The Relevance of Hyperbaric Oxygen to Combat Medicine

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At the Davis Hyperbaric Laboratory, Brooks AFB, TX we have embarked on a series of research protocols designed to determine the efficacy of hyperbaric oxygen treatment (HBO) in combat wounds. Our research has been directed towards finding ways to minimize the extent of combat injury, reduce the consumption of medical resources, speed healing of combat wounds, and improve the result in the healed wound. In this presentation the basic science related to the use of HBO in treating combat wounds will be presented and our current research efforts will be discussed.

Actions of HBO

Several of the cellular and molecular actions of HBO make it an attractive adjunct to combat wound treatment. Hyperbaric oxygen therapy has been shown to expedite wound healing by hastening angiogenesis, increasing or restoring the bactericidal properties of polymorphonuclear lymphocytes and macrophages, speeding the migration of macrophages, and hastening wound epithelialization and contraction[1,2,3]. These effects have been clinically useful and proven for diabetic wounds, poorly vascularized tissue, infected tissue, osteomyelitis, and irradiated tissue[4,5]. In full thickness, skin grafts and flaps, hyperbaric oxygen has been shown to speed healing and enhance flap take and graft survival, especially when compromised[6,7,8,9,10,11]. In burn patients undergoing grafting procedures, hyperbaric oxygen has been shown to shorten hospital stay, enhance donor site and graft healing, and reduce the number of grafting procedures required for wound closure[12,13,14]. The salvaging effect of hyperbaric oxygen on failing flaps and full thickness skin grafts has been demonstrated in numerous studies[15,16,17].

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[1] Tibbles, P. M., and Edelsberg, J. S. *Hyperbaric Oxygen Therapy.* N Eng Jmed 334: 1642-1648, 1996.
[2] Kindwall, E. P., Gottlieb, L. J., and Larson, D. L. *Hyperbaric oxygen therapy in plastic surgery: a review article.* Plast Reconstr Surg 88:898-908, 1991.
[3] Thom, S.R., Mendiguren, I., Hardy, K., Bolotin, T., et al. *Inhibition of human netrophil □$_2$-integrin-dependent adherence by hyperbaric O_2.* Am J Physiol 272 (Cell Physiol 41): C770-C777, 1997
[4] Tibbles, 1996
[5] Kindwall, 1991
[6] Perrins, D. J. D. *Influence of hyperbaric oxygen on the survival of split skin grafts,* Lancet 1967 Apr 22: 868-871.
[7] McFarlane, R. M., Wermuth, R. E., *The use of hyperbaric oxygen to prevent necrosis in experimental pedicle flaps and composite skin grafts.* Plast Reconstr Surg 37:422-430, 1966.
[8] Gruber, R. P., Brinkley, F. B., Amato, J. J., and Mendelson, J. A. *Hyperbaric oxygen and pedicle flaps, skin grafts, and burns.* Plast. Reconstr. Surg. 45: 24-30, 1970
[9] Shulman, A. G., and Krohn, H. L. *Influence of hyperbaric oxygen and multiple skin allografts on the healing of skin wounds.* Surgery 62: 1051-1058, 1967.
[10] Bowersox, J. C., Strauss, M. B., and Hart, G. B. *Clinical experience with hyperbaric oxygen therapy in the salvage of ischemic skin flaps and grafts.* Jour Hyperbar Med 1: 141-149, 1986.
[11] Jurell, G., and Kaijser, L. *The influence of varying pressure and duration of treatment with hyperbaric oxygen on the survival of skin flaps.* Scand J Plast Reconstr Surg 7: 25-28, 1973.
[12] Cianci, P., Williams, C., Lee, H.,Shapiro, R., et al. *Adjunctive hyperbaric oxygen in the treatment of thermal burns. An economic analysis.* J Burn Care Rehab 11: 140-143, 1990.
[13] Grossman, A. R. *Hyperbaric oxygen in the treatment of burns.* Ann Plast Surg 1: 163-171, 1978.
[14] Nylander, G., Nordstrom, H., and Eriksson, E. *Effects of hyperbaric oxygen on oedema formation after a scald burn.* Burns 10: 193-196, 1984.
[15] Tibbles, 1996.
[16] Kindwall, 1991.
[17] Rubin, J.S., Marzella, L., Myers, R. A., Suter, C., et al. *Effect of hyperbaric oxygen on the take of composite skin grafts in rabbit ears.* J Hyperbar Med 3: 79-88, 1988.

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HBO is capable of favorably influencing a number of cytokines and growth factors integral to wound healing. When administered after wounding, HBO up-regulates collagen synthesis through pro-al (I) mRNA expression[18]. In rabbit ear wounds HBO has been shown to up-regulate mRNA for the PDGFβ receptor[19]. This effect has been further born out in clinical studies. In ischemic flaps HBO up-regulates fibroblast growth factor (FGF) causing an increased effect over that seen with fibroblast growth factor alone[20]. In situations where FGF is ineffective, HBO can render it highly effective[21]. This is an effect different than up-regulation. In patients with Crohn's disease IL-1, IL-6, and TNFα levels were diminished during HBO treatment[22]. TNF levels in normal rats became elevated after a single exposure to HBO[23]. Perhaps under different physiologic conditions HBO may cause up or down regulation of cytokines. Vascular endothelial growth factor (VEGF) is up-regulated by hypoxia, yet HBO also up-regulates this factor[24]. Transforming growth factor-β (TGF-β1) and platelet-derived growth factor ββ (PDGF-β) are synergistically enhanced by HBO[25].

The HBO paradox: up-regulation of events stimulated by hypoxia:

HBO thus acts in a paradoxical manner. Many of the processes that are stimulated by hypoxia are accelerated by the administration of HBO. The following biologic processes and factors are stimulated or up-regulated by hypoxia, and by HBO: angiogenesis, collagen synthesis, and osteoclastic activity. One known mechanism is that by which fibroblasts are stimulated to make collagen through peroxides, which occur, in the hypoxic wound and during HBO treatment[26]. Therefore the peroxides generated by HBO mimic one of the stimuli found in hypoxia. Another mechanism is the stimulation of cytokines by hypoxia and further upregulation of these cytokines under the hyperoxia, which occurs during HBO treatment. This is the case for some interleukines and for tumor necrosis factor (TNF). There is some confusion on the exact timing of the release of growth factors and cytokines; in one study VEGF, TNF-α, and TGF-β occurred in hypoxic wounds after they had been released in normoxia. VEGF, TGF-β, and PDGF-β have bi-phasic release patterns; their release is stimulated by hypoxia and hyperoxia, but is lowest during normoxia[27,28]. Furthermore, the activity of released VEGF is further enhanced during hyperoxia, especially in the presence of lactate[29]. It is clear that biologically active chemicals such as cytokines and growth factors have a complex array of stimuli to up and down regulate activity. Oxygen, cytokines, and biologically active chemicals and metals appear to have key roles in the expression of healing. As we learn more about the role of oxygen its role appears to be much more detailed than in a simple mass-action equation.

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[18] Ishii, Y., Myanaga, Y., Shimojo, H., Ushida, T., and Tateishi, T. *Effects of hyperbaric oxygen on procollagen messenger RNA levels and collagen synthesis in the healing of rat tendon laceration.* Tissue Eng 5: 279-86, 1999.

[19] Bonomo, S. R., Davidson, J. D., Yu, Y., Xia, Y. et al. *Hyperbaric oxygen as a signal transducer: upregulation of platelet derived growth factor-beta receptor in the presence of HBO2 and PDGF*. Undersea Hyperb Med 25: 211-6, 1998.

[20] Bayati, S., Russell, R. C., and Roth, A. C. *Stimulation of angiogenesis to improve the viability of prefabricated flaps.* Plast Reconstr Surg 101: 1290-5, 1998.

[21] Wu, L., Pierce, G. F., Ladin, D. A., Zhao, L. L., et al. *Effects of oxygen on wound responses to growth factors: Kaposi's FGF, but not basic FGF stimulates repair in ischemic wounds.* Growth Factors 12: 29-35, 1995.

[22] Weisz, G., Lavy, A., Adir, Y., Melamed, Y., et al. *Modification of in vivo and in vitro TNF-alpha, IL-1, and IL-6 secretion by circulating monocytes during hyperbaric oxygen treatment in patients with perianal Crohn's disease.* J Clin Immunol 17: 154-9, 1997.

[23] Lahat, N., Bitterman, H., Yaniv, N., Kinarty, A., and Bitterman, N. Exposure to hyperbaric oxygen induces tumor necrosis factor alpha (TNF-alpha) secretion from rat macrophages. Clin Exp Immunol 102: 655-9, 1995.

[24] Hunt, T. K. Oxygen and wound healing. Hyperbaric Medicine 2000, 8th Annual Advanced Symposium, Columbia, S. C. 14-15 April 2000

[25] Zhao, L. L., Davidson, J. D., Wee, S. C., Roth, S. I., and Mustoe, T. A. *Effect of hyperbaric oxygen and growth factors on rabbit ear ischemic ulcers.* Arch Surg 129: 1043-9, 1994.

[26] ibid.

[27] Haroon, Z. A., Raleigh, J. A., Greenburg, C. S., and Dewhirst, M. W. Early wound healing exhibits cytokine surge without evidence of hypoxia. Ann Surg 231: 137-147, 2000.

[28] Gleadle, J. M., and Ratcliffe, P. J. Hypoxia and the regulation of gene expression. Mol Med Today 4: 122-9, 1998.

[29] Haroon, 2000.

In reperfusion injury, HBO diminishes tissue damage caused by leukocyte activation. In muscle this effect of HBO is mediated by inhibiting synthesis of guanylate cyclase (cGMP) and subsequent leukocyte β–2 integrin dependent adhesion[30,31]. This adhesion of leukocytes to vessel walls initiates the reperfusion injury inflammatory cascade[32,33]. In cardiac muscle the action of leukocytes is thought to be largely responsible for the reperfusion injury of myocardial infarction[34]. When the activation of leukocytes is blocked, they do not adhere to the β–2 integrin receptor on the surface of vascular endothelium and reperfusion injury is prevented[35,36]. HBO acts to prevent this activation and adhesion[37].

In addition to the above mechanisms the primary reason for administration of HBO is the oxygenation of poorly vascularized tissue – a situation present in at least a small way in nearly every wound. In addition to the provision of tissue oxygenation levels many times the normal level, oxygen is a potent vasoconstrictor and is capable of reducing the edema in injured tissue, facilitating blood flow and further oxygenation.

Uses of HBO for combat wounds

With these cellular and molecular effects in mind we have been looking at ways of applying HBO to the clinical situations encountered in combat. We developed a rat skin graft – open wound model which allowed us to test the effectiveness of HBO in treating open wounds which had been partially covered with mesh grafts. We saw no difference other than a slight increase in granulation tissue in the HBO treated group at one week, probably due to technical problems with the model and the short time period to evaluation.

We have hypothesized that HBO will shorten the time to healing of split thickness skin grafts by increasing the tensile strength of these grafts. This would allow for earlier mobilization and discharge of grafted patients. In the pig model we have developed we will also be able to test a number of treatments for open wounds designed to shorten epithelialization times.

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[30] Wyatt, T. A., Lincoln, T. M., and Pryzwansky, K. B. Regulation of neutrophil degranulation by LY-83583 and L-arginine: role of cGMP-dependent protein kinase. Am J. Physiol 265: C201-211, 1993.

[31] Thom, S. R., Mendiguren, I., Hardy, K., Bolotin, T. et al. Inhibition of human neutrophil β-2 integrin-dependent adherence by hyperbaric O_2. Am J Physiol 272: C770-C777, 1997.

[32] Maxwell, S. R. J., and Lip, G. Y. H. Reperfusion injury: a review of the pathophysiology, clinical manifestations and therapeutic options. Int J Cardiol 58: 95-117, 1997.

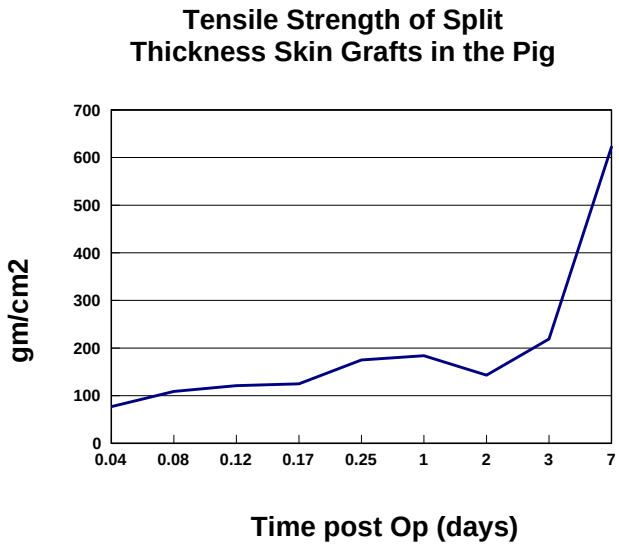
[33] Virkhaus, R. Lucchesi, B. R., Simpson, P.J., and Shebuski, R. J. The role of adhesion molecules in cardiovascular pharmacology: Meeting review. J Pharm Exp Ther 273: 569-565, 1995.

[34] Jordan, J. E., Zhao, Z-Q, and Vinten-Johansen, J. The role of neutrophils in myocardial ischemia-reperfusion injury. Cardiovasc Res 43: 860-878, 1999.

[35] Thomas, M. P., Brown, L. A., Sponseller, D. R., Williamson, S. E. et al. Myocardial infarct size reduction by the synergistic effect of hyperbaric oxygen and recombinant tissue plasminogen activator. Am Heart J 120: 791-800, 1990.

[36] Dolan, R., Hartshorn, K., Andry, C., Tablante, J., et al. In vivo correlation of neutrophil receptor expression, ischemia-reperfusion injury, and selective 5-lipoxygenase inhibition in guinea pigs. Arch Otolaryngol Head Neck Surg 124:1377-1380, 1998.

[37] Zamboni, W. A., Wong, H. P., and Stephenson, L. L. Effect of hyperbaric oxygen on neutrophil concentration and pulmonary sequestration in reperfusion injury. Arch Surg 131: 736-760, 1996.



We have begun two protocols testing the effect of HBO on the healing of fractures in long bones. In our clinical protocol we are testing the effect of HBO on the time to fracture healing in patients with lower extremity fractures. It is too early to assess results but we are hypothesizing that we will see a 20% reduction in healing time with a lessened need for secondary procedures and a lower complication rate in the HBO treated group. In a rabbit study we are testing the tensile strength of the rabbit tibia after osteotomy and compression plate fixation in control and HBO treated groups.

We have postulated that HBO will reduce the recovery time in nerve injuries and possibly improve the end result based on animal studies showing that nerves subjected to division, ischemia, and crush injury recover faster when treated with hyperbaric oxygen, axonal growth is stimulated, and the end result of nerve injury is superior to those animals not treated with HBO[38,39,40,41]. We have developed a post radical prostatectomy protocol investigating the incidence and rate of recovery of impotence following the procedure in HBO and control groups. In addition we have carpal tunnel syndrome and nerve laceration protocols under consideration.

In our facility we see a large number of chronic open wounds from a variety of causes – diabetes, peripheral vascular disease, and radiation are the major contributors. HBO has a role in accelerating the healing of these wounds, but we have very little knowledge on the interplay of cellular and biochemical events in wound healing and how these are affected by HBO. We have designed a human study and two rodent studies to evaluate the role of growth factors and biomarkers in wound healing and their ability to predict a favorable result. In our human work we have found that individual patients have slow and fast healing phases, sometimes alternating, and that the appearance of nitric oxide by products in the urine is a reliable predictor of wound closure.

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[38] Haapeniemi, T., Nylander, G., Kanje, M., and Dahlin, L. *Hyperbaric oxygen enhances regeneration of the rat sciatic nerve.* Exp Neurol 149: 433-8, 1998.
[39] Bradshaw, P.O., Nelson, A.G., Fanton, J.W., Yates, T., et al. *Effect of hyperbaric oxygenation on peripheral nerve regeneration in adult male rabbits.* Undersea Hyperb Med 23: 107-13, 1996.
[40] Tibbles, P. M., and Edelsberg, J. S. *Hyperbaric-oxygen therapy.* N Eng J Med 334: 1642-1648, 1996.
[41] Mukoyama, M., Iida, M., and Sobue, I. *Hyperbaric oxygen therapy for peripheral nerve damage induced in rabbits with clioquinol.* Exp Neurol 47: 371-80, 1975.

HBO has long been known to favorably affect the result of muscular compartment syndrome, lessening the degree of muscle necrosis and even eliminating the need for fasciotomy[42,43,44,45]. We have proposed a rabbit compartment syndrome study evaluating biomarkers of compartment syndrome, the effect of HBO in oxygenating ischemic muscle, and the end result of HBO treated animals with compartment syndrome. We hope that the judicious and prompt use of HBO following injury may eliminate the need for surgery in some cases and improve surgical results.

HBO can be lifesaving in extreme blood loss where resuscitation with blood products is not possible. We have wondered if HBO could be useful in less severe blood loss, perhaps eliminating or reducing the need for blood transfusion. The reduction of blood use in the field has particular appeal because of the logistical problems in supplying blood to a forward location and the ability to avoid contaminated blood. We have designed a rabbit study in which animals with a 50% blood loss are given HBO to determine if the recovery from blood loss is accelerated over the control group.

It is our hope that in time we will be able to position hyperbaric chambers in the forward medical facility and reduce the severity of wounds, hasten healing times, reduce the need for blood and surgical procedures, and lessen complication rates. Our current work is directed to understanding the events in injury and wound healing and identifying the parameters where HBO may be of use.

[42] Strauss, M. B., Hargens, A. R., Gershuni, D. H., Greenburg, D. A., et al. Reduction of skeletal muscle necrosis using intermittent hyperbaric oxygen in a model compartment syndrome. J Bone Joint Surg 65-A: 656-662, 1983.
[43] Buachour, G., Cronier, P., Gouello, J. P. Toulemonde, J. L. et al. Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. J. Trauma 41: 333-339, 1996.
[44] Mathieu, D., Wattel, F., Bouachour, G., Billard, V., and Defoin, J. F. Post-traumatic limb ischemia: prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. J. Trauma 30: 307-314, 1990.
[45]Skyhar, M. J., Hargens, A. R., Strauss, M. B., Gershuni, M. D., et al. Hyperbaric oxygen reduces edema and necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hypotension. J. Bone Joint Surg 68-A: 1218-1224, 1986.

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