WOUND HEALING LITERATURE

Pharmacoeconomics. 2008;26(12):1019-35. doi: 10.2165/0019053-200826120-00005.

Management and prevention of diabetic foot ulcers and infections: a health economic review.

Chow I, **Lemos EV**, **Einarson TR**.

Diabetic foot ulcers and infections are common and incur substantial economic burden for society, patients and families. We performed a comprehensive review, on a number of databases, of health economic evaluations of a variety of different prevention, diagnostic and treatment strategies in the area of diabetic foot ulcers and infections. We included English-language, peer-reviewed, cost-effectiveness, cost-minimization, cost-utility and cost-benefit studies that evaluated a treatment modality against placebo or comparator (i.e. drug, standard of care), regardless of year. Differences were settled through consensus. The search resulted in 1885 potential citations, of which 20 studies were retained for analysis (3 cost minimization, 13 cost effectiveness and 4 cost utility). Quality scores of studies ranged from 70.8% (fair) to 87.5% (good); mean = 78.4% +/- 5.33%.In diagnosing osteomyelitis in patients with diabetic foot infection, magnetic resonance imaging (MRI) showed 82% sensitivity and 80% specificity. MRI cost less than 3-phase bone scanning + Indium (In)-111/Gallium (Ga)-67; however, when compared with prolonged antibacterials, MRI cost $US120 (year 1993 value) more without additional quality-adjusted life-expectancy. Prevention strategies improved life expectancy and QALYs and reduced foot ulcer rates and amputations.Ampicillin/sulbactam and imipenem/cilastatin were both 80% successful in treating diabetic foot infections but the latter cost $US2924 more (year 1994 value). Linezolid cure rates were higher (97.7%) than vancomycin (86.0%) and cost $US873 less (year 2004 value). Ertapenem costs were significantly lower than piperacillin/tazobactam ($US356 vs $US503, respectively; year 2005 values). Becaplermin plus good wound care may be cost effective in specific populations. Bioengineered living-skin equivalents increased ulcer-free months and ulcers healed, but costs varied between countries. Promogran((R)) produced more ulcer-free months than wound care alone (3.75 vs 3.41 months, respectively). Treatment with cadexomer iodine resulted in higher rates of healed ulcer (29% vs 11%) and lower weekly treatment costs (Swedish krona [SEK]903 vs SEK1421; year 1993 values) than standard care. Filgrastim decreased hospital stays, time to resolution and costs (36% lower) compared with usual care. Adjunctive hyperbaric oxygen produced an incremental cost per QALY at year 1 of $US27 310 and $US2255 at year 12 (year 2001 values).Overall, preventive strategies were shown to be cost effective and potentially cost saving. Various antibacterial regimens are cost effective but empiric choices should be based on local resistance patterns. MRI was cost effective compared with three-phase bone scanning + In-111/Ga-67 but not against prolonged antibacterial therapy. Other innovations (becaplermin, bioengineered living-skin equivalents, filgrastim, cadexomer iodine ointment, hyperbaric oxygen, Promogran((R))) may be cost effective in this population but more studies are needed to confirm these findings.

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J Appl Physiol. 2008 Oct 9. [Epub ahead of print]
Oxidative stress is fundamental to hyperbaric oxygen therapy.
Thom SR.
The goal of this review is to outline advances addressing the role that reactive species of oxygen and nitrogen play in therapeutic mechanisms of hyperbaric oxygen. The review will be organized around major categories of problems or processes where controlled clinical trials have demonstrated clinical efficacy for hyperbaric oxygen therapy. Reactive species are now recognized to play a major role in cell signal transduction cascades, and the discussion will focus on how hyperbaric oxygen acts through these pathways to mediate wound healing and ameliorate post-ischemic and inflammatory injuries.

Med Hypotheses. 2008 Nov;71(5):776-80. Epub 2008 Aug 22.
The effect of hyperbaric oxygen therapy on blood vessel function in diabetes mellitus.
Unfirer S, **Kibel A**, **Drenjancevic-Peric I**.
Prolonged untreated diabetes mellitus leads to microangiopathy, tissue hypoxia and ischemic lesions; it increases the risk for stroke and exacerbates brain tissue damage following ischemia. Patients exhibit advanced atherosclerosis in coronary and cerebral arteries as well as enhanced vascular responsiveness to vasoconstrictors, an attenuated response to vasodilators and impaired autoregulation of cerebral blood flow. Altered endothelial function of arterioles and an impaired vasomotor function of resistance vessels could contribute to altered regulation of regional blood flow and insufficient tissue perfusion in diabetes mellitus. Hyperbaric oxygen therapy is shown to contribute to the healing of ischemic ulcerations in diabetic patients and to improvement of several other pathologic conditions. However, information about the mechanism of how this therapy works is still very limited. We postulate that hyperbaric oxygen therapy has an effect on vascular function by modulating mechanisms of vascular responses to various dilator and constrictor agonists in cerebral resistance vessels, leading to restored vascular reactivity. In accordance to this, the therapy affects production of vasodilators and vasoconstrictors, as well as the vessel-sensitivity to these factors. Furthermore, we hypothesize that hyperbaric oxygen therapy would restore cerebral blood flow regulation that is impaired in diabetics, whereas in contrast to that, chronic intermittent hypoxia would lead to impaired cerebral blood flow. These proposed mechanisms would, if confirmed, represent a valuable advancement in the understanding of this subject.

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J Surg Res. 2008 Nov;150(1):11-6. Epub 2008 Jan 22.
Reperfusion-induced neutrophil CD18 polarization: effect of hyperbaric oxygen.
Khiabani KT, **Bellister SA**, **Skaggs SS**, **Stephenson LL**, **Nataraj C**, **Wang WZ**, **Zamboni WA**.
BACKGROUND: Hyperbaric oxygen (HBO) inhibits ischemia reperfusion (IR) -induced neutrophil adhesion to endothelium through an unknown mechanism. This study evaluates the effect of HBO on IR-stimulated neutrophil adhesion and polarization of expressed CD18 adhesion molecules using a novel in vitro adhesion assay and confocal microscopy. MATERIALS AND METHODS: Neutrophils from normal animals were isolated from whole blood and incubated with plasma from rat gracilis muscle flaps on coverslips pretreated with ICAM. Percent adherence to ICAM and CD18 polarization was evaluated in the following five groups: (1) Nonischemic control, n = 15; (2) 4 h ischemia (IR, n = 15); (3) 4 h ischemia with HBO treatment (100% oxygen at 2.5 atmospheres absolute (IR + HBO, n = 15)); (4) 4 h ischemia with 100% oxygen at room temperature and pressure (RTP) (IR + normobaric hyperoxia, n = 5); and (5) 4 h ischemia with 8% oxygen at 2.5 atmospheres absolute (IR + hyperbaric normoxia, n = 5). Direct HBO treatment of neutrophils was also evaluated. RESULTS: Neutrophils exposed to IR plasma showed a significant increase in percent adherent (0.8 +/- 0.1% versus 16.7 +/- 2.2%, $P < 0.05$) and polarized cells (6.2 +/- 1.7% versus 43.9 +/- 12.2%, $P < 0.05$) compared to controls. Hyperbaric oxygen significantly reduced the adhesion and polarization to 1.6 +/- 0.3 and 4.1 +/- 2.5%, respectively ($P = < 0.05$). Normobaric hyperoxia and hyperbaric normoxia did not affect neutrophil adherence or CD18 polarization following IR. Direct HBO treatment of neutrophils did not change the percent of polarized cells in IR. CONCLUSIONS: Hyperbaric oxygen inhibits IR-induced neutrophil adhesion by blocking CD18 surface polarization and requires plasma exposure to HBO. Treatment with oxygen or pressure alone is not effective.

Antioxid Redox Signal. 2008 Nov;10(11):1869-82.
Hyperoxia, endothelial progenitor cell mobilization, and diabetic wound healing.
Liu ZJ, **Velazquez OC**.
Diabetic foot disease is a major health problem, which affects 15% of the 200 million patients with diabetes worldwide. Diminished peripheral blood flow and decreased local neovascularization are critical factors that contribute to the delayed or nonhealing wounds in these patients. The correction of impaired local angiogenesis may be a key component in developing therapeutic protocols for treating chronic wounds of the lower extremity and diabetic foot ulcers. Endothelial progenitor cells (EPCs) are the key cellular effectors of postnatal neovascularization and play a central role in wound healing, but their circulating and wound-level numbers are decreased in diabetes, implicating an abnormality in EPC mobilization and homing mechanisms. The deficiency in EPC mobilization is presumably due to impairment of eNOS-NO cascade in bone marrow (BM). Hyperoxia, induced by a clinically relevant hyperbaric oxygen therapy (HBO) protocol, can significantly enhance the mobilization of EPCs from the BM into peripheral blood. However, increased circulating EPCs failed to reach to wound tissues. This is partly a result of downregulated production of SDF-1alpha in local wound lesions with diabetes. Administration of exogenous SDF-1alpha into wounds reversed the EPC homing impairment and, with hyperoxia, synergistically enhanced EPC mobilization, homing, neovascularization, and wound healing.

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WOUND HEALING LITERATURE

J Invest Dermatol. 2008 Aug;128(8):2102-12. Epub 2008 Mar 13.
Hyperbaric oxygen attenuates apoptosis and decreases inflammation in an ischemic wound model.
Zhang Q, **Chang Q**, **Cox RA**, **Gong X**, **Gould LJ**.
The molecular mechanisms whereby hyperbaric oxygen (HBO) improves ischemic wound healing remain elusive. In this study, a rat model of wound ischemia was used to test the hypothesis that HBO enhances wound healing by modulating hypoxia-inducible factor-1alpha (HIF-1alpha) signaling. Male Sprague-Dawley rats underwent creation of a previously validated ischemic flap. Three groups underwent daily treatment: HBO (90 minutes, 2.4 atm); systemic administration of the free radical scavenger, N-acetylcysteine (NAC 150 mg kg(-1) intraperitoneal); control (neither HBO nor NAC). HBO treatment improved healing of the ischemic wounds. Analysis of ischemic wound tissue extracts demonstrated significantly reduced expression of HIF-1alpha, p53, and BNip3. Additionally, HBO increased expression of Bcl-2 while decreasing cleaved caspase-3. DNA fragmentation was abolished and the number of TUNEL-positive cells was reduced compared to the other groups. Vascular endothelial growth factor, cyclooxygenase-2, and neutrophil infiltration were reduced in ischemic wounds treated with HBO. These results indicate that HBO improves ischemic wound healing by downregulation of HIF-1alpha and subsequent target gene expression with attenuation of cell apoptosis and reduction of inflammation.

Wound Repair Regen. 2008 May-Jun;16(3):321-30.
The use of hyperbaric oxygen therapy to treat chronic wounds: A review.
Thackham JA, **McElwain DL**, **Long RJ**.
Chronic wounds, defined as those wounds which fail to proceed through an orderly process to produce anatomic and functional integrity, are a significant socioeconomic problem. A wound may fail to heal for a variety of reasons including the use of corticosteroids, formation of squamous cell carcinoma, persistent infection, unrelieved pressure, and underlying hypoxia within the wound bed. Hypoxia appears to inhibit the wound healing process by blocking fibroblast proliferation, collagen production, and capillary angiogenesis and to increase the risk of infection. Hyperbaric oxygen therapy (HBOT) has been shown to aid the healing of ulcerated wounds and demonstrated to reduce the risk of amputation in diabetic patients. However, the causal reasons for the response of the underlying biological processes of wound repair to HBOT, such as the up-regulation of angiogenesis and collagen synthesis are unclear and, consequently, current protocols remain empirical. Here we review chronic wound healing and the use of hyperbaric oxygen as an adjunctive treatment for nonhealing wounds. Databases including PubMed, ScienceDirect, Blackwell Synergy, and The Cochrane Library were searched for relevant phrases including HBOT, HBO/HBOT, wound healing, and chronic/nonhealing wounds/ulcers.

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Int J Technol Assess Health Care. 2008 Spring;24(2):178-83.
Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. - Chuck AW, **Hailey D**, **Jacobs P**, **Perry DC**.
BACKGROUND: Hyperbaric oxygen therapy (HBOT) has been proposed as an adjunct to standard methods of care for diabetic foot ulcers (DFU). Its use may decrease the risk of infection and lower extremity amputations (LEAs). As part of a Canadian assessment, we estimated the cost-effectiveness and budget impact of HBOT in this application. METHODS: We developed a decision model comparing adjunctive HBOT with standard care alone. The population was a 65-year-old cohort with DFU. The time horizon was 12 years taken from a Ministry of Health perspective. The health states were a healed wound with or without a minor LEA, an unhealed wound with no related surgery, and a major LEA. Efficacy data were based on outcomes reported in studies included in a literature review. Cost and capacity needs for treating DFU patients in Canada were estimated using prevalence data from the literature, and cost and utilization data from government records. RESULTS: The 12-year cost for patients receiving HBOT was CND$40,695 compared with CND$49,786 for standard care alone. Outcomes were 3.64 quality-adjusted life-years (QALYs) for those receiving HBOT and 3.01 QALYs for controls. Estimated cost to treat all prevalent DFU cases in Canada was CND$14.4-19.7 million/year over 4 years. If seven-person HBOT chambers were used, a further nineteen to thirty-five machines would be required nationally. CONCLUSIONS: Adjunctive HBOT for DFU is cost-effective compared with standard care. Additional HBOT capacity would be needed if it were to be adopted as the standard of care throughout Canada.

Singapore Med J. 2008 Feb;49(2):105-9.
Hyperbaric oxygen therapy in the management of diabetic lower limb wounds.
Ong M.
INTRODUCTION: Hyperbaric oxygen therapy (HBOT) involves the inhalation of 100 percent oxygen at pressures greater than at sea level. One of the most common indications for HBOT is to aid healing of diabetic foot wounds. METHODS: All cases of diabetic foot wounds that were seen by the Hyperbaric Medicine Centre in Tan Tock Seng Hospital from May 2005 to March 2006 were analysed in terms of outcome (wound healing) after HBOT. RESULTS: A total of 45 cases of foot ulcers/wounds were analysed. 32 patients had a favourable outcome, giving a success rate of 71 percent. The remaining 13 (28 percent) did not have a favourable outcome to HBOT. The success rate was even more significant as a large number of these patients (34 [77 percent]) were told by their specialist that they were at high risk of a further amputation. No major complications were noted. CONCLUSION: The experience of the Hyperbaric Medicine Centre in Singapore is consistent with that reported in other centres. With proper patient selection, HBOT, together with a multidisciplinary team of vascular and orthopaedic surgeons, podiatrists, infection disease physicians and endocrinologists, can help reduce the numbers and severity of amputations as well as downtime due to increased wound healing.

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Handchir Mikrochir Plast Chir. 2007 Oct;39(5):328-32.
The use of oxygen as drug and its relevance for wound healing
Andel H, **Kamolz L**, **Andel D**, **Brenner L**, **Frey M**, **Zimpfer M**.
Plastic surgeons often have to deal with problematic wounds. In reconstructive surgery, as well as in chronic wounds, tissue oxygen supply is often critically low. Similarly in the treatment of severely burned patients, perfusion and oxygen supply to the areas beneath burn wounds are often critical. This paper explains the mechanisms and impact of oxygen for wound healing. It is important to mention that it has been shown that oxygen even used at ambient pressure can improve wound healing. Whereas treatment with oxygen under hyperbaric conditions is not everywhere available, at least normobaric oxygen is cheap and ubiquitously available and should therefore be used routinely. Oxygen treatment under hyperbaric conditions, especially in critically ill patients, needs a special infrastructure and is quite more expensive. Therefore, it has to be evaluated whether the potential benefit for the patient meets the risk and costs of treatment. In 2006, at the Hyperbaric Centre of the Medical University of Vienna almost 2200 hyperbaric treatments including 330 in critically ill patients have been performed. Beside 2 patients suffering from Fournier's gangrene, 2 suffering from gas gangrene and 4 patients with severe carbon monoxide intoxications, all other intensive-care patients were treated for severe burns. Indications for less severely ill patients mainly included problem wounds mostly of diabetic patients, osteomyelitis of the mandible and less severe carbon monoxide poisoning. Our experience with the use of oxygen under hyperbaric conditions so far has been good enough to consider this kind of therapy at least in our centre as an option in the adjunctive treatment for the so far used indications. However, it has to be mentioned that there is still lack of prospective randomised controlled studies to introduce this kind of therapy as a level 1 indication in clinical routine.

Adv Skin Wound Care. 2007 Jul;20(7):382-8.
Hyperbaric oxygen therapy mediates increased nitric oxide production associated with wound healing: a preliminary study.
Boykin JV Jr, **Baylis C**.
OBJECTIVE: The objective of this preliminary study was to document general somatic and wound nitric oxide (NO) levels during and after hyperbaric oxygen therapy (HBOT). DESIGN: The study evaluated 6 chronic wound patients that responded favorably to HBOT treatment (20 treatments; 2.0 atmosphere absolute [ATA] x 90 minutes). Successful HBOT was associated with increased wound granulation tissue formation and significantly improved wound closure. Wound fluid and fasting plasma samples were obtained for measurement of nitrate and nitrite (NOx), the stable oxidation products of NO; plasma L-arginine (L-Arg); and asymmetric dimethylarginine (ADMA). NOx measurements were obtained before treatment (baseline), after 10 and 20 treatments, and at 1 and 4 weeks after therapy. RESULTS: Wound fluid NOx levels tended to increase during treatments, were significantly elevated at 1 and 4 weeks after therapy, and correlated with reductions in wound area. Plasma L-Arg and ADMA were unchanged during and after HBOT. CONCLUSION: This preliminary study documents a significant increase in local wound NO levels (by NOx measurements) after successful HBOT and suggests that this mechanism may be an important factor in promoting enhanced wound healing and wound closure associated with this therapy.

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J Wound Care. 2007 Jun;16(6):245-50.
Retrospective study of factors affecting non-healing of wounds during hyperbaric oxygen therapy.
Oubre CM, **Roy A**, **Toner C**, **Kalns J**.
OBJECTIVE: To identify potential factors, including cigarette smoking and diabetes status, that affect wound-healing outcomes during a six-week course of hyperbaric oxygen therapy (HBOT). METHOD: Seventy-three patients with 85 non-healing lower extremity wounds were treated with hyperbaric oxygen therapy (100% oxygen, 2.4 atmosphere absolute, (ATA), for 90 minutes).The wound area was evaluated over the six-week treatment period. RESULTS: A non-hierarchical clustering analysis of normalised wound-area data revealed that healing responses could be segregated into three groups: robust healing (n=31, over 50% reduction in area), minimal healing (n=33, 15% reduction) and non-healing (n=21,60% increase in area). Further analysis revealed that cigarette smoking was associated with poor response ($p<0.0001$), whereas diabetes was not. Robust responders had higher blood levels of creatinine and urea nitrogen, increased peripheral oxygenation (TcpO2), and were younger than less responsive patients. CONCLUSION: The results suggest that response to HBOT is variable and some patients do not benefit from it. Clinicians should evaluate available laboratory values, age and social history to determine if a patient is likely to benefit from HBOT.

Scand J Plast Reconstr Surg Hand Surg. 2006;40(5):257-60.
Effect of hyperbaric oxygen on survival of composite grafts in rats.
Fodor L, **Ramon Y**, **Meilik B**, **Carmi N**, **Shoshani O**, **Ullmann Y**.
Most treatment with hyperbaric oxygen (HBO) in plastic surgery is for wounds, burns, crush injuries, and infections. We aimed to find out if HBO increases the survival of composite grafts in rats. Twenty Sprague-Dawley rats were randomly assigned to two equal groups (treatment and control). A template 30 x 30 mm was placed on the skin and a composite graft taken from the upper back was harvested and then resutured to the fascia in situ. The treated group was placed in a hyperbaric chamber set at 202 kPa and 100% oxygen for 90 minutes daily for two weeks. Control animals were given no treatment. After death the mean surviving internal surface area of the graft was 372.5 (117.9) mm2 in the control group and 561.3 (85.7) mm2 in the experimental group ($p=0.001$). Treatment with HBO improved the surviving area of composite grafts in rats, and the beneficial effect was prominent only on the inner surface of the graft.

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Plast Surg Nurs. 2005 Apr-Jun;25(2):72-80
Understanding hyperbaric oxygen therapy and its use in the treatment of compromised skin grafts and flaps.
Phillips JC.
Nonhealing wounds represent a problem involving inadequate oxygenation of the tissues that can lead to hypoxic injury. Hyperbaric oxygen therapy can be used as an adjunctive therapy for compromised grafts and flaps that have failed to show improvement with standard wound therapy and offer additional physiologic benefits in the reversal of wound hypoxia and hypoperfusion. A literature review confirms the efficacy of hyperbaric oxygen therapy in nonhealing wounds and compromised skin grafts and flaps. The purpose of this article is to review the role of oxygen and physiological effects of hyperbaric oxygen therapy in wound healing and to provide an overview of the hyperbaric oxygen therapy experience including indications, types of chambers, patient preparation, complications, and treatment protocols. This article is intended to provide nurses working in plastic surgery the information necessary to consider the benefits that hyperbaric oxygen therapy can offer to improve the healing potential of patients with compromised skin grafts and flaps.

Br J Surg. 2005 Jan;92(1):24-32.
Systematic review of hyperbaric oxygen in the management of chronic wounds.
Roeckl-Wiedmann I, **Bennett M**, **Kranke P**.
BACKGROUND: Many therapeutic options exist for chronic wounds. Hyperbaric oxygen therapy (HBOT) is one such option. It may be used for diabetic, venous, arterial and pressure ulcers. METHODS: Following a systematic search of the literature, pooled analyses of predetermined clinical outcomes of randomized controlled trials involving the use of HBOT for chronic wounds were performed. Relative risks (RR) and number needed to treat (NNT) with 95 per cent confidence intervals (c.i.) were calculated. RESULTS: Six studies met the inclusion criteria. No appropriate trials were located for arterial and pressure ulcers. Pooled data from five trials on diabetic ulcers (118 patients) suggested a significant reduction in the risk of major amputation with HBOT (RR: 0.31; c.i. 0.13 to 0.71) with a NNT of 4 (c.i. 3 to 11). Sensitivity analyses did not alter the results. Ulcer healing and the rate of minor amputation were not influenced by HBOT. Data from one trial on venous ulcers suggested significant wound size reduction at the end of the treatment, but not at follow-up. CONCLUSIONS: There is evidence that HBOT reduces the risk of major amputation in diabetic patients. For venous, arterial or pressure ulcers there is a lack of data. Further trials may be warranted.

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Cochrane Database Syst Rev. 2004;(2):CD004123.
Hyperbaric oxygen therapy for chronic wounds. - Kranke P, **Bennett M**, **Roeckl-Wiedmann**
BACKGROUND: Chronic wounds are common and present a health problem with significant effect on quality of life. The wide range of therapeutic strategies for such wounds reflects the various pathologies that may cause tissue breakdown, including poor blood supply resulting in inadequate oxygenation of the wound bed. Hyperbaric oxygen therapy (HBOT) has been suggested to improve oxygen supply to wounds and therefore improve their healing. OBJECTIVES: To assess the benefits and harms of adjunctive HBOT for treating chronic ulcers of the lower limb (diabetic foot ulcers, venous and arterial ulcers and pressure ulcers). SEARCH STRATEGY: We searched the Cochrane Wounds Group Specialised Trial Register (searched 6 February 2003), CENTRAL (The Cochrane Library Issue 1, 2003), Medline (1966 - 2003), EMBASE (1974 - 2003), DORCTHIM (1996 - 2003), and reference lists of articles. SELECTION CRITERIA: Randomised studies comparing the effect on chronic wound healing of therapeutic regimens which include HBOT with those that exclude HBOT (with or without sham therapy). DATA COLLECTION AND ANALYSIS: Three reviewers independently evaluated the quality of the relevant trials using the validated Oxford-Scale (Jadad 1996) and extracted the data from the included trials. MAIN RESULTS: Five trials contributed to this review. Diabetic foot ulcer (4 trials, 147 patients): Pooled data of three trials with 118 patients showed a reduction in the risk of major amputation when adjunctive HBOT was used, compared to the alternative therapy (RR 0.31, 95% CI 0.13 to 0.71). Sensitivity analysis for the allocation of dropouts did not significantly alter that result. This analysis predicts that we would need to treat 4 individuals with HBOT in order to prevent 1 amputation in the short term (NNT 4, 95% CI 3 to 11). There was no statistically significant difference in minor amputation rate (pooled data of two trials with 48 patients). Healing rates were reported in one trial (Abidia 2003) which showed a significant improvement in the chance of healing 1 year after therapy (RR for failure to heal with sham 2.3, 95%CI 1.1 to 4.7, P=0.03), although no effect was determined immediately post HBOT, nor at 6 months. Further, the beneficial effect after 1 year was sensitive to allocation of dropouts.Venous ulcer: (1 trial, 16 patients): This trial reported data at six weeks (wound size reduction) and 18 weeks (wound size reduction and healing rate) and suggested a significant benefit of HBOT in terms of reduction in ulcer area only at 6 weeks (WMD 33%, 95%CI 19% to 47%, P<0.00001). Arterial and pressure ulcers: No trials that satisfied inclusion criteria were located. REVIEWERS' CONCLUSIONS: In people with foot ulcers due to diabetes, HBOT significantly reduced the risk of major amputation and may improve the chance of healing at 1 year. The application of HBOT to these patients may be justified where HBOT facilities are available, however economic evaluations should be undertaken. In view of the modest number of patients, methodological shortcomings and poor reporting, this result should be interpreted cautiously however, and an appropriately powered trial of high methodological rigour is justified to verify this finding and further define those patients who can be expected to derive most benefit from HBOT. Regarding the effect of HBOT on chronic wounds associated with other pathologies, any benefit from HBOT will need to be examined in further, rigorous randomised trials.

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World J Surg. 2004 Mar;28(3):294-300. Epub 2004 Feb 17.
Oxygen in wound healing--more than a nutrient.
Tandara AA, **Mustoe TA**.
This article provides an overview of the role of oxygen in wound healing. The understanding of this role has undergone a major evolution from its long-recognized importance as an essential factor for oxidative metabolism, to its recognition as an important cell signal interacting with growth factors and other signals to regulate signal transduction pathways. Our laboratory has been engaged in the study of animal models of skin ischemia to explore in vivo the impact of hypoxia as well as the use of oxygen as a therapeutic agent either alone or in combination with other agents such as growth factors. We have demonstrated a synergistic effect of systemic hyperbaric oxygen and growth factors that has been substantiated by Hunt's group. Within the past 10 years research in the field of wound healing has given new insight into the mechanism of action of hypoxia and hyperoxia as modifiers of the normal time-course of wound healing. The article concludes with a discussion of why hypoxia and hyperoxia intercurrently play an important role in wound healing. Hypoxia-inducible factor 1 is crucial in that interplay.

Ann Plast Surg. 2004 Aug;53(2):141-5.
The effect of hyperbaric oxygen therapy on composite graft survival.
Li EN, **Menon NG**, **Rodriguez ED**, **Norkunas M**, **Rosenthal RE**, **Goldberg NH**, **Silverman RP**.
Auricular composite grafts are a useful reconstructive option, particularly for nasal reconstruction. This study evaluates the effect of hyperbaric oxygen (HBO) therapy on auricular composite graft survival in rabbits. Circular chondrocutaneous composite grafts of 0.5, 1, or 2 cm in diameter were resected from the ears of rabbits. The grafts were sutured back into position. Half the rabbits in each group received HBO postoperatively, consisting of 90 minutes at 2.4 atm. Rabbits received 7 treatments in 5 days. Control rabbits did not receive HBO. On day 21 the percentage area of graft survival was calculated from gross and histologic examination. Two-centimeter grafts treated with HBO (n = 8) had a mean graft survival rate of 85.8 +/- 15.7% compared with a survival rate of 51.31 +/- 38.5% for the control group (n = 8; P = 0.0478). There was no such benefit in smaller grafts. HBO could prove clinically useful for larger composite grafts.

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Ann Plast Surg. 2003 Nov;51(5):478-87.

The effect of hyperbaric oxygen on ischemia-reperfusion injury: an experimental study in a rat musculocutaneous flap.

Hong JP, **Kwon H**, **Chung YK**, **Jung SH**.

The effect of hyperbaric oxygen is known to increase survival of ischemic tissue but its mechanism is not fully understood. The purpose of this study was to evaluate the effect of hyperbaric oxygen on a rat musculocutaneous flap versus ischemia-reperfusion injury, focusing on the mechanism involving the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) of endothelial cells and CD18 of neutrophils. A transverse rectus abdominis musculocutaneous (TRAM) flap (6 x 5 cm) supplied by a single superior epigastric vascular pedicle was elevated in 100 Sprague-Dawley rats. The rats were divided into 4 groups: group 0, sham (n = 10); group I, 4 hours of ischemia followed by reperfusion (n = 30); group II, 4 hours of ischemia and hyperbaric oxygen (100% oxygen, 2.5 atm absolute, during the last 90 minutes of ischemia before reperfusion) followed by reperfusion (n = 30); and group III, 4 hours of ischemia followed by reperfusion and hyperbaric oxygen (100% oxygen, 2.5 atm absolute, after reperfusion for 90 minutes; n = 30). The study consisted of gross examination for flap survival, histology, immunohistochemical staining, myeloperoxidase assay, flow cytometric study of CD18, and Northern blot analysis on ICAM-1 messenger ribonucleic acid expression. Gross measurement of the flap showed increased survival in groups II and III compared with group I ($P < 0.05$). The leukocytes adherent to the endothelium were counted at 24 hours and on day 5. Group I leukocytes were significantly increased compared with groups II and III ($P < 0.05$). The myeloperoxidase assay of TRAM flaps at 24 hours revealed a significant increase in group I compared with groups II and III ($P < 0.05$). The expression of CD18 was similar between groups I, II, and III. Immunohistochemical staining for ICAM-1 and Northern blot analysis on ICAM-1 messenger ribonucleic acid showed decreased expression in groups II and III compared with group I. Throughout the analysis, groups II and III did not show any significant differences. These results suggests that hyperbaric oxygen reduces the accumulation of leukocytes in the TRAM flap, but not enough to prevent adhesion of neutrophils on endothelial cells; ischemia-reperfusion injury increases the expression of CD18 and ICAM-1 and causes increased adhesion of leukocytes on the endothelium; hyperbaric oxygen does not alter the expression of CD18 but decreases the expression of ICAM-1; and the point of application for hyperbaric oxygen, whether applied before or after reperfusion, did not show any differences in outcome. In conclusion, the application of hyperbaric oxygen against ischemia-reperfusion injury increases flap survival and the beneficial effect may be explained by a protective mechanism involving downregulation of ICAM-1 on endothelial cells.

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Ann Plast Surg. 2003 Aug;51(2):210-8.
A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation.
Hess CL, Howard MA, Attinger CE.
Chronic or non-healing wounds may develop in the setting of many diseases and are the source of considerable morbidity as well as health costs. These wounds demand an aggressive, multifactorial approach including surgical debridement, revascularization, antibiotics and dressings. In addition several adjuvant treatment methods have been developed to further stimulate healing. Whirlpool, although used frequently, has not been proven to be of benefit. However, pulsed lavage does show a promising future. Ultrasound has demonstrated beneficial effects but further controlled studies are needed. Subatmospheric pressure therapy is associated with few complications and is fast becoming a mainstay of adjuvant therapy. Hyperbaric oxygen therapy has been shown to be effective for many types of wounds. Unfortunately, cost and access to chambers may prohibit its use on a routine basis. Finally, electrostimulation may be one of the up and coming therapies for the future. Though, more studies are needed to determine the mode of delivery for various types of wounds.

Clin Plast Surg. 2003 Jan;30(1):67-75.
Hyperbaric oxygen and wound healing.
Zamboni WA, **Browder LK**, **Martinez J**.
Problem wounds, which fail to respond to traditional medical and surgical therapy, can be challenging to the plastic surgeon. Surgical, outpatient, and inpatient wound care costs can be exorbitant. Indirect costs, such as those related to patient productivity, disability, and premature death, can also be significant. The underlying problem in failure of a wound to heal is usually hypoxia and infection. HBO treatments in selected patients can facilitate healing by increasing tissue oxygen tension, thus providing the wound with a more favorable environment for repair. Therefore, HBO therapy can be an important component to any comprehensive wound care program.

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Microsurgery. 2002;22(2):49-52.
Beneficial effect of hyperbaric oxygen on island flaps subjected to secondary venous ischemia. Gampper TJ, **Zhang F**, **Mofakhami NF**, **Morgan RF**, **Amiss R**, **Hoard MA**, **Angel MF**.
The potential for hyperbaric oxygen therapy (HBO) to decrease the untoward effects of a secondary ischemic event was studied in the rat superficial epigastric flap model. The secondary venous ischemic flap was created by cross-clamping the vascular pedicles for 2 h. Twenty-four hours later, the flap was reelevated and the venous pedicle was occluded for 5 h. Thirty-two rats were divided into three groups. In experimental group 1, animals received HBO treatment immediately prior to the initial flap elevation and ischemia at 2 atmosphere pressures for 90 min. In experimental group 2, the rats underwent a similar course except for a second 90-min HBO course immediately prior to the secondary venous occlusion. The rats without HBO therapy were used as controls. The results showed that all control flaps were nonviable at 1 week by clinical inspection and fluorescein injection. Complete flap survival occurred in 20% of group 1 flaps and 30.8% of group 2 flaps. Partial flap survival occurred in the rest of the flaps in these two groups, with mean survival areas of 48% and 55%, respectively. In conclusion, HBO treatments significantly increase the survival of flaps subjected to a secondary ischemia, even if administered before the primary ischemia. Administering HBO prior to secondary venous ischemia was marginal, which may be due to the effect of O(2) given by HBO not lasting longer than 5 h.

Otolaryngol Clin North Am. 2001 Aug;34(4):753-66, vi.
Applications of hyperbaric oxygen in otolaryngology head and neck surgery: facial cutaneous flaps. Bill TJ, **Hoard MA**, **Gampper TJ**.
Hyperbaric oxygen therapy is of significant benefit in the setting of an ischemic flap of the head and neck. Mechanistically, hyperbaric oxygen decreases local tissue edema and improves oxygen delivery to compromised tissues. Both capillary and fibroblast in-growth occur at a greater rate with hyperbaric oxygen therapy, and there is an increase in the tensile strength of the wound. Additional indications in the head and neck include traumatic composite amputations, necrotizing soft-tissue infections, and osteoradionecrosis of the facial skeleton.

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Arch Surg. 2000 Oct;135(10):1148-53.

Enhancement of wound healing by hyperbaric oxygen and transforming growth factor beta3 in a new chronic wound model in aged rabbits.

Bonomo SR, **Davidson JD**, **Tyrone JW**, **Lin X**, **Mustoe TA**.

HYPOTHESIS: Although hyperbaric oxygen (HBO) has been used clinically for 3 decades, there have been few controlled clinical trials. Animal models have not been adequate to test the efficacy of HBO in the treatment of chronic wounds, either by itself or in combination with growth factors. We hypothesize that HBO is as efficacious as a prototype growth factor in improving wound healing in a new animal model of ischemic chronic wounds. DESIGN: Twenty-five aged rabbits and 3 young rabbits had their ears rendered chronically ischemic and ulcers were created down to the level of cartilage. These ulcers were treated in 1 of 3 ways: with HBO, 90 minutes per day, Monday through Friday, for 4 weeks; with transforming growth factor beta(3) at 1 microg/cm(2); or with both modalities combined. Controls were treated with vehicle or hyperbaric room air or both. RESULTS: This model created an aged/ischemic wound that failed to heal spontaneously up to 26 days after wounding (88% reduction compared with aged/nonischemic controls). Hyperbaric oxygen alone and transforming growth factor beta(3) alone both improved healing rate (only 38% reduction in healing compared with aged/nonischemic controls). Combined therapy produced no additional improvement over either modality by itself. CONCLUSIONS: In aged animals, HBO and transforming growth factor beta(3) were equally effective in improving wound healing. Our data suggest that HBO alone may be more effective in the chronic wound than in the acute wound. There was no additive benefit to combining modalities as has been reported in the same wound model in young rabbits.

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Plast Reconstr Surg. 1998 Apr;101(5):1290-5.

Stimulation of angiogenesis to improve the viability of prefabricated flaps.

Bayati S, **Russell RC**, **Roth AC**.

The cutaneous area in a prefabricated myocutaneous flap surviving after elevation is dependent on the rate and amount of vascular ingrowth that occurs from the underlying muscle. Two modalities, basic fibroblast growth factor and hyperbaric oxygen, were used separately and together in a prefabricated myocutaneous flap animal model to improve flap survival. The semimembranous muscle, based on the saphenous vessels of 40 female Wistar rats weighing between 250 and 325 grams, was tunneled under the ipsilateral abdominal skin and sutured in place. A 3 x 5-cm silicone sheet was placed beneath the muscle flap, and the ipsilateral epigastric vessels were ligated. Four groups of 10 animals each received one of the following treatment regimes: a 1-ml normal saline infusion into the saphenous arterial pedicle, a 1-ml infusion of basic fibroblast growth factor (1.0 microg/gm of muscle), a 1-ml normal saline infusion and 14 hyperbaric oxygen treatments, or a 1-ml basic fibroblast growth factor infusion and 14 hyperbaric oxygen treatments. After 1 week, the muscle, still based on the saphenous vessels, was elevated with a 3 x 5-cm abdominal skin paddle. The flap was sutured back in place, leaving the silicone sheet intact. The surviving area of each flap was measured 1 week later after it had demarcated into viable and necrotic regions. Laser Doppler skin perfusion measurements were taken before and after flap elevation and before animal euthanasia. Sixteen flaps, 4 in each group, were examined histologically for vascularity by means of hematoxylin and eosin staining. There was a statistically significant increase in flap survival area when either basic fibroblast growth factor or hyperbaric oxygen was used alone. Further improvement was noted with combination therapy. Histology confirmed improved vascularity in the basic fibroblast growth factor and hyperbaric oxygen-treated flaps. This study shows a significant and reliable increase in the area of prefabricated myocutaneous flap survival using either basic fibroblast growth factor or hyperbaric oxygen. There is a further complementary effect when these two modalities are combined, leading to near complete flap survival through improved vascularity.

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Clin Podiatr Med Surg. 1998 Jan;15(1):117-28.

Wound healing. New modalities for a new millennium.

Williams RL, **Armstrong DG**.

Common to all studies of wound healing modalities is the need to convert the chronic wound into an acute wound and to maintain the wound in an acute state while subsequently using adjunctive therapy. Hence, precise control and documentation of wound care is extremely important in order to avoid contamination of the effects of a specific modality with the effects of good wound care. Falanga has noted that neuropathy of diabetes has been given wide support as the primary pathogenic component of diabetic ulcers, whereas less recognition has been made of the wound-healing failure component. The therapies discussed in this article considered the wound-healing failure component. Oxygen is a drug. The use of oxygen under normobaric conditions at higher than normal inspired partial pressures is standard operating procedure when clinicians are faced with patients with respiratory embarrassment or heart failure. The use of oxygen under hyperbaric conditions, however, remains estranged from the mainstream thoughts of most clinicians. Abnormally hypoxic wounds may benefit from specific oxygen therapy in hyperbaric dosage ranges. However, correction of abnormal wound oxygen tension alone does not guarantee healing. Hyperbaric studies have been criticized for the lack of well-defined wound care protocols, the absence of precise wound healing measures, and poorly defined wound healing endpoints. Studies with growth factors and human skin equivalents exclude patients typically referred for hyperbaric therapy. Patients referred for hyperbaric therapy often have larger wounds with greater severity of peripheral vascular disease with ABIs < 0.7 and TcPO2 < 30 to 40 mm Hg, are often on medications known to inhibit wound healing (e.g., steroids), or have concomitant medical disorders (collagen vascular disease, renal failure) associated with poor healing. No hyperbaric study has controlled stringently for all of these factors. Nevertheless, HBO2 is more specific and successful for the intended purpose of correction of abnormal tissue oxygen tensions than are growth factors for the intended purpose of growth. Similarly, skin substitutes are limited in their application and have not been tried in patients with ABIs < 0.7 or TcPO2 values < 30 mm Hg. In our view, hyperbaric therapy probably can be combined successfully with allogenic grafts and human skin equivalents in this group of patients. Hyperbaric therapy can generate a sufficient granulation base in which these products should be able to close properly selected wounds successfully. No studies of this combined modality approach exist. Finally, regardless of the modality used to aid in wound closure, long-term outcomes probably depend more on neuropathy and large vessel disease than on microangiopathy and local wound-healing defects. The modalities presented in this article must prove to be both cost effective and practical before they are widely disseminated. Nevertheless, the ability to manipulate the local wound environment is no longer inviolate as was once presumed, and current investigations continue to advance therapeutic options in this most fascinating and challenging discipline.

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Undersea Hyperb Med. 1997 Sep;24(3):175-9.
Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study.
Zamboni WA, **Wong HP**, **Stephenson LL**, **Pfeifer MA**.
The purpose of this study was to prospectively evaluate the effect of hyperbaric oxygen (HBO2) on the healing of diabetic lower extremity wounds. Ten consecutive insulin-dependent diabetic patients with chronic lower extremity wounds were referred for HBO2 treatment. The control group consisted of five patients, two claustrophobic and three rural. The latter refused HBO2 treatments because of logistic reasons. Five patients underwent 30 HBO2 treatments in the problem wound protocol (100% oxygen, 2 atm abs, 2 h/day, 5 days/wk). All patients were evaluated with transcutaneous oxygen measurements and had an initial surgical debridement of the wound. Weekly tracings of the wound surface area were made by a nurse or resident who was blinded to the group assignment. At the end of 7 wk, the mean wound area expressed as a percentage of pretreatment baseline area was compared between groups (analysis of variance, Duncan's post hoc). No significant differences were noted between groups with respect to age, gender, baseline wound area, wound site O2 tension, or presence of osteomyelitis. At the completion of each of the 7-wk treatment periods, a significantly greater reduction in wound surface area was noted in the HBO2 vs. the control group ($P < 0.05$). HBO2 treatment significantly reduced wound size compared to controls in this small, non-randomized prospective study. These results should serve as a basis for larger multicenter prospective, randomized, double-blind controlled studies to definitively evaluate the effect of HBO2 on the healing of diabetic foot wounds.

Ann Plast Surg. 1992 Apr;28(4):339-41.
The effect of hyperbaric oxygen on reperfusion of ischemic axial skin flaps: a laser Doppler analysis.
Zamboni WA, **Roth AC**, **Russell RC**, **Smoot EC**.
This study evaluates the microvascular reperfusion of ischemic skin flaps with and without acute hyperbaric oxygen (HBO) treatment. Thirty-two axial pattern epigastric skin flaps (3 x 6 cm) in male Wistar rats were subjected to 8 hours of global ischemia by pedicle clamp occlusion. The rats were divided into the following control and two experimental groups: Control (n = 12) with ischemia, no HBO; Group 1 (n = 11) with HBO treatment (three 1.75-hour dives, 2.5 absolute atm, 100% O2) during ischemia; and Group 2 (n = 9) with HBO treatment (two 1.75-hour dives) immediately after ischemia. Laser Doppler flows were recorded in two distal standardized flap locations at 0.5, 2, 4, and 18 hours after reperfusion in control rats and Group 1 rats and at 18 hours only in Group 2 rats, using a Med-Pacific 6000 laser Doppler unit. Mean distal flap laser Doppler flows (mV) were Control: 0.5 hours = 23.2 +/- 11.9, 2 hours = 52.8 +/- 27.3, 4 hours = 53.6 +/- 32.1, 18 hours = 40.2 +/- 36.2; Group 1: 0.5 hours = 71.8 +/- 30.9 (p less than 0.05 vs. control), 2 hours = 74.3 +/- 27.3, 4 hours = 67.4 +/- 20.6, 18 hours = 79.1 +/- 40.3 (p less than 0.05 vs. control); and Group 2: 18 hours = 90.3 +/- 47.9 (p less than 0.05 vs. control). It is concluded that acute HBO treatment of ischemic rat skin flaps improves distal microvascular perfusion as measured by laser Doppler flowmetry. This effect is observed for HBO treatment given either during or immediately after prolonged global ischemia.(ABSTRACT TRUNCATED AT 250 WORDS)

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