Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy?

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There have been many advances in the treatment of wounds made in the last decade. Innovative techniques of wound closure, topical agents, aggressive vascular repair, focused wound care management, and adjunctive hyperbaric oxygen therapy are but a few of these improvements. The vital role of oxygen in wound healing is becoming better understood, in no small part, due to Dr. T. K. Hunt and his colleagues at the Wound Healing Laboratory at the University of California, San Francisco. Elements of that contribution will be examined in this article. How these elements may be applied to improve wound healing will be explained and the possible role of adjunctive hyperbaric oxygen therapy based on sound science in the management of the difficult diabetic foot wound, will be highlighted. (WOUND REP REG 2004;12:2–10)

Diabetes mellitus affects 5–6 percent of the population, half of whom are undiagnosed. The annual cost of care exceeded $92 billion in 1999. Recent data from a study at a major health maintenance organization involving more than 17,500 diabetic patients showed they consumed 2.4 times more health care dollars than nondiabetic controls ($480,660 718 vs. $197,948 887). The federal government has become increasingly aware of this problem. Indeed, in an address to the House of Representatives in March 1998, Newt Gingrich stated that diabetics account for 27 percent of the federal medical budget. At any given time, there are perhaps a million diabetic patients suffering from lower extremity ulcers. Twenty percent of hospital admissions of diabetics are because of lower limb problems. The incidence of amputation is 6 per 1000; therefore, diabetics account for 50–70 percent of the annual non-traumatic amputations in the United States. From 1993 to 1995, approximately 67,000 amputations were performed yearly among people with diabetes. Nine percent required amputation of a foot, 31 percent of the lower leg, and 30 percent at or above the knee. The cost of amputation was reported to be in excess of $40,000 in 1986. Medicare reimbursement for primary amputation varies widely but is approximately $12,500.

There is little appreciation of the morbidity and mortality associated with amputation, which is significant. Ipsilateral, often higher amputation occurs in 22 percent of cases, and contralateral amputation occurs at a rate of approximately 10 percent per year. Sixty-eight percent of elderly amputees will be alive at 4 years, although only 40–50 percent of elderly amputees can be successfully rehabilitated. The length of hospital stay for primary amputation varies widely but has been reported to average 22 days. Six to nine months may be necessary to maximize walking ability. In 1997 dollars the cost of amputation is in excess of $2.7 billion yearly. Readmission within 2 years for stump modification or re-amputation may represent an additional $1.5 billion exposure. The mortality associated with amputation at a major teaching hospital...
was recently reported as 4 percent. Morbidity, including myocardial infarction, arrhythmia, or congestive heart failure requiring therapy was shown to be 14 percent. Clearly, these data show that primary amputation is far from an expeditious solution to the problem of foot wounds in diabetics. Total cost for patients who achieved healing and did not have critical ischemia in a recent study was $16,000 compared to $63,000 for patients requiring major amputation. An aggressive multidisciplinary team approach to diabetic foot management can result in improved salvage and significant cost savings.

We have utilized the following regimen at our community hospital since 1983. Patients are quickly evaluated, seen by appropriate specialists, revascularized aggressively when necessary, and, when indicated, given adjunctive hyperbaric oxygen therapy. There have been many advances in the treatment of the diabetic foot over the last two decades, and these include improvement in diabetic control; aggressive revascularization techniques, both percutaneously and through surgical bypass; focused wound care; and the use of topical agents. Despite this progress, many limbs are lost with the attendant long-term costs, both in dollars and quality of life. Recently, the importance of hypoxia as a major determinant of limb loss has been appreciated. The single best predictor of limb loss is transcutaneous oxygen (TcPO2) values below 30 mmHg while breathing room air. Clearly, any method of improving oxygen delivery, be it through improvement in circulation or increasing oxygen delivery or both, would be beneficial.

**PATHOPHYSIOLOGY OF THE DIABETIC FOOT**

The diabetic foot is characterized by sensory, motor, and autonomic neuropathy and macro- and microvascular disease, which can ultimately lead to ulceration, infection, gangrene, and amputation. Motor neuropathy may cause pressure distribution perturbation; foot deformities and altered sensation can result in ulceration. The classic plantar ulcer is caused by loss of sensation and painless trauma. This can occur in the absence of ischemia and frequently heals, in this instance, with conservative measures such as unweighting and aggressive wound management. Autonomic neuropathy may cause alterations in blood flow and diversion of nutritive flow resulting in cutaneous ischemia. Ulcers associated with ischemia may show pathophysiologic alterations involving small cutaneous vessels in addition to the contribution of major arterial insufficiency. Many diabetics have areas of low flow and hypoxia in their feet and ankles, even in the presence of palpable pulses. Contributing factors include platelet aggregation, altered blood viscosity, accelerated capillary growth, and adherence of leukocytes to capillary endothelial walls. Progressive capillary wall hyalinization leads to small vessel obstruction. Surgical re-vascularization can often provide the necessary substrate for wound healing. However, some wounds, in spite of reestablishment of adequate circulation, fail to heal, even when tissue perfusion appears adequate.

Defective wound healing is a major factor contributing to limb loss. Thrombosis also predisposes to ulceration and gangrene. Joseph and LeFrock reported that in the diabetic, response to local tissue stresses is by thrombosis and necrosis as opposed to inflammatory response in nondiabetics. Tight diabetic control appears to delay the onset or prevent the progression of microvascular complications. The crucial role of endothelium in the regulation of local microvascular hemodynamics is now apparent. Injury to the endothelium due to increased pressure and flow ultimately leads to sclerosis. The role of nitric oxide and white cell adherence in this process is being elucidated. Recent data suggest that hyperbaric oxygen may have a direct beneficial effect on the endothelium by preventing or modulating white cell adherence. This, in effect, is mediated in part through increased levels of endothelial nitric oxide. These findings are in agreement with observed clinical results. Regardless of the mechanisms, however, the net result of excessive adherence is hypoxia that involves regions of the foot, ankle, or toes.

**RATIONALE FOR THERAPY—ROLE OF OXYGEN IN HEALING**

Dr. Hunt and colleagues have helped to elucidate the basic mechanisms of wound healing and have increased our understanding of means to modify the process. He showed that injuries that damage the microvasculature initiate several chemoattractant and growth factor pathways, including the coagulation and complement cascades. Consequently, inflammatory cells that consume large amounts of oxygen collect at the wound site. Thus, most injuries and infections create energy-poor environments characterized by poor local perfusion, low oxygen tensions, increased oxidant production, low pH, and high lactate. Macrophages sense this environment and, because of it, release potent growth factors resulting in brisk angiogenesis and multiplication of fibroblasts at the wound margins. High lactate also stimulates growth factor secretions by inflammatory cells and appears to be sufficient stimulus to maintain wound healing when oxygen tension increases. As macrophages move into the injured area, fibroblasts begin to multiply and migrate after...
them. Endothelial buds then follow, largely from venules, and follow fibroblasts into hypoxic, highly lactate-rich areas. Under the influence of growth factors that respond to lactate, or the influence of lactate on the cellular microenvironment, fibroblasts transcribe collagen genes and synthesize collagen. Most of these events can proceed in very low oxygen tensions. A variety of mechanisms, clotting, complement activation, oxidant release, and others, stimulate release of growth factors. However, fibroblasts must modify the collagen they synthesize so it can be secreted into the extracellular space and become polymerized. This vital step can only be accomplished when oxygen is present at rather high partial pressures (Figure 1). Collagen is deposited most rapidly when both lactate and oxygen concentrations are high. Dr. Hunt’s laboratory has shown that the idea that this process can be initiated by lactate as a signal of energy deficit and accelerated by hyperoxia is not a paradox because macrophages release lactate, even in well-oxygenated environments, and continue to produce it in well-oxygenated wounds. This stimulus to collagen production remains, therefore, even during hypoxia. The need for oxygen, however, persists well into the healing process because new collagen must be deposited as old collagen is lysed. Production must accommodate the degradation if wounds are to heal and maintain strength. O₂ availability is rate limiting in at least two important steps in collagen biosynthesis. In the synthetic pathway of collagen, proline and lysine are incorporated into the growing peptide chain and are hydroxylated later when peptides enter the endoplasmic reticulum. These hydroxylation reactions are necessary for the polymerization and cross-linkage of procollagen strands and the transport of collagen molecules to the extracellular space. This process proceeds at one-half the normal rate at an oxygen tension (PO₂) of 20 mmHg and at 90 percent of the maximal rate at about 200 mmHg (Figure 1). Thus, collagen deposition, the process that fills new tissue growth in wound defects and supports new blood vessels, proceeds in proportion to local oxygen tensions, even throughout and beyond the entire physiologic range.

Cell replication also requires oxygen. Fibroblasts and vascular endothelial cells have been reported to replicate most rapidly at about 40 mmHg, whereas epidermal cells replicate best at about 700 mmHg. Hehenberger et al. have reported that diabetic fibroblasts show diminished cell turnover when compared to normal controls. Hyperbaric oxygen exposure resulted in dramatic increases in cell proliferation which were proportional to O₂ tensions, a maximum effect being seen at 2.5 ATA (atmospheres absolute; the pressure equivalent of breathing 100 percent oxygen at 45 feet of sea water) (Figures 2 and 3). Of note, pressures beyond 2.5 ATA were associated with a drop-off in proliferation, indicative of possible O₂ toxicity. Any interference with oxygen delivery to wounds also increases susceptibility to infection. Wounds of the

![Figure 1](image1.png)

**FIGURE 1.** Kinetics of prolyl hydroxylase (Km = 25 mmHg). Reaction velocity of prolyl hydroxylase depends on the concentration of oxygen in the endoplasmic reticulum, with half maximal velocity (Km) at about 20 mmHg. Normally, the PO₂ there varies between a few to perhaps 50 mmHg. Normal mean probably is in the region of 30–40 mmHg. In foot lesions in diabetics the number of focal areas at which PO₂ is zero increases markedly, and the mean may fall close to zero. Clearly, there is better collagen deposition at somewhat higher levels. (Courtesy of T. K. Hunt, MD)

![Figure 2](image2.png)

**FIGURE 2.** DNA content, expressed as fluorescence units, of human fibroblasts derived from normal skin (filled bars) and from chronic diabetic wounds (shaded bars) 24 hours after a 1-hour treatment at multiple oxygen pressures. Values represent the mean ± standard deviation of five different patients, each assayed in triplicate. Significant difference (*p < 0.05, **p < 0.01) compared with 21 kPa (untreated cells). (Reprinted from 48 with permission)
extremities are often infected, whereas those of tissues that have higher blood flow and thus higher tissue oxygen tensions, such as the tongue or face, are rarely infected. The difference between these sites is blood flow and PO2 in the wounds. Blood flow in extremities may be low due to regional arterial obstructions, small vessel disease, sympathetic nervous perturbation, cold, pain, or dehydration. Leukocytes kill bacteria most effectively when supplied with abundant oxygen (Figure 4). Phagocytosis stimulates a huge, often five-fold increase in oxygen consumption, the so-called "respiratory burst." At least 98 percent of this oxygen is converted to superoxide anion, peroxide, and other reactive oxygen species (oxygen radicals) which, when released into phagosomes, are lethal to many bacteria. This oxidative mechanism is most effective in high PO2, even up to several hundred millimeters of mercury. The key enzyme that converts oxygen to superoxide anion has kinetics similar to those of prolyl hydroxylase, but the k_m is even higher (k_m about 50). It fails rapidly as tissue PO2 falls to less than 30–40 mmHg. Hunt et al. showed that oxidative and antibiotic killing of bacteria are independent mechanisms and are additive in wounds. Several investigators also demonstrated that random flaps, which have low distal oxygen tensions analogous to those measured near diabetic foot ulcers, are susceptible to infection and suffer a high degree of necrosis, and that oxygen administration to elevate PO2 values to more than 100 mmHg minimizes infection/necrosis. Borer has seen significant improvement in diabetic white cell function when exposed to elevated doses of oxygen. This effect seems to be mediated by both adherence molecules, e.g., intercellular adhesion molecule, and increased levels of nitric oxide (NO). We are also beginning to elucidate the vital role of reactive oxygen species on cell signaling and stimulation of growth factors in support of wound healing.
WOUND ANGIOGENESIS

Stimulation and regulation of angiogenesis are similar in principle to that of collagen synthesis and deposition. Increased lactate concentration and production of oxidants such as NO, hydrogen peroxide, and O₂ stimulate macrophages to produce angiogenic substances that are both chemoattractant and growth factors to endothelial cells. The most important of these in wounds appears to be vascular endothelial growth factor (VEGF). VEGF secretion responds to mild exposure to oxidants and lactates, stimulants that are not inhibited by hyperoxia. In fact, they are enhanced by elevated oxygen tensions (Figure 5). As noted previously, hyperoxia does not lower lactate in wounds. From both clinical observation and laboratory experience, there is no longer any doubt that angiogenesis occurs most rapidly in well-oxygenated animals. In recent studies, Hunt and colleagues have shown that anti-VEGF antibody was found to abrogate the effects of hyperbaric oxygen on angiogenesis in a Matrigel model. Hyperbaric oxygen stimulates angiogenesis and leads to an increase in new vessel concentration. As this occurs, transcutaneous PO₂ values increase, and this increase seems to be long lasting. Again we see that there is a dose–response curve as levels increase to a pressure (oxygen dose) of 2.5 ATA, then drop as pressure increases, indicative of probable O₂ toxicity (Figure 5).

CLINICAL OBSERVATIONS

Hyperbaric oxygen has been utilized in the treatment of selected diabetic foot wounds for more than 20 years. The clinical observations were in agreement with and often based on findings from Dr. Hunt’s lab that showed restoration of TcPO₂ to normal or slightly raised levels, enhanced angiogenesis, fibroplasia, collagen deposition, bacterial killing, and epithelialization. While controversy remains as to whether specific cellular immunity is diminished in diabetics in the absence of hypoglycemia, no one disputes that hypoxia increases morbidity from infection resulting in sepsis, loss of life or limb, or both. While hyperbaric exposure in the clinical setting is brief, perhaps 2–3 hours daily, oxygen tensions remain elevated for some time after cessation of therapy (Figure 6). Siddiqui and colleagues have demonstrated that subcutaneous oxygen tensions remain elevated for several hours after exposure, and that over time this phenomenon disappears as angiogenesis progresses (Figure 7). In the long run, the effect of hyperbaric oxygen on angiogenesis may be the fundamental one. Sheffield elegantly demonstrated improvement in capillarity, measuring TcPO₂ levels over healing tissue in diabetic feet. His data clearly documented the slow improvement in blood flow over the first 3 weeks of therapy as evidenced by rising oxygen tensions in the tissues, especially during hyperbaric oxygen sessions. Faglia et al. have shown a highly significant and apparently permanent increase in TcPO₂ values in diabetic patients who have benefited from hyperbaric oxygen therapy. Marx et al. have demonstrated the same changes in ischemic irradiated tissue, indicative of improved vascularity.

Adjunctive hyperbaric oxygen therapy

Several groups have reported increased limb salvage utilizing adjunctive hyperbaric oxygen therapy.
Baroni et al.\textsuperscript{78} reported in 1987 a statistically significant reduction in morbidity (amputation) in hyperbaric oxygen-treated patients. Sixteen of 18 patients in their treated group healed, whereas only 1 of the 10 controls healed. The amputation rate was 40 percent in controls vs. 12.5 percent in the treated group (\(p < 0.001\)). Hyperbaric oxygen–treated patients were sufficiently improved to be discharged in 62 days, and 16 went on to complete healing. Nine of the 10 control patients had not healed 82 days later. In a continuation of this study,\textsuperscript{76} 62 patients in the treated group were compared with 18 controls. A 95 percent salvage rate was achieved in the hyperbaric oxygen–treated group in which there were three amputations. The control group suffered six amputations (33 percent, \(p\text{-value < 0.001}\)). The incidence of amputation in the untreated group was essentially unchanged from a historical group of patients treated ten years earlier without adjunctive hyperbaric oxygen therapy. There were no statistical differences in any of the groups relating to age, glycemic control, or diabetic complications. In 1988 our group reported a series of 19 diabetic patients as a subset of 39 patients with serious lower limb lesions (Wagner grade 3–5).\textsuperscript{13} We noted a salvage rate of 89 percent. Forty-two percent of these patients had undergone successful re-vascularization yet had failed to heal. We defined salvage as bipedal ambulation if two limbs were originally present and wound coverage for at least 1 year. Hyperbaric oxygen costs at that time were $12,668 and were reflected in a total hospital charge of $34,370, with an average stay of 35 days. Faglia et al., in a prospective, randomized, and blinded study, showed an 8.6 percent amputation rate in hyperbaric oxygen–treated patients vs. 33.3 percent in controls (\(p\text{-value < 0.016}\)).\textsuperscript{71} Of note, TcPO\textsubscript{2} measurements significantly improved in the hyperbaric oxygen–treated group (14 mmHg ± 11.8 vs. 5 mmHg ± 5.4) over the nontreated group (\(p\text{-value < 0.002}\)). These investigators concluded that hyperbaric oxygen therapy in conjunction with an aggressive multidisciplinary protocol is effective in severe ischemic diabetic foot lesions and that improvements in TcPO\textsubscript{2} values indicative of angiogenesis are probably permanent. There were no differences in any other parameters of the study, including the presence of neuropathy, glycemic control, or other modalities of treatment. Zamboni et al. showed a statistically significant reduction in wound area over an observation period of 7 weeks when hyperbaric oxygen was utilized.\textsuperscript{79} At every point in the study, hyperbaric oxygen–treated patients had smaller wounds. Statistical analysis showed a \(p\text{-value < 0.05}\) at each interval of wound measurement in the hyperbaric-treated patients\textsuperscript{70} (Figure 8). Doctor et al. showed a 10 percent major amputation rate in a series of patients being treated with hyperbaric oxygen therapy vs. 43 percent in the control group.\textsuperscript{80} Hunt and Cianci showed that an aggressive program including adjunctive hyperbaric oxygen therapy resulted in a durable repair. Ninety-four percent of patients maintained an intact limb at 55 months postclosure (Table 1).\textsuperscript{6} These data were borne out by the observations of Kalani et al.\textsuperscript{81} in a randomized study performed at the Karolinska Institute. They showed in a group of diabetic hypoxic foot wounds with initial TcPO\textsubscript{2} lower than 40 mmHg a 76 percent healing rate and intact skin at a follow-up of 3 years in the oxygen-treated group vs. 48 percent healing in the control group. A 33 percent amputation rate was noted in the control group vs. 12 percent in the hyperbaric oxygen-treated patients. Abidia et al. have shown in a double blind, randomized, controlled trial complete epithelialization in 13 of 19 diabetic ulcers treated with hyperbaric oxygen therapy vs. 4 of 14 in the control group.\textsuperscript{82} The decrease in wound size was 96 percent at 12 weeks in the treated group vs. 41 percent in the untreated group (\(p = 0.043\)). Fife and colleagues have shown the predictive value in TcPO\textsubscript{2} measurements
in selecting those patients who might benefit from adjunctive hyperbaric oxygen therapy as part of a comprehensive program. These data are in agreement with Wattel et al. (Figure 9).\textsuperscript{84}

**Recent recommendations**

The value of adjunctive hyperbaric oxygen therapy in the treatment of the diabetic foot has recently been recognized by major insurers, learned organizations, and governmental agencies as evidenced by favorable technology assessments by the British Medical Journal and, of particular note, the American Diabetes Association, which in 1999 endorsed the use of adjunctive hyperbaric oxygen therapy in severe diabetic ischemic lesions that have not responded to more traditional care.\textsuperscript{85,86} The Center for Medical Services, formerly HCFA, has recognized and agreed to reimburse for adjunctive hyperbaric oxygen therapy for Wagner scale grades 3 or greater diabetic foot lesions effective April 1, 2003.\textsuperscript{87} We must continue, however, to refine our patient selection criteria to ensure the most cost-effective use of this resource.

**SUMMARY**

Adjunctive hyperbaric oxygen therapy as part of a comprehensive program of wound care based on sound surgical and medical principles and corroborated both at the basic science level— in no small part due to the numerous contributions of Dr. Hunt and his collaborators over the last 30 years—and concurrently by numerous clinical studies, show that this is an effective means of dealing with an otherwise very difficult and expensive problem and provides us with a new tool in the treatment of severe (Wagner grade 3–5) nonhealing diabetic wounds. The pioneering work of T. K. Hunt and members of his team has made a major contribution to our understanding of the role of oxygen in wound healing. We are now able to utilize the modality more effectively in the treatment of difficult wounds such as the diabetic foot.

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