Hyperbaric Oxygenation Accelerates the Healing Rate of Nonischemic Chronic Diabetic Foot Ulcers

A prospective randomized study

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OBJECTIVE — To study the effect of systemic hyperbaric oxygenation (HBO) therapy on the healing course of nonischemic chronic diabetic foot ulcers.

RESEARCH DESIGN AND METHODS — From 1999 to 2000, 28 patients (average age 60.2 ± 9.7 years, diabetes duration 18.2 ± 6.6 years), of whom 87% had type 2 diabetes, demonstrating chronic Wagner grades I–III foot ulcers without clinical symptoms of arteriopathy, were studied. They were randomized to undergo HBO because their ulcers did not improve over 3 months of full standard treatment. All the patients demonstrated signs of neuropathy. HBO was applied twice a day, 5 days a week for 2 weeks; each session lasted 90 min at 2.5 ATA (absolute temperature air). The main parameter studied was the size of the foot ulcer measured on tracing graphs with a computer. It was evaluated before HBO and at day 15 and 30 after the baseline.

RESULTS — HBO was well tolerated in all but one patient (barotraumatic otitis). The transcutaneous oxygen pressure ($TcPO_2$) measured on the dorsum of the feet of the patients was 45.6 ± 18.1 mmHg (room air). During HBO, the $TcPO_2$ measured around the ulcer increased significantly from 21.9 ± 12.1 to 454.2 ± 128.1 mmHg ($P < 0.001$). At day 15 (i.e., after completion of HBO), the size of ulcers decreased significantly in the HBO group (41.8 ± 25.5 vs. 21.7 ± 16.9% in the control group [$P = 0.037$]). Such a difference could no longer be observed at day 30 (48.1 ± 30.3 vs. 41.7 ± 27.3%). Four weeks later, complete healing was observed in two patients having undergone HBO and none in the control group.

CONCLUSIONS — In addition to standard multidisciplinary management, HBO doubles the mean healing rate of nonischemic chronic foot ulcers in selected diabetic patients. The time dependence of the effect of HBO warrants further investigations.

Diabetes Care 26:2378–2382, 2003

Lower-extremity ulcers are responsible for 20% of the hospital admissions of diabetic patients; the incidence of amputation is 6 per 1,000 (1). Foot ulcer represents one of the major causes of lower-extremity injuries in the 220 million people suffering from diabetes worldwide, 2.5% of whom will develop a foot ulcer each year (2). Moreover, duration of hospitalization attests to the high morbidity of this condition (3), which has been shown to require as long as ~26 weeks for full recovery (4) despite a multidisciplinary approach (associating glycemia control, daily local care, foot offloading antibiotic therapy, and surgical revascularization).

The diabetic foot is characterized by sensory, motor, and autonomic neuropathies leading to alteration of pressure distribution, foot deformities, and ulcerations. Metabolic control and infection treatments are of primary importance to control the evolution of the diabetic foot. Hyperbaric oxygenation (HBO) has previously been proposed as an adjunctive treatment for the diabetic foot because it improves in vitro the complex processes underlying healing (5–7). It has also been reported that HBO reduces the incidence of major amputation in diabetic patients with a gangrenous foot (8). The actual value of HBO on diabetic foot healing is, however, still a matter of discussion because conflicting data exist in the literature (9–13) on its true therapeutic effect. The difficulty in controlling the different parameters (metabolic, vascular, infectious, and foot off-loading) involved in the evolution of the diabetic foot and the lack of prospective randomized studies on the effect of HBO on this pathophysiological condition make it difficult to recognize HBO as an incontrovertible treatment.

Recently, Méchine et al. (14) have reported on the effect of HBO on the acceleration of angiogenesis and on a stimulation of neovascularization in an experimental model of wound healing in the rat. On the other hand, Wattel et al. (15) showed that the effectiveness of HBO on healing in nondiabetic patients was dependent on the peripheral arterial disease. Consequently, the purpose of this study was to evaluate the effect of HBO on

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Received for publication 18 April 2002 and accepted in revised form 9 May 2003.

Abbreviations: HBO, hyperbaric oxygenation; $TcPO_2$, transcutaneous oxygen tension.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

the healing of nonischemic chronic diabetic foot ulcer in a prospective controlled and randomized study on the basis of the experimental protocol proposed by Méchine et al.

RESEARCH DESIGN AND METHODS

Patients

The protocol was approved by our local ethics committee, and written consent was obtained from each patient.

From January 1999 to January 2000, 28 type 1 and type 2 diabetic patients consecutively admitted in our ward for chronic foot ulcers (Wagner grades I, II, and III) were prospectively included in this study. Their ulcers (depth <2 mm) were characterized by the absence of favorable evolution for at least 3 months despite the stabilization of glycemia, the absence of clinical local infection, and satisfactory off-loading measures. In 17 patients, the ulcers were located on the heels or soles and were mainly due to an initial hyperkeratosis area complicated with cutaneous fissures. When the ulcers were located on the toes, the initial provoking causes were a traumatism or blister resulting from ill-fitting shoes ($n = 11$). In 13 cases the ulcers were associated with an aperture with chronic deep infection. The initial size of ulcers was 2.56 ± 1.83 cm^2. Clinical signs of arteriopathy were absent (the palpation of arterial pulses at lower extremities was normal). Doppler scans of lower limbs were normal and the transcutaneous oxygen tension ($TcPo_2$) measured at the dorsum of the foot exhibiting the ulcer was >30 mmHg. Each patient was asked to keep weight off the affected foot. The patients had a stabilized nonproliferating retinopathy. During the study period, 64 diabetic patients were admitted to our unit for foot ulcers. Of them, 34 patients were excluded, 8 due to gangrenous ulcer with severe sepsis, 22 patients due to severe arteriopathy (TcPo2 <30 mmHg), and 4 due exclusion criteria for HBO (emphysema, proliferating retinopathy, claustrophobia). Among the 30 selected patients, 2 patients refused to participate. The 28 patients selected were randomized to standard treatment or standard treatment plus HBO according to a randomization table. The HBO and control groups involved 15 and 13 diabetic patients, respectively.

Study protocol

On inclusion, physical examination was performed on patients, including palpation of the arterial pulses, evaluation of pinprick, light touch, and vibratory sensations in feet, and testing for Achilles' tendon reflexes. Lower-limb vascularization was evaluated by Doppler scan, and baseline $TcPo_2$ was simultaneously measured on the dorsum of the foot with a modified Clark electrode (Kontron Instruments, Watford, U.K.). The sensorimotor neuropathy of lower extremities was assessed by electromyography. In case of abnormalities of the foot X-ray, magnetic resonance imaging was performed to evaluate chronic bone infection.

At the study outset, patients of both groups were hospitalized for 2 weeks in the department of diabetology for conventional treatment, regardless of their association. They were then followed as outpatients for 2 weeks. During the hospitalization, the patients randomized for HBO underwent two 90-min daily sessions of 100% O_2 breathing in a multiplace hyperbaric chamber (Comex Pro, Comex, Marseille, France) pressurized at 2.5 ATA (absolute atmosphere air). This regimen lasted 5 days a week for 2 consecutive weeks according to Méchine et al. (14). In brief, HBO sessions included a period of compression in air for 15 min followed by three 30-min breathing periods, at $Fio_2 = 1$, separated by 5-min intervals of air breathing ($Fio_2 = 0.21$) and then a decompression period of 15 min. The conventional additional treatment was applied to both groups of patients during hospitalization and the ambulatory period. Each patient was provided with an orthopedic device to remove mechanical stress and pressure at the site of the ulcer during walking (Barouk shoes) (2). In both groups, the optimization of metabolic control required subcutaneous insulin administration (two or three injections or bedtime treatment) for the majority of patients. In the case of chronic infection, patients were given antibiotics according to microbiological tests.

After the 1st and the 20th sessions of HBO, $TcPo_2$ was measured in room air and during the hyperbaric session in a standardized fashion: first in noninflamed skin located 1 cm from the wound edges and second in the second intercostal space as a reference (16,17). At baseline (i.e., before HBO was started), and 2 and 4 weeks (day 15 and 30, respectively), the aspect of ulcers (color, outline) was evaluated by standardized photographs. Weekly tracings of the surface area of the ulcer onto gridded transparent film were performed by a physician blinded to the patient's group assignment. Tracings were digitally treated for measurement using a computer program (Mouseyes version 1.1, 1995, Dr. RJ Taylor, Salford, U.K.). Baseline wound ulcer surface area was expressed in centimeters squared, and its evolution was quoted as a percentage of the reduction of the wound ulcer surface area between baseline and day 15, between day 15 and 30, and between baseline and day 30.

Statistical analysis

Data were expressed as mean ± SD. For the comparison between HBO and control groups, *P* values were determined by a χ^2 two-tailed Fisher's exact test for discrete variables and by an unpaired Student's *t* test for continuous variables. Comparison of wound ulcer area reduction and $TcPo_2$ between HBO-treated and -untreated patients was performed using the Student's *t* test.

RESULTS — HBO was well tolerated in all but one patient, who demonstrated a barotraumatic otitis, for which he was discharged from the study.

As shown in Table 1, HBO patients and control patients did not differ in their baseline characteristics (i.e., age, sex, type and duration of diabetes, micro- and macrovascular complications, bone lysis, and treatment). Of interest is the fact that ulcer surface area was not statistically different between groups at the beginning of the study.

Influence of HBO on the $TcPo_2$

As shown in Fig. 1, the $TcPo_2$ measured around the ulcer significantly increased from 21.9 ± 12.2 in room air to 454.1 ± 128.1 mmHg during the 1st session of HBO ($P < 0.001$) and from 25.6 ± 12.8 to 549.6 ± 232.9 mmHg after the 20th session ($P < 0.001$). When the $TcPo_2$ was measured in the second intercostal space, these values significantly increased from 67.9 ± 16.4 to 1,119.6 ± 180.2 mmHg and from 67.2 ± 12.7 to 1,074 ± 112.3 mmHg, respectively, after the 1st and the 20th sessions of HBO ($P < 0.001$). There was no significant difference between the

Table 1—*Clinical characteristics of control and HBO-treated patients*

	HBO group	Control group	*P*
n	14	13	
M/F	10/4	9/4	
Age (years)	60.2 ± 9.7	67.6 ± 10.5	0.29
BMI (kg/m^2)	29.9 ± 3.1	29.1 ± 5.9	0.68
Type 1 diabetes (%)	2/14 (14)	2/13 (15)	0.72
Type 2 diabetes (%)	12/14 (86)	11/13 (85)	0.72
Diabetes duration (years)	18.2 ± 13.2	22.1 ± 13.1	0.38
Ulcer surface area (cm^2)	2.31 ± 2.18	2.82 ± 2.43	0.42
Insulin therapy (%)	13/14 (92.8)	12/13 (92.3)	0.62
Oral agent (%)	1/14 (7.2)	1/13 (7.7)	0.62
Stabilized retinopathy (%)	10/14 (71)	11/13 (84.6)	0.75
Renal impairment (%)	5/14 (35.7)	6/13 (46.1)	0.70
Coronary artery disease (%)	2/14 (14.2)	4/13 (30.8)	0.38
Carotid arteriopathy (%)	1/14 (7.1)	1/13 (7.6)	1.00
$TcPO_2$ (mmHg) foot dorsum	45.6 ± 18.1	45.2 ± 24.2	0.61
Sensorimotor neuropathy (%)	14/14 (100)	13/13 (100)	1.00
HbA_{1c} (%), normal range (4.4–5.8)	9.4 ± 2.4	8.1 ± 1.4	0.31
Bone lysis (%)	7/14 (50)	6/13 (46.1)	0.76
Antibiotic therapy (%)	8/14 (57.1)	9/13 (69.2)	0.69

Data are means ± SD unless indicated otherwise. Renal impairment was defined as a creatinine clearance <60 ml/min; coronary artery disease was confirmed by abnormalities at coronarography, carotid arteriopathy by abnormalities at carotid echography; sensorimotor neuropathy was clinically defined by abnormalities of pinprick, light touch, and a decrease in vibratory sensations and in the testing for Achille's tendon reflexes together with abnormalities in more than two nerves at electromyography (velocity <45 m/s); bone lysis was determined by X-ray findings.

increase in $TcPO_2$ at the beginning and end of the HBO treatment.

Wound ulcer surface area measurements

After 2 weeks of treatment, the reduction of the ulcer surface area in HBO patients was significantly greater than in control patients (41.8 ± 25.5 vs. 21.7 ± 16.9%) ($P = 0.037$). Two weeks later, the reduction of the ulcer size was comparable between the groups (48.1 ± 30.3 vs. 41.7 ± 27.3%). After a 4-week period, there was no difference in the reduction of ulcer surface area between groups (61.9 ± 23.3 vs. 55.1 ± 21.5%).

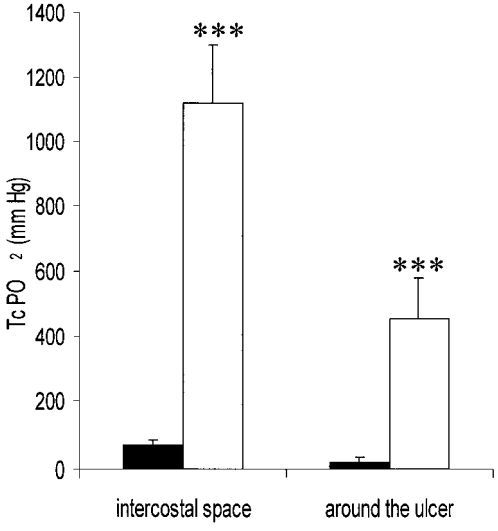

Figure 1—*$TcPO_2$ MEASUREMENTS IN THE SECOND INTERCOSTAL SPACE AND AROUND THE ULCER IN PATIENTS UNDERGOING HBO IN ROOM AIR (■) AND AFTER THE FIRST HYPERBARIC SESSION (□). ***P < 0.001.*

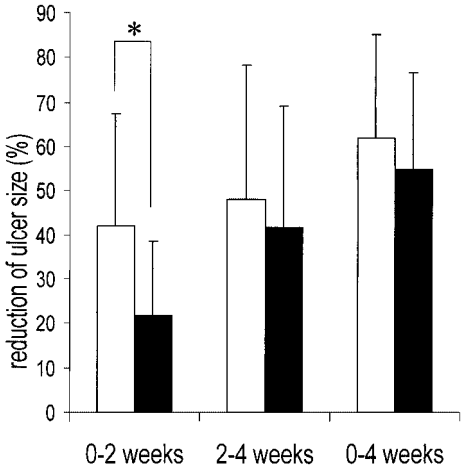

Figure 2—*Reduction of ulcer size in patients of HBO (□) and control (■) group after 2 and 4 weeks. (*P = 0.037)*

After 4 weeks, healing was completed in two HBO patients but in none of the control subjects.

CONCLUSIONS — This prospective randomized study provides evidence that HBO doubles the mean healing rate of nonischemic chronic foot ulcers in selected diabetic patients. In addition, it suggests the possibility of shortening hospitalization time in these patients.

The rationale for the use of HBO as an adjunctive treatment for the diabetic foot stems from its beneficial effects on the microenvironment of the wound. If high oxygen pressure over a long time period (several days) stimulates an abnormal angiogenesis (as demonstrated in the eyes of newborns), several studies have reported that cycling high and low oxygen pressure over a short period (1 or 2 h) stimulates a physiological angiogenesis at the site of the ulcer. This is due, in part, to the release of collagen from fibroblasts and vascular growth factors by macrophages (18,19). The vascular response to high O_2 tension is usually vasoconstriction. However, the promotion of new vessel growth follows the withdrawal of the high oxygen with relative hypoxia in the constricted tissues area. Furthermore, hyperoxia can trigger the onset of signal transduction pathways of regulating the gene expression of growth factors or their receptors, like platelet-derived growth factor (20). Moreover, oxygen is able to strengthen microbiocidal capacity of endogenous defense mechanisms in addition to its direct antianaerobic activity (21). HBO cannot

dramatically increase the O_2 transported by hemoglobin, but it significantly increases the fraction of O_2 dissolved in plasma (22) and delivered throughout the organism, as demonstrated by $TcPo_2$ measurements. In our patients, in ambient air, the $TcPo_2$ of the foot dorsum was >30 mmHg, which is the threshold value usually accepted as the cutoff point, beyond which the wound can heal without adjuvant surgical treatment (23).

It is important to note that the type 2 diabetic patients included in our study were patients in their late fifties with a long diabetes duration (average 20 years). All of these patients had neuropathy, as shown by clinical and electromyographic data, but they demonstrated a mild peripheral lower-limb arteriopathy according to their $TcPo_2$ values of 45 mmHg (normal values >60 mmHg). Before HBO the $TcPo_2$ around the ulcer was only ~22 mmHg, which indicates that the wound ulcer tissues were unlikely to be supplied with enough O_2 to undergo a correct healing. In our study, the $TcPo_2$ value is reduced around the ulcer when compared with the values measured on the dorsum of the foot. This difference can be explained by the existence in these patients of a peripheral arteriopathy reaching the small arteries associated with a reduction of the capillary vascularization and a modification of the tissues around the lesion. In agreement with others, we observed a 20-fold increase of ulcer tissue O_2 tension under hyperbaric conditions (24); this effect can be explained by the selection of patients who did not demonstrate clinical and Doppler signs of macroangiopathy. In such conditions, Wattel et al. (15) have already shown that the effectiveness of HBO on healing is dependent on the $TcPo_2$ increase during the session.

Elevation of O_2 tension in hypoxic wound ulcers enhances neutrophil oxidative killing of bacteria and stimulates fibroblast proliferation, collagen production, neovascularization, and epithelialization (20). In addition, O_2 is directly toxic to anaerobic organisms (13). Despite these findings, few controlled prospective clinical studies have been able to support the use of HBO for chronic nonhealing wound ulcers. HBO has probably been distrusted because previous studies have involved several different kinds of lower-limb injuries that may not have identically benefited from an increase in local O_2 pressure. Only two randomized controlled clinical trials evaluating HBO in the diabetic foot (11,12) are available. In these studies, the authors have demonstrated that HBO is effective in decreasing major amputations in diabetic patients with severely prevalent ischemic foot ulcers. Recently, in a prospective nonrandomized study, Zamboni et al. (11) evaluated the influence of HBO on the healing of lower-extremity wounds in 10 type 1 diabetic patients. The HBO group underwent 30 sessions over a period of 7 weeks. This study shows a greater reduction of the wound surface area in the HBO group together with a complete healing in 80% of the patients over the entire 7-week period. In our study, a significant acceleration of the healing was observed in the HBO group. However, among the 14 patients who underwent the 20 sessions of HBO, only two patients had their ulcers healed after 4 weeks. The smaller number of HBO sessions could explain these differences. In both studies, no amputations were reported in either control or HBO patients. In our study, the matched patients were comparable regarding the status of diabetes, the presence of chronic bone infection, the size of wound ulcers, and the follow-up. Indeed, during the initial period of treatment, each and every patient was hospitalized and then followed in ambulatory care. During the 3 months preceding the study, the absence of favorable evolution observed in patients of both groups was observed in ambulatory care. After randomization, the acceleration of the healing in the control group is probably due to the conditions of hospitalization, during which the metabolic control, the local cares, and the removal of metabolic stress are better. After the 2 weeks of hospitalization, the improvement observed in ambulatory care can be explained by the intensive follow-up of patients. During the first 2 weeks of the study, the healing rate was improved only in patients undergoing HBO treatment. For a further 2 weeks, patients of both groups followed as outpatients received similar conventional treatment. In this time, the healing rate was comparable between the two groups, further supporting the effect of HBO since its suspension resulted in the absence of further benefit on the healing rate. The apparent faster healing observed in the control group at the end of the study could be explained by the kinetics of the healing process, which begins slowly and then increases (5). In a nonrandomized study, Baroni et al. (25) showed that HBO accelerates the healing of diabetic chronic foot ulcer. However, since 18 of the 28 patients were hospitalized, and since 23 had gangrene of the foot and 5 presented neuropathic ulcers, the study population was too heterogenous to draw any reliable conclusions.

A long-lasting effectiveness of HBO has been suggested in some pathophysiological conditions involving irradiated tissues (26). It is noteworthy that the effect of HBO could no longer be observed in our patients once the treatment had been discontinued. This is in keeping with the experimental model of Méchine et al. (14) and raises questions about the mechanisms involved in such a phenomenon. Whether longer periods of HBO sessions would result in better healing remains to be established. In the rat, the effect of HBO is suggested to be less effective after 2 weeks of treatment, possibly as a deleterious consequence of pressure itself.

The tolerance of HBO was fairly acceptable; of the 14 patients of the HBO group, only 1 was discharged due to a mild barotraumatic otitis, from which he recovered without sequelae. The costs of the technique must, of course, also be taken into account. Data reported by Marroni et al. (27) suggest that the cost of HBO is equivalent to other new treatments (local topic of human growth factor) in the diabetic foot and may be more effective.

HBO seems effective in accelerating the healing rate of nonischemic chronic diabetic foot ulcers. In humans, its effect is observed only during the treatment, which suggests a similar mechanism of action to that in the experimental model of Méchine et al. This result reinforces the interest of HBO in selected diabetic patients with chronic foot ulcers associated with neuropathy but without severe macroangiopathy.

Acknowledgments— This study was supported by grant from The Centre européen d'étude du Dìabète (CeeD).

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