Trauma 2001; **3**: 133–141

Hyperbaric medicine in soft tissue trauma

Helen Cosgrove[a] and **Phil Bryson**[b]

Severe crush injuries of the soft tissues can result in tears of the large vessels and destruction of the microcirculation. This produces ischaemia and tissue necrosis and contributes to the development of oedema and compartment syndromes. All these factors compromise tissue survival. Immediately following a crush injury some areas of tissue are obviously irreversibly damaged, and others undamaged. It is common to have a 'grey area' between these, where there is uncertainty as to what will survive. Management of crush injury must involve surgical repair of vessels and soft tissues, debridement of obviously dead tissue, and bone stabilization. At the same time tissue perfusion must be maintained by manoeuvres such as fluid replacement and diminution of oedema, and when necessary fasciotomy. It has been proposed that hyperbaric oxygen therapy has a role, as an adjunct, in the maintenance of tissue oxygenation under these conditions, and will improve survival of tissues in the grey area, and thus minimize tissue loss. Hyperbaric oxygen therapy involves breathing 100% oxygen at pressures greater than one atmosphere. Presently, the pressures most often used are in the range 2–3 atmospheres absolute.

Key words: crush injury, hyperbaric oxygen and white cell function

History

Hyperbaric therapy, with air, has existed since 1662, when a British clergyman built a sealed chamber in which he could vary the pressure with a set of bellows. He thought that acute illnesses would respond to increased pressure, and chronic diseases to reduced pressures (Sheridan and Shank, 1999). In the nineteenth century air pressure chambers became fashionable around Europe and competed with the spas and mineral waters of health resorts (Sheridan and Shank, 1999).

During the second world war research was conducted into hyperbaric oxygen therapy to support the diving operations of the military. This research was continued in the post-war years as hyperbaric therapy was used to support cardiac surgery. With the advent of cardiopulmonary bypass the need to operate under conditions of hyperbaric oxygen no longer existed and both research and the number of chambers declined (Kindwall, 1999a). During the late 1970s hyperbaric oxygen therapy was inappropriately overused and fell into disrepute.

More recently, with increased understanding of cell physiology and the mechanisms of injury at molecular level, interest has once again been focused more carefully on hyperbaric oxygen. There are a number of conditions that should theoretically respond to the hyperoxygenation produced by hyperbaric therapy. In this article we aim to look at some of this theoretical background and then examine the evidence for the use of hyperbaric oxygen as an adjunct to the management of soft tissue injury.

The Undersea and Hyperbaric Medical Society publish a list of conditions for which hyperbaric oxygen is indicated, often in conjunction with other treatment (see the Appendix).

[a]A & E Department, Torbay Hospital, Torquay, UK. [b]DDRC, Hyperbaric Medical Centre, Tamar Science Park, Research Way, Plymouth, UK. A registered charity. No. 279652.

Address for correspondence: P Bryson, DDRC, Hyperbaric Medical Centre, Tamar Science Park, Research Way, Plymouth PL6 8BU, UK. Tel: 01752 209999. Website: www.ddrc.org

1460–4086(01)TA108OA

Normal cell metabolism

All cell functions are energy dependent. The energy is created from glucose, amino acids and fatty acids via acetyl coenzyme A and the Kreb's cycle and stored as adenosine triphosphate (ATP). The ATP is used throughout the cell to fuel all functions. Under aerobic conditions one mole of glucose will produce 38 moles of ATP (Guyton and Hall, 1997) (see Figure 1).

The cells of the body depend on the circulation of extracellular fluid for nutrients. There is a constant exchange of fluid between the plasma and the interstitial spaces. When oxygen is insufficient, the cell can produce limited amounts of energy by anaerobic glycolysis. This is not an efficient method of producing energy, it harnesses only about 3% of the available energy from each mole of glucose also leads to a build up of lactic acid which diffuses out of the cell. When oxygen is restored the lactate is converted back to pyruvate and enters the Kreb's cycle (Guyton and Hall, 1997).

When the energy supplies are exhausted, the cell is no longer able to perform its functions. Once the active transport mechanisms are paralysed, due to lack of ATP, the internal milieu of the cell breaks down and fluid and electrolytes move across the cell membrane down their concentration gradients. This results in a net increase in intracellular fluid and is rapidly followed by cell death (Guyton and Hall, 1997).

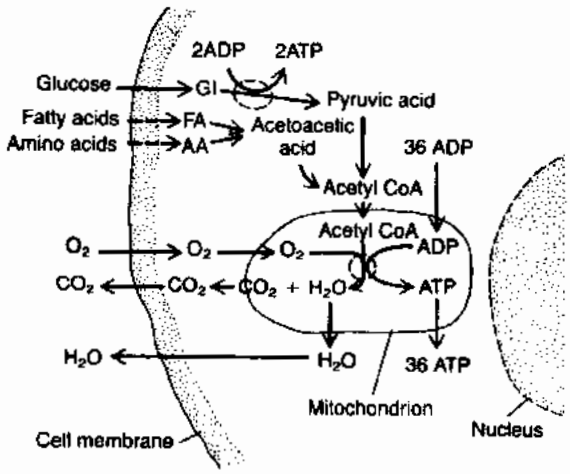

Figure 1 Formation of adenosine triphosphate (ATP) in the cell, showing that most of the ATP is formed in the mitochondria

Regulation of the tissue blood supply

Under normal conditions the supply of oxygen and glucose is regulated to meet the needs of the cells. Blood supply to the tissues is controlled locally and systemically, and occurs both acutely and over the longer term.

Acutely, the local control is governed by oxygen availability. As the oxygen supply reduces, the blood flow increases (Guyton and Hall, 1997).

The development of oedema is multifactorial. It requires an increase in local blood flow and also includes local damage to blood and lymphatic vessels (Wright, 1992).

The pressure exerted by oedema can compromise the capillary circulation. When the pressure in the surrounding tissue approaches or exceeds that in the capillary, then capillary blood flow will slow and cease.

Oedema also contributes to tissue hypoxia by increasing the distance between the capillary and the cells. Under normal conditions most cells are less than 50 μm from the nearest capillary and this is sufficient to supply their metabolic needs. If the distances between functioning capillaries and cells are increased, either by capillary destruction, or by interstitial oedema, then the furthest cells may not be adequately supplied. As described above, these cells will then have to utilize anaerobic glycolysis to supply their energy needs. This will, in turn, contribute to the escalation of damage.

The diffusion of oxygen from the capillary through extracellular tissue fluid is proportional to the square root of the oxygen concentration in the capillary (Peirce, 1969). Thus an increase in capillary oxygen content will result in an increase in cell oxygen delivery in tissues further from the capillary.

Pathophysiology of soft tissue trauma

The acute response to any injury involves inflammation and attempted repair. Inflammation is the process whereby serum proteins and phagocytes gain access to the damaged tissue and any invading organisms. Local vasodilation increases blood flow and together with an increase in vascular permeability, increases extravascular proteins, fluid and produces swelling. This swelling contributes to the pain felt. Phagocytes respond to various mediators and migrate

Table 1 Classification of soft tissue injuries

Type I	Wound <1 cm long and clean
Type II	Laceration >1 cm long without extensive soft tissue damage, flaps or avulsions
Type IIIA	Adequate soft tissue coverage, despite extensive lacerations or flaps, or high energy trauma, irrespective of the wound size
Type IIIB	Extensive soft tissue injury with periosteal stripping and bone exposure
Type IIIC	Arterial injury requiring repair

Derived from Gustillo *et al.* (1984).

into the area of inflammation (Wright, 1992). Neutrophils enter the capillary circulation and adhere to the walls – a process called margination. They then migrate out of the vessel and once in the extravascular space they phagocytose debris in the area of injury.

Crush injury is a severe traumatic injury to the tissues. Two or more tissues must be involved, e.g. bone, muscle, skin, connective tissue, nerve and vessels. Injury is so severe that tissue survival is questionable and there is a gradation of damage within the injured area (Wattel *et al.*, 1998). Soft tissue injuries have been graded according to a system proposed by Gustillo (1984) (see Table 1). Crush injuries have a varying degree of vascular disruption (both of large vessels and the microcirculation); with devitalized tissues, tissue hypoxia and oedema.

A characteristic series of events takes place in the microcirculation of tissues, which are reperfused after a period of ischaemia. On reperfusion there is an initial vasodilation followed after about 1 hour by a progressive and severe vasoconstriction, most marked in the arterioles closest to venules. It has been proposed that the arteriolar vasoconstriction is as a result of the local conditions produced by the neutrophil-damaged venule.

Loss of fluid from the capillaries increases the viscosity of the blood; and this coupled with margination of neutrophils and platelets on the vessel wall may result in a slowing, or cessation, of flow in the capillary. This may be more marked for red blood cells than for plasma and will contribute to the developing hypoxia of the injured area (Wright, 1992).

Wound healing

The healing of any injured area includes inflammation, regeneration and repair in varying proportions. Initially the influx of phagocytes removes debris and micro-organisms from the damaged area. Contamination with bacteria follows tissue injury and this may progress to infection. As part of the inflammatory process phagocytes enter the injured tissue and engulf bacteria. The destruction of the phagosome involves a combination of degranulation and the initiation of the respiratory burst. During the respiratory burst a metabolic pathway is activated which produces microbicidal agents by the partial reduction of oxygen. When stimulated, all phagocytes demonstrate an increase in oxygen consumption, and at least some of this is converted to hydrogen peroxide and superoxide. Superoxide production in the respiratory burst of neutrophils is depressed by hypoxia in the range found in wounds, and rises as the ambient oxygen concentration rises. Hydrogen peroxide is one of the agents employed by the phagocyte in microbial killing (Babior, 1978). Allen *et al.* (1997) have shown that oxygen tension is the most important local factor affecting the neutrophil respiratory burst in clinical conditions. They measured the utilization of oxygen and the production of superoxide by neutrophils from healthy donors and from the drains of mastectomy patients. They tested a range of different conditions and found that glucose concentration (range 2–40 mmol/l); ambient temperature (range 30–37°C); and pH (range 7.0–7.3) have relatively little effect on the neutrophil respiratory burst. They showed that the maximum rate of oxygen consumption occurred at a concentration of more than 300 mmHg. They extrapolate this to mean that by improving the tissue oxygen tension in wounds we can reduce the rate of infection.

Two or three days after the injury there is a migration of fibroblasts into the area; these divide and produce large amounts of collagen and ground substance. The production of collagen is energy dependent and active fibroblasts are confined to areas where the oxygen tension is more than 15 mmHg (usually 50–70 μm from the nearest functioning capillary). Angiogenesis takes place down a gradient from high oxygenation to lower oxygenation and up the gradient from an area of low lactate to an area of higher lactate (Guyton and Hall, 1997).

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is administered either in small monoplace chambers which are usually filled with 100% oxygen at pressure; or in multiplace cham-

bers which are compressed with air and the patient breaths 100% oxygen through a mask, hood or endotracheal tube (Grim *et al.*, 1990). Figures 2 and 3 show a patient entering, and then within a multiplace chamber; Figure 4 is a monoplace chamber.

Monoplace chambers are generally small constructions and allow one patient to lie supine within a transparent tube and access to the patient whilst the chamber is under pressure is not possible.

Multiplace chambers can accommodate 2–14 people, and allow attendants to be present in the chamber during treatment, which adds to patient safety. They also have a chamber lock entry system, which allows entry to, and exit from, the chamber without altering the pressure within the chamber (Grim *et al.*, 1990).

Most treatment regimes use pressures of between 2.0 and 3.0 atmospheres absolute (ATA) for up to 120

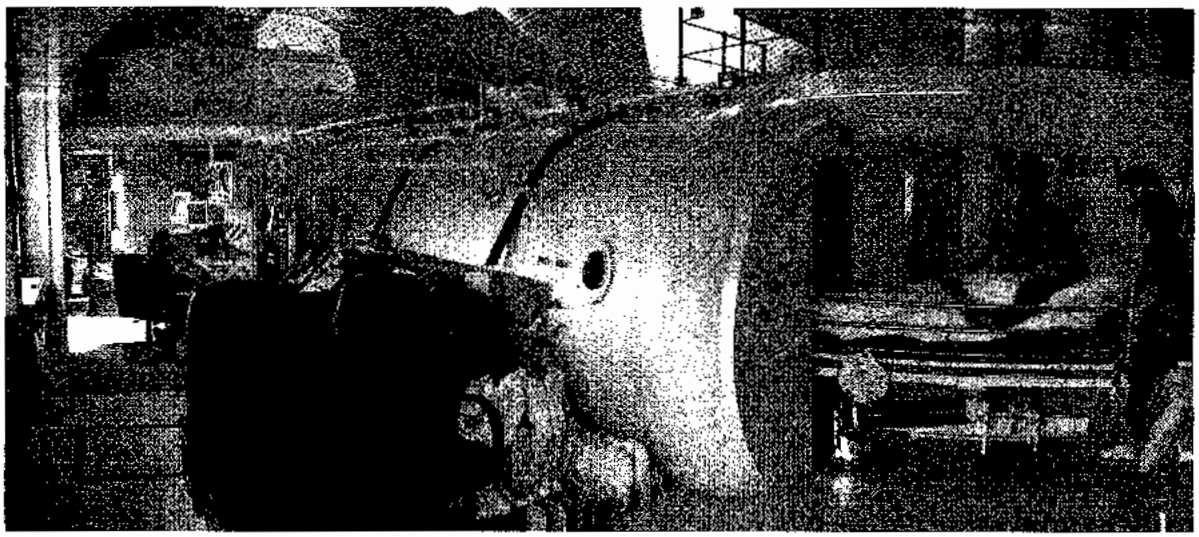

Figure 2 Patient entering a multiplace chamber

Figure 3 Patient inside a multiplace chamber

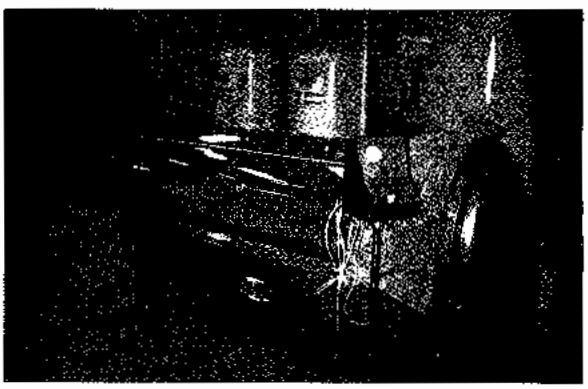

Figure 4 A monoplace chamber

min. These regimes have 'air breaks' built into them when the patient breathes the chamber compressed air for 5–10 min every 30 min. This allows about 90 min of 100% oxygen at the specified pressure per treatment.

Air is composed of approximately 21% oxygen and 79% nitrogen. Dalton's law states that in a gaseous mixture the partial pressure of each gas is a product of the proportion of the total volume of gas and the total pressure. Thus the partial pressure of oxygen in air at sea level (atmospheric pressure = 760 mmHg) is:

$$760 \times (21/100) = 160 \text{ mmHg}$$

and of nitrogen is:

$$760 \times (79/100) = 600 \text{ mmHg}$$

Henry's law states that the concentration of a gas dissolved in a liquid is a product of the pressure and a gas-dependent solubility coefficient. The solubility coefficient varies for different liquids and is temperature dependent.

When breathing air at normal atmospheric pressure (760 mmHg or 1 ATA) very little oxygen (approximately 0.3 ml per 100 ml of plasma (vol%)) is dissolved in plasma, but as the pressure rises more oxygen dissolves. At 2 ATA, breathing 100% oxygen, the dissolved oxygen increases significantly to 4.44 vol% and at 3 ATA breathing 100% oxygen the dissolved oxygen rises to 6.80 vol% (Jain, 1999) (Figure 5). This is a simple linear physical effect.

At rest, under conditions of normal perfusion, human tissues require approximately 6 ml of oxygen per 100 ml of blood flow. At a pressure of 3 ATA the oxygen dissolved in plasma is approximately 6 ml/100 ml which is enough to supply the resting requirements of the tissues without a contribution from the oxygen bound to haemoglobin (Leach *et al.*, 1998). The oxygen dissolved in plasma is utilized more readily than that bound to haemoglobin. Among other effects, this means that adequate tissue oxygenation can be maintained in the presence of profound anaemia for short periods of time. As the flow in the capillary slows in areas of injury as described above, the plasma flows more readily than the red cells. Under conditions of hyperbaric oxygenation the oxygen carried in the plasma will ensure that the tissues in the injured area become less hypoxic than they otherwise would. The diffusion distances of oxygen also become important under conditions of hyperoxia as stated above. As the oxygen concentration increases, cells further from the capillary are more adequately oxygenated.

Adverse effects of hyperbaric therapy

These can be thought of in two main categories: the effects of the oxygen, and the effects of pressure. When administered at pressures greater than 1 ATA oxygen behaves like a drug (Zamboni, 1993). The

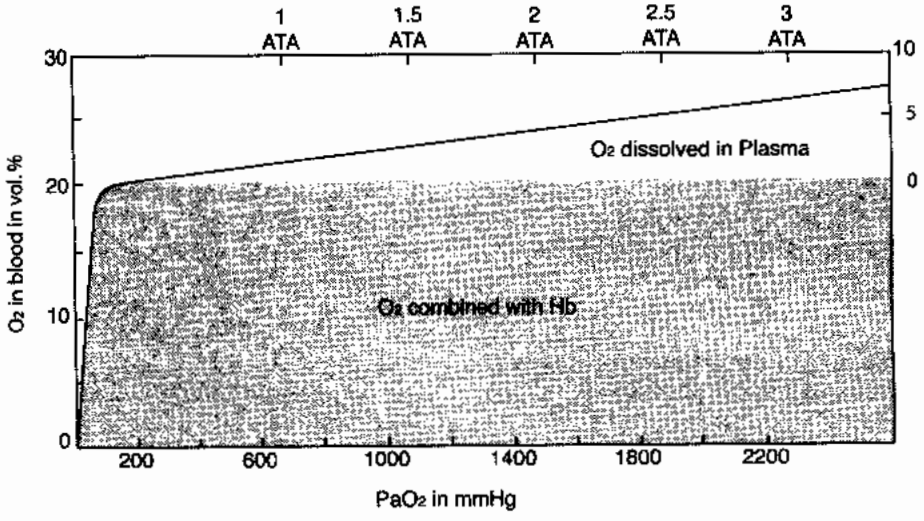

Figure 5 The effect of pressure on oxygen solubility in blood

effects are dose dependent and include detrimental as well as beneficial manifestations. When oxygen is administered at pressures greater than 3 ATA the side-effects often outweigh the advantages. The most serious adverse effect of hyperbaric oxygenation are seizures. These are variably quoted as occurring in 10% of patients undergoing treatment at 3ATA for 90 min (Sheridan and Shank, 1999); or 1.3 per 10 000 patient treatments at 2.5 ATA when 5-min air breaks are given every 20 min (Kindwall, 1999b). These seizures are said to be more common in febrile patients, but are self-limiting and not harmful (Sheridan and Shank, 1999; Tibbles and Edelsberg, 1996).

Pulmonary oxygen toxicity is a theoretical risk, and is manifest by substernal chest pain, cough and a decreased vital capacity. Prolonged exposure is necessary to produce pulmonary oxygen toxicity and with treatment times under two hours and regular air breaks it is not seen. However, if the patient is maintained on an FiO_2 of more than 50% between treatments then the risk increases (Kindwall, 1999b).

Other side-effects of oxygen which resolve after cessation of treatment include finger paraesthesias and visual refractory disturbances (Kindwall, 1999b; Tibbles and Edelsberg, 1996).

Barotrauma will rarely cause life-threatening conditions such as tension pneumothorax (Kindwall, 1999b; Tibbles and Edelsberg, 1996). However, the more common effects of barotrauma are problems relating to the ear, sinuses, and teeth. Pain in any of these areas is relieved by slowing the rate of compression, and in the ear by equalizing the pressures with manoeuvres which clear the Eustachian tube, or by the use of myringotomies or grommets (Kindwall, 1999b; Sheridan and Shank, 1999; Tibbles and Edelsberg, 1996).

In the smaller chambers claustrophobia can be a problem.

Evidence for efficacy of HBO in soft tissue trauma: animal studies

At present there is more experimental evidence for the efficacy of HBO in animal models than there is in humans. The bulk of animal experiments are done on rats and dogs and involve inducing ischaemia of a limb with arterial clamps or limb tourniquets (Nylander *et al.*, 1985, 1986; Haapaniemi *et al.*, 1996); or creating a compartment syndrome by infusing an autologous plasma solution into an isolated leg compartment (Skyhar *et al.*,1986; Strauss *et al.*, 1983, 1986).

The studies looking at ischaemia are all similar in design. Groups of anaesthetized laboratory rats were subjected to global ischaemia of a limb for 1.5, 3, or 4 hours by application of a tourniquet or arterial clamp. Subgroups of these rats were treated with hyperbaric oxygen therapy at various time intervals after reperfusion of the limb. Muscle biopsies were taken from the ischaemic and non-ischaemic limbs at predetermined times up to 48 hours after reperfusion. The muscle biopsies were analysed for water content (as an indication of oedema) (Nylander *et al.*, 1985), ATP, lactate and phosphocreatine (Nylander *et al.*, 1986; Haapeniemi *et al.*, 1996); or binding of ^{99m}technetium pyrophosphate (^{99m}technetium pyrophosphate is absorbed by the calcium deposits of necrotic cells and its accumulation reflects irreversible ischaemic injury) (Hargens *et al.*, 1981). These studies conclude that a series of hyperbaric oxygen treatments after ischaemic injury improve outcome as measured by the amount of muscle oedema, high energy compounds and the binding of ^{99m}technetium pyrophosphate.

Other investigators have looked at the outcome following artificial creation of a standardized compartment syndrome in dogs (Strauss *et al.*, 1983, 1986; Skyhar *et al.*, 1986). Autologous plasma was infused into a hind limb muscle compartment at a rate that maintained the compartment pressure at a predetermined level. The raised compartment pressures were maintained for 6 (Skyhar *et al.* 1986) or 8 (Strauss *et al.*, 1983, 1986) hours, under anaesthesia. The dogs were then allowed to recover and those in the experimental group were subjected to 100% oxygen at 2 ATA for 1 hour, this was repeated twice at four hourly intervals. In addition Skyhar (1986) had a subgroup of hypotensive dogs, and Strauss (1986) a group subjected to delayed hyperbaric oxygen (2 hours after termination of the raised compartment pressure). Forty-eight hours after the onset of raised compartment pressure the dogs were injected with ^{99m}technetium pyrophosphate and 3 hours after this they were killed. The muscles of the hind limbs were again analysed for water content and radioactivity. All papers conclude that hyperbaric oxygen therapy significantly improves the outcome after compartment syndrome in terms of muscle oedema and necrosis. In addition hyperbaric oxygen improves the outcome after compartment syndrome with hypotension; and when its administration is delayed by 2 hours.

These six studies all provide evidence that hyperbaric oxygen therapy may have a role in the treatment of ischaemic conditions of the limb. Under the standardized and artificial conditions of the laboratory, hyperbaric oxygen given soon after the ischaemic insult appears to improve muscle survival in rats and dogs. None of the dissection or analysis would appear to have been done blind, which raises the possibility of bias. The most obvious opportunity for this bias to occur would be when the muscle groups were dissected out for weighing, for analysis of water content.

These artificial models of injury are much simpler than that which occurs in trauma. Most accidental injuries produce a combination of vessel occlusion and raised compartment pressures as well as soft tissue destruction. There is no guarantee that injured human tissues will respond in the same way as that of rats and dogs. Therefore we cannot extrapolate these results directly to the injured human population. However, the evidence provided marks a beginning that needs to be followed up with good quality human trials.

Zamboni *et al.* (1993) used an *in vivo* preparation to visualize the circulation in rat gracilis muscle during and after ischaemia and hyperbaric oxygen therapy. They have shown that, upon reperfusion after 4 hours of ischaemia, there is a short period of vasodilation followed at 1 hour by progressive vasoconstriction. This is most marked in arterioles closest to venules and they hypothesize that this is a leucocyte effect. There is also a marked adherence of leucocytes to the venule wall. Hyperbaric oxygen therapy reduces the vasoconstriction and leucocyte adherence. It had been proposed that the reduction in leucocytes seen in the ischaemic muscle was as a result of leucocyte sequestration in other, more oxygen sensitive, tissues such as the lung. This would appear not to be the case (Zamboni *et al.*, 1996).

Human studies into the use of increased oxygenation in soft tissue injuries

As already stated there are fewer quality studies of the use of hyperbaric oxygen therapy in human soft tissue injuries, but they do exist. There are a large number of retrospective case reports and series which suggest a benefit from hyperbaric oxygen in terms of wound healing, lack of infection or improved tissue salvage. As these studies were not controlled, and are all anecdotal, they are not considered further.

Hopf *et al.* (1997) did a non-interventional prospective study in surgical patients at risk of postoperative wound infection. They measured the tissue oxygen tension of a subcutaneous arm wound in patients undergoing a wide range of general surgical operations. They showed a clear correlation between lower oxygen tension in the surrogate wound and infection in the surgical wound, and conclude that the subtle changes in wound oxygenation are important to wound immune mechanisms. An obvious drawback to this study is that they were not measuring the oxygen tension directly in the surgical wound, but were making assumptions based on the information from the surrogate arm wound. However, it is likely that the arm wound was at least as well perfused and oxygenated as the surgical wound.

Grief *et al.* (2000) performed a randomized controlled trial into the use of supplemental peri-operative oxygen and the incidence of wound infection. Five hundred patients were randomly assigned to receive 30% or 80% oxygen during and for 2 hours after colorectal surgery. The anaesthetist knew the patient group, but surgical and nursing staff did not. Patients were followed for 2 weeks and wounds were considered infected if organisms were cultured from pus. There was a significant reduction ($p = 0.01$) in wound infection in the 80% oxygen group compared with the 30% oxygen group. They conclude that improved perioperative tissue oxygenation reduces the incidence of wound infection. This is a well-conducted paper that has an important message.

However, all of these papers have just looked at oxygen supplementation under standard atmospheric pressure, none of them have considered the question of hyperoxygenation.

Bouachour (1996) conducted a prospective, randomized, placebo controlled, double blind trial into the use of hyperbaric oxygen in crush injury of the limb. Over a 2-year period he recruited 36 patients with a severe (grade II or III on the Gustillo score) limb injury. After initial surgical management the patients were transferred to the hyperbaric centre. They were randomized to receive 100% oxygen at 2.5 ATA for 90 min twice daily for 6 days (with 5-min air breaks); or air at 1.1 ATA for 90 min twice daily for 6 days. By subjecting the placebo group to 1.1 ATA they were able to simulate compression and the effects on the ears. Neither the patients nor the surgical team knew to which group they were allocated. Operative management was standardized as far as possible and was all performed by the same team, routine antibiotics and low molecular weight heparin were given as standard. Tissue oxygen tensions were measured in the wound and in the corresponding place on the opposite limb and a ratio between the two was calculated. There were no adverse effects of hyper-

baric therapy reported. The two groups were found to be statistically similar in terms of injury, pre-existing problems and age. There was a statistically significant ($p \leq 0.01$) greater rate of complete wound healing in the hyperbaric oxygen group when compared with placebo. Repeat surgical procedures were significantly ($p \leq 0.05$) more common in the placebo group than the hyperbaric group. There was no difference between the two groups in terms of length of hospital stay; time to healing or number of dressings needed.

This was a well-conducted prospective, randomized, controlled double blind trial which has shown an improvement in outcome of severe crush injuries when treated with adjunctive hyperbaric oxygen. They used patients as they presented rather than simulating patterns of injury as has been done before. Hard end points were used such as number of additional operations, and number of wounds healed completely. These are clinically important and relevant outcomes and are more useful than secondary measurements such as wound oxygen tension. However, despite the fact that the study was conducted over 2 years the sample size was still small. This reflects the fact that severe crush injuries are relatively rare. The authors did not perform any power calculations prior to starting the study, and we are not told how randomization was done.

Overall this is an important trial providing valuable evidence about the effect of hyperbaric oxygen therapy, as an adjunct, in the management of crush injuries. It has not yet been repeated.

Evidence for conventional treatments of soft tissue injuries

By convention the management of severe soft tissue injuries includes debridement of dead tissue, fasciotomy and manoeuvres designed to reduce swelling such as ice and elevation. The evidence to support these is patchy, and there would appear to be no class 1 evidence at all.

Surgical treatment for compartment syndrome has been practiced since 1888 (Moore and Friedman, 1989). Urgent fasciotomy is widely quoted as the 'gold standard' management of compartment syndrome (Moore and Friedman, 1989; Mabee, 1994), and rightly so. However, we should not forget that the evidence to support its use does not withstand the tests of scientific rigour demanded of other, newer treatments. The evidence to support ice and elevation is weaker still even though its use may appear logical.

Conclusion

There are good theoretical reasons why hyperbaric oxygen therapy has a useful role in the management of severe soft tissue injury, which are supported by evidence from animal studies. Good quality trials involving injured humans are fewer, but the evidence is supportive of the use of hyperbaric oxygen. Conventional treatments of crush injuries are also not supported by class 1 evidence.

We would recommend that the use of hyperbaric oxygen therapy is considered, as an adjunct, when planning the management of patients with severe crush injuries, however we are aware of the small number of facilities in the UK.

Presently, there are 25 chambers in the UK of varying capabilities, which are members of the British Hyperbaric Association (BHA). The phone number of the BHA is via its chairman on 0151 648 8000.

Acknowledgement

The authors acknowledge the assistance of HSM Engineering Ltd of Loughborough, chamber engineering suppliers and consultants to DDRC.

References

Allen DB, Maguire JJ, Mahdavian M *et al.* 1997. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* **132**: 991–96.

Babior BM. 1978. Oxygen dependent microbial killing by phagocytes (part 1). *NEJM* **298**: 659–67.

Bouachour G, Cronier P, Gouello JP *et al.* 1996. Hyperbaric oxygen therapy in the management of crush injuries: a randomised double-blind placebo controlled clinical trial. *J Trauma* **41**: 333–39.

Grief R, Ozan A, Horn EP *et al.* 2000. Supplemental perioperative oxygen to reduce the incidence of surgical wound infection. *NEJM* **342**: 161–67.

Grim PS, Gottlieb LJ, Boddie A *et al.* 1990. Hyperbaric oxygen therapy. *JAMA* **263**: 2216–20.

Gustillo RB, Mendoza RM, Williams DN. 1984. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma* **24**: 742.

Guyton AC, Hall JE eds. 1997. *Human physiology and mechanisms of disease,* 6th edn. WB Saunders, Philadelphia, PA, 9–21 and 551–559.

Haapaniemi T, Nylander G, Sirsjo A *et al.* 1996. Hyperbaric oxygen reduces ischemia induced skeletal muscle injury. *Plast. Reconstr. Surg* **97**: 602–607.

Hargens AR, Schmidt DA, Evans KL *et al.* 1981. Quantitation of skeletal muscle necrosis in a model compartment syndrome. *J Bone Joint Surg* **63A**: 631–39.

Hopf HW, Hunt TK, West JM *et al.* 1997. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg* **132**: 997–1005.

Jain KK. 1999. Physical, physiological and biochemical aspects of hyperbaric oxygenation. *Textbook of hyperbaric medicine*, 3rd edn. Hogrefe & Huber, Seattle, WA: 19–20.

Kindwall EP. 1999a. A history of hyperbaric medicine. In Kindwall EP, Whelan HT eds. *Hyperbaric medicine practice*, 2nd edn. Best Publishing, 1–20.

Kindwall EP. 1999b. Contraindications and side effects to hyperbaric oxygen treatment. Kindwall EP, Whelan HT eds. *Hyperbaric medicine practice*, 2nd edn. Best Publishing, 83–98.

Leach RM, Rees PJ, Wilmshurst P. 1998. ABC of oxygen. Hyperbaric oxygen therapy. *BMJ* **317**: 1140–43.

Nylander G, Lewis D, Nordstrom H *et al.* 1985. Reduction of postischemic edema with hyperbaric oxygen. *Plast. Reconstr Surg* 76: 596–601.

Nylander G, Nordstrom H, Lewis D *et al.* 1986. Metabolic effects of hyperbaric oxygen in post-ischemic muscle. *Acta Chir Scand.* suppl 533.

Mabee JR. 1994. Compartment syndrome: a complication of acute extremity trauma. *J Emerg Med* **12**: 651–56.

Peirce EC. 1969. Pathophysiology, apparatus, methods, including the special techniques of hypothermia and hyperbaric oxygen. *Extra-corporeal circulation for open heart surgery*. Charles C Thomas, Springfield, IL, 53–63.

Moore RE, Friedman RJ. 1989. Current concepts in pathophysiology and diagnosis of compartment syndromes. *J Emerg Med* 7: 657–62.

Skyhar MJ, Hargens AR, Strauss MB *et al.* 1986. Hyperbaric oxygen reduces edema and necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hypotension. *J Bone Joint Surg* **68**: 1218–24.

Sheridan RL, Shank ES. 1999. Hyperbaric oxygen treatment: A brief overview of a controversial topic. *J Trauma* **47**: 426–35.

Strauss MB, Hargens AR, Gershuni DH *et al.* 1983. Reduction of skeletal muscle necrosis using intermittent hyperbaric oxygen in a model compartment syndrome. *J Bone Joint Surg* **65**: 656–62.

Strauss MB, Hargens AR, Gershuni GH, *et al.* 1986. Delayed use of hyperbaric oxygen for treatment of a model anterior compartment syndrome. *J Orthop Research* **4**: 108–11.

Tibbles PM, Edelsberg JS. 1996. Hyperbaric oxygen therapy. *NEJM* **334**: 1642–48.

Wattel F, Neviere MR, Bocquillon N. 1998. Acute peripheral ischaemia and compartment syndromes: a role for hyperbaric oxygenation. *Anaesthesia* **53** (suppl 2): 63–65.

Wright NP. 1992. The response to injury. In McGee JO'D, Isaacson P, Wright N eds. *Oxford textbook of pathology*. Oxford University Press, Oxford, 351–78.

Zamboni EP. 1993. Hyperbaric oxygen. *BMJ* **307**: 515–16.

Zamboni WA, Roth AC, Russell RC *et al.* 1993. Morphologic analysis of the microcirculation during reperfusion of ischaemic skeletal muscle and the effect of hyperbaric oxygen. *Plast Reconstr Surg* **91**: 1110–23.

Zamboni WA, Wong HP, Stephenson LL. 1996. Effect of hyperbaric oxygen on neutrophil concentration and pulmonary sequestration in reperfusion injury. *Arch Surg* **131**: 756–60.

Appendix: Undersea and Hyperbaric Medical Society 1999 committee report. Indications for use of hyperbaric oxygen

1. Air or gas embolism.
2. Carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning.
3. Clostridial myositis and myonecrosis (gas gangrene).
4. Crush injury, compartment syndrome and other traumatic ischaemias.
5. Decompression sickness.
6. Enhancement of healing in selected problem wounds.
7. Exceptional blood loss (anaemia).
8. Intracranial abscess.
9. Necrotizing soft tissue infections.
10. Refractory osteomyelitis.
11. Delayed radiation tissue damage (soft tissue and bone necrosis).
12. Compromised skin grafts and flaps.
13. Thermal burns.