Hyperbaric Oxygen Therapy – An Adjunct to Optimal Combat Trauma Management

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INTRODUCTION

Although wound statistics from Operation Iraqi Freedom are still being analyzed, a preliminary analysis of casualty data demonstrates that approximately 70% of the injured combatants sustained trauma to their extremities.(Malcolm 2004) During the acute management of these injuries at Echelon II and III medical facilities, approximately 75 - 100 major vascular reconstructions and 180 limb amputations were performed. Anecdotal reports reveal that a number of the wounded combatants required tissue grafting, flap reconstruction, revision amputation or treatment for resistant infection subsequent to their evacuation to tertiary care facilities. Indeed, of the 560 surgical procedures performed for combat related injuries aboard the USNS Comfort, approximately 31% were noted to be sufficiently complicated by persistent tissue necrosis, wound infection, graft failure or delayed wound healing that further surgical management was required.(Helmers 2004) Residual ischemia has been shown to play a role in each of these processes. Hyperbaric Oxygen (HBO_2) has been shown to be an effective in reversing ischemia and limiting wound healing complications in hospital-based, clinical care settings. It is proposed that HBO_2 therapy could be applied in Echelon II and III operational environments to similarly limit the extent of surgical debridements, improve tissue flap and graft survival, decrease wound infection rates, speed complex wound healing and, ultimately, reduce the morbidity experienced by wounded combatants. This paper discusses the physiologic mechanisms underlying HBO_2 therapy's clinically beneficial effects, examines potential roles for HBO_2 in the optimal management of combat-related trauma, and provides practical suggestions for HBO_2 treatment chamber deployment into operational environments.

MECHANISMS OF HBO_2 THERAPY

Reversal of Acute Ischemia

All wounds are characterized by a state of relative hypoxia.(Hunt, Twomey et al. 1967) Local oxygen tensions in the vicinity of a wound are approximately half the values observed in normal, non-wounded tissue.(Sheffield 1998) Musculoskeletal injuries secondary to crush, blast and penetrating trauma each produce local tissue ischemia, hypoxic gradients from zones of necrotic to healthy tissue and, when inadequately treated, the potential for propagation of ischemic injury into adjacent healthy tissues.(Warriner and Hopf 2003) Clinically, HBO_2 therapy can be used to correct tissue hypoxia. This is accomplished when a patient breathes 100% oxygen at elevated atmospheric pressure. Physiologically, a directly proportional

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increase in plasma oxygen tensions is produced and, at 2 - 2.5 atmospheres absolute pressure, arterial PO_2 elevations in excess of 1500 mmHg are achieved.(Warriner and Hopf 2003) As a result, tissue oxygen tensions are also elevated and the diffusion of oxygen into areas of relative hypoxia markedly enhanced.(Strauss 2003; Niinikoski 2004) This significant level of hyperoxygenation allows for the reversal of localized tissue hypoxia and corrects the pathophysiology related to oxygen deficiency. This improved tissue oxygenation translates into the ability to limit the duration and progression of ischemic tissue necrosis(Zamboni, Roth et al. 1989; Bouachour, Cronier et al. 1996; Ramon, Abramovich et al. 1998), improve demarcation between necrotic and viable tissue(Isakov Iu, Atroshchenko et al. 1979; Rosenthal, Benderly et al. 1985; von Schroeder and Botte 1998; Murphy, Banwell et al. 2000), temporize against exceptional blood loss anemia(Hart 1974; Sherman, Sennik et al. 1989; Bitterman, Reissman et al. 1991; Greensmith 2000; MacFarlane, Cronje et al. 2000; Stark, Coatesworth et al. 2003) and enhance the survival of reconstructive tissue grafts and flaps.(Tai, Birely et al. 1992; Gampper, Zhang et al. 2002; Kalani, Jorneskog et al. 2002; Ulkur, Yuksel et al. 2002; Richards, Lineaweaver et al. 2003)

Reduction of Reactive Edema Formation

Post-traumatic vasogenic edema develops as a direct consequence of acute soft tissue injury and, as the injured, hypoxic tissues lose their ability to regulate intracellular water, it becomes accentuated by the formation of cytogenic edema.(Strauss 2003) The resultant extracellular fluid accumulation increases diffusion distances between oxygen-carrying capillaries and surrounding cells, reducing total oxygen delivery and perpetuating cytogenic edema formation. In closed tissue compartments, increases in insterstitial pressure cause collapse of the microcirculation, further exacerbating existing ischemia and threatening previously uninvolved, healthy tissues. Clinically, this pathologic process is recognized as compartment syndrome. HBO_2 therapy has been shown to be an effective adjunct in the management of compartment syndrome. Three distinct processes contribute to this clinical effectiveness. First, by reversing acute tissue hypoxia, HBO_2 breaks the cycle between cellular ischemia and progressive edema formation, limits the total volume of soft tissue necrosis.(Nylander 1986; Skyhar, Hargens et al. 1986; Nylander, Nordstrom et al. 1988; Zamboni, Roth et al. 1993) Second, HBO_2-induced vasoconstriction produces a 20% decrease in arterial blood flow.(Bird and Telfer 1965; Bird and Telfer 1966) Edema reduction occurs because filtration of capillary fluid is decreased, while vascular outflow and improved oxygen delivery are maintained. Finally, the affected soft tissues are protected from reperfusion injury, a topic covered more fully in the next section.(Haapaniemi, Sirsjo et al. 1995) From the clinical standpoint, HBO_2 therapy can be used to prophylax against suspected or impending compartment syndrome.(Myers 2000; Strauss 2003) Where a compartment syndrome is already established, HBO_2 can be used to decrease the extent of required surgical fasciotomy, accelerate resolution of residual edema, and speed primary wound closure.(Bouachour, Cronier et al. 1996; Fitzpatrick, Murphy et al. 1998; Lindstrom, Gullichsen et al. 1998; Assenza, Borromeo et al. 2001; Van Poucke, Leenders et al. 2001; Gold, Barish et al. 2003)

Optimizing Host Antibacterial Defenses

Beyond the occurrence of frank necrosis, pathologic levels of hypoxia are correlated with increased rates of wound infection and, consequently, delayed wound healing.(Niinikoski 1969; Silver 1977) HBO_2 therapy has been shown to be effective in limiting the incidence of wound infection, speeding resolution of refractory infections, and decreasing the morbidity and mortality associated with malignant infections. Several discrete mechanisms account for the beneficial effects of HBO_2 in controlling infection. First, neutrophils required tissue oxygen tensions of 30-40 mmHg to destroy bacteria by oxidative killing mechanisms.(Mandell 1974; Hohn 1977) Leukocyte-mediated killing of aerobic gram-positive and anaerobic gram-negative organisms is restored when the pathologically low tissue oxygen tensions characteristic of wounded and infected tissues are

increased to physiologic or supraphysiologic levels by HBO_2 treatment.(Mader 1987; Knighton, Fiegel et al. 1990) Second, aminoglycoside and cephalosporin antibiotic transport across the bacterial cell wall does not occur if tissue oxygen tensions are below 20-30 mmHg. Therefore, HBO_2 therapy may enhance transport and augment antibiotic efficacy.(Park, Muhvich et al. 1991; Hirn 1993; Mendel, Reichert et al. 1999) Third, hyperoxygenation of the tissues surrounding areas of malignant infection may be of significance in preventing the extension of invading microorganisms.(Korhonen, Hirn et al. 1998; Korhonen 2000) Clinically, the most dramatic benefits are seen in reducing the morbidity and mortality of necrotizing fasciitis and gas gangrene, where treatment with HBO_2 results in clinical improvement even when standard measures have failed.(Schreiner, Tonjum et al. 1974; Bakker 1985; Riseman, Zamboni et al. 1990) Such benefits have been demonstrated for combat casualties.(Shupak, Halpern et al. 1984; Pailler and Labeeu 1986) Clinical improvements have also been noted in the management of peritonitis.(Bogomolova and Bol'shakov 1996) HBO_2 therapy is useful as a rescue treatment of refractory bone infections.(Aitasalo, Niinikoski et al. 1998; Maynor, Moon et al. 1998; Chen, Shih et al. 2003) In addition, HBO_2 is effective in reducing the need for re-operations in neurosurgical procedures complicated by infected grafts.(Eltorai, Hart et al. 1984; Larsson, Engstrom et al. 2002)

Prophylaxis Against Reperfusion Injury

The body of scientific literature continues to elucidate the multiple biochemical mechanisms behind HBO2 therapy's ability to limit and prophylax against ischemia-reperfusion (I/R) injury. These include upregulation of TGF-beta1 which ameliorates reperfusion injury by up-regulating bcl-2 and inhibiting TNF-alpha production (Yang, Bosco et al. 2001; Grunenfelder, Miniati et al. 2002), catalase induction (Kim, Choi et al. 2001), inhibition of intracellular adhesion molecule (ICAM-1) formation (Buras, Stahl et al. 2000) and stimulation of the fibrinolytic enzymes tissue plasminogen activator (t-PA), urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type one (PAI-1).(Tjarnstrom, Holmdahl et al. 2001) While it is not possible to say at this point which of these mechanisms is most predominant in the beneficial effects of HBO2 in limiting I/R injury, the preponderance of models consistently demonstrate this effect.(Buras 2000) Such inducible I/R protection has been demonstrated even when HBO2 treatment was delayed two to eight hours.(Murakami, Horinouchi et al. 2001; Tjarnstrom, Holmdahl et al. 2001; Agir, Mersa et al. 2003) Pretreatment with HBO2 has also been shown to be protective against subsequent periods of ischemia in neural and musculoskeletal tissues.(Murakami, Horinouchi et al. 2001; Dong, Xiong et al. 2002) Clinically, prophylaxis against I/R injury could be used to help improve post-surgical outcomes in patients undergoing peripheral vascular repairs, flap and grafting, and primary closure of large tissue defects.(Chen, Chen et al. 1998; Mazariegos, O'Toole et al. 1999; Myers 2000)

Improving Tissue Repair Rates

As noted previously, the hypoxic nature of all wounds has been demonstrated and, when pathologically increased, is correlated with impaired wound healing.(Hunt, Twomey et al. 1967; Niinikoski 1969; Gottrup 2004) Fibroblast replication, collagen deposition and angiogenesis are all oxygen sensitive responses that are necessary to proper wound healing.(Hunt and Pai 1972; Knighton, Silver et al. 1981; LaVan and Hunt 1990; Ishii, Miyanaga et al. 1999) Induction of several oxygen dependent growth factors has been elucidated in this process. Specifically, the production of nitric oxide (NO), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), angiopoietin-2 (ANG-2) and their respective tissue receptors are all upregulated in the presence of HBO_2.(Zhao, Davidson et al. 1994; Bonomo, Davidson et al. 1998; Boykin 2000; Sheikh, Gibson et al. 2000; Lin, Shyu et al. 2002; Kang, Gorti et al. 2004) These effects have been shown to persist after patient removal from the hyperbaric environment.(Siddiqui, Davidson et al. 1997) Additionally, the degree of wound healing induced by HBO_2 therapy appears to be

either superior to or synergistic with topically applied growth factors.(Bonomo, Davidson et al. 2000; Boykin 2000; Chen, Lai et al. 2002) In animal models, acceleration of wound healing has been noted for both wounds in both regionally ischemic and normal tissue beds.(Uhl, Sirsjo et al. 1994) Improvements in healing have also been demonstrated for orthopedic and neurosurgical procedures.(Atesalp, Komurcu et al. 2002; Chen, Lai et al. 2002) Clinically, HBO_2 therapy has been shown to improve rates of wound healing and reduce amputation rates in patients sustaining injuries in both civilian and combat environments.(Bialik, Fishman et al. 1987; LaVan and Hunt 1990; Radonic, Baric et al. 1995; Porcellini, Bernardo et al. 1997; Atesalp, Komurcu et al. 2002; Wang, Li et al. 2002; Warriner and Hopf 2003; Zamboni, Browder et al. 2003)

Hyperbaric Effects Summary

For hypoxic, complex wounds such as those induced by combat trauma, the net effect of serial hyperbaric exposures is improved local host immune response, increased clearance of infection, enhanced tissue growth, angiogenesis and wound epithelialization. When applied as an adjunct to surgical interventions, antibiotics and other clinically indicated therapies, HBO therapy is effective adjunct in the management of severe and refractory musculoskeletal problems. Indeed, the timely application of hyperbaric oxygen can be a limb- and life-saving therapy. (Wang, Li et al. 2002) More practically, adding HBO_2 treatment to other standard of care therapies can reduce the number and extent of required surgical procedures, decrease the duration of hospitalization and recovery time, improve post recovery function and, ultimately, enhance the wounded patient's prospects for full recovery.

Combat-Related Treatment Indications:

	Reduce Acute Tissue Ischemia	Minimize Edema Formation	Reperfusion Injury Prophylaxis	Improve Host Antibacterial Defenses	Improve Tissue Healing Rates
Musculoskeletal Trauma	Indicated Practical	Indicated Practical	Indicated Practical	Indicated Practical	Indicated Practical
Compartment Syndrome	Indicated Practical	Indicated Practical	Indicated Practical	Indicated Practical	Indicated Practical
Compromised Grafts / Flaps	Indicated Practical	Indicated Practical	Indicated Practical	Indicated Practical	Indicated Practical
Major Vascular Injury	Indicated Practical	Indicated Practical	Indicated Practical	N/A	N/A
Necrotizing Infections	Indicated Practical	Indicated Practical	Unknown	Indicated Practical	Indicated Practical
Antibiotic Resistant Infection	N/A	N/A	N/A	Indicated Practical	Indicated Practical
Acute Blood Loss Anemia	Indicated Not Practical	N/A	Unknown	N/A	N/A

Operational Deployment of HBO_2 Chambers:

The use of HBO_2 therapy for the management of combat related trauma has been suggested by a number of authors.(Cramer 1985; Spichev and Gostev Iu 1987; Rudge 1993; Broome 1997; Radonic, Baric et al. 1997; Fitzpatrick, Murphy et al. 1998; MacFarlane, Cronje et al. 2000) The primary difficulty with employment of this therapeutic modality is providing ready access of combat casualties to hyperbaric chamber facilities. As noted from the mechanistic discussions above, the acute benefits of HBO_2 therapy are best achieved when the therapy is provided within a few hours of injury. However, for the diseases and injuries presented, treatment with HBO_2 is generally considered to be an adjunct to appropriate antibiotic therapy and standard surgical management. Thus, whenever possible, initial treatment with HBO_2 should be timed to occur immediately after definitive surgical interventions have taken place, between planned surgical procedures, or when lack of OR availability allows HBO_2 therapy to be used as a temporizing measure. Unfortunately, logistical issues complicate deployment of hyperbaric chambers into the combat environment. Indeed, size, safety and mobility constraints render co-location of hyperbaric chambers at Echelon I treatment levels impractical. In contrast, at least two hyperbaric systems are available for use at Echelon II level treatment facilities. The most portable of these systems is the single person (i.e. a monoplace chamber) folding hyperbaric stretcher. This foldable, lightweight chamber, called the Emergency Evacuation Hyperbaric Stretcher (EEHS), has received certification for use within DoD. While the majority of these systems were initially intended for use in the remote treatment of decompression sickness and submarine escape and rescue operations, their potential application to combat trauma cases has been noted.(Locklear 2002) Deployment of U.S. Navy's Transportable Recompression Chamber System (TRCS), as was used by the Special Medical Response Team in August 2002 to treat miners trapped in a Pennsylvania coal mine. This later chamber has the advantage of being large enough to allow a medical attendant to accompany the patient during treatment (i.e. a multiplace chamber). At Echelon III level treatment facilities, multiple hyperbaric treatment options could be employed. These could include those chamber systems already mentioned as well as larger chamber systems such as the Fly Away Recompression Chamber (FARC). For maritime operations, a multiplace hyperbaric chamber could be stationed aboard amphibious ships or designated hospital ships, such as USNS Comfort and USNS Mercy. HBO_2 therapy used in support of reconstructive procedures and complex wound management can be arranged by medevac of select patients to regional Echelon IV treatment facilities that have fixed multiplace and monoplace chamber facilities. Such hospital-associated HBO_2 treatment capabilities can be found in most industrialized nations. Many of the chamber complexes are associated with existing tertiary care, military treatment facilities.

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