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# The Adjunctive Role of Hyperbaric Oxygen Therapy in the Treatment of Lower Extremity Wounds in Patients With Diabetes

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### In Brief

Diabetic foot wounds are one of the major complications of diabetes, resulting in substantial morbidity and mortality. One mode of therapy is hyperbaric oxygen therapy (HBO). This therapy is designed to increase oxygen delivery to local ischemic tissue and, by a variety of primary and secondary mechanisms, to facilitate wound healing in the high-risk foot. This article reviews the adjunctive benefits of HBO treatments in the diabetic wound.

Diabetes mellitus is the seventh leading cause of death in the United States and is widely prevalent in American society, affecting nearly 16 million people, or 6% of the U.S. adult population.<sup>1</sup> Moreover, it is estimated that 7.2% of all hospitalizations in the United States involve diabetes, with more than 20% of these because of peripheral vascular disease and its related tissue damage in the lower extremities.<sup>3</sup>

Nearly 50% of all nontraumatic lower extremity amputations performed in the United States are due to diabetes, with an annual incidence of 37–137 per 10,000 patients with this disease.<sup>1</sup> Of these amputations, 9% are of a foot, 31% are of the lower leg, and 30% are at or above the knee.<sup>4</sup> Ipsilateral higher amputations occur in 22% of cases. Contralateral amputations occur at a rate of 10% per year. After 5 years, amputees with diabetes have a 50% chance of bilateral amputation, often due to increased wear on the remaining limb. At any given time, perhaps 1 million patients with diabetes suffer from lower extremity ulcers. Wounds of the lower extremities are thus one of the major complications of diabetes, resulting in substantial morbidity and mortality.

The personal and economic costs of this problem are staggering. The cost of a primary amputation in 1986 dollars was reported to be more than \$40,000.<sup>5</sup> Current Medicare reimbursement for primary amputation is approximately \$10,000.<sup>6</sup> Sixty-eight percent of elderly amputees will be alive after 4 years, and only 40–50% will be successfully rehabilitated.<sup>7,8</sup> The length of hospital stay for primary amputation varies widely but has been reported to range from 22 to 40 days.<sup>3,9</sup> Six to nine months may be necessary to maximize walking ability.<sup>10</sup> Rehabilitation costs can add an additional \$40,000–50,000.<sup>11</sup> The total cost of amputation due to diabetes in the United States is nearly \$1.5 billion per year.<sup>11</sup> Readmission within 2 years for stump modification or re-amputation may represent an additional \$1 billion expenditure.<sup>11</sup>

Primary amputation is far from an expeditious solution to the problem of foot wounds, particularly in patients with diabetes. The U.S. Department of Health has set a goal of reducing the amputation rate among patients with diabetes by 40% by 2000.<sup>12</sup> Any treatment modality that would substantially

reduce the morbidity of diabetic lower extremity wounds would have a profound effect on health-care costs. An aggressive, multidisciplinary team approach to diabetic foot management, in which patients are seen by appropriate specialists and undergo aggressive revascularization when indicated, has resulted in improved salvage and a significant cost benefit.<sup>11,13</sup>

### **Pathophysiology of Diabetic Foot Wounds**

The diabetic foot is characterized by sensorimotor and autonomic neuropathies that lead to alteration of pressure distribution, foot deformities, and ulceration. The classical *mal perforans* ulcer is caused by loss of sensation and painless trauma. This can occur in the absence of ischemia and frequently heals with conservative measures, such as aggressive wound management and unweighting. Primary management is directed to patient education and foot care. Autonomic neuropathy may cause alterations in blood flow, resulting in islands of cutaneous ischemia.<sup>14</sup>

In patients with large-vessel obstruction, the mechanism of wound development is clear, and only the restoration of pulsatile blood flow will allow adequate healing. However, some patients with diabetes who have large-vessel perfusion and palpable pulses will still develop wounds that appear to be hypoxic/ischemic and will fail to heal.<sup>15,16</sup> In these cases, the mechanism of wound development is less clear.

Even in the presence of palpable pulses, patients with diabetes can have areas of low flow and hypoxia in their feet and ankles. Contributing factors may include increased blood viscosity, increased platelet aggregation, and accelerated capillary endothelial growth.<sup>17-19</sup> Capillary wall hyalinization can lead to capillary obstruction,<sup>20,21</sup> and capillary hyperperfusion and vasodilatation can lead to injury via subendothelial deposition of macromolecules.<sup>19</sup> Additionally, patients with diabetes respond to local tissue stresses through thrombosis and necrosis, as opposed to the inflammatory response that occurs in the nondiabetic population.<sup>22</sup> Regardless of the mechanism involved, the net result is focal hypoxia that can involve regions of the ankle, foot, or toes.

Investigators believe that tight control of blood glucose concentration may slow or even reverse this pathological process, and periodic elevation of tissue oxygen tensions can also favorably influence this process. Surgical revascularization, particularly with *in situ* vein grafts, can frequently provide the necessary substrate for wound healing. However, in some cases, wound-healing failure occurs despite restored circulation. This suggests a problem with the wound-healing process itself, and indeed, defective wound healing has been demonstrated to be a major factor in the nonhealing diabetic ulcer.<sup>23</sup>

### **The Wound-Healing Process**

The wound-healing process is a complicated one and is initiated by a complex series of events that include chemoattraction, growth-factor pathways, complement generation, and the energy-poor environments created by low oxygen tensions, low pH, and high lactate concentrations.<sup>24</sup> Macrophages attracted to such environments release lactate aerobically, as well as anaerobically, and generate potent growth factors, resulting in brisk angiogenesis and multiplication of fibroblasts at wound margins. These events can take place in a low-oxygen environment. However, the modification of collagen by fibroblasts so that it can be polymerized and secreted into the extracellular space can be accomplished only when oxygen is present at high partial pressures. Therefore, collagen is deposited most rapidly when both lactate and oxygen concentrations are high. The need for oxygen persists well into the healing process, since new collagen must be deposited as old collagen is lysed. Production and remodeling must be in balance if wounds are to maintain tensile strength.

The mechanisms of oxygen enhancement of wound healing involve the hydroxylation of proline and lysine residues in procollagen. As mentioned above, these hydroxylation processes are necessary for polymerization and cross-linkage of procollagen strands and the transport of collagen molecules to the extracellular space. This process proceeds at one-half maximal rate at a PO<sub>2</sub> (partial pressure of oxygen) of 20 mmHg and at 90% maximal rate at 200 mmHg.<sup>25</sup> Thus, collagen deposition, the process that fills tissue defects and supports new blood vessels, proceeds in proportion to tissue oxygen levels.<sup>26</sup> Cell replication also requires oxygen. Fibroblasts and vascular endothelial cells

replicate most rapidly at a  $PO_2$  of 40 mmHg; epidermal cells may replicate best at 700 mmHg.<sup>27</sup>

Leukocytes kill most effectively when supplied with abundant oxygen,<sup>28</sup> as their most effective killing is accomplished through the oxidative pathway. This mechanism is most efficient in high oxygen concentrations and fails rapidly as tissue oxygen tensions fall below 30–40 mmHg. Therefore, susceptibility to infection increases as tissue oxygen tensions decrease. Accordingly, wounds of the extremities are often infected, while infections are rare in those tissues that have higher flow and higher tissue oxygen tensions, such as in the face, tongue, and anal area. Similarly, well perfused and oxygenated flaps are resistant to infection and infectious gangrene, whereas random flaps, which have low oxygen tensions in their distal portions (analogous to the situation noted in the diabetic foot), are susceptible to infection and suffer a high degree of infectious necrosis.<sup>29-32</sup> Oxidative killing is an important aspect of wound healing and is additive to the effect of appropriate antibiotics.<sup>33,34</sup> Periodic oxygen administration to elevate  $PO_2$  above 100 mmHg enhances this process.

Angiogenesis is a fundamental requirement of healing, and the observations of Rohr and associates demonstrate the importance of oxygen in this process and are compatible with clinical observations of accelerated angiogenesis using oxygen at pressure.<sup>35</sup> Angiogenesis occurs most rapidly when it proceeds from a high oxygen tension to a low one and from a low-lactate environment to a high one.<sup>24,36</sup> The data of Marx and associates<sup>36</sup> and Knighton and associates<sup>24</sup> suggest that angiogenesis is proportional to the gradient of  $PO_2$  from capillary to wound space (i.e., a high tissue oxygen tension at the periphery of a wound and a low tissue oxygen tension at its center enhances angiogenesis). Therefore, restoration of  $PO_2$  to normal or supranormal levels enhances not only epithelialization, fibroplasia, collagen deposition, and bacterial killing, but also capillary proliferation and advancement into the wound space.

### **Principles of Hyperbaric Oxygen Therapy**

The Undersea and Hyperbaric Medical Society, an international scientific organization and the leading authority for diving and hyperbaric medicine in the United States, defines hyperbaric oxygen therapy (HBO) as the intermittent administration of 100% oxygen inhaled at a pressure greater than sea level. (Topical oxygen therapy rendered in small limb-encasing devices is not considered HBO and has been demonstrated to be ineffective. It may, in fact, decrease oxygen delivery to affected limbs.<sup>37,38</sup>)

HBO is not new, having been used since 1943.<sup>39</sup> Modern therapy dates to the early 1960s, when Dutch investigators demonstrated the efficacy of HBO in gas gangrene and anemic states.<sup>40,41</sup> HBO is presently used as primary treatment for decompression illness (the bends), air embolisms, and severe carbon monoxide poisoning.<sup>42-44</sup> Adjunctive indications include clostridial myonecrosis, crush injury and traumatic ischemias, enhancement of healing in selected problem wounds, necrotizing soft tissue infections, chronic refractory osteomyelitis, radiation damage to soft or hard tissue, compromised skin grafts or flaps, and thermal burns. All of these conditions share a common pathophysiology of local or focal hypoxia.<sup>36,45-66</sup>

HBO is designed to increase oxygen delivery to local ischemic tissue and, by a variety of primary and secondary mechanisms, to facilitate wound healing. It is a physiological process, in which a patient breathes 100% oxygen intermittently while the pressure of the external environment is increased to a greater-than-normal-sea-level pressure, usually 2.0–2.4 atmospheres absolute (ATA) or 33–45 feet of sea water (fsw). HBO may be implemented in a walk-in (multiplace) chamber, compressed to depth with air while the patient breathes 100% oxygen with a head tent, face mask, or endotracheal tube, or, alternatively, the patient may be treated in a one-person (monoplace) chamber pressurized to depth with oxygen. In either case, the arterial partial pressure of oxygen will approach 1,500 mmHg at the pressure equivalent of 33 fsw (10 m, or 2 ATA).

At normal atmospheric pressures, most of the oxygen in blood is carried by hemoglobin, with minimal additional oxygen dissolved in the plasma. By giving high concentrations of oxygen under increased pressure (2.0–2.4 ATA), the dissolved oxygen in the blood can be significantly increased,

resulting in an ~30% increase in oxygen-carrying capacity. These levels of dissolved oxygen have been shown to maintain life in the absence of hemoglobin.<sup>40</sup> At a standard treatment pressure of 2.4 ATA, an arterial PO<sub>2</sub> of 1500 mmHg can be achieved, which increases the driving pressure for diffusion of oxygen into the tissue and increases the diffusion distance by three- to fourfold.

HBO protocols vary depending on the severity of the situation. In the absence of infection, HBO once per day at 2.0–2.4 ATA for 90–120 minutes is sufficient to stimulate wound healing. In the presence of infection or a high risk of limb loss, treatment twice per day is recommended. Even though treatment sessions are relatively brief, oxygen tensions may remain elevated in subcutaneous tissue for several hours after exposure.<sup>67-69</sup>

By increasing tissue oxygen levels, HBO can attack the deleterious effects that hypoxia has on wound healing. The exact mechanism by which this is accomplished is not yet fully understood. However, there is evidence that suggests that HBO stimulates angiogenesis. Sheffield has demonstrated improvement in capillaries, measuring transcutaneous oxygen over healing tissue in the diabetic foot, and has clearly documented the slow improvement in blood flow over the first 3 weeks of HBO, as evidenced by rising tissue oxygen tensions.<sup>70</sup> This is particularly true during HBO sessions. Marx has shown similar changes in ischemic irradiated tissue.<sup>36</sup>

### **Studies Investigating the Efficacy of HBO**

Numerous retrospective studies have shown the efficacy of HBO. Davis reviewed a clinical series of 168 patients with compromised refractory diabetic foot wounds treated over a 7-year period.<sup>71</sup> Utilizing the parameter of limb salvage, a success rate of 70% was obtained. Thirty percent failed to respond and required amputation above or below the knee. Failures were most common in older individuals without palpable pedal pulses and with large-vessel occlusion at or above the ankle diagnosed by angiography. Cianci treated 19 patients with diabetes in a subset of 39 lower extremity lesions in 1988, with a salvage rate of 89%.<sup>11</sup> Forty-two percent of these patients had undergone successful revascularization and were referred because of persistent infection or nonhealing wounds. Salvage was defined as bipedal ambulation if two limbs were originally present and intact wound coverage remaining for at least 1 year. HBO costs were \$12,668 and were reflected in total hospital charges of \$34,370, with an average length of stay of 35 days.

More recently, another series of 41 patients with diabetes, who averaged 63 years in age, was analyzed.<sup>72</sup> Thirty-nine patients (97%) were suffering limb-threatening lesions. Fifty-five percent of the patients had undergone revascularization. An average Wagner score of 4, indicating gangrene of the toes or forefoot, was obtained. Thirty-one patients (78%) had their lower extremities salvaged. HBO charges in this series were \$15,900, total hospital charges were \$32,000, and the average length of stay was 27 days, which compare favorably with the cost of primary amputation.

Avoidance of rehabilitation costs and the additional savings involved in prevention of re-amputation or stump revision has been an additional benefit. The follow-up of these patients over 1-6 years (average of 30 months) has shown a 92% durability; that is, ambulation without further lesions or problems. Two of the patients have suffered below-the-knee amputations.

In 1992, Oriani reported a 10-year experience that showed 80% salvage in a group that received HBO versus 40% in controls ( $P < 0.001$ ).<sup>73</sup> Initial treatment of 15 sessions and reevaluation was recommended, as significant improvement in wound healing should be apparent at that time. If improvement was noted, treatment was continued for an additional 10 sessions. If absent, HBO was discontinued. Gismondi has noted the importance of careful, aggressive debridement and meticulous wound care in reducing hospital stay, the number of HBO treatments, and ultimately, cost of care.<sup>74</sup>

In 1993–94, a pilot study was undertaken to examine the results of hyperbaric oxygen therapy in patients with diabetes seen at our centers. Data were collected in a retrospective manner utilizing 1,633 consecutive patients who were treated in our Dallas clinics over a 33-month period (March 1992 through November 1994). Five hundred and one patients (31%) presenting with diabetes and ischemic wounds were identified by diagnosis codes and confirmed by chart review. Patients were grouped by treatment modality: hyperbaric oxygen therapy ( $n = 119$ ) versus conservative treatment alone ( $n = 382$ ), which was administered according to the clinical judgment of the treating physician.

Limb salvage (defined as bipedal ambulation if two limbs were present) was used as the endpoint for the study.

Hyperbaric treatment consisted of oxygen therapy delivered at an individualized rate, duration, and ATA for each patient. Complete follow-up was available on 73% (87 of 119) of the patients receiving hyperbaric oxygen. Some patients were referred from outside centers, and, therefore, their records were unavailable for review (n = 32).

Conservative treatment was based on the standard of care and individualized to include, if necessary: revascularization, dietary modification, smoking cessation, antibiotics, behavioral modification, wound debridement, glycemic control, and offloading.<sup>75</sup> Patients referred for HBO had larger wounds (mean  $\pm$  SE area:  $2,533 \pm 987$  vs.  $1,199 \pm 61$  mm<sup>3</sup>, P = 0.18), more wounds per patient (3.8 vs. 2.4, P < 0.0001), and a greater percentage recommended for amputation (31% vs. 19%, P = 0.002). Despite having the more serious wounds, the limb salvage rate was greater in the HBO patients (72% vs. 53%, P < 0.002).

The results of multiple other retrospective studies involving approximately 500 patients have been consistent and indicate a 70–90% success rate in patients who had been refractory to other modes of therapy, with success defined as the avoidance of amputation and, in many cases, complete wound healing.<sup>76-79</sup>

Baroni and associates prospectively treated 28 patients, 18 of whom received HBO.<sup>80</sup> Unfortunately, the patients were not randomized. They were placed in the control group if they had claustrophobia, ischemic heart disease, paresthesia, or were felt to be unmotivated. All patients received daily debridement of ulcers to bleeding tissue with removal of necrotic tissue. Physicians performing the debridements were blinded to group assignment. Sixteen of the 18 patients (89%) in the treatment group completely healed and remained healed at a follow-up of 1-36 months ( $13.5 \pm 10.1$ ). Only one (10%) of the patients in the control group healed. The amputation rate was 12.5% in the treated group versus 40% in the control group (P < 0.001). The HBO patients were sufficiently improved to be discharged in 62 days, and 16 completely healed. Nine of ten of the control group had not healed 82 days later.

In a follow-up study in 1990, 62 of 80 patients (78%) received a course of HBO.<sup>81</sup> Ninety-six percent of the HBO patients went on to heal versus 66% of the control group. The amputation rate in the HBO group was 4.8% versus 33% in the control group (P < 0.001). The incidence of amputation in the untreated group was essentially unchanged from a group of patients treated nearly 10 years earlier without the benefit of adjunctive HBO. There were no statistical differences in any of the groups relating to age, glycemic control, or diabetes complications.

In a recently reported study, individuals with diabetes with nonhealing foot ulcers were consecutively admitted to a hospital for treatment.<sup>82</sup> They were randomly assigned to either an HBO group or a control group. Two individuals, one in each group, did not complete the protocol and were excluded from analyses. A total of 35 individuals received HBO. Three (8.6%) of them underwent major amputation (the outcome variable) versus eleven (33.3%) in the nonHBO group (P = 0.016). The relative risk for the treated group was 0.26 (95% CI 0.08–0.84). Multivariate analysis confirmed the protective role of HBO (odds ratio 0.084, P = 0.033, 95% CI 0.008–0.821) and indicated as negative prognostic determinants low ankle-brachial index values (odds ratio 1.715, P = 0.013, 95% CI 1.121–2.626) and high Wagner grade (odds ratio 11.199, P = 0.022, 95% CI 1.406–89.146).

To our knowledge, there has been only one double-blind, prospective, randomized study investigating the utility of HBO, which was performed in nondiabetic patients with chronic leg wounds.<sup>83</sup> Individuals receiving HBO had a 35.7% (SD  $\pm$  17%) reduction in wound size at 6 weeks compared with 2.7% (SD  $\pm$  11%) in control subjects (P < 0.001).

These studies indicate that HBO is an effective method for treating diabetic foot wounds in carefully selected cases of lower extremity lesions. They support the recommendation that HBO should be considered as an adjunct to wound healing and as part of multidisciplinary wound care. Additional studies to further define the role of HBO are underway.

One such study, funded by the American Diabetes Association, is in progress at our institution.<sup>84</sup> This study will employ a prospective, randomized, placebo-controlled, double-blind design. All patients will receive standard wound care, which includes but is not limited to revascularization, offloading, glycemic control, infection control, debridements, and education and lifestyle modification. In addition, patients will be randomized into two groups: the treatment group (HBO) and the control group (no HBO). Both groups will receive treatment at 2.4 ATA (45 fsw) for a period of 100 minutes. The HBO group will be receiving 100% oxygen during the breathing periods. The control patients will be exposed to the same hyperbaric environment, but will breathe a gas mixture equivalent to breathing air on the surface. We hypothesize that a defined course of intermittent increased tissue concentrations of oxygen will result in: 1) reduction in amputation rate; 2) increase in number of wounds that are completely healed; and 3) more rapid healing rates. The study will also evaluate whether there are specific subgroups of patients with diabetic wounds who will benefit most from HBO. This patient population will be analyzed according to age, objective evidence of adequacy of limb perfusion (severely compromised, moderately compromised, and preserved), presence or absence of peripheral neuropathy, and glycemic control.

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**Note:** Health-care professionals wishing to learn more about hyperbaric oxygen therapy may contact Dr. Stone by sending e-mail to [Stone@wound.com](mailto:Stone@wound.com).

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