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Hyperbaric oxygen therapy for nonhealing vasculitic ulcers

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Summary

Background. Cutaneous nonhealing ulceration is a threatening manifestation of vasculitis. Hyperbaric oxygen (HBO), frequently used as adjuvant therapy for patients with ischaemic ulcers, exerts additional beneficial effects on the vascular inflammatory response.

Aim. To evaluate the effect of HBO on vasculitis-induced nonhealing skin ulcers.

Methods. The study population comprised 35 patients aged ≥ 18 years with severe, nonhealing, vasculitis-induced ulcers that had not improved following immunosuppressive therapy. Baseline ulcer tissue oxygenation was evaluated at room air concentration (21% O_2), at 1 atmosphere absolute (ATA) breathing 100% O_2, and at 2 ATA breathing 100% O_2. The baseline treatment protocol consisted of a 4-week course of 100% O_2 for 90 min at 2 ATA, five times/week.

Results. The mean baseline ulcer tissue oxygenation (3.1 ± 2.4 kPa at room air concentration), was significantly increased to 13.9 ± 11.9 kPa at 1 ATA breathing 100% O_2 ($P < 0.001$), and subsequently increased further to 59.1 ± 29.8 kPa at 2 ATA breathing 100% O_2 ($P < 0.001$). At the end of the hyperbaric therapy, 28 patients (80%) demonstrated complete healing, 4 (11.4%) had partial healing and 3 (8.6%) had no improvement. None of the patients had any side-effects related to the HBO therapy.

Conclusion. HBO therapy may serve as an effective safe treatment for patients with vasculitis having nonhealing skin ulcers. Further studies are needed to evaluate its role as primary therapy for this group of patients.

Introduction

Vasculitides are defined by the presence of leucocytes in the vascular vessel wall, with reactive damage to mural structures leading to tissue ischaemia and necrosis. Cutaneous presentation of vasculitis includes purpura, erythema, urticaria, noduli, bullae and skin infarction leading to ulceration. Cutaneous ulceration is usually caused by vasculitis in medium to small-sized vessels.[1] Persistent or progressive ulceration due to vasculitis is an indication for systemic immunosuppressive therapy, although evidence of efficacy of the latter is based only on case reports and uncontrolled trials.[2] Even though vasculitis is a rare cause of nonhealing skin ulcers, its impact on comorbidity, mortality and therapy cost is significant.

Hyperbaric oxygen (HBO) has been used as primary or adjunctive therapy for a variety of medical conditions.[3] Most of the benefits of HBO are explained by the simple physical relationships determining gas concentration, volume and pressure. By altering conditions of local hypoxia, HBO facilitates the wound-healing energy-consumption processes.[4] HBO has also been used as an adjunct to antibiotics, debridement and revascularization in the therapy of chronic nonhealing wounds associated with diabetes or nondiabetic vascular insufficiency.[5] Hyperoxia has an anti-inflammatory

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effect in the vascular bed.[6] The aim of the current study was to investigate the effect of HBO therapy in patients with vasculitis-induced nonhealing skin ulcers.

Methods

Patients

The study population comprised patients with vasculitis-induced severe nonhealing ulcers who were admitted to the Institute of Hyperbaric Medicine and Wound Care Clinic at Assaf Harofeh Medical Center, Israel between January 2001 and May 2005. The inclusion criteria were: histologically or serologically proven vasculitis, age range ≥ 18 years and immunosuppressive treatment for at least 3 months. Patients having chest pathology incompatible with pressure changes, inner ear disease, or suffering from claustrophobia, were excluded from the study. All patients gave written informed consent before starting the HBO therapy.

Study protocol

All participants underwent a complete physical examination, and their medications (immunosuppressives, analgesics or antibiotics) were recorded. Baseline ulcer tissue oxygenation was evaluated by three measurements of transcutaneous O_2 ($TCpO_2$) performed using a pulse oximeter (Novametrix 840; Novametrix Medical Systems Inc. Wallingford, Connecticut, USA). The hyperbaric oxygen was given via the hyperbaric chamber at Assaf Harofeh Medical Center (Israel) and the following protocol was applied: (i) 20 min exposure to room air oxygen concentration; (ii) 20 min exposure to 100% oxygen at 1 atmosphere absolute (ATA) pressure; and (iii) 20 min exposure to 100% oxygen at 2 ATA pressure.

Baseline treatment protocol consisted of a 4-week administration of 100% O_2 for 90 min at a pressure of 2 ATA, five times/week. All patients received the basal 20 HBO treatments, following which additional treatments were added according to clinical response. Wound dressings were changed according to the clinical situation, but never less often than three times/week.

Ulcer classification

To evaluate ulcer severity, we used the University of Texas Wound Classification System.[7] The classification uses a matrix of wound grade (depth) and wound stage (infection and/or ischaemia) to categorize wounds by severity. In brief, the wounds were graded by depth, according to the following criteria: grade 0, a pre- or post-ulcerative site that had healed; grade 1, superficial wounds through the epidermis or epidermis and dermis that did not penetrate to tendon, capsule or bone; grade 2, wounds that penetrated to tendon or capsule; and grade 3, wounds that penetrated to bone or into the joint. Within each wound grade, the following four stages were distinguished: A, clean wounds; B, non-ischaemic infected wounds; C, ischaemic noninfected wounds; and D, infected ischaemic wounds. Complete healing was determined as grade 0, stage A. Partial healing was defined as improvement by at least one grade and one stage. In addition to the above, wound inflammation signs (redness, oedema, pain) were also recorded. Ulcers were photographed before and after the HBO therapy.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 11; SPSS Inc., Chicago, IL, USA). Parametric data were expressed as means ± standard deviations and compared by the paired sample *t*-test. Non-parametric data were compared using the χ^2 test. Differences between results yielding P values < 0.05 were considered statistically significant.

Results

Between January 2001 and May 2005, 41 patients with vasculitis-induced severe nonhealing ulcers were referred to the Institute of Hyperbaric Medicine and Wound Care Clinic of Assaf Harofeh Medical Center (Israel). Six patients were excluded from the study: three patients did not had histolgical confirmation of vasculitis process on biopsy and did not met the diagnostic criteria of any known vasculitis disease, two had inner ear disease, and one had an abnormal chest X-ray. All 35 patients included in the study completed the protocol. None demonstrated any side-effects related to the hyperbaric therapy.

Baseline patient characteristics are summarized in Table 1. The mean age of the patients was 53.5 ± 17.8 years; 76% of the participants were women. The most common types/causes of vasculitis were cutaneous leukocytoclastic vasculitis (8 patients; 22.8%), systemic lupus erythemathosus (7; 20%), rheumatoid arthritis (6; 17.1%) and inflammatory bowel disease (6; 17.1%). The mean daily prednisone dosage at the beginning of the hyperbaric therapy was 0.57 ± 0.33 mg/kg, and there were 16 patients (45.7%) concomitantly treated with other immunosuppressive

Table 1 Baseline patient characteristics.

Characteristic	Patients (%)*
Mean ± SD age (years)	53.5 ± 17.8
Males/females	9/26 (26/74%)
Type of vasculitis	
Cutaneous leukocytoclastic vasculitis	8 (22.8%)
Systemic lupus erythematosus	7 (20%)
Rheumatoid arthritis	6 (17.1%)
Inflammatory bowel disease	6 (17.1%)
Mixed connective tissue disease	3 (8.6%)
Henoch–Schonlein purpura	2 (5.7%)
Giant cell arteritis	2 (5.7%)
Mixed cryoglobulinaemia	1 (2.9%)
Concomitant diseases	
Diabetes mellitus	7 (20%)
Hypertension	4 (11.4%)
Chronic renal failure	3 (8.6%)
Congestive heart failure	2 (5.7%)
Mean ± SD daily prednisone dose (mg/kg)	0.57 ± 0.33
Concomitant immunosuppressive drug prescription†	
Azathioprine	6 (17.1%)
Cyclophosphamide	5 (14.3%)
Methotrexate	2 (5.7%)
Hydroxychloroquine sulfate	2 (5.7%)
Ciclosporin	1 (2.9%)
Classification of ulcers (stage and grade)‡	
1C	1 (2.9%)
1D	1 (2.9%)
2A	2 (5.7%)
2B	7 (20%)
2C	10 (28.6%)
2D	8 (22.9%)
3C	4 (11.4%)
3D	2 (5.7%)

*n=35; †in addition to prednisone; ‡University of Texas Wound Classification System.

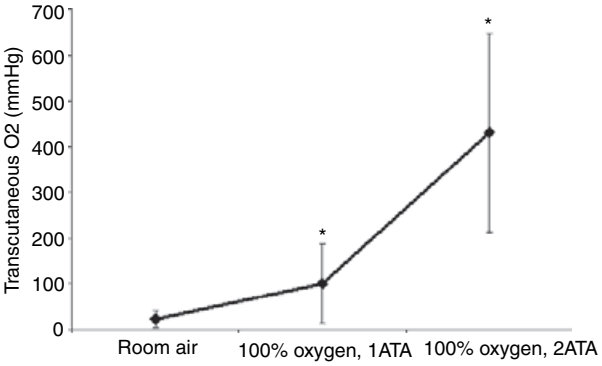

Figure 1 Baseline ulcer tissue oxygenation at room air concentration, after 20 min exposure to 100% oxygen at 1 atmosphere absolute (1 ATA) and after 20 min exposure to 100% oxygen at 2 ATA. Note: ulcer tissue oxygenation was evaluated by transcutaneous O_2 pressure ($TCpO_2$) measurements using a pulse oximeter. *$P < 0.001$ when compared with any of the other two mean $TCpO_2$ values.

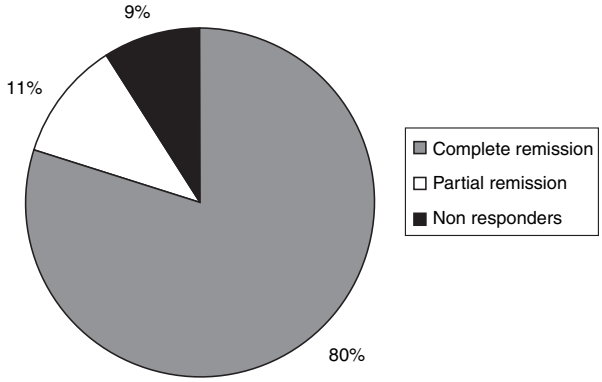

Figure 2 Clinical response to hyperbaric oxygen therapy ($n = 35$). Note: complete healing was defined as grade 0, stage A according to the University of Texas Wound Classification; partial healing defined as improvement of at least one grade and one stage.

drugs. The mean duration of the nonhealing ulcer from its occurrence until the start the HBO therapy was 11.8 ± 22.6 months (range 4–62).

All ulcers were moderate to severe, ranging from 1C to 3D, according to the University of Texas Wound Classification, with a preponderance of class 2C (10 patients, 28.6%), 2D (8; 22.9%) and 2B (7; 20%). The majority of ulcers occurred in the lower limbs (32; 91%), one patient had an ulcer on the hand, and one had an ulcer on the head at the mandibular angle. Baseline ulcer tissue oxygenation as determined by $TCpO_2$ measurements was 3.1 ± 2.4 kPa at room air concentration. It was significantly elevated in 1 ATA of 100% O_2 (13.9 ± 11.9 kPa, $P < 0.001$) and increased further at 2 ATA of 100% O_2 (59.1 ± 29.8 kPa, $P < 0.001$). The mean changes in $TCpO_2$ are summarized in Fig. 1.

At the end of the hyperbaric therapy 28 patients (80%) demonstrated complete healing and 4 (11.4%) showed partial healing. Three patients (8.6%) did not respond to the basal 20 HBO treatments. The results of their clinical outcome are summarized in Fig. 2.

The examples of vasculitis ulcers before and after HBO therapy are presented in Fig. 3. Mean duration of the HBO therapy was 7.08 ± 2.68 weeks (five sessions per week). At the end of the HBO therapy, there was a significant decrease in the daily prednisone dose (from 0.57 ± 0.33 to 0.22 ± 0.18 mg/kg, $P = 0.002$).

Four patients demonstrated only partial resolution of the ulcer. However, by observation, despite the incomplete healing, the redness and oedema around the ulcer were completely resolved. Moreover, there was significant improvement in the ulcer-related pain, so that the amount of painkillers used could be reduced.

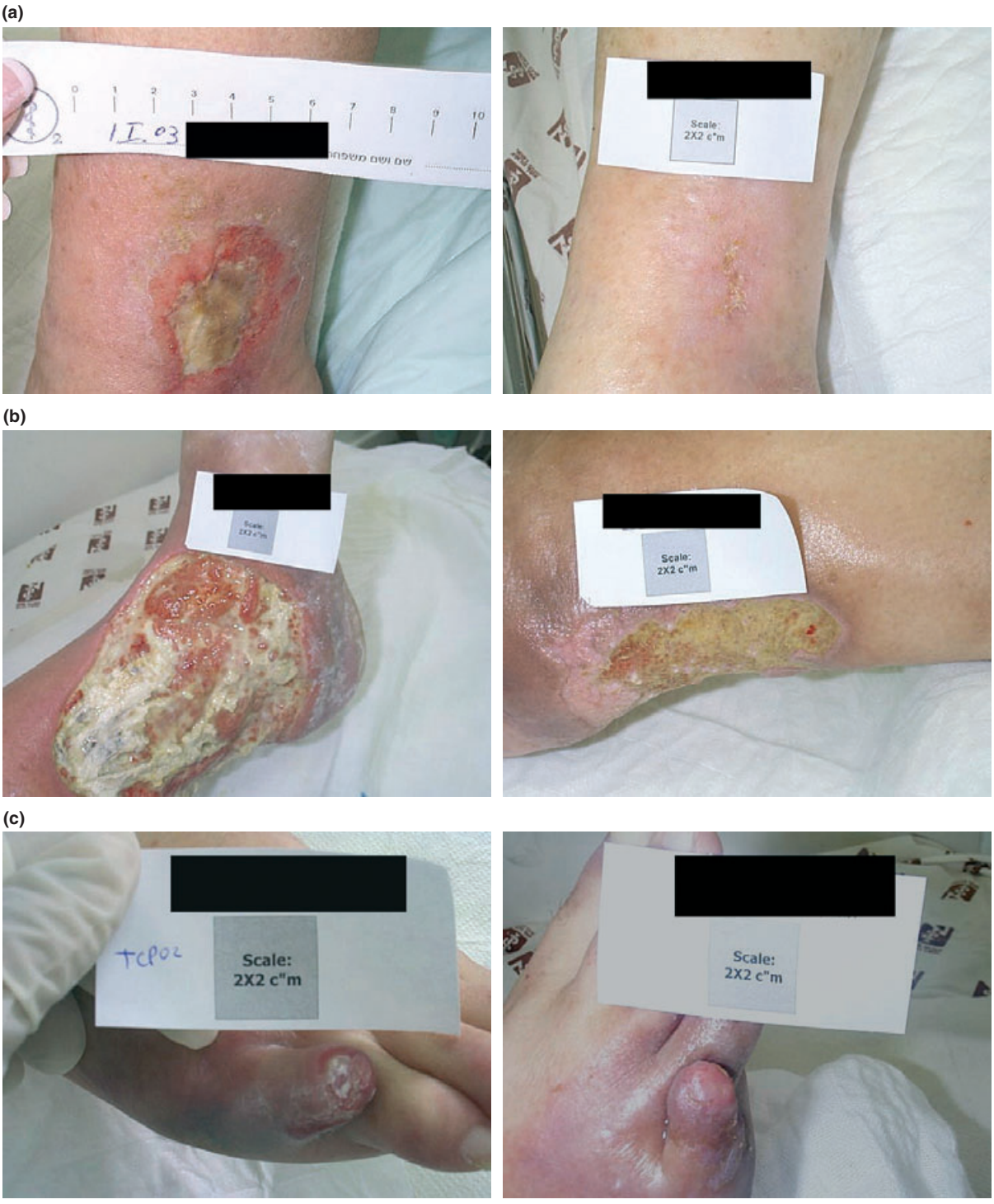

Figure 3 (a–c) Representative close-up photographs of ulcers of three patients with vasculitis-induced skin ulcers (left) at baseline and (right) at the end of the hyperbaric oxygen therapy.

One of the three patients who did not respond to the HBO treatment had pyoderma gangrenosum due to inflammatory bowel disease, the second had systemic lupus erythematosus and the third had cutaneous leukocytoclastic vasculitis. Baseline characteristics of the patients who clinically responded to HBO treatment

did not differ from those of the nonresponders. Likewise, there was no significant difference between the responders and nonresponders with respect to the measurements of $TCpO_2$ breathing room air, breathing 100% oxygen at 1 ATA and breathing 100% oxygen at 2 ATA (3.0 ± 2.5 kPa vs. 4.3 ± 3.3 kPa, 12.9 ± 11.1 kPa vs. 24.9 ± 16.7 kPa and 57.3 ± 28.3 kPa vs. 75.2 ± 44.2 kPa, respectively).

Discussion

Cutaneous nonhealing ulceration is a threatening manifestation of vasculitis. The standard of medical care includes the use of systemic immunosuppressive drugs, although the evidence for this therapy is scanty.[2] In the present study we evaluated the effect of HBO therapy on nonhealing ulcers in 35 patients with vasculitis unresponsive to immunosuppressive drugs. HBO therapy was found to be extremely effective, with 80% of the patients experiencing complete healing and 11% demonstrating partial healing. None of the patients participating in this study had any side-effects related to the HBO therapy.

HBO can be used as adjuvant therapy for patients with ischaemic ulcers.[5] Using HBO, the circulating haemoglobin is fully oxygenated and the oxygen dissolves in the plasma, correlating with the partial pressure of oxygen. Under HBO of 2–2.5 ATA, the amount of dissolved oxygen in the plasma increases more than 10-fold, exceeding the tissue oxygen requirements.[8] This primary effect of HBO generates a favourable gradient for oxygen diffusion from functioning capillaries to ischaemic tissue sites. By altering conditions of local hypoxia, HBO facilitates the wound-healing processes such as fibroblast proliferation or angiogenesis.[4] The increase in tissue oxygenation, as measured by $TCpO_2$, is the most important predictive parameter used to identify patients who are likely to benefit from HBO therapy.[9] In our study there was a significant sequential increase in the ulcer tissue oxygenation, in accordance with the increase in inhaled oxygen pressure. The oxygen pressure increased from 3.1 ± 2.5 kPa at room air concentration to 59.1 ± 29.8 kPa at 2 ATA of 100% oxygen, $P < 0.001$ (Fig. 1). This significant increase in tissue oxygenation appeared to be one of the major components responsible for the high cure rates in our patients.

In addition to the physical relationships determining the local gas concentration, volume and pressure, HBO has a beneficial effect in nonischaemic ulcers.[10] The effect of hyperoxia on vascular inflammatory responses has already been studied in a considerable number of experimental models. HBO reduces rolling and adhesion of polymorphonuclear cells in the microcirculation of skeletal muscle,[11] small bowel,[12] brain,[13] skin flaps[14] and liver.[15] Furthermore, HBO has been demonstrated to affect polymorphonuclear–endothelial cell adhesion via modification of CD receptors,[16] thus downregulating the functions of CD11/18.[16] HBO has been reported to exert beneficial effects in other inflammatory conditions, including experimental colitis,[17] Crohn's disease,[18] carrageenan-induced paw oedema[19] in a rat model of systemic inflammatory response, and in a model of circulatory shock induced by intraperitoneal injection of zymosan.[20] In the current study, the major process responsible for the development of the vasculitis ulcer was inflammation in the vessel walls followed by reactive damage of mural structures. We therefore suggest that the anti-inflammatory effect of HBO, especially in the vessel walls, could serve as an additional mechanism responsible for its beneficial outcome in the vasculitis patients.

While 80% of the patients experienced complete healing, three patients (8.6%) did not respond to the therapy. No significant difference of the baseline patient characteristics or tissue oxygenation was observed between the nonresponders and those having complete healing. Consequently, based on current knowledge we are unable to predict who will or will not benefit from HBO therapy. Further studies are needed to elucidate this question.

HBO therapy is generally safe and well tolerated. Most side-effects are mild and reversible, although adverse events can occur in rare cases (reversible myopia, symptomatic otic barotraumas, pulmonary barotraumas or pulmonary oxygen toxicity, as well as seizures due to central nervous system oxygen toxicity).[21,22] In the current study, HBO treatment was found to be very safe. None of the vasculitis patients participating in the current study had any side-effects related to the therapy.

The costs of the technique must be taken into consideration. Marroni *et al.* reported that while the cost of HBO is equivalent to other new treatments used for nonhealing ulcers (e.g. local topic treatment of human growth factor), HBO therapy might prove more effective.[23] Taking into consideration the long-term immunosuppressive therapies usually prescribed to subjects with vasculitis-induced nonhealing skin ulcers, the lack of major side-effects and the relatively low cost of HBO make the latter extremely advantageous for this patient category.

Conclusion

HBO treatment is an effective and safe therapy for vasculitis patients suffering from nonhealing skin ulcers.

As this is the first study evaluating the effects of HBO in vasculitis-induced ulcers, further studies are needed to evaluate whether HBO can be use as primary therapy for this group of patients.

References

1 Lotti T, Ghersetich I, Comacchi C *et al.* Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.
2 Ryan TJ. Management issues in vasculitis. *Adv Exp Med Biol* 1999; **455**: 327–30.
3 Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *QJM* 2004; **97**: 385–95.
4 Roth RN, Weiss LD. Hyperbaric oxygen and wound healing. *Clin Dermatol* 1994; **12**: 141–56.
5 Abidia A, Laden G, Kuhan G *et al.* 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**: 513–18.
6 Waisman D, Brod V, Wolff R *et al.* Effects of hyperoxia on local and remote microcirculatory inflammatory response after splanchnic ischemia and reperfusion. *Am J Physiol Heart Circ Physiol* 2003; **285**: H643–52.
7 Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* 1998; **21**: 855–9.
8 Boerema I, Meyne NG, Brummelkamp WH *et al.* [Life without blood]. *Ned Tijdschr Geneeskd* 1960; **104**: 949–54.
9 Grolman RE, Wilkerson DK, Taylor J *et al.* Transcutaneous oxygen measurements predict a beneficial response to hyperbaric oxygen therapy in patients with nonhealing wounds and critical limb ischemia. *Am Surg* 2001; **67**: 1072–9.
10 Kessler L, Bilbault P, Ortega F *et al.* Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care* 2003; **26**: 2378–82.
11 Haapaniemi T, Nylander G, Sirsjo A *et al.* Hyperbaric oxygen reduces ischemia-induced skeletal muscle injury. *Plast Reconstr Surg* 1996; **97**: 602–7.
12 Tjarnstrom J, Wikstrom T, Bagge U *et al.* Effects of hyperbaric oxygen treatment on neutrophil activation and pulmonary sequestration in intestinal ischemia-reperfusion in rats. *Eur Surg Res* 1999; **31**: 147–54.
13 Thom SR. Functional inhibition of leukocyte B2 integrins by hyperbaric oxygen in carbon monoxide-mediated brain injury in rats. *Toxicol Appl Pharmacol* 1993; **123**: 248–56.
14 Kaelin CM, Im MJ, Myers RA *et al.* The effects of hyperbaric oxygen on free flaps in rats. *Arch Surg* 1990; **125**: 607–9.
15 Chen MF, Chen HM, Ueng SW *et al.* Hyperbaric oxygen pretreatment attenuates hepatic reperfusion injury. *Liver* 1998; **18**: 110–16.
16 Buras J. Basic mechanisms of hyperbaric oxygen in the treatment of ischemia-reperfusion injury. *Int Anesthesiol Clin* 2000; **38**: 91–109.
17 Akin ML, Gulluoglu BM, Uluutku H *et al.* Hyperbaric oxygen improves healing in experimental rat colitis. *Undersea Hyperb Med* 2002; **29**: 279–85.
18 Lavy A, Weisz G, Adir Y *et al.* Hyperbaric oxygen for perianal Crohn's disease. *J Clin Gastroenterol* 1994; **19**: 202–5.
19 Sumen G, Cimsit M, Eroglu L. Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats. *Eur J Pharmacol* 2001; **431**: 265–8.
20 Luongo C, Imperatore F, Cuzzocrea S *et al.* Effects of hyperbaric oxygen exposure on a zymosan-induced shock model. *Crit Care Med* 1998; **26**: 1972–6.
21 Fitzpatrick DT, Franck BA, Mason KT *et al.* Risk factors for symptomatic otic and sinus barotrauma in a multiplace hyperbaric chamber. *Undersea Hyperb Med* 1999; **26**: 243–7.
22 Plafki C, Peters P, Almeling M *et al.* Complications and side effects of hyperbaric oxygen therapy. *Aviat Space Environ Med* 2000; **71**: 119–24.
23 Marroni A, Oriani G, Wattel FE. Evaluation of cost-benefit and cost-efficiency of hyperbaric oxygen therapy. In: *Handbook of Hyperbaric Medicine*. Berlin: Springer-Verlag, 1996: 879–86.

