EDITORIAL (SEE LÖNDAHL ET AL., P. 998)

# Hyperbaric Oxygen Therapy for Diabetic Foot Wounds

## Has hope hurdled hype?

"*One must always hope when one is desperate, and doubt when one hopes.*" Gustave Flaubert.

Hyperbaric oxygen therapy (HBOT) has been promoted as an effective treatment for diabetic foot wounds, and the first controlled trial for this indication was reported (in *Diabetes Care*) over 20 years ago (1). Advocates have suggested that the experimentally demonstrated effects of HBOT on improving wound tissue hypoxia, enhancing perfusion, reducing edema, downregulating inflammatory cytokines, promoting fibroblast proliferation, collagen production, and angiogenesis make it a useful adjunct in clinical practice for "problem wounds," such as diabetic foot ulcers (2,3). HBOT is also touted for eradicating difficult to treat soft tissue and bone infections by mechanisms that include killing microorganisms, improving leukocyte and macrophage function, and enhancing the effect of antimicrobials (4). If realized clinically, these beneficial effects, although requiring expensive technology, might powerfully reduce the risk of lower-extremity amputation in diabetic patients with foot wounds. Thus, rigorously assessing the clinical effectiveness of HBOT in diabetic foot ulceration is an important enterprise. But, because both patients and clinicians are strongly motivated to avoid the devastating outcome of amputation, there is a high potential for bias in poorly designed trials. Proof of benefit requires properly conducted clinical trials that minimize the possibility that preexisting prejudices will influence the allocation of patients, diligence of foot care, or other key management decisions.

Most of the published reports on the effect of HBOT for treating diabetic foot wounds have been case series or nonrandomized trials with major methodological limitations. Although these are a poor source of evidence, the consistency of positive results is noteworthy. More recently, several randomized controlled trials have been conducted. A Cochrane database systematic review published in 2004 concluded, based on results from four such trials, that "HBOT significantly reduced the risk of major amputation and may improve the chance of healing at 1 year" but, ". . . the small number of studies . . . modest numbers of patients, methodological and reporting inadequacies . . . demand a cautious interpretation" (5). A more recent systematic review and meta-analysis that included 10 studies (6 of which were not randomized, controlled trials) concluded that HBOT reduces the risk of amputation (odds ratio 0.24, seven studies) and increases the likelihood of wound healing (odds ratio 10.0, six studies) (6).

But there are concerns. HBOT is available in only a minority of communities, is very expensive (a full course of treatment in the U.S. typically costs $50,000 [Medicare] to $200,000 [private pay]), and is time-consuming (an average of 60 total hours in the chamber). Limited economic analyses using the flawed primary clinical data have suggested, however, that HBOT is potentially cost-effective (7,8) or even cost-saving (9). The more skeptical view is best summarized in a counterpoint commentary (10) on hyperbaric oxygen treatment for diabetic foot wounds published 4 years ago that concluded "[it] is time that the advocates of this therapy organized large, randomized, placebo-controlled trials to provide definitive answers to the questions: which, if any, patients would benefit from HBOT for a diabetic foot wound, and how great is any measurable benefit?" Have there been investigations designed to answer these questions published since that challenge, and, specifically, has the study from Lund, Sweden, by Löndahl et al. (11) in this issue of *Diabetes Care* provided the proof that HBOT naysayers are seeking?

One new study that addressed this issue by Duzgun et al. (12) was published in 2008. This randomized trial compared the effects of HBOT with standard wound care alone on 100 patients with a diabetic foot ulcer that had not responded to a month of appropriate treatment. They found that HBOT was associated with statistically significantly higher rates of wound healing (66% vs. 0%), lower rates of operative interventions (debridement, amputation, or skin flap or graft; 16% vs. 100%), and fewer lower extremity amputations (8% vs. 82%). This study, in common with most others previously published, had several important limitations, including a lack of investigator or patient blinding, minimal descriptions of the types of wounds enrolled, and disparities in treatment allocation that were presumed to be by chance. Nevertheless, it provided useful data and increased by two-thirds the number of patients on which the previously cited Cochrane systematic review of HBOT for diabetic wounds reported.

The study by Löndahl et al. (11) builds on work their team began in the early 1990s, when they demonstrated in a randomized controlled study of 16 nondiabetic patients with a nonischemic chronic leg ulcer, that HBOT significantly reduced the size of the wounds during a 6-week observation period (13). This study, unlike all previous ones except that by Abidia et al. (9), was double-blinded; all enrolled patients were treated in a multiplace hyperbaric chamber, but the masks for half the subjects delivered air while those for the other half delivered 100% oxygen. This method, although technically complex, allowed for a placebo-controlled and blinded evaluation of HBOT, thus eliminating many of the potential confounders that plagued other trials. Fortunately, the investigators kept this design for the current trial in patients with diabetic foot ulcers. In this study, the authors enrolled 94 diabetic patients with a foot ulcer (Wagner grades 2–4) that had been present for at least 3 months and who did not need or could not have reconstructive vascular surgery. They excluded only those patients for whom HBOT was contraindicated or who had a substance abuse problem and stratified enrolled patients by their arterial toe blood pressure. Hyperbaric sessions were given for 8 to10 weeks (aiming for 40 sessions), in conjunction with appropriate foot care provided by a multidisciplinary diabetic foot clinic. The primary end point was ulcer healing, properly defined as complete epithelial regeneration, and

patients were followed for a year. Patients randomized to the two treatment groups were similar at baseline; of note is that over half had previously had vascular surgery to the affected lower limb. It was disappointing that only 56% of eligible patients were enrolled, and only 57% of those enrolled completed the 40 treatments (although most had at least 35).

The results of the Löndahl study clearly support the benefit of HBOT. Complete ulcer healing at the 1-year follow-up was noted in significantly more HBOT-treated than hyperbaric air-treated patients (52% vs. 29% [$P = 0.03$] in the intention-to-treat analysis, and 61% vs. 27% [$P = 0.009$] in the per-protocol analysis). The number needed to treat to avert nonhealing was only 4.2 (3.1 in the per-protocol analysis). Among their secondary outcomes, the rates during the study period of major amputation (~4%) and death (~7%) were relatively low (for these elderly diabetic patients with a high prevalence of comorbidities) and were similar for the two groups. Although patients with infected wounds (presumably including osteomyelitis) could be enrolled, and ~70% of the patients were receiving oral antibiotic therapy at the time of enrollment, the authors, unfortunately, did not comment on the rates or speed of resolution of infection in the two groups. The rate of adverse reactions to hyperbaric therapy in this study was notable; one patient died (in the HBOT group, possibly related to treatment), 5% had significant barotrauma, and 6% had symptomatic hypoglycemia (one of whom was hospitalized), a known potential risk of HBOT.

The authors of this study are certainly to be commended on the strong study design they used—it was fully blinded and placebo-controlled, with concealed allocation that was maintained until the end of a 1-year follow-up period, the exclusion criteria were limited, and patients were stratified by arterial vascular status. The number of patients enrolled was larger than any but the methodologically inferior study by Duzgun et al. (12). There were, however, some important limitations. Only 55% of potentially eligible patients were available for analysis at the 1-year follow-up. The Wagner system used to grade wound severity, while also used in previous HBOT studies and by Medicare to determine eligibility for treatment, has largely been superseded by other systems that provide more information (14,15). We are given no information regarding how many patients in each group had osteomyelitis, a clinically important variable that was neither a reason for exclusion nor used for stratification of enrolled patients. The enrolled patients were relatively unique in some ways: the mean age was a decade older than in most studies of patients with diabetic foot ulcers, all had ulcers that had failed prolonged attempts at treatment, and most had previously had vascular surgery on the affected leg. The description of the severity of infection in the two groups, or how HBOT affected the resolution of infection, was inadequate. There were too few amputations to judge the effect of HBOT on this crucial end point. No data supporting the statement that arterial toe blood pressure did not predict outcomes were provided, and transcutaneous oxymetry would have been a better means of determining adequacy of wound perfusion and oxygenation than toe pressures (16). Finally, the authors made no attempt to address the cost-effectiveness of this expensive technology.

What are we to conclude about the place of HBOT in treating patients with diabetic foot wounds? It seems clear that in a center of excellence of both HBOT and diabetic foot care, like the one in Lund, HBOT can help heal refractory wounds. It is unnecessary for the great majority of patients, however, who will respond to appropriate wound care (cleansing, debridement, off-loading, antimicrobials, as needed). But, for chronic diabetic foot wounds that are not responding to months of appropriate therapy, the present study, together with most of those previously published, suggests that HBOT improves long-term healing. Although HBOT is approved in the U.S. for treatment of chronic osteomyelitis, there is little published support for this treatment for treating infectious complications in the diabetic foot. The potential benefit of HBOT comes at a high financial cost; it would be reasonable for payers to ask if treating four patients to deliver one additional healed ulcer at 1 year is cost-effective. Further randomized controlled trials would, of course, be welcomed. In light of the expense of conducting properly designed clinical trials, alternative methods of assessment, such as theoretical modeling, may be helpful (17).

The study by Löndahl et al., standing on the shoulders of previous trials, has placed HBOT on firmer ground. While this article may not be the one to untie the purse strings of health care payment agencies, it does provide cause for hope and serves to prove that large, properly designed trials are both possible and necessary. Key issues that we must yet address to better understand the place of HBOT in treating diabetic foot wounds include developing robust criteria to determine which patients are likely to benefit, determining at what point in their treatment HBOT should be considered (or abandoned), and deciding which treatment protocols are most appropriate (18). This landmark study at last demonstrates not only that answering these questions is possible using standards of evidence appropriate for the 21st century, but that seeking the answers to these questions is no longer of interest only to the hyperbaric industry. The answers are important for, and eagerly awaited by, all "stakeholders" in the diabetic foot world.

**Benjamin A. Lipsky, MD, FACP, FIDSA, FRCP[1]**
**Anthony R. Berendt, BM, BCH, FRCP[2]**

From the [1]University of Washington, VA Puget Sound, Seattle, Washington; and the [2]Bone Infection Unit, Nuffield Orthopaedic Centre NHS Trust, Oxford, U.K.

Corresponding author: Benjamin A. Lipsky, dblipsky@hotmail.com.

DOI: 10.2337/dc10-0393



**Acknowledgments**— No potential conflicts of interest relevant to this article were reported.

**References**

1. 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; 10:81–86
2. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM 2004;97:385–395
3. Barnes RC. Point: hyperbaric oxygen is beneficial for diabetic foot wounds. Clin Infect Dis 2006;43:188–192
4. Cimşit M, Uzun G, Yildiz S. Hyperbaric oxygen therapy as an anti-infective agent. Expert Rev Anti Infect Ther 2009;7:1015–1026
5. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2004;1:CD004123
6. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a sys-

tematic review. PM R 2009;1:471–489
7. Chow I, Lemos EV, Einarson TR. Management and prevention of diabetic foot ulcers and infections: a health economic review. Pharmacoeconomics 2008;26: 1019–1035
8. Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. Int J Technol Assess Health Care 2008;24:178–183
9. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA, McCollum PT. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 2003;25:513–518
10. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective. Clin Infect Dis 2006;43:193–198
11. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010;33:998–1003
12. Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. J Foot Ankle Surg 2008;47:515–519
13. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plast Reconstr Surg 1994;93:829–833
14. Gul A, Basit A, Ali SM, Ahmadani MY, Miyan Z. Role of wound classification in predicting the outcome of diabetic foot ulcer. J Pak Med Assoc 2006;56:444–447
15. Parisi MC, Zantut-Wittmann DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. Eur J Endocrinol 2008;159:417–422
16. Niinikoski J. Hyperbaric oxygen therapy of diabetic foot ulcers, transcutaneous oxymetry in clinical decision making. Wound Repair Regen 2003;11:458–461
17. Flegg JA, McElwain DL, Byrne HM, Turner IW. A three species model to simulate application of hyperbaric oxygen therapy to chronic wounds. PLoS Comput Biol 2009;5:e1000451
18. Wang C, Schwaitzberg S, Berliner E, Zarin DA, Lau J. Hyperbaric oxygen for treating wounds: a systematic review of the literature. Arch Surg 2003;138:272–279