An Evidence-Based Appraisal of the Use of Hyperbaric Oxygen on Flaps and Grafts

H. I. F. Friedman, M.D., Ph.D.
M. Fitzmaurice, M.D.
J. F. Lefaivre, M.D.
T. Vecchiolla, M.S.N.
D. Clarke

Columbia, S.C.

Summary: Hyperbaric oxygen has been advocated, both as an adjunctive or primary form of treatment, for a variety of disorders, including gas gangrene, osteoradionecrosis, and carbon monoxide poisoning. It has also been used to improve ischemic wounds before skin grafting and to support ischemic flaps. In this review, we analyze the available literature that investigates the use of hyperbaric oxygen for composite grafts, skin grafts, random flaps, distant flaps, and free flaps. An appraisal of the level of evidence for each of these uses of hyperbaric oxygen is offered. Although there are a significant amount of animal data supporting the application of hyperbaric oxygen for grafts and flaps, there is very little clinical information other than case reports and series to sustain its choice over other modalities of therapy. Multicenter prospective clinical studies are clearly needed comparing hyperbaric oxygen to other mechanical or pharmacologic interventions to improve wound healing for grafting or to support flap survival. (*Plast. Reconstr. Surg.* 117 (Suppl.): 175S, 2006.)

A considerable body of information exists to demonstrate the efficacy of hyperbaric medicine in the treatment of a variety of clinical problems, including carbon monoxide poisoning,[1] gas gangrene,[2] osteoradionecrosis of the mandible,[3] and diabetic foot ulcers.[4] Hyperbaric oxygen has also been used for the management of wounds requiring skin grafting and for the treatment of ischemic flaps.[5,6]

However, the information supporting the use of hyperbaric oxygen for these latter indications may be less definitive. The question thus becomes whether there is enough substantive information available to demonstrate efficacy in treating patients with compromised flaps and grafts with hyperbaric oxygen to warrant the cost and potential risk to the patients of such therapy.

Sackett and Rosenberg[7] define evidence-based medicine as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. To determine the validity or relative importance of information about the efficacy of a given treatment for a clinical problem, analytic studies with experimental designs carry more weight than simple observational extrapolations. Thus, randomized, controlled trials provide the standard against which other forms of evaluations are measured.

A number of systems of data evaluation have evolved to help provide a grading methodology for practitioners to use when comparing forms of therapy in clinical situations. The Oxford Center for Evidence-Based Medicine has one of the most well-known and detailed schemata for evaluating published data, along with a grading system for recommendations (www.cebm.net). However, the Center ranks experimental animal studies in the lowest level of the evaluation scheme, along with expert opinion without critical appraisal or based on physiology or bench research. Since most of the current published literature on the use of hyperbaric oxygen for flaps and grafts derives from animal studies, it would seem reasonable to use a system that included animal data in the evaluation. For this reason, we have chosen the American Heart Association Emergency Cardiovascular Care Levels of Evidence[8] to evaluate current information on the efficacy of hyperbaric oxygen to treat flaps and grafts.

This system divides published data into eight levels of evidence broadly defined as follows:

Level 1. Statistically significant randomized controlled clinical trials
1a. Meta-analysis of multiple positive ran-

From the Department of Education, Sisters of Charity Providence Hospital; and the Department of Hyperbaric Medicine, Palmetto Health Richland Hospital
Received for publication July 7, 2004.

DOI: 10.1097/01.prs.0000222555.84962.86

domized controlled clinical trials; statistically significant results
1b. One or more positive randomized controlled clinical trials; statistically significant results
1c. Meta-analysis with inconsistent but significant results
Level 2. Statistically insignificant randomized controlled clinical trials
2a. Meta-analysis of positive randomized controlled clinical trials but not statistically significant
2b. One or more positive randomized controlled clinical trials; not statistically significant
2c. Meta-analysis of inconsistent randomized controlled clinical trials; not statistically significant
Level 3. Prospective, controlled, but not randomized cohort studies
Level 4. Historic, nonrandomized cohort or case-control studies
Level 5. Human case series
Level 6. Animal or mechanical model studies
6a. Well designed; demonstrate a homogeneous pattern of results
6b. Less powerful designs, or demonstrate equivocal or heterogenous patterns of results
Level 7. Reasonable extrapolations from existing data; quasi-experimental designs
Level 8. Rational conjecture (common sense); historical acceptance as standard practice

To apply this system to the data regarding flaps and grafts, the available literature was reviewed and an effort made to categorize and compare the published investigations according to the type of tissues involved and a number of other variables in the application of hyperbaric oxygen. In this manner, flaps have been divided into local rotation, distant, and free flaps. Within the category of local rotation flaps, a further subdivision was made based on whether the study addressed random pedicled flaps or axial pedicled flaps and the composition of tissues included, such as skin and/or muscle. In the case of grafts, a distinction was made between split- or full-thickness skin grafts and composite grafts. Similarly, hyperbaric oxygen therapy was evaluated based on whether it was delivered preoperatively or postoperatively, the timing of onset of treatment, the length of time of each individual treatment, the total number of treatment days, the number of treatments per day, the concentration of oxygen, and the atmospheric depth of each treatment. Finally, in an effort to further evaluate the efficacy of hyperbaric oxygen therapy, the studies were compared where possible to results using other forms of intervention that also strive to positively affect graft or flap survival. In the following review, these issues are analyzed to determine whether the available published data are sufficient to support the use of hyperbaric oxygen for compromised flaps and grafts, and at what level of confidence hyperbaric oxygen exerts an effect.

COMPOSITE GRAFTS

Hyperbaric oxygen is usually employed in the case of grafts to develop a granulating wound base that will then support the application of a split- or full-thickness skin graft. Thus, hyperbaric oxygen is administered preoperatively. However, when using composite grafts that may contain subcutaneous fat and cartilage as well as full-thickness skin, hyperbaric oxygen is generally applied in the postoperative period to promote survival of the graft. It is well recognized that most composite grafts will take if no portion of the graft is more than 0.5 cm from a blood supply. Usually this limits composite grafts to approximately 1 cm in diameter to ensure their complete survival.[9] There are four techniques for improving the survival of larger grafts: increasing the surface area of contact between the graft and the recipient bed (surgical), cooling the graft, using pharmacologic agents, and using hyperbaric oxygen.

Animal Studies

Most animal models have used rabbit or rodent ears for the creation of composite graft models. These composite grafts are fashioned in a number of ways. In one technique, a circular full-thickness cutout is removed and the resulting graft is then sutured back into the original defect. In this fashion, the blood supply to the graft re-enters it from the 360-degree perimeter of the wound edge. In another model, the ear tip is amputated and then re-applied. In this case, blood flow is reestablished into the graft along only one edge. Finally, the graft can be harvested from the lateral border of the ear as a rectangle and then sutured back into its original position. In this case, blood supply re-enters the graft from three sides. Obviously, the ear amputation model is the most severe test of composite graft survival.

Aden and Biel[10] used the full-thickness 2-cm circular composite graft model to evaluate the use

of methylprednisolone, chlorpromazine (membrane stabilizers), dimethyl sulfoxide and superoxide dismutase (superoxide radical scavengers), and indomethacin (a nonsteroidal anti-inflammatory) to improve graft survival. The methylprednisolone-treated group was further subdivided into two regimens: animals that received both preoperative and postoperative steroid injections and those that received only postoperative steroids. Control animals were injected with normal saline and had an average area of necrosis of 76.6 percent. The group that received the preoperative steroids displayed the least necrosis (28.75 percent) and this result was significant at the $p < 0.001$ level. The groups receiving indomethacin for 3 days, chlorpromazine, and dimethyl sulfoxide also had significantly smaller zones of necrosis compared with controls, but only at the $p < 0.01$ levels. One might argue that 57.67 percent, 61.31 percent, and 56.06 percent areas of total necrosis, respectively, did not represent a true biologically significant improvement compared with the controls (76.69 percent).

Fann et al.[11] performed a very similar study. Two centimeter circular full-thickness composite grafts were harvested from rabbit ears and then rotated 180 degrees and replaced. Animals received either (1) preoperative and postoperative steroids, (2) postoperative steroids only, (3) salvage steroid therapy started 3 days postoperatively, (4) a cyclooxygenase lipoxygenase inhibitor, or (5) surgical delay of the recipient site with creation of a 2-cm defect and placement of a contralateral 2-cm ear graft 7 days later. The control animals displayed approximately 10 percent graft survival. The only real improvements were observed with steroid therapy administered preoperatively (65.8 percent) or postoperatively (47.8 percent).

Using an ear tip amputation model of 2 cm, Henrich et al.[12] looked at graft survival with postoperative steroids, topical fibroblast growth factor, and delayed reimplantation for 90 minutes with cooling and methylprednisolone. Three weeks postoperatively the control animals had only 1.3 percent survival, while steroid therapy increased the take of these grafts to 23.2 percent. Cooling and steroid therapy also helped to improve survival to 15.5 percent.

Chen et al.[13] used a slightly different model in which only the dorsal skin and auricular cartilage were harvested and then sutured back onto the ventral rabbit ear skin. As one might expect, control animal composite graft survival for a 2-cm graft was significantly better (80 percent) than observed in the previously described studies, since the recipient site contact with the graft occurred over a much larger surface area. However, when the graft was 2.5 cm, survival was only 17 percent of the total graft. In the latter case, intragraft injections with heparin for 7 days improved survival to 64 percent.

These studies yield some indication of the amount of improvement that can be achieved with pharmacologic intervention for composite graft take when the graft is larger than can be supported by eventual blood supply ingrowth. Furthermore, steroid therapy, particularly when administered preoperatively, appears to provide the greatest benefit.

In 1988, Rubin et al.[14] performed the first investigation of the effect of hyperbaric oxygen on composite grafts using rabbits. The composite graft contained the posterior skin and cartilage, measured 4 × 2 cm, and was immediately sutured back onto the anterior skin. This study mimicked that of Chen et al.,[13] only it used a much larger graft. Expected take based on the latter study, therefore, should be 17 percent or less for the control animals. Treated rabbits received hyperbaric oxygen twice daily for 21 treatments at 2.0 ATA (absolute atmospheres below sea level) for 90 minutes each. Nine days postoperatively, mean survival for control animals was 16.2 percent and that for the group treated with hyperbaric oxygen was 46.9 percent ($p = 0.01$). However, after hyperbaric oxygen was terminated, although there was a trend toward greater survival in the hyperbaric oxygen group, the difference between control and experimental animals decreased to the point that at 18 days the p value was not significant (19.8 percent versus 30.5 percent survival). The authors postulated that continued treatment with hyperbaric oxygen for longer than the 10 days employed might have yielded greater benefit.

Ten years later Zhang et al.[15] asked the same question about whether or not hyperbaric oxygen potentiated the survival of composite tissues. Utilizing rat ears, they harvested grafts composed of skin, subcutaneous tissue, and cartilage and sutured them, with the cartilage side down, onto the posterior auricular surface of the opposite ear, where a similar size skin defect was made. The grafts were only 1 × 0.5 cm. In the design of this study, therefore, there was a fairly large contact surface between the graft and the recipient site. The experimental group received hyperbaric oxygen continuously for 4 hours the first postoperative day and then 6 continuous hours for an additional 5 days at 2.0 ATA. Average percent surface

area of survival was 26.5 percent for the control group and 82 percent for the hyperbaric oxygen–treated animals ($p < 0.01$). Thus, hyperbaric oxygen therapy did improve graft take. The reason the authors gave for using one continuous treatment per day, instead of the more clinically common twice daily therapy, was the weak tolerance of rats to pressurization and decompression.

Lim et al.[16] looked at the effects of dimethyl thiourea, melatonin, and hyperbaric oxygen on the survival of reimplanted rabbit composite grafts. Both dimethyl thiourea and melatonin are oxygen free radical scavengers. This model differed from the previously described studies in that the tip of the rabbit ear was amputated, producing a full-thickness composite graft measuring approximately 4 cm across and 2 cm wide. The graft was then sutured back into place. Thus, blood vessel reconnection with the graft could only take place along the amputated edge. This study was therefore very similar to the one performed by Henrich et al.[12] in which steroids increased survival from 1.3 percent total surface area in control animals to 23.2 percent. Hyperbaric oxygen was administered only once per day for 5 days for 90 minutes at 2.5 ATA. Animals received dimethyl thiourea or melatonin by intraperitoneal injection daily for 5 days. Photographic analysis at 3 weeks after intervention showed no improvement in survival for any treatment group. Although hyperbaric oxygen animals had 15.38 percent graft survival and control animals had 10.79 percent, these numbers were not statistically significant. One criticism of this study was that hyperbaric oxygen was only administered once per day, while usual therapy is 90 minutes twice per day. Furthermore, hyperbaric oxygen was only given for 5 days, while usual therapy is considerably longer. A similar criticism could be leveled at the length of time of therapy with dimethyl thiourea or melatonin. Finally, the amputation of the tip of the ear and its replacement as a large composite graft is a maximum test of the take of any composite graft, since there is only one surface edge available for reperfusion of the graft. This model does not reflect the usual clinical situation in which an elective composite graft is planned. Rather, it more closely mimics the emergent reattachment of an amputated part.

In support of this argument was the investigation by McClane et al.[17] Again, using rabbits, they either amputated the tip as in the Henrich et al. study[12] or performed a rectangular cut out from the lateral border of the ear (1.5 cm wide × 4.0 cm long). In the latter case, there are now three borders from which the composite graft can acquire blood flow, and although the graft is 4 cm long, no area is less than 1.5 cm from a potential blood supply. The treated animals received hyperbaric oxygen for 90 minutes at 2.0 ATA twice per day for 4 days and then daily for 6 more days. By postoperative day 18 there were no tip grafts surviving in either the control or hyperbaric oxygen treated groups. However, in the lateral cutout group, while seven of eight grafts failed in the control animals (0.31 percent mean surface area survival), only one of 10 rabbits in the hyperbaric oxygen group had complete loss (mean surface area survival of 15.97 percent).

In a totally different model, McFarlane and Wermuth[18] looked at hyperbaric oxygen and its effect on composite musculocutaneous grafts in a rat model. A flap was elevated on the back of a rat and then the pedicle was divided and the flap replaced. Seventeen control animals had total necrosis of the graft. Hyperbaric oxygen was administered to 16 other rats for 2 hours per day at 3.0 ATA for 5 days. Four animals died in the group treated with hyperbaric oxygen. Of the remaining 12, six had partial necrosis of the graft while the other six had complete graft survival. This study does demonstrate some efficacy for the use of hyperbaric oxygen in this composite graft model. Using a similar model, Gruber et al.[19] measured transcutaneous oxygen tension in large composite grafts on the backs of rats given hyperbaric oxygen. They were able to raise the oxygen tension to normal levels with approximately 1.5 ATA. They only gave one treatment and therefore did not study the effect on the tissues of a significant course of hyperbaric oxygen.

Based on this review of the available animal data regarding the use of hyperbaric oxygen on composite grafts, we think it is safe to conclude that (1) hyperbaric oxygen improves partial survival of composite grafts if administered often enough and for a long enough period of time; (2) if the graft is too large or too distant from its potential blood supply, a portion or all of it will die regardless of the use of hyperbaric oxygen; (3) other treatment modalities (such as steroids, heparin, and so on) may also potentiate graft survival; (4) more information is needed regarding the potential of combining synergistic therapies to increase composite graft survival (steroids, cooling, hyperbaric oxygen, and so on); (5) these experiments provide evel VI data of the American Heart Association's levels of evidence in support of the use of hyperbaric oxygen for the treatment of composite grafts.

Clinical Studies

Unfortunately, there are no prospective, randomized studies that investigate the use of hyperbaric oxygen for larger than normal and therefore high-risk composite grafts. Rather, the only information that is available comes from case reports. In 1986, Gonnering et al.[20] described the use of hyperbaric oxygen in six case studies of periorbital reconstructions of which three were larger than normal composite grafts (17 × 5 mm, 20 × 7 mm, 22 × 5 mm). The treatment regimen was 100% oxygen at 2.0 ATA for 2 hours twice per day for 4 to 5 days. All of the grafts survived.

In 1991 Nichter et al.[21] reported the successful reimplantation of a traumatically amputated nose as a large composite graft with adjuvant hyperbaric oxygen. Approximately 10 years later, Rapley et al.[22] successfully applied a large (2 cm) composite graft from the ear to the nasal tip of a 5-year-old boy following traumatic amputation. Hyperbaric oxygen was administered twice per day at 2.0 ATA for 3 days to assist with complete graft take.

Finally, Friedman et al.[23] used adjunctive hyperbaric oxygen in a series of six patients undergoing nasal reconstruction with composite grafts for either cleft nasal defects or cancer reconstruction. All grafts showed complete take, except for that in one patient who did not get hyperbaric oxygen and suffered loss of a large graft (1.5 cm). The procedure was then repeated successfully in the same patient with the use of hyperbaric oxygen. In this latter case, there was some limited central epidermolysis that required application of an additional full-thickness skin graft to prevent contracture of the composite graft. The reason for using adjunctive hyperbaric oxygen in this series of patients was that the composite graft was from the ear lobule. The lobule graft was split down its center and a second cartilage graft placed inside of it, thus adversely affecting the normal vascular architecture of the graft.

Even though there are less data available from these clinical reports than that obtained from animal studies, the information provided suggests the efficacy of hyperbaric oxygen at level IV of the American Heart Association's levels of evidence scheme: historic, nonrandomized cohort, or case control studies. Again, these are clearly not level I data. However, we conclude that hyperbaric oxygen *may* have efficacy in supporting the take of relatively large composite grafts in patients, provided the graft size does not completely overwhelm the ability of the recipient site to provide revascularization. It is important to emphasize, however, that there are no other clinical studies with other modalities of therapy that would support the take of larger than normal composite grafts. This level IV evidence is therefore the best evidence available for adjunctive management of these grafts.

SKIN GRAFTS

The issue regarding split- and full-thickness skin grafts is less clear than with composite grafts. Usually, hyperbaric oxygen is administered preoperatively to patients with inadequately vascularized recipient sites to stimulate sufficient angiogenesis to support the take of a skin graft. The mechanism by which hyperbaric oxygen exerts its effect is to increase the oxygen gradient between the underlying blood vessels and the recipient site, thereby stimulating vessel proliferation.[24,25] It may also reduce bacterial contamination[26–28] that normally would be a danger to graft survival. Most surgeons applying skin grafts today would not administer hyperbaric oxygen during the time of graft take, but would terminate it just before the application of the graft once the recipient site was felt to be adequate for grafting. Providing hyperbaric oxygen during the actual take of the graft is usually not necessary. In addition, transfer to and from the hyperbaric oxygen chamber can introduce the potential for trauma to the graft, thereby negating its perceived benefit.

Animal Studies

The first study that evaluated the use of hyperbaric oxygen and skin grafts was by Shulman and Krohn in 1967.[29] They reasoned that skin grafts were relatively anoxic for the first 5 days after application of the graft. Therefore, by providing 100% oxygen under pressure they would provide a more favorable oxygen environment at the wound surface. They created standardized partial-thickness and full-thickness wounds on the backs of rats and separated the animals into four treatment groups. The first served as controls and were left open. The second group received serial split-thickness allografts every 24 hours. Each 24 hours the old graft was removed and a new one placed. The third graft was left in place and not removed. The third group of animals had the partial- and full-thickness wounds made and were treated with hyperbaric oxygen at 2.5 ATA for 1.5 hours per day for 9 to 10 days. They were not grafted. The final group received grafting as in group 2 combined with hyperbaric oxygen as in group three. The time it took for the wounds to

completely heal either by scar contracture or re-epithelialization was the endpoint. Rats in group 1 demonstrated healing in 16.8 and 29.3 days for partial- and full-thickness wounds, respectively. Allografted animals had better results, with healing times of 14.0 and 25.6 days. Hyperbaric oxygen shortened these times to 11.7 and 19.7 days, while the combination of hyperbaric oxygen and serial allografting reduced wound-healing times further to 8.8 and 18.7 days.

The authors speculated that the application of both grafts and hyperbaric oxygen might have reduced bacterial contamination, thereby allowing faster healing.[29] In addition, the application of hyperbaric oxygen may have improved survival of the serially applied grafts that in turn provided a more favorable environment for the proliferation of epithelial elements in the partial-thickness wounds.

This study clearly does not replicate the clinical situation in which one is trying to obtain improved skin graft take. Rather, it addresses the issue of improving wound healing with the application of serial grafts and hyperbaric oxygen. It therefore cannot be included in data that would support the use of hyperbaric oxygen for take of full- or split-thickness skin grafts.

Similarly, Erdmann et al.[30] recorded their observations on the use of hyperbaric oxygen and cyclosporine on the take of immunohistoincompatible skin grafts. In their first study, hyperbaric oxygen was administered for 1 week preoperatively and 2 weeks after applying an allograft to a denuded back wound. Hyperbaric oxygen significantly delayed rejection of the allografts. In the second study, the hyperbaric oxygen effect was potentiated by cyclosporine.[31] Again, these studies imply that hyperbaric oxygen has an immunosuppressive capability, but they do not address the central issue of improved graft take with hyperbaric oxygen.

Hosgood et al.[32] looked directly at the effect of hyperbaric oxygen on full-thickness skin grafts in dogs. In this study, hyperbaric oxygen was administered with either hydroxy-ethyl penta fraction starch or deferoxamine combined with hydroxy-ethyl penta fraction starch and hyperbaric oxygen. The rational for using deferoxamine was that it would prevent hydroxyl radical formation that could be induced by hyperbaric oxygen alone. Deferoxamine alone causes hypotension, but combing it with hydroxy-ethyl penta fraction starch mitigates this phenomenon. The hydroxy-ethyl penta fraction starch also prolongs intravascular half-life 10-fold. Hyperbaric oxygen was administered postoperatively (2.0 ATA, 60 minutes, twice daily, 10 days). Hyperbaric oxygen with hydroxy-ethyl penta fraction starch had a detrimental effect on graft survival, while the addition of deferoxamine improved this result somewhat. There were two problems with the study. Again, hyperbaric oxygen was only administered postoperatively and that does not mimic the usual clinical situation. The authors also relied on historical data from other investigators to determine the usual percent take of full-thickness grafts in dogs. There was no arm of their study that just examined skin graft take without hyperbaric oxygen/hydroxy-ethyl penta fraction starch or hyperbaric oxygen/hydroxy-ethyl penta fraction starchdeferoxamine.

Clinical Studies

Perrins did the only clinical study that addresses the use of hyperbaric oxygen and skin grafting in 1967.[33] This investigation was a prospective randomized blinded trial of hyperbaric oxygen in which 24 patients received hyperbaric oxygen postoperatively and 24 other control patients did not. The hyperbaric oxygen was administered for 2 hours on the evening of the operation and then thereafter twice per day for 3 days at 2.0 ATA. The surgeon performing the grafts did not know which patients were to get the hyperbaric oxygen. One graft failed due to heavy contamination with b-hemolytic streptococci. There was an overall 29 percent improvement in graft survival. Complete graft take as defined by greater than 95 percent total surface area take occurred in 64 percent of hyperbaric oxygen–treated patients and only 17 percent of the controls. There was a greater than 60 percent take in 100 percent of the patients treated with hyperbaric oxygen and yet only 60 percent take in 64 percent of the control patients.

Although this is the only published study looking at the efficacy of hyperbaric oxygen on skin graft take, it clearly demonstrates a benefit to postoperative application of hyperbaric oxygen. In fact, this study reaches level 1B of the American Heart Association levels of evidence. Unfortunately, most plastic surgeons today would routinely expect greater than a 90 percent take of most skin grafts applied electively without the use of hyperbaric oxygen in the postoperative time period. It therefore becomes difficult to recommend the use of hyperbaric oxygen during the period of graft take unless there are extenuating circumstances, such as poor perfusion or oxygen-

ation of the recipient site or perhaps in patients with sickle cell disease. However, no data are available about the use of hyperbaric oxygen for sickle cell ulcers and skin grafting.

In summary, there are no clinical or laboratory data that specifically demonstrate improved skin graft survival with the preoperative application of hyperbaric oxygen. The same may be said for other modalities of therapy that improve angiogenesis, such as wound vacuum or growth factors. Although rational conjecture (level 8 of American Heart Association's levels of evidence scheme) would suggest that improved angiogenesis, before the application of a skin graft to an otherwise compromised wound, should improve graft take, the ability of hyperbaric oxygen to stimulate angiogenesis in a compromised wound thus argues for its application in certain clinical cases. Again, the supporting data are either weak or nonexistent.

RANDOM FLAPS

To attempt to compare studies of the efficacy of hyperbaric oxygen on flap survival, it is necessary to categorize the investigations as to the type of flap undergoing evaluation. Thus, studies of random flaps must be distinguished from those looking at distant or free flaps. Axial pattern flaps that have a distal portion that is ischemic can be considered with random flaps, since the ischemic portion is actually the random part of the flap.

Animal Studies

Eleven animal studies utilized the dorsal random flap in the rat model. This tissue is a pedicled flap, a portion of which is normally predicted to undergo necrosis at its distal end. In other words, the flap is larger than its blood supply territory. This flap usually contains the panniculus carnosus muscle, which is elevated with the skin, and as such, it is truly a musculocutaneous flap. In 1965 McFarlane et al.[34] designed a flap on the dorsum of the rat (10 cm long × 4 cm wide) that would reliably undergo a known amount of necrosis at its distal end (one half to one quarter of the flap). The efficacy of hyperbaric oxygen in preventing necrosis was then evaluated varying the treatment pressure, treatment intervals, and number of treatments per day.[18,35] At 2.0 ATA for 3 to 4 hours continuously each day for 4 days, there was a significant reduction in the amount of necrosis. However, the animal mortality rate was high due to oxygen toxicity. When the length of exposure was reduced to 2 hours for 5 days, approximately 83 percent of the flaps had complete survival.

In a similar fashion, Wald et al.[36] created a distally based flap measuring 3 × 10 cm on the dorsum of rats. A portion of this flap predictably died. Treatment with hyperbaric oxygen for 2 hours four times per day for 5 days yielded a 22 percent increase in the area of flap survival.

Arturson and Khanna[37] based their 6.5 × 2.0 cm skin flap cranially on the backs of rats. They then treated the animals with hyperbaric oxygen, dimethylsulfoxide applied topically, or Complamin (nicotinic acid and theophylline base) intraperitoneally for 2 days. Hyperbaric oxygen was administered once or twice per day at 2.0 or 3.0 ATA. One group received both dimethylsulfoxide and hyperbaric oxygen and another group received Complamin and hyperbaric oxygen. Both dimethylsulfoxide and hyperbaric oxygen significantly increased the area of survival, as did the combination of the two. The best results were obtained with hyperbaric oxygen. However, the authors noted that the improvement in flap survival, although statistically significant, was really only marginal. Calculation of their data would indicate about a 19 percent increase in flap survival over controls with twice-daily therapy at 2.0 ATA. However, there was still a 30 percent area of flap necrosis.

Niinikoski[38] designed an experiment in which he eliminated the effect of the underlying raw surface area of the resutured dorsal flap from contributing to flap survival by tubing this flap. His design was a cranially based flap measuring 9 cm × 1.5 cm wide. The flap was sutured to itself, and the distal end was ligated 3.5 cm from its caudal end, thereby making the flap actually 5.5 cm long. Experimental animals received hyperbaric oxygen at 2.5 ATA, twice daily for five treatments beginning immediately after surgery. Control rats breathed room air. There was a 51 percent increase in the length of flap survival in the hyperbaric oxygen–treated group over the controls.

Jurell and Kaijser[39] made an effort to evaluate the optimum pressure, exposure time, and duration of hyperbaric oxygen therapy on cranially based flaps 7 cm × 1 cm wide. There were nine treatment groups. ATA was varied between 2 and 3. The number of treatments varied between one and eight, the duration of exposure varied between 1 and 6 hours, and air breathing between treatments varied between 4 and 7 hours. Starting treatment immediately after surgery yielded greater flap survival than delaying treatment (24 hours). Two ATA provided better flap survival im-

provement than 3.0 ATA. Animals had breathing difficulties when the exposure to hyperbaric oxygen was for 4 hours with only 4-hour breaks (room air) compared with 2 hours of hyperbaric oxygen and 6-hour breaks. Again, the improvement in length of flap survival over control animals was approximately 33 to 36 percent.

Manson et al.[40] elevated a 3.5 × 9 cm cranially based flap on the backs of guinea pigs. They compared hyperbaric oxygen subjected animals (2.5 ATA, 2-hour duration) treated four times per day on the day of surgery and then three times on postoperative day 2, followed by two times on day 3 and once on day 4, to control animals. There was an approximately 22 percent improvement in the length of flap survival with hyperbaric oxygen therapy. The investigators also found a marked improvement in capillary ingrowth in these skin flaps as well as epithelial regeneration.

A 22 percent increase in flap survival was also found by Nemiroff et al.[41] in cranially based dorsal flaps measuring 3 × 9 cm and treated with hyperbaric oxygen (2.5 ATA, for 2 hours, with half hour intervals between for four treatments). The hyperbaric oxygen was administered either before or after flap creation. Certain animal groups were also given 1000 rads to the dorsum either before or after flap elevation. Radiation did not seem to affect flap survival in either control or hyperbaric oxygen–treated animals. However, when hyperbaric oxygen administration was delayed for 48 hours, there was no improvement over control animals.

Nemiroff[42] also studied the synergistic effects of pentoxifylline and hyperbaric oxygen on cranially based dorsal flap survival (9 × 3 cm). Pentoxifylline had been shown to increase red blood cell deformability and lower blood viscosity. Pentoxifylline was administered before and after flap elevation. The hyperbaric oxygen regimen was 2.5 ATA for 2 hours, three times per day the first 2 days and then twice per day for the next 4 days (total of 14 treatments). Hyperbaric oxygen and pentoxifylline increased the percent of flap survival over controls by 24 and 28 percent, respectively. Synergistically, the two treatments increased the percent of flap survival over control animals by 45 percent, to almost 96 percent survival of the entire flap.

Esclamado et al.[43] also studied the synergy of two treatments: hyperbaric oxygen and methylprednisolone in the cranially based dorsal rat flap (9 × 3 cm). The steroids (30 mg/kg) were administered 24 hours and 1 hour before flap elevation and 24 and 48 hours after the flap was resutured to its bed. The hyperbaric oxygen regimen was two 90-minute treatments at 2.4 ATM separated by 5 hours of room air. Hyperbaric oxygen was administered for 3 consecutive days. Individually, the steroid- and hyperbaric oxygen–treated groups had 17 and 20 percent increases in the area of flap survival respectively, over control animals. Combining the two therapies did not further improve the area of survival. The authors note that their regimen of two 90-minute treatments more closely resembles that used in humans.

Stewart et al.[44] also analyzed the combined efficacy of a number of therapies to improve the length of flap survival. Their flap was cranially based and rather long, 12 × 3 cm, compared with those in other studies. The longest flap previously used, in other investigations, was 9 cm. There were 10 treatment groups. Hyperbaric oxygen was administered for 90 minutes only once per day at 2.5 ATA presumably for 7 days. Other treatment modalities included superoxide dismutase, which is an oxygen free radical scavenger, catalase, a hydrogen peroxide scavenger, allopurinol, a xanthine oxidase inhibitor, alpha tocopherol, another oxygen free radical scavenger, and topical silver sulfadiazine, a topical antimicrobial. The nontopical interventions were given at varying dosage regimens intraperitoneally. In this animal model, control flaps demonstrated approximately 50 percent length survival. Hyperbaric oxygen did not significantly improve flap survival. The only statistically significant results were obtained with hyperbaric oxygen combined with tocopherol, an increase to 66 percent of total flap survival, or the combination of hyperbaric oxygen with superoxide dismutase and catalase (62.5 percent). These therapies increased the amount of survival over controls by 18 and 16 percent, respectively. What is a little surprising is the lack of response to hyperbaric oxygen alone. This fact may be related to one of two things; hyperbaric oxygen was only administered once per day and the flap was particularly long. In the previously referenced study by Niinikoski,[38] he measured tissue oxygen tensions during and after hyperbaric oxygen therapy and found that tissue oxygen concentrations rapidly declined with hyperbaric chamber decompression. Many of the other studies that demonstrated improved flap survival with hyperbaric oxygen administered it several times per day. Clearly hyperbaric oxygen had a synergistic effect with various oxygen radical scavengers as it did with pentoxifylline, as observed in Nemiroff's study.[42]

In another report, Frigerio et al.[45] created a 1.5 × 6.0-cm rectangular flap on the backs of rats. The hyperbaric oxygen group received twice-daily

treatments of 2.0 ATA for 2 hours with air breaks at 20-minute intervals for 1 week. The control group received no therapy. Treatment with hyperbaric oxygen increased the total length of survival from 13 mm to 27.4 mm (27.4 percent).

Summarizing the results of the various rodent dorsal random flap experiments, it would seem that hyperbaric oxygen does increase the length of flap survival in a model where a portion of the flap is predicted to fail. This increase in the length of flap survival was on the order of 18 to 25 percent of total flap length. The best result was obtained when hyperbaric oxygen was combined with pentoxifylline.

Tan et al.[46] first evaluated flaps positioned on the ventral surface by developing a neurovascular skin flap measuring 8 × 8 cm on the entire abdominal wall of rats. One epigastric pedicle was divided, leaving the blood supply to the flap based on the other single epigastric pedicle. Treated animals received hyperbaric nitrogen-oxygen mixture (92 %, 8%), hyperbaric air (21 % oxygen), or hyperbaric 100% oxygen (all at 2.5 ATA, 90 minutes twice daily for 5 days). These various mixtures when administered under pressure yielded total oxygen pressures of 21 percent, 50 percent and 100 percent, respectively. Control animals that did not get hyperbaric therapy had 36 percent survival of the random portion of the flap (i.e., that portion that was contralateral to the pedicle). The nitrogen/oxygen mixture had 32 percent viability, while hyperbaric air and hyperbaric oxygen at 100 % yielded 64 and 60 percent viability, respectively. The authors concluded that the flaps could get equal benefit from air under hyperbaric pressure (equivalent to 50 % oxygen mixture) as could be obtained from 100 % oxygen at hyperbaric pressures. Using air at hyperbaric pressures would eliminate the risk of oxygen toxicity. This principle is now used in patients who get air-breaks during hyperbaric oxygen therapy.

Ueda et al.[47] published a study in which hyperbaric oxygen was utilized in a number of patients for treatment of ischemic flaps. As part of their investigation into the mechanism of action of hyperbaric oxygen, the investigators created an island epigastric flap in the lower abdomen of rats and then made the flaps ischemic for 60 minutes by clamping the feeding vessels. After the clamp was removed and flow was restored, one group received hyperbaric oxygen at 2.0 ATA for 60 minutes while the control group did not. In the latter animals, blood flow decreased to approximately 12 percent of preclamp levels and remained there for the period of measurement (1 hour), as measured by laser Doppler flow. Blood flow increased in the hyperbaric oxygen–treated group to 32 percent. The authors postulated that hyperbaric oxygen first improves hypoxia-induced edema, thereby subsequently increasing circulation. We now know that there is a probability that hyperbaric oxygen improved flow by inhibiting reperfusion injury mediated by neutrophils.[48]

Zamboni et al.[49] pushed the above ischemia model to a greater extreme by developing a 3 × 6 cm epigastric flap that was made ischemic for 8 hours. Control animals demonstrated 28 percent necrosis of the area of the flap. Animals given hyperbaric oxygen (2.0 ATA, 1.75 hours per dive, 30 minutes between treatments) during the period of ischemia (three treatments) or immediately afterward (two treatments) had a significantly smaller area of necrosis (9 to 12 percent). When a coated Mylar bag separated the flap, to prevent local diffusive effects of hyperbaric oxygen, the area of necrosis was similarly reduced (5 percent). These investigators suggested that neutrophil sequestration in the lungs with hyperbaric oxygen therapy might have prevented the neutrophils from contributing to reperfusion injury in the flaps. The conclusion that the concentration of leukocytes and neutrophiles in arterial inflow to ischemic flaps is reduced by hyperbaric oxygen was proven in a subsequent study of ischemic gracilis muscle.[50] Of interest, however, is the fact that hyperbaric oxygen only partially improves flap survival. There was still a significant amount of necrosis of the distal ends of the epigastric flaps.

The rat epigastric flap (7 × 7 cm) was also utilized by Collins et al.[51] to compare the efficacy of hyperbaric oxygen with nicotinamide in preserving flap tissue length. Animals were either given saline or nicotinamide injections for 14 days preoperatively and 1 day postoperatively. After flap elevation, one group received hyperbaric oxygen (three treatments at 2.5 ATA for 60 minutes with 30-minute breaks at 1.0 ATA air) in addition to the saline injections and another received nicotinamide in addition to hyperbaric oxygen. The other groups were only treated with saline or nicotinamide. Flap survival with only saline injections was approximately 45 percent. The addition of nicotinamide increased this to 85 percent, while hyperbaric oxygen increased it to 76 percent. The combination of hyperbaric oxygen and nicotinamide yielded about 91 percent, which was not statistically significant from either treatment alone.

Ramon et al.[52] evaluated the effect of hyperbaric oxygen on the transverse rectus abdominis

muscle (TRAM) flap in the rat. The flap was a 6 × 2.5 cm transversely oriented skin island on an inferiorly based pedicle of rectus abdominis muscle. Control animals had 38.5 percent survival. This number improved to 52.5 percent with hyperbaric oxygen (2.5 ATA, 90 minutes for five treatments over 48 hours). The improvement represented an increase of about 25 percent in the area of surviving skin ($p = 0.1$). On angiographic analysis there was an increase in capillary network in the flaps receiving hyperbaric oxygen.

Thus, summarizing the efficacy of hyperbaric oxygen in various rodent epigastric flap models, it would appear that hyperbaric oxygen improves total flap survival by roughly 20 to 30 percent. This improvement is certainly similar to that observed with hyperbaric oxygen therapy in the studies of the dorsal random flaps.

Kernahan et al.[53] created random dorsally based flaps in pigs measuring 6 × 3 inches. This procedure created a flap in which the distal 3 inches was noted to demarcate after 1 day and to go on to necrosis. When hyperbaric oxygen was provided at 3 ATA twice per day for 2 days, a slight improvement in flap survival (2 cm) was noted. Converting the inches to centimeters, this would translate into an increase of 26 percent of the area of flap survival, certainly in the range of that recorded for rodents.

Similarly, Pellitteri et al.[54] raised six medially based random flaps (9.5 × 3.0 cm) on the dorsal surface of each of 12 animals and divided them into two groups. The pigs receiving hyperbaric oxygen were treated for 90 minutes at 2.0 ATA six times on the first postoperative day, five treatments on the second day, four treatments on the third day, three on the fourth day, two treatments on the fifth, and one on the sixth day. Animals serving as controls did not receive hyperbaric oxygen. The animals receiving hyperbaric oxygen had a 12 percent mean total survival area increase over the control or 35 percent less necrosis ($p < 0.001$).

In contrast to these results, Caffee and Gallagher[55] examined pedicled, random, and musculocutaneous flaps in a pig model. Hyperbaric oxygen therapy consisted of 24 hours of 4-hour cycles of hyperbaric oxygen at 2.0 ATA alternating with 4 hours of room air. There was no significant difference between control and treated animals in the amount of flap survival of the random and pedicled flaps. There was complete survival of the musculocutaneous flaps in both groups, so that this was not an effective test of hyperbaric oxygen. The authors note that continued therapy beyond 24 hours was not tested in this experiment to see if further treatment would have been of benefit.

In the case of rabbits, Champion et al.[56] studied five different animal groups. An epigastric flap island flap of 3.25 inches with a pedicle of 1.5 inches was elevated and replaced. Control animals had no further treatment and 40 percent of the flap area became necrotic. Rabbits in the second group received hyperbaric oxygen at 2.0 ATA for 4 hours, two times per day for 5 days. The flaps completely survived. Animals in the third group had the same protocol, except the hyperbaric oxygen was administered for only 2 hours for each treatment. Again, the flaps survived completely. In a fourth group, the chamber was pressurized to 3.0 ATA with 100% oxygen, yet the animals were breathing 19.5% FIO2 via an endotracheal tube. In the final group, the chamber was pressurized with room air and the animals inspired 100% oxygen. All flaps survived in these latter two groups, although there was some evidence of epidermolysis that subsequently healed. These results would seem to indicate that the pressurization was perhaps more important than the concentration of inspired oxygen, supporting the results of Tan et al.[46] with rat abdominal epigastric flaps

In complete contrast to these results, Gruber et al.[57] repeated the previous study with the same flap and was able to vary the conditions of hyperbaric oxygen exposure and inspired oxygen content. There was no significant difference in flap survival in any of 11 different treatment groups, varying the ATA, the duration of exposure, or the oxygen concentration. The reason for this discrepancy in results is not clear.

One study was performed in cats.[58] A caudal superficial epigastric flap was created with the arterial inflow partially occluded with sutures. Treatment with hyperbaric oxygen was carried out for 14 days using a regimen of 2.0 ATA for 90 minutes once per day. Unfortunately, the flap was probably not large enough to provide a significant test, as three of six control animals that did not get hyperbaric oxygen and five out of six animals that did get hyperbaric oxygen had 100 percent flap survival. Although this trend was in favor of hyperbaric oxygen therapy, there was not enough of a sample size for statistical significance.

Again, in summary, it would seem that most of the animal experiments indicate a small but significant improvement with the use of hyperbaric oxygen to salvage a portion of an ischemic flap. In these animal models, the improvement in flap survival, although statistically significant, is some-

what modest in total size, on the order of a few centimeters. If one then transposes these findings to the clinical situation for an ischemic flap, then perhaps only a few additional centimeters of flap survival beyond the well-perfused tissues could be expected with hyperbaric oxygen therapy. Clearly, however, hyperbaric oxygen will not support flap tissue that is significantly distant from a source of adequate circulation. In this fashion it could be stated that although the results satisfy level 6 criteria of the American Heart Association's levels of evidence schemata in support of the use of hyperbaric oxygen for compromised flaps, the area of compromise must be relatively small.

Clinical Studies

As in the case of grafts, there is a paucity of information regarding the effectiveness of hyperbaric oxygen on clinically compromised flaps. There are no prospective randomized trials in the literature. Hyperbaric oxygen is usually administered after the operative procedure, when it is apparent that a portion of the random or pedicled flap has some form of vascular inflow compromise.

Perrins[59] noted that in a personal communication, a physician in Amsterdam informed him of the use of hyperbaric oxygen to salvage several flaps of "doubtful viability" in 1967. This information combined with the animal studies mentioned above led him to perform a prospective nonrandomized clinical investigation. The hyperbaric pressure for each patient varied between 2.0 and 3.0 ATA depending on the response of the tissues. The number of treatments varied from four per day to only two total treatments. The onset of treatment once the flap was seen to be ischemic also varied considerably. In one case where the hyperbaric oxygen therapy failed it was begun 16 hours after it was discovered that the flap was in difficulty. Perrins[59] notes that about 150 flaps per year were performed at his institution in London. In total, in a 1-year period of time, there were 11 incidents of possible flap necrosis in 10 patients and only one failed to respond to hyperbaric oxygen as noted. During this period the total percent of flap failures was 4.5. Most of these failures did not receive hyperbaric oxygen. In contrast, in the preceding 5 years the flap failure rate without hyperbaric oxygen was 8.5 to 11.8 percent. Thus, his retrospective analysis led him to believe that hyperbaric oxygen was extremely efficacious in treating ischemic flaps. In regard to the use of hyperbaric oxygen, he states, "flaps showing signs of failure can be saved and that a problem that has exercised the minds and ingenuity of surgeons since the technique was first introduced has finally been solved." Obviously, this opinion was overly enthusiastic in the absence of carefully executed controlled studies.

Bowersox and colleagues[60] performed a retrospective review of all patients who received hyperbaric oxygen for the threatened failure of skin flaps or grafts from 1976 to 1983. Sixty-five patients had flaps. The reasons for implementing hyperbaric oxygen therapy included (1) clinical appearance of the flap that suggested it was at risk, (2) a history of previous flap failure, or (3) other factors that are recognized as compromising wound healing or infection control. Hyperbaric oxygen therapy was administered at 2.0 ATA for 90 minutes twice per day until sustained clinical improvement was noted (about 5 to 7 days) and then once per day for 120 minutes. The results were graded as complete healing (no flap necrosis), marked improvement (minimal flap necrosis), or failure (flap necrosis requiring another procedure or healing by secondary intent). In these group of flaps, 55 percent healed completely, and an additional 34 percent showed marked improvement. Of those patients who failed with hyperbaric oxygen therapy, it was noted that these patients were 12 years older on average than the successful group and the onset of treatment was markedly delayed (19.8 days versus 4.6 days). Unfortunately, it is impossible to determine from their data how many patients actually had ischemic flaps and what percent of these responded favorably to hyperbaric oxygen versus those patients who just had risk factors as the indication for hyperbaric oxygen. Furthermore, 12 patients were terminated prematurely because of barotrauma or failure to stop nicotine. These patients might have served as a control population, yet we have no data as to their outcomes.

Ueda and colleagues[47] reported on 26 patients from the Department of Oral Surgery in Nagoya University Hospital in whom flap ischemia developed immediately after surgery. These cases covered an 8-year period from 1977 to 1985. The flaps included Abbé flaps to correct lip deformities after cleft surgery and nasolabial, deltopectoral, cervical, sternocleidomastoid, and pectoralis major musculocutaneous flaps for intraoral cancers. In addition there were cases using forehead flaps, tongue flaps, and Estlander and mucosal flaps. Twenty-three were deemed axial pattern flaps and three were random flaps. Again, the use of hyperbaric oxygen varied. Mild ischemic conditions were treated with 2.0 ATA for 60 minutes, once per

day, 6 days per week. Patients with severely ischemic tissues were treated with 2.0 ATA for 60 minutes or 3.0 ATA for 60 minutes twice per day.

Unfortunately, the number of treatments varied for each patient from three to 46. The onset of treatment also varied from the same day as the operation to the postoperative day 14. Most patients were begun by the postoperative day 4 (the average was 2.6 days). Eleven patients had 100 percent flap recovery, and five had 95 percent recovery. Partial necrosis of 15 to 20 percent was noted in the rest. There was an average improvement of 92.1 percent. The authors did note better success when hyperbaric oxygen was administered soon after the flap was created and observed to be in difficulty.

Finally, Schweitzer, and Burtka[61] presented a case of flap necrosis with a cochlear implant exposure that was salvaged with preoperative and postoperative hyperbaric oxygen and another flap. It is not clear that this case has significant relevance to the general application of hyperbaric oxygen for ischemic flaps, as it is uncertain whether the hyperbaric oxygen therapy or the repeated flap procedure or both improved eventual outcome.

In summary, the data available in the literature reaches level 4 of the American Heart Association levels of evidence format (i.e., historic, nonrandomized, cohort or case control studies). Clearly, there are no well-controlled randomized clinical studies to suggest that hyperbaric oxygen has a beneficial effect on ischemic flaps. Perhaps, by combining the animal and clinical data, the best one could say is that hyperbaric oxygen when applied immediately postoperatively and continued for an undetermined period of time, *may* increase the amount of surviving tissue in an ischemic flap that otherwise would become necrotic. How much tissue survival improvement occurs in tissues a given distance from areas with intact blood supply is not clear. In the clinical case series, those flaps that demonstrated 100 percent or even less survival may have done as well without hyperbaric oxygen. Again, there is no way of knowing without controlled trials. If one were to take the data from the rodent studies noted above, a calculation could be made that suggests hyperbaric oxygen improves survival in ischemic tissues for a distance of about 2 cm from the area of usual demarcation without hyperbaric oxygen. In certain clinical situations where distal portions of flaps are at risk, 1 to 2 cm may be all that is needed to prevent additional operative intervention. However, even this number may be dependent on the strength of the blood flow proximal to the area of ischemia. Another issue is the flap that has marginal blood flow but is underperfused as opposed to tissue that is not perfused. The underperfused flap may progress to demonstrate epidermolysis or partial necrosis at its distal end. There are no animal models or clinical studies that investigate the efficacy of hyperbaric oxygen or other modalities for this scenario.

DISTANT FLAPS

Distant flaps require the growth of new blood supply from surrounding tissues into the distal end of the flap before the division of the donor proximal pedicle. In this fashion, portions of vascularized flaps are transferred from one site to another. The usual period of time of connection of the flap between the donor and recipient site is 3 to 4 weeks.

Animal Studies

There is only one animal study that looks at the issue of hyperbaric oxygen and distant flaps, those flaps that require attachment to both donor and recipient sites for a period of time before division of the pedicle. Bayati et al.[62] tunneled the semimembranosus muscle into a pocket under the ipsilateral abdominal skin. A silicone sheet was placed under the muscle to prevent vascular ingrowth from anywhere beneath the abdominal skin except the muscle, and the ipsilateral epigastric vessels were ligated to produce relative ischemia as a stimulus for neovascularization. Through a femoral catheter, fibroblast growth factor or saline was infused, or animals received hyperbaric oxygen or both fibroblast growth factor and hyperbaric oxygen. The latter was administered at 2.5 ATA for 90 minutes every 12 hours for 7 days. After 1 week, the abdominal skin (3 × 5 cm) was elevated along with the muscle and then sutured back in place without disturbing the silicone sheet. After 7 more days the amount of flap survival was determined. Both hyperbaric oxygen and fibroblast growth factor improved the percent of flap survival and the two treatments together were synergistic. Control animals displayed 10.6 percent survival, while hyperbaric oxygen improved this to 36.7 percent, fibroblast growth factor to 55.3 percent, and the combination yielded survival of 64.6 percent. Similarly, laser Doppler flow in the flaps and angiogenesis were also better with the synergistic treatment of hyperbaric oxygen and fibroblast growth factor. It should be noted here, however, that hyperbaric oxygen was

administered before flap division rather than after. This scenario does not entirely match the clinical situation unless one were to suspect that division of the pedicle would risk a flap failure and therefore hyperbaric oxygen would be needed before rather than after flap division.

Clinical Studies

The only clinical investigation looking at distant flaps was the previously mentioned report by Ueda et al.[47] in patients undergoing Abbé flap lip reconstructions. Again, there were no control subjects and there is some likelihood that the flaps would have survived without hyperbaric oxygen.

Only these two studies address the issue of distant flaps. The animal data would suggest some benefit to the use of hyperbaric oxygen, specially combined with fibroblast growth factor, thus supporting hyperbaric oxygen at level 6, while the case series would raise the level of support to five of the American Heart Association's levels of evidence criteria. Clearly, there are no prospective randomized trials that would give solid support to hyperbaric oxygen use in these situations.

FREE FLAPS

All of the data regarding free flaps are found in animal experiments. Manson and colleagues[63] in 1986 published one of the first investigations of improved free flap survival with prolonged storage. Groin flaps measuring 3 × 5 cm were harvested from rats along with the branches of the epigastric vessels. The flaps were stored at room temperature for 21 to 24 hours and then anastomosed to the contralateral epigastric vessels. Just before reperfusion the flaps were either perfused with saline (control) or with superoxide dismutase, a scavenger of free radicals. The control flaps had an incidence of survival of only 38 percent, while flaps treated with superoxide dismutase had a survival rate of 76 percent. This improvement provides a baseline against which to compare the effects of hyperbaric oxygen, which also counteracts oxygen free radicals. Thus, Kaelin et al.[64] looked at the effect of hyperbaric oxygen on rat free flaps stored for 18, 21, and 24 hours at 24°C and then revascularized. Hyperbaric oxygen therapy was administered within 4 hours of reperfusion and consisted of 90-minute dives at 2.0 ATA twice per day for 7 days. Control animals were maintained in room air. Flap survival for the later group was 20, 10, and zero percent for each of the time periods of storage. Animals given hyperbaric oxygen had improvement in survival rates to 66, 67, and 40 percent. In another arm of the same study the investigators developed island flaps of the entire abdominal skin based on the epigastric vessels on only one side. Control animals demonstrated 35 percent survival of the random portion of the flap. Postoperative treatment with hyperbaric oxygen raised the survival rate to 64 percent, consistent with the improvement noted in other rodent studies.

In a somewhat different approach, amputated rat limbs were either stored in hyperbaric oxygen at 2.9 ATA or in room air for 3.5 hours and then replanted.[65] Limbs stored in room air had a 50 percent survival rate while those stored under hyperbaric conditions demonstrated 100 percent survival. A similar study by Tai et al.[66] investigated the storage of free groin skin flaps in room air verses hyperbaric oxygen for 18 hours. Survival improved from 10 to 60 percent with the use of hyperbaric oxygen. Angel et al.[67] combined cold with hyperbaric oxygen storage and was able to increase flap survival after storage for 72 hours from 20 to 70 percent.

Although these animal investigations showed a benefit for flap storage under hyperbaric conditions, this scenario better reflects the clinical situation where a part, such as a finger, is amputated and cannot undergo immediate replantation. In the case of free flaps, the usual situation is that the tissue undergoes prolonged ischemia in the operating room and then after the vessel anastomoses are completed, circulation is not restored to the entire piece of tissue, or thrombosis, kinking of the pedicle, or edema results in another period of ischemia.

Stevens et al.[68] designed a study that better reflects this situation. Unilateral adipocutaneous flaps were elevated based on the superficial inferior epigastric vessels in rats. Applying a clamp for 6 hours to the vascular pedicle induced normothermic ischemia. Subsequently, the clamp was removed and the flaps reperfused for 2 hours. The clamp was then reapplied for another 6, 10, or 14 hours and the rats were placed into one of three groups after the clamp was again removed. The animals breathed either normobaric air, 100% oxygen under normobaric conditions, or hyperbaric oxygen (2.0 ATA, 90 minutes, twice daily) for 7 days. Flap survival was an all or none phenomenon. The secondary ischemia time that provided 50 percent flap survival was calculated. This time for control and animals breathing 100% oxygen was 6 hours. It increased to 10 hours with the use of hyperbaric oxygen ($p < 0.1$). The increase in tolerance to secondary ischemia was on the order

of 170 percent. Thus hyperbaric oxygen reduced the incidence of flap loss in this animal model, but it did not completely prevent it. At 14 hours of secondary ischemia, 14 out of 18 flaps still underwent necrosis. At 10 hours, six out of 13 animals had complete flap loss and at 6 hours three out of 12 animals had flap loss. At each period of time there was an advantage to using hyperbaric oxygen versus 100% oxygen or room air, but still flap necrosis occurred in 25 percent, 46 percent, and 78 percent of flaps after secondary ischemia for 6, 10, and 14 hours respectively.

On the basis of the above animal experiments, it would appear that hyperbaric oxygen does provide some protection from ischemia reperfusion injury for free flaps with prolonged primary or secondary ischemia. However, again there has been no prospective randomized clinical trial to document efficacy in the clinical situation. Therefore, the level of evidence reached is only level 6 of the American Heart Association's levels of evidence evaluation scheme.

SUMMARY

Although there would seem to be significant animal data to support the use of hyperbaric oxygen in the treatment of ischemic flaps, composite grafts, and perhaps for preparing wounds for skin grafting, there does not seem to be a single clinical prospective randomized clinical trial to give this information absolute validity. If you couple this fact with the potential, albeit infrequent complications of hyperbaric medicine,[69] including ear trauma, seizures, worsening of heart failure, pneumothorax, and so on. and the cost of therapy, it becomes difficult, when faced with an individual clinical problem, to determine whether a trial of hyperbaric medicine is warranted. This dilemma is certainly true in the case of preparation of a wound for skin grafting when there are other techniques that seem to also promote angiogenesis and granulation tissue, such as Regranex,[70] wound vacuum,[71–73] and serial dressing changes. For example, just as in the case of hyperbaric oxygen, there are no prospective clinical trials that demonstrate the efficacy of the wound vacuum specifically for skin grafting. However, both hyperbaric oxygen and wound vacuum have been shown, with prospective randomized clinical trials, to be effective in helping diabetic lower extremity ulcers to heal.[4,72] This increased wound healing was presumably through the development of granulation tissue and wound contracture in both instances. Although in a recent animal model study of an acute wound, vacuum therapy appeared superior to hyperbaric oxygen in the development of granulation tissue.[73]

In the same vein, there are pharmacologic interventions for flaps that could be applied preoperatively or postoperatively that may give equal benefit as hyperbaric oxygen, such as steroid injections, or oxygen free radical scavengers. Finally, arguments could be made for combined therapies including hyperbaric oxygen, yet there are no clinical data to support any of these approaches.

This review of the available literature regarding the efficacy of hyperbaric oxygen utilization for flaps and grafts underscores the paucity of clinical information available that would support a strong recommendation for its application in these clinical situations. Does this mean that hyperbaric oxygen lacks efficacy or should not be employed to help with graft or flap preservation? In a recent article in the *British Medical Journal*, Smith and Pell[74] published an article with the provocative title of "Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomized Controlled Trials." In this article they argue that there are no prospective randomized controlled trials available to suggest that the use of a parachute when jumping from a plane yields any better clinical results than free-falling without one. Yet no one would argue that observational data support the use of the parachute. Similarly, at this time, there is enough animal evidence and observational data to warrant the application of hyperbaric oxygen in selective situations, either alone or in combination with other modalities that enhance the take of skin grafts in compromised recipient sites, or unusually large composite grafts, or aid in the survival of compromised flaps.

To develop stronger guiding principles for individual clinical situations, better data are required. More than likely, a single institution will not be able to generate sufficient numbers of patients to undertake controlled randomized trials and multicenter studies will be needed. The Undersea and Hyperbaric Medical Society, whose interest is the application of hyperbaric medicine to clinical problems, should be charged with coordinating such endeavors. Until that time when clinicians have clear-cut clinical data on which to base an informed decision for therapy, we will be relying on laboratory experiments, expert opinion, experience, and trial and error to see if hy-

perbaric oxygen provides significant benefit in these scenarios.

Harold I. Friedman, M.D., Ph.D.
Division of Plastic Surgery, Department of Surgery
University of Southern California School of Medicine
No. 2 Medical Park Road, Suite 402
Columbia, S.C. 29203
hfriedmandr@sc.rr.com

REFERENCES

1. Weaver, L. K., Hopkins, R. O., Chan, K., et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N. Engl. J. Med.* 347: 1057, 2002.
2. Hirn, M. Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotizing fasciitis. *Eur. J. Surg. Suppl.* 570: 1, 1993.
3. Curi, M. M., Dib, L. L., and Kowalski, L. P. Management of refractory osteoradionecrosis of the jaws with surgery and adjunctive hyperbaric oxygen. *Int. J. Oral Maxillofac. Surg.* 29: 430, 2000.
4. Faglia, E., Favales, F., Aldehgi, A., et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: A randomized study. *Diabetes Care* 19: 1338, 1996.
5. Zamboni, W. A. Applications of hyperbaric oxygen therapy in plastic surgery. *In G. Oriani and A. Marroni (Eds.),Handbook on Hyperbaric Medicine.* Springer-Verlag: New York, N.Y., 1996. P. 443.
6. Zamboni, W. A., and Broder, L. K. Hyperbaric oxygen and wound healing. *Clin. Plast. Surg.* 30: 67, 2003.
7. Sackett, D. L., and Rosenberg, W. M. C. Evidence-based medicine: What it is and what it isn't. *Br. Med. J.* 312: 71, 1996.
8. American Heart Association Emergency Cardiovascular Care Levels of Evidence. *J.A.M.A.* 268: 2172, 1992.
9. Converse, J. M. Full-thickness loss of nasal tissue. In J. M. Converse (Ed.), *Reconstructive Plastic Surgery: Principles and Procedures in Correction, Reconstruction, and Transplantation.* 2nd Ed. Philadelphia: Saunders, 1977. P. 1220.
10. Aden, K. K., and Biel, M. A. The evaluation of pharmacologic agents on composite graft survival. *Arch. Otolaryngol. Head Neck Surg.* 118: 175, 1992.
11. Fann, P. C., Hartman, D. F., and Goode, R. L. Pharmacologic and surgical enhancement of composite graft survival. *Arch. Otolaryngol. Head Neck Surg.* 119: 313, 1993.
12. Henrich, D. E., Logan, T. C., Lewis, R. S., and Shockley, W. W. Composite graft survival. An auricular model. *Arch. Otolarygol. Head Neck Surg.* 121: 1137, 1995.
13. Chen, C. I., Yang, R. S., Ou, L. F., Tang, Y. W., and Jian, M. J. The influence of intro-graft heparin injection on the survival of composite grafts. *Chin. Med. J.* 61: 346, 1998.
14. Rubin, J. S., Marzella, L., Myers, R. A., Suter, C., Eddy, H., and Kleiman, L. Effect of hyperbaric oxygen on the take of composite skin grafts in rabbit ears. *J. Hyperbaric Med.* 3: 79, 1988.
15. Zhang, F., Cheng, C., Gerlach, T., Kim, D. Y., Lineaweaver, W. C., and Buncke, H. J. Effect of hyperbaric oxygen on survival of the composite ear graft in rats. *Ann. Plast. Surg.* 41: 530, 1998.
16. Tan Lim, A. A., Wall, M. P., and Greinwald, J. H. Effects of dimethylthiourea, melatonin, and hyperbaric oxygen therapy on the survival of reimplanted rabbit auricular composite grafts. *Otolaryngol. Head Neck Surg.* 121: 231, 1999.
17. McClane, S., Renner, G., Bell, P. L., and Early, E. K. Pilot study to evaluate the efficacy of hyperbaric oxygen therapy in improving the survival of reattached auricular composite grafts in the New Zealand White rabbit. *Otolaryngol. Head Neck Surg.* 123: 539, 2000.
18. McFarlane, R. M., Wermuth, R. E. The use of hyperbaric oxygen to prevent necrosis in experimental pedicle flaps and composite skin grafts. *Plast. Reconstr. Surg.* 37: 422, 1966.
19. Gruber, R. P., Brinkley, F. B., Amato, J. J., and Mendelson, J. A. Hyperbaric oxygen and pedicle flaps, skin grafts and burns. *Plast. Reconstr. Surg.* 45: 24, 1970.
20. Gonnering, R. S., Kindwall, E. P., and Goldmann, R. W. Adjunct hyperbaric oxygen therapy in periorbital reconstruction. *Arch. Ophthalmol.* 104: 439, 1986.
21. Nichter, L. S., Morwood, D. T., Williams, G. S., and Spence, R. J. Expanding the limits of composite grafting: A case report of a successful nose replantation assisted by hyperbaric oxygen therapy. *Plast. Reconstr. Surg.* 87: 337, 1991.
22. Rapley, J. H., Lawrence, W. T., and Witt, P. D. Composite grafting and hyperbaric oxygen therapy in pediatric nasal tip reconstruction after avulsive dog-bite injury. *Ann. Plast. Surg.* 46: 434, 2001.
23. Friedman, H. I., Stonerock, C., and Brill, A. Composite earlobe grafts to reconstruct the lateral nasal ala and sill. *Ann. Plast. Surg.* 50: 275, 2003.
24. Machine, A., Rohr, S., Toti, F., et al. Wound healing with hyperbaric oxygen: Experimental study of the angiogenesis phase in the rat. *Ann. Chir.* 53: 307, 1999.
25. Lin, S., Shyu, K. G., Lee C. C. et al. Hyperbaric oxygen selectively induces angiopoietin-2 in human umbilical vein endothelial cells. *Biochem Biophys. Res. Commun.* 296: 710, 2002.
26. Hunt, T. K., Lindsey, M., Sonne, M., et al. Oxygen tension and wound infection. *Surg. Forum* 23: 47, 1972.
27. Knighton, D. R., Halliday, B., and Hunt, T. Oxygen as an antibiotic: The effect of inspired oxygen on infection. *Arch. Surg.* 119: 199, 1984.
28. Park, M. K., Myers, R. A. M., and Marzella, L. Oxygen tensions and infections: Modulation of microbial growth, activity of antimicrobial agents, and immunologic responses. *Clin. Infect. Dis.* 14: 720, 1992.
29. Shulman, A. G., and Krohn, H. L. Influence of hyperbaric oxygen and multiple skin allografts on the healing of skin wounds. *Surery.* 62: 1051, 1967.
30. Erdmann, D., Roth, A. C., Hussmann, J., et al. Skin allograft rejection and hyperbaric oxygen treatment in immune-histoincompatible mice. *Undersea Hyperbaric Med.* 22: 395, 1995.
31. Erdmann, D., Roth, A. C., Hussmann, J., et al. Hyperbaric oxygen and cyclosporine as a combined treatment regimen to prevent skin allograft rejection in immunohistoincompatible mice. *Ann. Plast. Surg.* 36: 304, 1996.
32. Hosgood, G., Hodgin, E. C., Strain, G. M., Lopez, M. K., and Lewis, D. D. Effect of deferoxamine and hyperbaric oxygen on free, autogenous, full-thickness skin grafts in dogs. *Am. J. Vet. Res.* 56: 241, 1995.
33. Perrins D. J. D. Influence of hyperbaric oxygen on the survival of split skin grafts. *Lancet* 868, 1967.
34. McFarlane, R. M., DeYoung, G., and Henry, R. A. The design of a pedicle flap in the rat to study necrosis and its prevention. *Plast. Reconstr. Surg.* 35: 177, 1965.
35. McFarlane, R. M., DeYoung, G., and Henry, R. A. Prevention of necrosis in experiemental pedicle flaps with hyperbaric oxygen. *Surg. Forum* 16: 481, 1965.
36. Wald, H. I., Georgiade, H. G., Angelollo, J., and Saltzman, H. A. Effect of intensive hyperbaric oxygen therapy on the survival of experimental skin flaps in rats. *Surg. Forum* 19: 497, 1968.

37. Arturson, G., and Khanna, N. N. The effects of hyperbaric oxygen, dimethyl sulfoxide and Complamin on the survival of experimental skin flaps. *Scand. J. Plast. Surg.* 4: 8, 1970.
38. Niinikoski, J. Viability of ischemic skin flaps in hyperbaric oxygen. *Proc 5th Int. Hyperbaric Conf.* 1: 244, 1974.
39. Jurell, G., and Kaijser, L. Influence of varying pressure and duration of treatment with hyperbaric oxygen on survival of skin flaps. *Scand. J. Plast. Surg.* 7: 25, 1973.
40. Manson, P. N., Im, M. J., Myers, R. A. M., and Hoopes, J. E. Improved capillaries by hyperbaric oxygen in skin flaps. *Surg. Forum* 31: 564, 1980.
41. Nemiroff, P. M., Merwin, G. E., and Brant, T. Effects of hyperbaric oxygen and irradiation on experimental skin flaps in rats. *Otolaryngol. Head Neck Surg.* 93: 485, 1985.
42. Nemiroff, P. M. Synergistic effects of pentoxifylline and hyperbaric oxygen on skin flaps. *Arch. Otolaryngol. Head Neck Surg.* 114: 977, 1988.
43. Esclamado, R. M., Larrabee, W. F., and Zel, G. E. Efficacy of steroids and hyperbaric oxygen on survival of dorsal skin flaps in rats. *Otolaryngol. Head Neck Surg.* 102: 41, 1990.
44. Stewart, R. J., Moore, T., Bennett, B., Easton, M., Newton, G. W., and Yagamuchi, K. T. Effect of free-radical scavengers and hyperbaric oxygen on random-pattern skin flaps. *Arch. Surg.* 129: 982, 1994.
45. Frigerio, D., Lovisetti, G., Lovisetti, L. Effect of hyperbaric oxygenation on the survival of experimental skin flaps in rats. *Proc. 10th Int.Cong. Hyperbaric Med.* 199, 1990 .
46. Tan, C. M., Im, M. J., Myers, R. A. M., and Hoopes, J. E. Effects of hyperbaric oxygen and hyperbaric air on the survival of island skin flaps. *Plast. Reconstr. Surg.* 73: 27, 1984.
47. Ueda, M., Kaneda, T., Takahashi, H., et al. Hyperbaric oxygen therapy of ischemic skin flaps: Clinical and experimental study.9th Internat. Symp. Underwater Hyperbaric Physiol. UHMS 1987: 823,
48. Buras, J. Basic mechanisms of hyperbaric oxygen in the treatment of ischemia-reperfusion injury. *Int. Anesth. Clin.* 38: 91, 2000.
49. Zamboni, W. A., Roth, A. C., Russell, R. C., Nemiroff, P. M., Casas, L., and Smoot, E. C. The effect of hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. *J. Reconstr. Microsurg.* 5: 343, 1989.
50. Zamboni, W. A., Wong, H. P., and Stephenson, L. L. Effect of hyperbaric oxygen on neutrophil concentration and pulmonary sequestration in reperfusion injury. *Arch. Surg.* 131: 756, 1996.
51. Collins, T. M., Caimi, R., Lynch, P. R., et al. The effects of nicotinamide and hyperbaric oxygen on skin flap survival. *Scand. J. Plast. Surg.* 25: 5, 1991.
52. Ramon, Y., Abramovich, A., Shupak, A., et al. Effect of hyperbaric oxygen on a rat transverse rectus abdominis myocutaneous flap model. *Plast. Reconstr. Surg.* 102: 416, 1998.
53. Kernahan, D. A., Zingg, W., and Kay, C. W. The effect of hyperbaric oxygen on the survival of experimental skin flaps. *Plast. Reconstr. Surg.* 36: 19, 1965.
54. Pellitteri, P. K., Kennedy, T. L., and Youn, B. A. The influence of invasive hyperbaric oxygen therapy on skin flap survival in a swine model. *Arch. Otolaryngol. Head Neck Surg.* 118: 1050, 1992.
55. Caffee, H. H., and Gallagher, T. J. Experiments on the effects of hyperbaric oxygen on flap survival in the pig. *Plast. Reconstr. Surg.* 81: 751, 1988.
56. Champion, W. M., McSherry, C. K., and Goulian, D. Effect of hyperbaric oxygen on the survival of pedicled skin flaps. *J. Surg. Res.* 7: 583, 1967.
57. Gruber, R. P., Billy, L. I., Heitkamp, D. H., and Amato, J. J. Hyperbaric oxygenation of pedicle flaps without oxygen toxicity. *Plast. Reconstr. Surg.* 46: 477, 1970.
58. Kerwin, S. C., Hosgood, G., Strain, G. M., Vice, C. C., White, C. E., and Hill, R. K. The effect of hyperbaric oxygen treatment on a compromised axial pattern flap in the cat. *Vet. Surg.* 22: 31, 1993.
59. Perrins, D. J. D. The effect of hyperbaric oxygen on ischemic skin flaps. In W. C. Grabb and M. B, Myers (Eds.), *Skin Flaps.* Boston: Little, Brown, 1975. P. 53.
60. Bowersox, J. C., Strauss, M. B., and Hart, G. B. Clinical experience with hyperbaric oxygen therapy in the salvage of ischemic skin flaps and grafts. *J. Hyperbaric Med.* 1: 141, 1986.
61. Schweitzer, V. G., and Burtka, M. J. Hyperbaric oxygen therapy in the management of cochlear implant flap necrosis. *J. Hyperbaric Med.* 5: 81, 1990.
62. Bayati, S., Russell, R. C. and, Roth, A. C. Stimulation of angiogenesis to improve the viability of prefabricated flaps. *Plast. Reconstr. Surg.* 101: 1290, 1998.
63. Manson, P. N., Narayan, K. K., Im, M. J., Bulkley, G. B., and Hoopes, J. E. Improved survival in free skin flap transfers in rats. *Surgery* 99: 211, 1986.
64. Kaelin, C. M., Im, M. J., Myers, R. A. M., Manson, P. N., and Hoopes, J. E. The effects of hyperbaric oxygen on free flaps in rats. *Arch. Surg.* 125: 607, 1990.
65. Edwards, R. J., Im, M. J., and Hoopes, J. E. Effects of hyperbaric oxygen preservation on rat limb replantation: A preliminary report. *Ann. Plast. Surg.* 27: 31, 1991.
66. Tai, Y. J., Birely, B. C., Im, M. J., Hoopes, J. E., and Manson, P. N. The use of hyperbaric oxygen for preservation of free flaps. *Ann. Plast. Surg.* 28: 284, 1992.
67. Angel, M. F., Im, M. J., Chung, H. K., Vander Kolk, C. A., and Manson, P. N. Effects of combined cold and hyperbaric oxygen storage on free flap survival. *Microsurgery* 15: 648, 1994.
68. Stevens, D. M., Weiss D. D., Koller, W. A., and Bianchi, D. A. Survival of normothermic microvascular flaps after prolonged secondary ischemia: Effects of hyperbaric oxygen. *Otolaryngol. Head Neck Surg.* 115: 360, 1996.
69. Plafki, C., Peters, A. M., Almeling, M., Welslau, W., and Busch, R. Complications and side effects of hyperbaric oxygen therapy. *Aviat. Space Environ. Med.* 71: 119, 2000.
70. Horn, D. B., and Manivel, J. C. Promoting healing with recombinant human platelet-derived growth factor-BB in a previously irradiated problem wound. *Laryngoscope* 113: 1566, 2003.
71. Clare, M. P., Fitzgibbons, T. C., McMullen, S. T., Stice, R. C., Hayes, D. F., and Henkel, L. Experience with the vacuum assisted closure negative pressure technique in the treatment of non-healing diabetic and dysvascular wounds. *Foot Ankle Int.* 23: 896, 2002.
72. Eginton, M. T., Brown, K. R., Seabrook, G. R., Towne, J. B., and Cambria, R. A. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann. Vasc. Surg.* 17: 645, 2003.
73. Fabian, T. S., Kaufman, H. J., Lett, E., et al. The evaluation of subatmospheric pressure and hyperbaric oxygen in ischemic full-thickness wound healing. *Am. Surg.* 66: 1136, 2000.
74. Smith, G. S. C., and Pell, J. P. Parachute use to prevent death and major trauma related to gravitational challenge: Systematic review of randomized controlled trials. *Br. Med. J.* 327: 1459, 2003.