



# Hyperbaric oxygen therapy of diabetic foot ulcers, transcutaneous oxymetry in clinical decision making

JUHA NIINIKOSKI, MD, PhD

The foot ulcer is one of most common and devastating complications of diabetes and is associated with considerable morbidity and mortality. The major causes of these ulcers are ischemia/hypoxia, neuropathy, and infection, and they often coexist. Despite conventional therapy including revascularization procedures when appropriate, three situations lead frequently to amputation: persistent critical limb ischemia, soft tissue infection, and impaired wound healing from osteomyelitis. In these conditions, hyperbaric oxygen therapy may be used as an adjunctive treatment and is associated with a better outcome. Randomized, prospective, controlled trails have shown the benefit of hyperbaric oxygen therapy in diabetic ulcers of the lower extremity. Transcutaneous oxygen measurement performed under hyperbaric oxygen therapy has a prognostic significance when used to select patients who are the most likely to benefit from therapy. Hyperbaric oxygen should be added to conventional treatment if the transcutaneous oxygen tension close to the trophic lesion in 2.5 ATA hyperbaric oxygen is over 200 mmHg. Peri-wound transcutaneous oxygen tensions over 400 mmHg in 2.5 ATA hyperbaric oxygen or over 50 mmHg in normobaric pure oxygen predict healing success with adjuncted hyperbaric oxygen therapy with high accuracy. (**WOUND REP REG 2003;11:458-461**)

Diabetes is the most common underlying cause of lower extremity amputations in Europe and North America. Diabetes-related amputations represent 50–80% of all lower extremity amputations.<sup>1</sup> Diabetics have a 15- to 30-fold greater risk of lower extremity amputation than individuals without diabetes.<sup>2</sup> Diabetic foot ulcers are a major complication that affects 4–10% of the diabetic population.<sup>3,4</sup> Further, foot problems represent one of the most common reasons for hospitalization among diabetic patients. It is estimated that 50% of diabetic amputees require an amputation of the contralateral limb during the first four years after amputation of the first limb.<sup>5</sup>

The economic and emotional costs of amputation and rehabilitation easily exceed the cost of hyperbaric oxygen (HBO) therapy when successful.<sup>6</sup> In Europe, an amputation

ATA	Atmosphere absolute
HBO	Hyperbaric oxygen
TcPO <sub>2</sub>	Transcutaneous oxygen tension

in a diabetic patient has been estimated to cause a mean direct cost of €18,000 and a mean hospitalization of 41.8 days.<sup>7</sup>

In diabetic foot ulcers, major pathogenic factors include peripheral neuropathy, ischemia, and infection.<sup>8</sup> The neuropathic foot is warm, numb, dry, and usually painless, with palpable pulses. It leads to three complications: the neuropathic ulcer, which is found mainly on the sole of the foot, the neuropathic (Charcot) foot, and rarely, neuropathic edema. Ischemia results from atherosclerosis, which in the diabetic patient is often bilateral, multisegmental, and distal, involving arteries below the knee. In contrast to the neuropathic foot, the ischemic foot is cool and the pulses are absent. It is complicated by rest pain, ulceration, and gangrene.

Evaluation of the possibility of revascularization is mandatory in the overall treatment of diabetic foot ulcers. Infection often complicates ulceration in both the

*From the Department of Surgery, University of Turku, Turku, Finland.*

*Reprint requests: Juha Niinikoski, MD, PhD, Department of Surgery, University of Turku, FIN-20520 Turku, Finland. Fax: +358-2-3132284; Email: juha.niinikoski@tyks.fi.*

*Copyright © 2003 by the Wound Healing Society. ISSN: 1067-1927 \$15.00 + 0*

neuropathic and ischemic foot, as the ulcers are portals of entry for bacteria. These infections are often polymicrobial and may range from mild, localized infections to bone involvement or a limb-threatening necrotizing process with fasciitis.

## RATIONALE FOR HBO

Hyperbaric oxygenation is an important therapeutic adjunct in the management of wounds that exist in chronic oxygen deficiency and where the local oxygen tension is below that optimal for healing.<sup>9</sup> Many factors may cause impaired oxygenation in the diabetic foot.<sup>10,11</sup> Measurements of tissue oxygen tensions in nonhealing diabetic wounds have shown values far below those where healing could be expected. HBO therapy has been shown to increase tissue or transcutaneous oxygen tensions in diabetic patients with chronic wounds.<sup>12-14</sup> The greatest benefit of HBO therapy is achieved in situations where the nutritive flow and oxygen supply to repair tissue are compromised, but in which the regional vascular network, a prerequisite for oxygen to reach tissues, is only partially impaired. The main effects of HBO therapy on the healing of diabetic foot ulcers include stimulation of fibroblast proliferation and differentiation, increased collagen formation and crosslinking, augmented neovascularization, stimulation of leukocyte microbial killing,<sup>9,15-19</sup> lethal effects on certain anaerobic bacteria, and inhibition of toxin formation by certain pathogenic microorganisms.<sup>20</sup> Infected ischemic soft tissues also benefit from HBO through improved preservation of energy metabolism and reduction of edema.<sup>21</sup>

HBO is administered in either multiplace or monoplace hyperbaric chambers. The multiplace chamber is pressurized with air and the patient breathes oxygen through a mask or head tent. The monoplace chamber is pressurized with oxygen and the patient breathes pure oxygen directly. Normally, pressures of 2–2.5 atmosphere absolute (ATA) are used. Under HBO, hemoglobin in the circulating blood becomes fully oxygenated and, in addition, oxygen physically dissolves in plasma in direct proportion to the partial pressure of oxygen. Under hyperbaric oxygenation, enough oxygen can become physically dissolved in plasma to meet tissue oxygen requirements without support from hemoglobin-borne oxygen. At 2–2.5 ATA oxygen pressure, physically dissolved oxygen in plasma increases by more than 10 fold. This primary effect of hyperbaric oxygenation generates a favorable gradient for oxygen diffusion from functioning capillaries to ischemic tissue sites.<sup>22</sup>

HBO therapy cannot substitute for surgical revascularization or angioplasty in advanced arterial insufficiency.

In each patient with a diabetic foot ulcer the possibility for vascular construction has to be properly evaluated and the procedure performed if feasible.<sup>9</sup>

## CLINICAL PROSPECTIVE STUDIES

Previously published controlled, prospective trials have focused on the effects of adjunctive HBO therapy on ulcer healing and reduction of amputation rates in diabetic patients with chronic foot ulcers. Baroni and coworkers<sup>23</sup> reported that 89% (16 of 18 patients) healed in the HBO group, whereas only 10% (1 of 10 patients) healed in the control group. Oriani and coworkers<sup>24</sup> reported the effect of HBO treatment in a group of 62 patients. The matched control group consisted of 18 patients. There was no significant difference in age, severity, or duration of diabetes or its complications. Treatment was the same in both groups except for HBO. In the HBO group, 96% of patients healed and 5% underwent amputation, while in the control group the corresponding figures were 66% and 33%. In a small prospective, nonrandomized trial including 10 patients, Zamboni and coworkers<sup>25</sup> found significant improvement in the wound-healing rate in the HBO group vs. controls. The largest prospective, randomized, controlled study conducted thus far was published by Faglia et al.<sup>26</sup> A total of 68 patients with Wagner grades 2, 3, and 4 (deep ulcers, osteomyelitis and/or gangrene of toes or forefoot) were treated, 35 with HBO and 33 without HBO. Variables in patients did not differ significantly in any of their clinical characteristics. In patients treated with HBO, the amputation rate was 8.6% vs. 33.3% in controls ( $p < 0.016$ ). Among patients with Wagner grade 4 lesions (gangrene of toes or forefoot), the HBO group had a major amputation rate of 9.1% (2 of 22 patients) vs. 55% (11 of 20 patients) in the control group ( $p = 0.002$ ). In the study by Kalani and coworkers,<sup>27</sup> 38 diabetic patients with chronic foot ulcers were included in a prospective, controlled study. Seventeen patients underwent 40–60 sessions of HBO therapy, while 21 patients were treated conventionally. The follow-up time was 3 years. Seventy-six percent of the patients treated with HBO healed within the follow-up time. The corresponding value for patients treated conventionally was 48%. Two patients (12%) from the HBO group and seven patients (33%) from the controls underwent amputation. In Kalani and coworkers' study none of the patients had gangrene or deep infection, in contrast to the other studies referred to above.<sup>23-26</sup>

The jury of the European Committee on Hyperbaric Medicine Consensus Conference on HBO in the

treatment of foot lesions in diabetic patients<sup>28</sup> stated that there is some evidence from a number of trials, each of which suffers from methodological problems, to support the use of HBO therapy in ischemic limb-threatening problems in diabetic patients. It was further recognized that there is an urgent need for a collaborative international trial for the application of HBO in diabetic foot lesions. Patients with diabetic foot problems need treatment by foot care teams with careful evaluation of metabolic, neurologic, and vascular factors. Potential candidates for HBO therapy may include those with Wagner grade 3–4 lesions treated unsuccessfully by standard methods when amputation seems a possibility. Pretreatment evaluation should include an assessment of the probability of successful therapy that might include, for example, transcutaneous oxygen measurements in ambient pressure and under hyperbaric oxygen as well as assessment of peripheral circulation by invasive and noninvasive methods. Within the framework of the research network COST B 14, such a study has been developed.<sup>29</sup> In the study protocol, the objective is to evaluate the efficacy of HBO in the healing of foot ulceration in diabetic patients. In this prospective, randomized, controlled study patient enrollment takes place in two phases: preinclusion and inclusion. At the preinclusion phase patients with type I or II diabetes mellitus, diagnosed more than 2 years earlier, are accepted. The foot lesion, Wagner 2–4, should be present for more than 12 weeks. Proper evaluation of revascularization possibility has been done and there is no possibility of invasive procedures (angioplasty, vascular surgery). At the inclusion phase the patient will be enrolled in the study if the foot lesion persists for 3 weeks after preinclusion and conventional standard treatment has been correctly followed. The intervention phase of the study has three arms. In the first, the control arm, the patient receives conventional treatment and no HBO. In the second arm the patient receives one daily 90-minute session at 2.5 ATA oxygen pressure 5 days a week for 6 weeks. In the third arm the patient receives two daily 90-minute sessions at 2.5 ATA oxygen pressure 5 days a week for 6 weeks. In the evaluation phase, major end points include failure or success in healing after 6 weeks. Secondary end points include major amputation above the ankle, healing rate, infection disappearance rate, time for complete healing, disability scale, length of hospitalization, recurrence rate, and eventual adverse effects. The follow-up time is 1 year. The number of patients enrolled in the study will be 200. The study protocol has been implemented in eight European centers.

## TRANSCUTANEOUS OXYMETRY

Transcutaneous oxymetry provides a simple, reliable noninvasive diagnostic technique for the objective assessment of wound perfusion and oxygenation.<sup>30</sup> It can be used for serial assessment of tissue perfusion in the vicinity of the diabetic foot ulcer. Transcutaneous oxymetry may be used in the assessment of healing potential, selection of amputation level, and patient selection for HBO. Transcutaneous oxygen pressure monitoring uses a Clark polarographic electrode that has been modified to include a heating element and thermistor. The heating element should be preset at 44°C to allow maximum oxygen diffusion to the skin surface from the underlying capillaries. Serial determinations of peri-wound transcutaneous oxygen tension (TcPO<sub>2</sub>) are made while the patient is breathing room air, pure oxygen at sea level, and during hyperbaric oxygen therapy. Quigley and Faris<sup>31</sup> used TcPO<sub>2</sub> measurements to determine the severity and clinical progression of peripheral arterial occlusive disease, and values under 40 mmHg were associated with poor ulcer healing in diabetic patients.<sup>17</sup> Measurement of TcPO<sub>2</sub> while breathing pure oxygen or during HBO exposure has been used to select patients for HBO therapy. A significant rise in the peri-wound TcPO<sub>2</sub> predicts the beneficial effect of HBO therapy.<sup>17,32</sup> Fife and coworkers<sup>33</sup> performed a retrospective analysis of 1144 patients to determine reliability of TcPO<sub>2</sub> measurement in predicting outcomes of diabetics who underwent hyperbaric oxygen therapy for lower extremity wounds. Six hyperbaric facilities in the United States provided TcPO<sub>2</sub> data under several possible conditions: breathing air, breathing oxygen at sea level, and breathing oxygen in the chamber. Overall, 75.6% of the patients improved after HBO therapy. Baseline sea-level air TcPO<sub>2</sub> identified the degree of tissue hypoxia but had little statistical relationship with outcome prediction because some patients healed after HBO therapy despite very low prehyperbaric TcPO<sub>2</sub> values. Breathing oxygen at sea level was unreliable for predicting failure but 68% reliable for predicting success after HBO therapy. TcPO<sub>2</sub> measured in chamber under hyperbaric conditions provided the best single discriminator between success and failure of HBO therapy using a cut-off score of 200 mmHg. This test was 74% reliable. These data supported the use of in-chamber TcPO<sub>2</sub> as a screening tool as originally described by Wattel, Mathieu, and associates.<sup>34,35</sup> To summarize, the present scientific evidence suggests that the likelihood of healing with in-chamber TcPO<sub>2</sub> below 100 mmHg is very low, whereas the healing rate is high for patients whose in-chamber TcPO<sub>2</sub> is 400 mmHg or greater. HBO may be added to conventional treatment of diabetic foot ulcers if peri-wound TcPO<sub>2</sub> in 2.5 ATA HBO is over 200 mmHg.

## ACKNOWLEDGMENTS

The author thanks Professor Thomas K. Hunt, MD, for his cooperation and personal friendship over the past 3 decades. It has been a great pleasure to contribute to this memorable Festschrift issue of **Wound Repair and Regeneration** to honor Dr. Hunt's scientific achievements and his long, outstanding clinical career as an academic surgeon.

This work was supported by a grant (EVO Project 13714) from the Turku University Hospital, Turku, Finland.

## REFERENCES

1. Lavery LA, Ashry HR, Van Houtum W, Pugh JA, Harkless LB, Basu S. Variation in the incidence and proportion of diabetes-related amputations in minorities. *Diabetes Care* 1996;19:48–52.
2. Van Houtum WH, Lavery LA, Harkless LB. The impact of diabetes-related lower extremity amputations in Netherlands. *J Diabetes Compl* 1996;10:325–30.
3. Boulton AJM. The pathway to ulceration: aetiopathogenesis. In: Boulton AJM, Connor H, Cavanagh PR, editors. *The foot in diabetes*, (2nd edn). Chichester: John Wiley and Sons, 1995: 37–48.
4. Reiber G. The epidemiology of diabetic foot problems. *Diabetic Med* 1996;13:S6–S11.
5. Ebstov B, Josephsen P. Incidence of reamputation and death after gangrene of the lower extremity. *Prosthet Orthotics Int* 1980;4:77–80.
6. Cianci P, Petrone G, Drager S, Lueders H, Lee H, Shairo R. Salvage of the problem wound and potential amputation with wound care and adjunctive hyperbaric oxygen therapy: an economic analysis. *J Hyperb Med* 1988;3:127–41.
7. Van Houtum WH, Lavery LA, Harkless LB. The costs of diabetes-related lower extremity amputations in the Netherlands. *Diabetic Med* 1995;12:777–81.
8. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. *N Engl J Med* 1994;331:854–60.
9. Niinikoski J, Hunt TK. Oxygen and healing wounds; tissue-bone repair enhancement. In: Oriani G, Marroni A, Wattel F, editors. *Handbook on hyperbaric medicine*. Berlin: Springer Verlag, 1996: 485–507.
10. Williams RL. Hyperbaric oxygen therapy and the diabetic foot. *J Am Pod Med Ass* 1997;87:279–92.
11. Williams RL, Armstrong DG. Wound healing. New modalities for a new millenium. *Clin Pod Med Surg* 1998;15:117–28.
12. Sheffield PJ. Tissue oxygen measurements. In: Davis JC, Hunt TK, editors. *Problem wounds. The role of oxygen*. New York: Elsevier, 1998: 17–51.
13. Wattel F, Mathieu D, Coget JM, Billard V. Hyperbaric oxygen therapy in chronic vascular wound management. *Angiology* 1990;41:59–65.
14. Wattel F, Mathieu D, Fossati P, Nevière R, Coget JM. Hyperbaric oxygen in the treatment of diabetic foot lesions. Search for healing predictive factors. *J Hyperb Med* 1991;6:263–8.
15. Hunt TK. Disorders of wound healing. *World J Surg* 1980;4:271–7.
16. Hunt TK. The physiology of wound healing. *Ann Em Med* 1988; 17:1265–73.
17. Brakora MJ, Sheffield PJ. Hyperbaric oxygen therapy for diabetic wounds. *Clin Pod Med Surg* 1995;12:105–17.
18. LaVan FB, Hunt TK. Oxygen and wound healing. *Clin Plast Surg* 1990;17:463–72.
19. Rabkin JM, Hunt TK. Infection and oxygen. In: Davis JC, Hunt TK, editors. *Problem wounds: the role of oxygen*. New York: Elsevier, 1988: 1–16.
20. Bakker DJ. The use of hyperbaric oxygen in the treatment of certain infectious diseases especially gas gangrene and acute dermal gangrene. Thesis, University of Amsterdam. Wageningen: Drukkerij Veenman BV, 1984:1–118.
21. Nylander G, Nordström H, Eriksson E. Effects of hyperbaric oxygen on edema formation after a scald burn. *Burns* 1984;10:193–6.
22. Thom SR. Hyperbaric oxygen therapy. *J Intensive Care Med* 1989;4:58–74.
23. Baroni G, Porro T, Faglia E, Pizzi G, Mastropasqua A, Oriani G, Pedesini G, Favales F. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* 1987;10:81–6.
24. Oriani G, Meazza D, Favales F, Pizzi GL, Aldeghi A, Faglia E. Hyperbaric oxygen in diabetic gangrene. *J Hyperb Med* 1990;5:171–5.
25. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *J Hyperb Med* 1997;24:175–9.
26. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. *Diabetic Care* 1996;19:1338–43.
27. Kalani M, Jörneskog G, Nazanin N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in the treatment of diabetic foot ulcers. Long-term follow-up. *J Diabetes Compl* 2002;16:153–8.
28. Fourth Consensus Conference of the European Committee on Hyperbaric Medicine. 1998, December 4–5; London, United Kingdom. Hyperbaric oxygen in the management of foot lesions in diabetic patients. *Diabetes Nutr Metab* 1999;12:47–8.
29. Mathieu D. Working group 'HBO and diabetic foot lesion' of COST B14 action. Hyperbaric oxygen therapy in the treatment of diabetic foot lesions. A randomized controlled prospective study. The 28th Annual Meeting of the European Underwater and Baromedical Society; 2002, September 4–8; Brugge, Belgium. *Eur J Underwater Hyperb Med* 2002;3:65 [Abstract].
30. Matos LA, Nuñez AA. Enhancement of healing in selected problem wounds. In: Kindwall E, editor. *Hyperbaric medicine practice*, 1994. Flagstaff, AZ: Best Publishing Co., 1994: 589–612.
31. Quigley FG, Faris IB. Transcutaneous oxygen tension measurements in the assessment of limb ischemia. *Clin Physiol* 1991;11:315–320.
32. Mathieu D, Nevière R, Bocquillon N, Wattel F. Adjunctive hyperbaric oxygen therapy in the treatment of foot lesion in diabetic patient: selection of patients. In: Wattel F, Mathieu D, editors. *Proceedings of ECHM Consensus Conference on Hyperbaric Oxygen in the Treatment of Foot Lesions in Diabetic Patients*. 1998, December 4–5; London, United Kingdom. 1998, 139–50.
33. Fife CE, Buyukcakilir C, Otto GH, Sheffield PJ, Warriner RA, Love TL, Mader J. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1144 patients. *Wound Rep Reg* 2002;10:198–207.
34. Wattel F, Mathieu D, Fossati F, Nevière R, Coget JM. Hyperbaric oxygen in the treatment of diabetic foot. *Undersea Biomed Res* 1990;17 (Suppl.):160–1.
35. Mathieu D, Nevière R, Wattel F. Transcutaneous oxymetry in hyperbaric medicine. In: Oriani G, Marroni A, Wattel F, editors. *Handbook on hyperbaric medicine*. Berlin: Springer, 1996: 686–98.