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The effect of hyperbaric oxygen on different phases of healing of ischaemic flap wounds and incisional wounds in skin

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SUMMARY. **Several studies have revealed a positive effect of treatment of ischaemic wounds and flaps with hyperbaric oxygen. We studied the effect of 100% oxygen (2.4 ATA) for 90 min daily on different phases of healing ischaemic and normal incisional wounds in rats. Hyperbaric oxygen on day 0–3 significantly increased almost all the force parameters of ischaemic flap wounds by 41–57% after 10 days of healing. On the other hand, when the treatment was continued until day 9 the positive effect on the wound healing was abolished. Furthermore, when hyperbaric oxygen was given on days 4–9 there was a tendency towards a decrease in the biomechanical parameters. Hyperbaric oxygen had no effect on the healing of normal incisional wounds.**

Ischaemia is an important cause of impaired wound healing clinically and renders the wound more susceptible to infection,[1,2] thereby causing a further retardation of the healing. Although the hypoxia in the central space of a wound is one of the factors that stimulate the wound healing process,[2,3] oxygen is essential for the synthesis and maturation of collagen.[2,4,5] Thus, in an ischaemic wound less scar tissue will be formed, the wound line will be weaker, and consequently there is an increased risk for wound rupture. This means that the biomechanical (functional) properties of the wound will be impaired. In order to improve ischaemic wound healing it is important to investigate the effect of increasing oxygen supply. The purpose of this study was to investigate the effect of treatment with hyperbaric oxygen (HBO) on different stages of healing ischaemic wounds, by means of an ischaemic flap model evaluated previously.[6,7] Furthermore, for comparative purposes the influence of HBO was studied on normal healing incisional wounds as well.

Materials and methods

Eighty male Wistar rats (260–300 g) were used. One died under anaesthesia. The animals were acclimatised for 1 week before surgery and were kept in plastic cages, with 2 or 3 rats in each. There were no problems with having more than one rat in a cage and the bandages (see below) ensured that cannibalism never occurred. The room temperature and day-night cycles were kept constant and the animals were fed rat pellets and water ad libitum.

The animals were randomly divided into 8 groups, with 10 animals in each group. Ischaemic H-shaped double flaps and normal incisional wounds were treated with HBO, and tested biomechanically after 10 and 20 days, respectively. The treatment schedules are showed in Figure 1.

The oxygen treatments were performed in a monoplace chamber (Vickers). In the groups treated with HBO (except group 2) the therapy was started within 6 h from raising the flaps or incision of the linear wounds. 100% oxygen was given at 2.4 atmospheres absolute (ATA) every 24 h for 90 min on the above mentioned days, preceded by 5–5½ min of compression and followed by 5 min of decompression.

The rats were photographed to determine the degree of shrinkage of the test wounds on slides after 10 or 20 days of healing, as well as the length of surface necrosis on the flaps on day 10.

Operative procedure

The animals were anaesthetised with an injection of pentobarbital (50 mg/kg B.W.) i.p. After shaving of

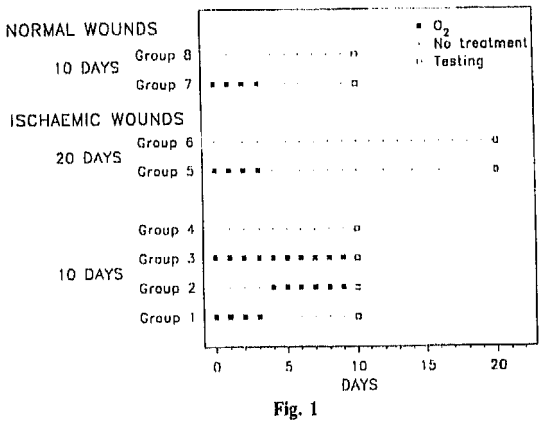

Fig. 1

Figure 1—The schedules for treatment with hyperbaric oxygen of ischaemic and normal wounds.

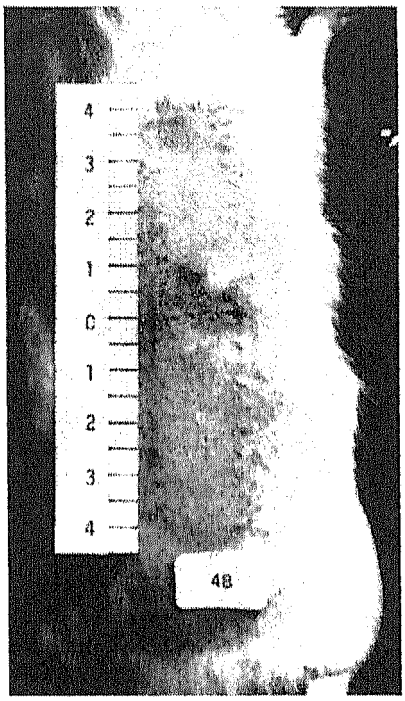

Fig. 2

Figure 2—The H-shaped double flap on the back of a rat after 10 days of healing. The dark areas are surface necroses.

the skin, the wound lines, together with suture sites (4 mm apart), were marked on the skin of the back of each animal. In the flap groups, 2 cm wide and 8 cm long H-shaped double flaps were created, each single flap having a length of 4 cm (Fig. 2). In the groups with incisional wounds, 2 cm long horizontal lines were marked on the site corresponding to the horizontal test wound in the double flap. The skin and panniculus carnosus were incised perpendicularly to the surface. After raising of the flaps, perforating branches from the central vein were cut. On the "free" apical edge of each flap the thickness of the dermis was measured (without panniculus carnosus) 0.5 cm from the midline on both sides, an average value of these 4 values was obtained, and the flaps were sutured back in position. Also in the incisional wound groups, each wound edge was measured and an average value was obtained. In all groups, the skin and panniculus carnosus were sutured in one layer with 5/0 polypropylene (Prolene®) sutures and the animals were bandaged with perforated film absorbent dressing (Melolin®) and elastic adhesive (Tensoplast®) for 5 days. The sutures were removed on day 10 postoperatively.

Sampling and biomechanical testing

After sacrifice of each animal with an overdose of pentobarbital, the skin with the wounds was removed *in toto*. Standardised 2 mm wide skin strips were cut perpendicularly to the test wounds in the double flaps and the incisional wounds, using a multibladed cutting instrument. From each wound 6 strip specimens were obtained (about 5 in the case of 20 days flap wounds). After removal of the panniculus carnosus, the specimens were mounted in a materials testing machine (Alwetron) by means of two clamps with rough surfaces, with the wound in the middle of the free space. The jaw space, i.e. the distance between the edges of the clamps, was 3 mm. With the deformation rate kept constant at 10 mm per minute, the specimens were loaded uniaxially until failure, while immersed in Ringer's solution (pH 7.4), and complete load-deformation curves were recorded by transducers coupled to bridges and sampled in a PC by an analog-digital converter. From these curves four sets of data were calculated: Load vs. strain, load*S vs. strain, stress vs. strain and stress*S vs. strain, where S indicates data corrected for shrinkage (see below). Stress is load divided by the cross-sectional area of the wound tissue, and strain is the extensibility which is deformation divided by original length of the wound strip specimen. Original length is the jaw space plus the length the specimen can be stretched before loading it (i.e. the jaw space plus possible slack at the mounting). From each of these data sets the following key parameters were calculated:[7-9] (1) Maximum load, load*S, stress and stress*S; (2) The energies at maximum load, load*S, stress and stress*S and at the breaking point (which we defined as the point where the force has dropped to half the maximum value); (3) Strain at maximum and breaking point. The most important parameters are the energies (calculated as the area under the curves), since forces applied to the tissue are absorbed as energy.[8-11]

In the case of ischaemic wounds, a certain shrinkage along the wound line took place by a factor $(1-S)$, where $S = TL/IL$ (TL = length at the time of biomechanical testing, and IL = length at the time of incision).[7] The force and energy parameters thus have to be multiplied with S since the biomechanical testing of a 2 mm wide specimen means that this strip was 2/S wide when healing started. Thus, for flap wounds the load-strain or stress-strain data corrected for shrinkage are the most interesting biomechanical parameters, since they express the functional properties of the flap wound that began to heal and thereby reflect the actual external forces that a wound can resist before breaking. These parameters are thus directly comparable with the load-strain and stress-strain data, respectively, of the incisional wounds.

All the operations, treatments and the biomechanical testing were performed by the same investigator.

Measurement of length of surface necrosis

The necroses on the flaps in this model are only confined to the surface[6,7] and the proximal delimitation is often irregular (Figs 2, 3). The contour of surface necrosis was drawn on a piece of paper by means of a magnifying apparatus (Fig. 3). The extrapolated length of proximal necrosis (L_p) and distal necrosis L_d was calculated by dividing the corresponding areas (A_p,A_d) with the width (W) of the

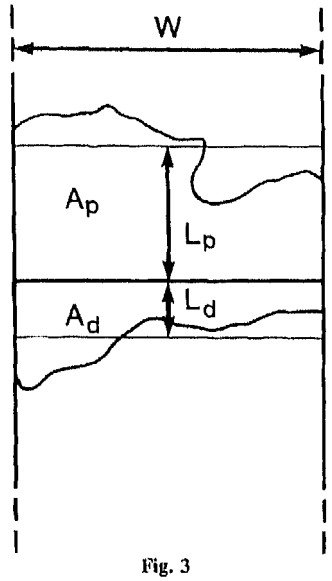

Fig. 3

Figure 3 -Schematic drawing of the contour of the surface necroses seen on the double flap in Figure 2.

flap, calibrated with the measuring device on the slide (Fig. 2). By using the length of surface necrosis and not the area, the differences in flap width could be eliminated.

Statistical analysis

To obtain variance homogeneity, the variables for the biomechanical parameters were transformed logarithmically. The effect of this transformation is visualized in Fig. 6A–D. One-way analysis of variance and Student's t-test were used to test any differences between the groups. Differences were considered significant when $p \leq 0.05$. The 95% confidence limits given in the figures are obtained from back-transformation of ($Mean_{log}$ −95% confidence limit) and ($Mean_{log}$ +95% confidence limit), where $Mean_{log}$ is the mean of the logarithmically transformed variables.

Results

The effect of ischaemia on the biomechanical properties after 10 days of healing is shown in Figure 4, where the control groups of normal incisional and ischaemic flap wounds are compared. This decrease in strength of the ischaemic wounds is in agreement with previous results derived from this model.[7]

After 10 days of healing of the flap wounds (Fig. 5, Fig. 6A–D) (only data corrected for shrinkage are shown), all force parameters significantly increased for group 1 ($p \leq 0.05$). Thus regarding the load*S-strain data, maximum load*S increased by 41% ($p < 0.05$), energy*S at maximum load by 54% ($p = 0.05$) (Fig. 6A–B) and breaking energy*S by 56% ($p < 0.05$), compared with the untreated control group. The

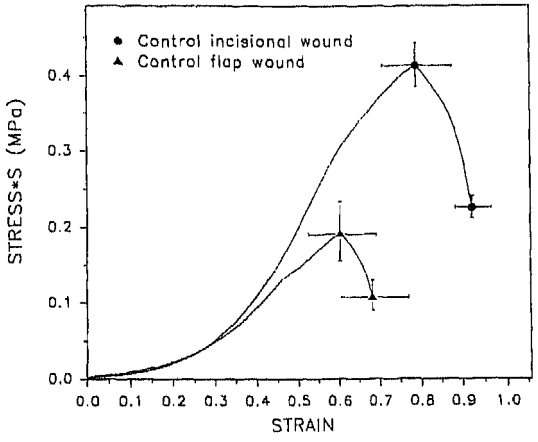

Fig. 4

Figure 4 The effect of ischaemia on the biomechanical properties after 10 days of healing. Control groups.

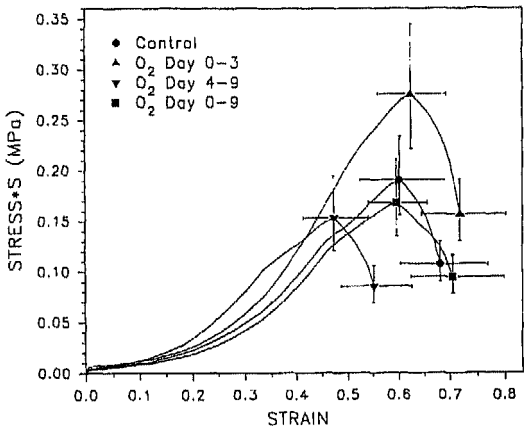

Fig. 5

Figure 5—Stress*S vs. strain curves for ischaemic flap wounds after 10 days of healing. The S indicates that the stress data have been corrected for shrinkage (see "Sampling and biomechanical testing"). The bars indicates 95% confidence limits. Note the axes are different from those of Figures 4, 7 and 8.

corresponding parameters calculated from the stress*S-strain curve (Fig. 5, Fig. 6C–D), maximum stress*S, energy*S at maximum stress and breaking energy*S, increased by 43%, 57% and 57%, respectively ($p < 0.05$). Strain at maximum stress*S and breaking strain remained unchanged in comparison with the control group. For group 2, on the other hand, strain at maximum stress*S significantly decreased by 21% and breaking strain by 19% ($p < 0.05$). Furthermore, maximum load*S, energy*S at maximum load, and breaking energy*S tended to decrease by 26%–33% ($p = 0.06$–0.07). In contrast, the stress*S-strain parameters for group 2 were not significantly changed (maximum stress*S: $p = 0.17$, energies at maximum stress*S: $p = 0.12$). For group 3, there were no significant differences in any of the biomechanical parameters of the flap wounds ($p > 0.2$).

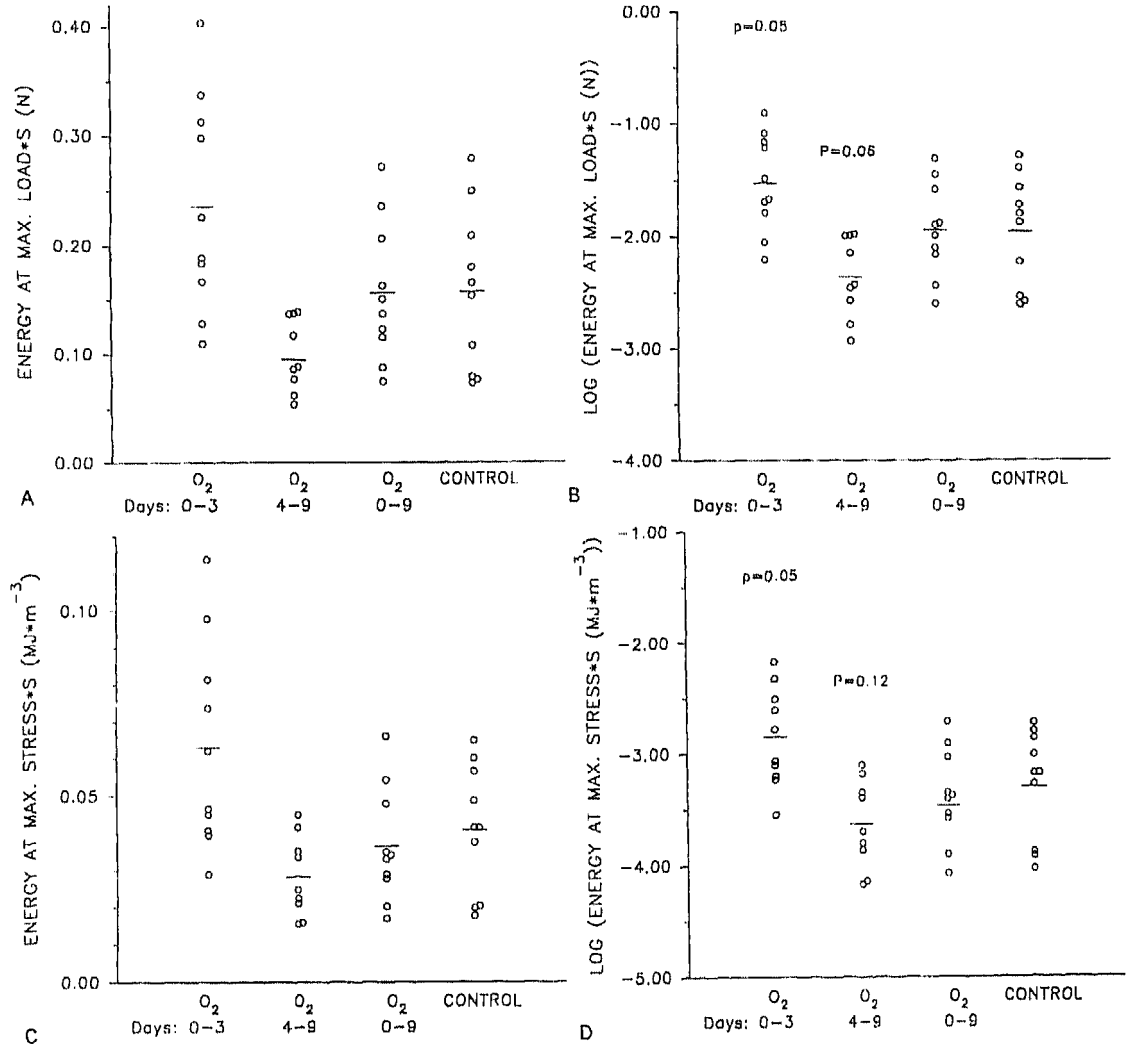

Fig. 6

Figure 6—Ischaemic flap wounds after 10 days of healing. (A, B) Energy at maximum load*S. (C, D) Energy at maximum stress*S. The means are indicated by bars. The S indicates that the force parameters have been corrected for shrinkage (see "Sampling and biomechanical testing"). Figs 6A and 6C shows a tendency of skewness to the right and an increased variance when the mean increases. Figs 6B and 6D show that after logarithmic transformation the skewness disappears and the differences in variances diminishes.

After 20 days of healing of the flap wounds (Fig. 7), all the biomechanical parameters remained unchanged after treatment with HBO on day 0–3, compared with those of the untreated control wounds ($p > 0.2$).

Treatment of normally healing incisional wounds with HBO on day 0–3 (Fig. 8) did not significantly affect the biomechanical characteristics after 10 days of healing ($p > 0.2$).

There were no differences between the length of surface necrosis in the various groups after 10 days of healing (Table 1). Likewise, there were no significant differences between the shrinkage of the wounds tested after 10 days of healing, nor after 20 days ($p > 0.2$) (Table 2).

The mean weight gain from the day of surgery until the biomechanical testing was: Group 1–3: 2–3%. Group 4: 4%. These gains were not significantly different ($p > 0.2$). Three animals in group 1 and one animal in each of the groups 2–4 had a weight loss of 2–4%. This small weight loss was not accompanied by a decrease in the biomechanical parameters. For group 5–6 the weight gain was 13–14%. The weight gain for group 7 was significantly less than for group 8 (6% versus 11%, $p < 0.05$). Furthermore, the weight gain for group 4 was significantly less than for group 8 ($p < 0.01$).

Discussion

The effect of HBO therapy on acute wound healing has only been investigated in one controlled clinical study by Perrins[12] who found that the survival of split skin grafts increased by administration of HBO (2 ATA 2 h × 2 daily for 3 days). The first randomised double-blind study of the effect of HBO (2.5 ATA 1.5 h daily for 30 days) on chronic leg ulcers was published recently[13] and showed a significant decrease in wound

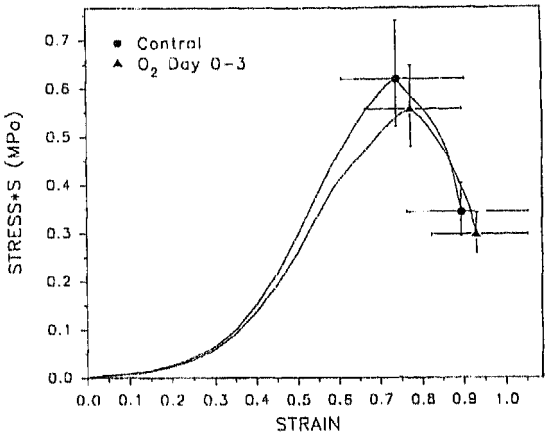

Fig. 7

Figure 7—Stress*S vs. strain curves for ischaemic flap wounds after 20 days of healing. The S indicates that the stress data have been corrected for shrinkage (see "Sampling and biomechanical testing"). The bars indicates 95% confidence limits.

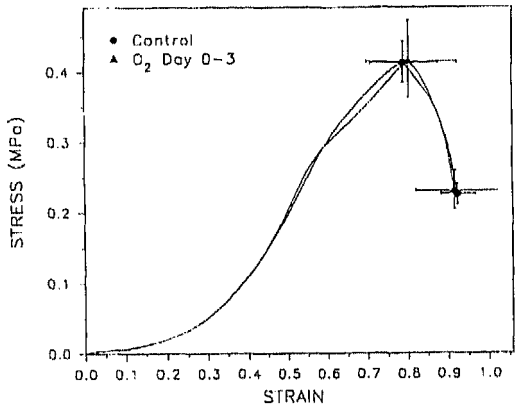

Fig. 8

Figure 8—Stress vs. strain curves for normal incisional wounds after 10 days of healing. The bars indicates 95% confidence limits. Note the vertical axis is different from those of Figures 4 and 7.

Table 1 Mean lengths of necrosis (in cm, 95% confidence limits) for proximal and distal flaps

	Proximal flap	*Distal flap*
Group 1	2.0 (1.3, 2.7)	0.5 (0.3, 0.7)
Group 2	2.0 (1.6, 2.4)	0.6 (0.4, 0.8)
Group 3	1.9 (1.4, 2.4)	0.4 (0.2, 0.6)
Group 4	1.9 (1.3, 2.5)	0.6 (0.4, 0.8)

Table 2 The mean shrinkage (in mm, 95% confidence limits) of the test flap wounds after 10 and 20 days of healing

After 10 days	
Group 1	2.1 (1.5, 2.7)
Group 2	1.9 (1.2, 2.6)
Group 3	2.2 (1.6, 3.0)
Group 4	2.2 (1.5, 2.7)
After 20 days	
Group 5	7.8 (7.1, 8.5)
Group 6	8.6 (7.8, 9.4)

area after 4 and 6 weeks compared with the control group. In contrast, a number of experimental studies have been published; HBO therapy seemed to decrease the tensile strength in normal healing incisional wounds but not in apparently ischaemic wounds in rats.[14] In another study in rats, HBO also decreased tensile strength of normal incisional wounds and subcutaneous implanted viscose cellulose sponges.[15] In contrast, Lundgren and Sandberg[16] showed that the decrease in tensile strength on day 5 of incisional wounds on hypovolemic and anaemic rats could be abolished by concomitant treatment with HBO. Furthermore, the tensile strength of abdominal wounds in dogs[17] and the bursting strength as well as angiogenesis in normal incisional wounds on rats were increased after treatment with HBO.[18] Finally, the effect of HBO has been studied on healing open wounds; the healing time of partial as well as full thickness skin wounds in rats was significantly decreased by HBO for 10 days.[19] In contrast, Kivisaari and Niinikoski[20] did not find any effect of HBO on the healing of normal open full thickness skin wounds but, if these were rendered ischaemic, the healing was significantly increased after 22 to 28 days. Thus, as in our study, only ischaemic wounds benefited from the elevated tissue oxygen tension from HBO. In a recent study of open wounds on mouse ears, the effect of HBO was also most pronounced for ischaemic wounds although HBO also reduced the time until closure for normal wounds.[21] In another study of ischaemic open wounds on rabbit ears, HBO therapy seemed to increase the formation of granulation tissue although the numbers of wounds in the statistical analyses are obscure.[22]

The ischaemic double flap model used in the present study was developed for biomechanical testing. The blood flow adjacent to the test wound, measured by the ^{133}Xe clearance method, decreased to an ischaemic level on day 1 postoperatively, compared with that of normally healing incisional wounds, and did not return to normal until day 16.[6] This drop in blood flow resulted in a significant delay of the healing of the test wound after 10 days as well as after 20 days of healing.[7] A healing time of 10 days was chosen since this is the earliest time of clinical importance, i.e. when the sutures are usually removed and the wound will be subjected to external forces on "its own". Furthermore, an improvement of healing occurring earlier will presumably still be seen then. A healing time of 20 days was also used, since it then can be ascertained whether a possible positive effect recorded after 10 days is an acceleration of early wound healing or a feature throughout the healing process. The rationale for treatment with HBO once a day is that during the hyperoxia the tissue oxygen increases, thereby optimising fibroblast proliferation,[4] while during the periods of relative hypoxia angiogenesis is stimulated.[3, 23] When the inhaled oxygen concentration is increased, the oxygen gradient from the capillaries to the central dead space gets steeper, thereby increasing the oxygen supply in the zone where cell division takes place.[5, 24] This may explain the stimulating effect in our study of treatment with HBO in the inflammatory phase. This effect was however abolished when the treatment was continued into the

phase of fibroplasia where the capillary buds start to join to functioning capillary loops.[25] Furthermore, if the oxygen therapy was started on day 4, i.e. in the beginning of the phase of fibroplasia, there was a tendency toward an impairment of healing, as measured after 10 days of healing. In contrast to open wounds, the central dead space in our test wound is only a slit. This means that in the phase of fibroplasia the wound space is filled with vascular granulation tissue and treatment with HBO in this phase of healing will affect the hypoxic drive negatively, thereby impairing collagen formation and maturation.

The weight gain of the animals was smaller for the flap groups than for the incisional groups, indicating that having a large ischaemic flap on the back is more stressing than having a smaller incisional wound. Theoretically an increased catabolism in the flap groups could contribute to a decrease in wound healing additional to that caused by ischaemia. Furthermore, the weight gain was slightly less in the HBO treated 10 day groups; for some reason the differences were most pronounced between the groups with normal incisional wounds. This indicates that the treatment procedure is stressing but as there was no significant effect of the procedure on the weight gain in the flaps groups this stressing effect does not have any practical importance.

The effect of HBO on skin flap survival has most often been studied in dorsal random flaps in rats. In most studies the length/area of necrosis decreased significantly with treatment with HBO.[26–32] One study found only a marginal effect[33] and in two studies no significant effect could be detected.[34, 35] In another study, HBO seemed to increase and/or maintain the number and possibly the size of the vessels in the microvasculature.[36] HBO therapy also increased the survival area of island abdominal flaps.[37–40] In guinea pigs, HBO decreased the length of epidermis necrosis of dorsal skin flaps and the capillary network seemed to increase.[41] In rabbits, HBO therapy decreased the area of necrosis on skin flaps[42] but these results could not be reproduced in another study.[43] Finally, the effect of HBO has been investigated on flaps in pigs; an intensive treatment schedule decreased the area of necrosis of random flaps[44] but in another study HBO had only a marginal effect on necrosis length.[45] Moreover, no effect of treatment with HBO was found on the survival of four types of flaps in pigs.[46]

Many different schedules of HBO therapy have been used; most of them increased healing of ischaemic wounds or survival of flaps. A treatment with 100% oxygen under a pressure of more than about 2–2.5 ATA for 2 hours twice a day would risk toxic side effects and does therefore not seem to be reasonable clinically in attempts to increase ischaemic wound healing or flap survival. We chose a treatment with 100% oxygen at 2.4 ATA for 90 min per day, or about 100 min when the compression and decompression period are included, since this treatment schedule is well tolerated in patients.[47] Since measurement of surface necrosis is used most often for evaluation of flap survival, we measured such necrosis too. We did not, however, find any differences in the length of flap surface necrosis between the groups, although the biomechanical parameters of the test wounds increased significantly. This apparent discrepancy in the results can be explained by the fact that the measured necroses are not full thickness necroses but are only limited to the surface[6, 7] and therefore do not reflect the degree of ischaemia in the healing dermis. This is confirmed by the finding that the extension of surface necroses does not correlate with the biomechanical parameters of the test wound.[6, 7] Furthermore, we have shown that dressing of the flaps significantly decreases the surface necroses (necrosis of epidermis and perhaps the uppermost part of the dermis)[48] and dressing of the flaps in the present study (to avoid biting of the sutures by other animals in the cage) has probably already salvaged some of the surface and no further reduction in the length of these necroses took place by means of HBO. Clinically more important than epidermis necrosis are the changes in the healing dermis. These changes can in the double flap model be detected accurately by measuring the biomechanical (functional) properties of the test wounds at different pharmacological and physical treatments.

In conclusion, HBO can significantly improve the healing of ischaemic incisional wounds if the treatment takes place during the first few days of wound healing. In contrast, HBO therapy has no effect on the healing of normal wounds.

Acknowledgements

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