickness Injury			
Average	5.2	5.6	
Range	0-18	0-20	$p < 0.96$ NS
Standard Deviation	6.1	6.2	
Surgeries			
Average	1.3	1.7	
Range	0-2	0-3	$p < 0.42$ NS
Standard Deviation	0.88	1.2	
Days Hospitalized			
Average	20.8	33.0	
Range	16-33	16-58	$p < 0.012$ *
Standard Deviation	6.7	13.1	
Cost of Burn Care			
Average	\$44,838	\$55,650	
Range	\$27,600-	\$21,500	$p, 0.47$ NS
	\$75,500	\$98,700	
Standard Deviation	\$9,200	\$11,300	
<i>NS, Not Significant</i>			
<i>*$p < .012$, significant (Mann-Whitney U test)</i>			

TABLE 2. COMPARISON OF CONTROLS AND HBO TREATED PATIENTS WITH 40-80% TBSA BURNS

Variable	Control (n=7)	HBO (n=11)	HBO Since '87 (n=6)
Age			
Average	26	31.3	35
Range	14-24	20-60	24-60
Total Body Surface Burn (%)			
Average	48%	61.8%	60%
Range	40-60%	45-80%	40-80%
Days Hospitalized			
Average	108	51.8	44.6
Range	47-184	22-95	22-80
Cost of Burn Care			
Average	\$391,000	\$215,000	\$200,000
Range	\$151,000- 801,000	\$72,000- 350,000	\$76,000- 394,000
Surgeries			
Average	7.8	2.1	1.1
Range	3-12*	0-6*	0-6*
Average HBO Tx			
Average	0	40	32
Range		13-77	13-64
HBO Cost*			
Average	0	\$16,600	\$17,000
Range		\$5,000- \$23,000	\$5,000- \$27,000
% Reduction			
Days Hospitalized		53	86
Surgeries		73	59
Care cost		46	49
<i>*p<0.03</i>			

Brannan et al. (7a) failed to show any reduction in length of stay or the number of surgical procedures in a recent study. The failure to demonstrate any reduction in surgical procedures is not surprising as both groups underwent very early and aggressive excision, thus invalidating an important study parameter. There was, however, a reduction in overall cost of care in the group treated with hyperbaric oxygen.

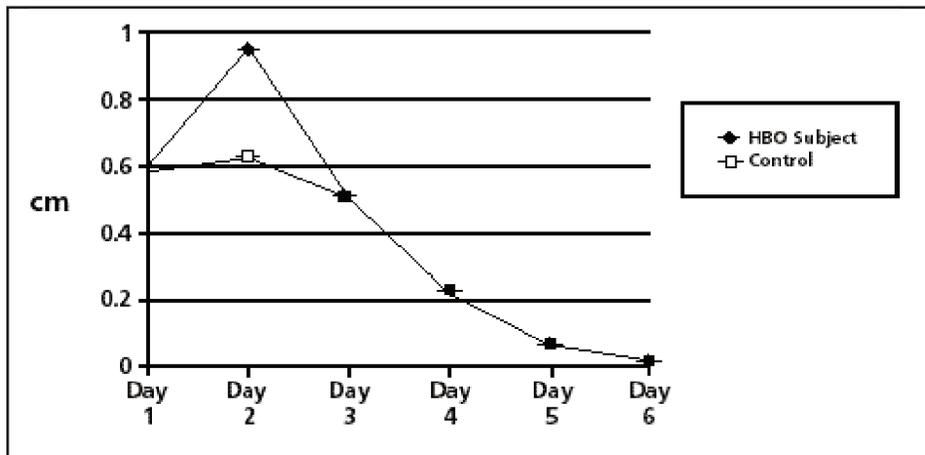


Figure 8. Hyperbaric Oxygen Therapy for Burns

Wound size measurements (cm) of ultraviolet-irradiated suction blister wounds in control group (□) and hyperbaric oxygen group (◆).

SURGICAL PERSPECTIVES

Over the past 30 years, the pendulum has rapidly 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 third-degree burns, especially to functionally important parts of the body.^(24a,44a) Hyperbaric oxygen, as adjunctive therapy, has allowed the surgeon another modality of treatment for these deep second-degree or so-called “indeterminant burns” of the hands and fingers, face and ears, and other areas where the surgical technique of excision and coverage is often difficult and imprecise. These wounds, not obvious third degree, are then best treated with topical antimicrobial agents, bedside and enzymatic debridement, and adjunctive hyperbaric oxygen therapy, allowing the surgeon more time for healing to take place and definition of the extent and depth of injury (Illustrations 1, 2).⁽⁹⁾ Adjunctive hyperbaric oxygen therapy has drastically reduced the healing time in the major burn injury, especially if the wounds are deep second degree (Illustration 3).^(7,9,10,34) There is some theoretical benefit of hyperbaric oxygen therapy for obviously less well defined third-degree burns.⁽²⁸⁾ Fourth-degree burns, most commonly seen in high voltage electrical injuries, are benefited by reduction in fascial compartmental pressures and need for fasciotomies as injured muscle swelling is lessened by preservation of aerobic glycolysis and, later, by a significant 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 this technique. Often the decision to use hyperbaric oxygen has been made intraoperatively as the surgeon is concerned about a compromised cutaneous or musculocutaneous flap. Patients are, in many instances, prepared preoperatively about the possibility of receiving this form of adjunctive therapy immediately after surgery.

PATIENT SELECTION

Hyperbaric oxygen therapy is presently utilized to treat serious burns, i.e., greater than 20% total body surface area, deep partial or full thickness injury, or with involvement of the hands, face, feet, or perineum. Patients with superficial burns or those not expected to survive are not accepted for therapy.

TREATMENT PROTOCOLS

We utilize a twice-a-day regimen of 90 minutes at 2 atmospheres plus descent and ascent time. Treatments typically take 105 minutes. Treatment is rendered as soon as possible after injury, often during initial resuscitation.



Illustration 1

- A. 23-year-old white female with facial burns from flaming gasoline and tar 12 hours after injury.**
- B. 24 hours later (36 hours after injury) after two HBO treatments. Note resolution of edema.**
- C. 72 hours later (84 hours after injury) after six HBO treatments.**
- D. Shortly before discharge.**



Illustration 2

- A.** A deep partial thickness of hand in 30-year-old male with 60% total body surface burn and inhalation injury, on admission.
- B.** Six days later.
- C.** At surgery, light debridement.
- D.** Immediately after surgery. Note preservation of dermal appendages.
- E.** Two weeks after admission. Note re-epithelialization.
- F.** Appearance on discharge 25 days post-injury. Healed without grafting.

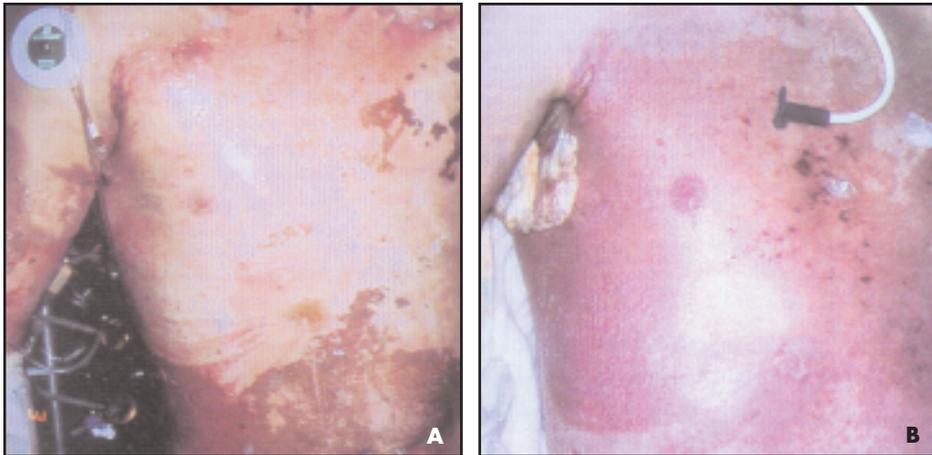


Illustration 3

A. 19-year-old white male with flame burn of chest from burning clothing estimated to be deep partial-to-full-thickness burn.

B. One month later with no grafting required. Patient received adjunctive HBO therapy twice daily.

Patients are carefully monitored during initial treatments until stable and as necessary thereafter. Children are treated for 45 minutes twice a day.⁽¹⁶⁾ In the monoplace configuration, we are now able to monitor blood pressure non-invasively using a special cuff. We attempt to treat three times in the first 24 hours and BID thereafter. Treatments are rendered twice during a normal workday, that is, a normal 8-10 hour period. Careful attention to fluid management is mandatory. Initial requirements of burn patients may be several liters per hour, and pumps capable of this delivery at pressure must be utilized in order to maintain appropriate fluid replacement. Patients can be maintained on ventilatory support during treatment. This is frequently the case in larger burns. Maintenance of a comfortable ambient temperature must be accomplished, and treating patients within two hours of tubing or dressing changes is not recommended as temperature control may be difficult. Febrile patients must be closely monitored and fever controlled as O₂ toxicity is reported to be more common in this group. We have not observed evidence of O₂ toxicity in the patients we have treated.

Patients may be treated in a multiplace or monoplace hyperbaric chamber. Monoplace chamber treatment appears to be easier in terms of maintaining the patient environment, especially in head and neck burns. A multiplace chamber is obviously preferable, if available, for those patients who are hemodynamically unstable. Movement over long distances is not recommended. Patients should not be transported to a hyperbaric chamber that is not within the burn center facility. Careful attention to infection control is mandatory. In large burns of 40% Total Body Surface Area (TBSA) 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 30

sessions is usually utilized to ensure graft take. While there is no absolute limit to the number of hyperbaric treatments rendered, it is rare to exceed 40-50 except in very unusual circumstances.

SIDE EFFECTS

Barotrauma to the ears is common, particularly in burns of the head and neck.⁽⁴³⁾ Routine ear, nose, and throat (ENT) evaluation and early myringotomy is recommended in this subset of patients. We have established capabilities for myringotomy in our hyperbaric unit as this will often facilitate more rapid and more comfortable treatment.

In larger burn injuries, adequate fluid and electrolyte resuscitation during the first 24 hours can be problematic. Certain patients have developed hypotension shortly after exiting the chamber. We feel this represents hypovolemia that was masked during hyperbaric oxygen treatments. Careful volume replacement and assessment is mandatory prior to, during, and immediately after hyperbaric treatment. We have elected to increase fluids during ascent to compensate for any masked hypovolemia. We have not seen O₂ seizures or pulmonary toxicity in our patients.

RECOMMENDATIONS

We recommend that units planning treatment of burn patients be thoroughly versed in the management of critical care patients in the hyperbaric setting and to the peculiar problems of burn patients prior to initiation of a therapy program. Patients with severe burns are among the most challenging encountered in medicine. The hyperbaric team must be experienced in the management and monitoring of central lines, ventilators, and all aspects of critical care in the hyperbaric chamber. HBO treatment must be carefully coordinated to work around the busy schedule of the burn center. Our hyperbaric department is an extension of the burn center. Our personnel are trained in burn care and hyperbaric medicine and are an integral part in the "team approach" to burn care.

SUMMARY

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.

FROSTBITE

Much has been said about frostbite injuries through the ages. Napoleon's problems are well known and often quoted in the literature, (13f) but the basic mechanism has remained little understood. As burns were once thought merely to represent direct thermal injury to cells, the mechanism of frostbite injury has been thought to be a direct effect of freezing on the tissue cells. At various times, ice crystals, either intracellular or extracellular, were thought to be the main cause of cellular damage.(19f) The outcome of frost-

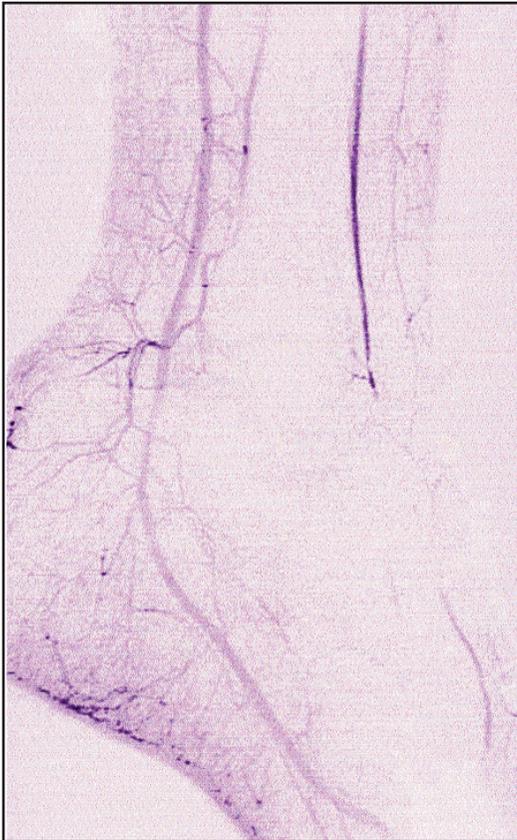


Illustration 4

Arteriogram of young, active-duty army soldier with a severe frostbite injury. Note occlusion of dorsalis pedis artery.

Photo courtesy of Dr. Bill Clem of the Hyperbaric Medicine Center, Presbyterian/St. Luke's Medical Center, Denver, Colorado.

bite injury was inevitable; and the basic treatment has been to thaw the tissue, cover it with a sheet, wait, and debride or amputate everything that turns black.(11f) Even in recent years, much effort has been made to speed up the amputation process by the use of nuclear imaging techniques to predict the level of needed amputation so the "wait" phase can be eliminated.(8f,15f) This has done little to provide insight into the mechanism of frostbite injury much less provide needed treatment options to prevent rather than to predict amputation.

The mechanism of frostbite injury on a cellular level is much more complex than previously believed. When a frozen limb is initially thawed, it appears viable; and various studies have shown that blood flow is reinstated after thawing.(12f,22f) Over the next few days, however, there is a process of progressive ischemia which can result in tissue necrosis depending on the severity of the injury. It is this progressive tissue ischemia which is most interesting. The pathophysiology of

ischemia-reperfusion injury is well studied and well described. (5f,7f,21f) Several studies have shown that many of the characteristics of frostbite pathophysiology are similar to ischemia-reperfusion injury, although they may be seen at different times in the injury process.(22f) These include neutrophil adhesion to the endothelial wall, breakdown of the endothelial cell membrane, erythrocyte extravasation, production of potent vasoconstrictors such as thromboxane A2 and prosta-glandin F2a, free radical generation, and the amelioration of some tissue damage with free radical scavengers such as deferoxamine and superoxide dismutase (SOD). (1f,10f,14f) Additionally, several studies have found that thrombus formation may play a significant role in the later stages of the ischemic injury process.

Although better understood than frostbite, it has been difficult to clinically intervene in the process of ischemia-reperfusion injury. This is partially due to the inability to stage the process in any individual patient. Likewise in frostbite injury, each patient may be in a different stage of injury and the degree of tissue injury varies from virtually uninjured to severely affected. The successful use of deferoxamine, SOD (at least experimentally), selective prostaglandin inhibitors, and thromboxane A2 inhibitors in frostbite treatment is encouraging.(10f,14f) One very interesting study by Salimi et al. (17f) as well as other studies (20f) have demonstrated extensive vascular thrombosis and subsequent tissue salvage using thrombolytic agents. Other clinical evidence, including emergent arteriography in recently thawed frostbite patients, has shown significant vascular thrombus formation, even in larger arteries such as the dorsal pedis artery (Illustration 4).(1f,4f,6f,18f) Unlike cardiac thrombolytic therapy where a guide wire can be used to first cannulate a thrombus, thrombolytic therapy in small and microvascular structures is more difficult due to the limited "face" that the clot presents to the thrombolytic agent. It may be that anticoagulation therapy, if given early in the process, can prevent the formation of microvascular thrombus. At present, there is sufficient clinical and experimental evidence to support the use of selective prostaglandin inhibitors (ibuprofen), deferoxamine, thromboxane A2 inhibitors (topical aloe vera), and anticoagulation in certain patients. Selective thrombolytic therapy may be beneficial if there is arteriography documented occlusion and the agent can be infused over many hours. Hyperbaric oxygen therapy, if used early and aggressively, may be beneficial when added to a regimen designed to minimize the production of vasoconstrictive agents and free radicals, limit endothelial damage, and prevent thrombosis. Hyperbaric oxygen therapy has been shown to increase capillary diffusion distance in ischemic tissue, helping to salvage marginal tissue until recanalization occurs. It also has been proven to reduce free radical production, stabilize and reverse lipid peroxidation of the cell wall, and prevent neutrophil adhesion to the endothelium, a major contributor to ischemia-reperfusion injury.(2f,3f,9f,55) Objections to its use have been made when it has been erroneously said to cause vasoconstriction and reduction of blood flow.(16f) This only occurs in healthy tissue. HBO actually reverses vasoconstriction in ischemic tissue.(20f) In all cases the hyperoxia induced by HBO overwhelms any potential reduction in blood flow. The benefits of hyperbaric oxygen therapy greatly outweigh any potential deleterious effects.

While it would be satisfying to recommend a single treatment for frostbite, it is clear that the mechanism is a cascade of causative factors. As different portions of the injured tissue are likely to be at different stages of injury, it is likely to be necessary to use a combination of agents, each intervening at a different stage of the injury. What is clear is that amputation should be considered an outcome, not an intervention.

The similarities of frostbite to thermal burns and reperfusion injury suggest that application of adjunctive hyperbaric oxygen in the treatment of frostbite, particularly if utilized in the early stages of injury, may prove an area of fruitful investigation.

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