COMPROMISED GRAFTS AND FLAPS

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Rationale

Hyperbaric oxygen therapy (HBOT) is neither necessary nor recommended for the support of normal, uncompromised grafts or flaps. However, in tissue compromised by irradiation or in other cases where there is decreased perfusion or hypoxia, HBOT has been shown to be extremely useful in flap salvage. Hyperbaric oxygen can help maximize the viability of the compromised tissue thereby reducing the need for regrafting or repeat flap procedures. The criteria for selecting the proper patients that are likely to benefit from adjunctive hyperbaric oxygen for graft or flap compromise is crucial for a successful outcome. Identification of the underlying cause for graft or flap compromise can assist in determining the proper clinical management and use of hyperbaric oxygen therapy. A number of studies have shown the efficacy of HBOT on enhancement of flap and graft survival in a variety of experimental and clinical situations.

Patient Selection Criteria

As hyperbaric oxygen therapy is only indicated in certain pathologic disorders, proper patient selection criteria begins by recognizing the underlying cause of the compromise of the flap or graft. While compromised skin grafts and composite grafts are often classified with compromised flaps, these two entities are distinctly different from a physiologic standpoint. All flaps, by definition, have an inherent blood supply whereas grafts are avascular tissues that rely on the quality of the recipient bed for survival and revascularization. Because of this dependence, the diagnosis of a compromised graft begins with proper assessment of the recipient wound bed.

The most effective treatment for the compromised graft is *prevention* by ensuring an appropriate recipient bed. Diagnosis and treatment of the problem wound that will benefit from hyperbaric oxygen therapy is addressed in a previous section of this report. There are instances, however, when a questionable recipient bed goes unrecognized or when the size of the harvested graft exceeds the dimensions that can be sustained by the recipient bed. These scenarios describe the compromised graft that suffers from hypoxia. These compromised grafts may be salvaged with prompt institution of HBOT. Hyperbaric oxygen can help maximize the viability of the compromised graft while revascularization takes place thereby reducing the need for re-grafting procedures which incur further operations and increased donor site morbidity.

There are many etiologies of flap compromise. These can range from random ischemia to venous congestion or occlusion to arterial occlusion. In addition, free tissue transfers describing a flap in which the arterial and venous blood supply is divided and reattached to another location by microsurgical anastomosis can have their own special problems. Free flaps can be exposed to both ischemia-reperfusion injury and secondary ischemic insults which can compromise the viability of the flap. In many cases, surgical re-exploration will identify and treat the etiology of flap compromise. However, in instances where there is no correctable mechanical cause of

decreased flap perfusion, HBOT can play an important role in flap salvage. The key to successful salvage is the prompt institution of HBOT which can help maximize tissue viability while perfusion is restored. Similar to its use in compromised grafts, HBOT can reduce the need for repeat flap procedures decreasing overall patient morbidity.

Evidence-Based Review

An evidence-based review of the benefits of hyperbaric oxygen therapy on compromised grafts and flaps encompasses a variety of experimental trials. These studies can be classified into animal studies and clinical studies.

Animal Studies

The role of HBOT in compromised wound beds vs. non-compromised wound beds has been examined experimentally. Kivisaari and Niinikoski[1] in a study on rats showed that HBOT at 2 atmospheres absolute (ATA) had no effect on the healing rate of non-compromised open wounds in which the circulation was left intact. However, when the wound edges were devascularized, HBOT significantly enhanced wound closure rates over control groups.

Shulman and Krohn,[2] in a study of healing tissues of full thickness and partial thickness wounds in rats, found that HBOT shortened the healing time significantly. Further, the combination of repeated skin grafting and HBOT reduced the healing time of partial thickness wounds to one-half of that of non-treated controls. No attempt at wound sterilization was made in performing these surgeries. Superficial contamination did occur in all animals, but infection was entirely absent in the groups treated with HBOT.

There are a number of experimental studies describing the effect of HBOT on compromised grafts, both skin grafts and composite grafts. Erdmann et al.[3,4] has evaluated the effect of HBOT as treatment from skin allograft rejection. Using a mouse skin allograft rejection model, these authors demonstrated that treatment with HBOT alone[3] or in combination with cyclosporine[4] lengthened the time to allograft rejection. This effect was more profound in animals receiving more frequent HBOT compared to animals receiving lower doses of HBOT.

Renner et al.[5] investigated the efficacy of HBOT in improving survival of reattached auricular composite grafts. A prospective, randomized, double-blind study using twenty New Zealand albino rabbits randomized to a treatment or control group. Their study represented a continued investigation following a pilot study, which suggested some enhancement of composite graft survival with the use of HBOT in the rabbit ear. Both experiments have demonstrated a slight survival benefit using HBOT in auricular composite grafts in the rabbit model.

Rubin et al.[6] studied the hyperoxic effects of composite skin grafts in rabbit ears. Experimental animals received 100% oxygen at 2 ATA twice daily for 21 treatments. Grafts in HBOT-treated animals demonstrated significantly greater survival than grafts in control animals. Similarly, Zhang et al.[7] examined the effects of HBOT on composite skin grafts in the rabbit ear model. Experimental animals received HBOT at 2 ATA daily for five days and demonstrated a

significantly increased 82% survival area compared to the 26.5% survival area in the control group.

Li et al.[8] investigated the efficacy of HBOT on rabbit auricular composite graft survival of different sizes. Circular chondrocutaneous composite grafts of 0.5, 1.0, or 2.0 cm in diameter were harvested and reattached to the rabbit ears. Experimental animals received HBOT for 90 minutes at 2.4 ATA for five days. Three weeks post-operatively, the 2.0 cm composite grafts treated with HBOT had a mean graft survival rate of 85.8% compared to the control group's 51.3% survival rate. There was no benefit seen in the smaller grafts. This suggests a benefit of HBOT for the larger size composite grafts which could be considered compromised and hypoxic.

Several early studies have demonstrated the benefits of HBOT on experimental skin flaps.[9-11] The effects of HBOT on compromised and ischemic random flaps have been studied experimentally as well. Niinikoski[12] found a 51% improvement in the length of the viable portion of tubed random skin flaps in rats treated with HBOT (2.5 ATA for 2 hours twice daily for 2 days) compared to air-breathing controls ($P<0.001$). The author suggested that enhanced diffusion of oxygen into the area of disturbed circulation was the mechanism for improvement of tissue viability. Gruber et al.[13] showed that in skin flaps in rats, HBOT at 3 ATA raised mean tissue oxygen tensions to 600mmHg, whereas 100% oxygen at sea level did not raise mean flap oxygen tension.

Pellitteri et al.[14] demonstrated the effect of HBOT in a pig model of random skin flap survival. Random skin flaps in swine were designed to result in a predictable length of necrosis and the experimental animals were treated with HBOT for 90 min at 2.0 ATA over six days. The compromised flaps in the treatment animals demonstrated a mean survival of 77% which correlated to 35% less necrosis when compared to the control animals.

Arturson and Khanna,[15] in an experimental study on standard dorsal random skin flaps in rats designed to give a predictable and a constant degree of necrosis, revealed that HBOT had a significant improvement in flap survival over untreated controls ($P<0.05$). Other flap-enhancing agents were studied, and in some cases enhanced flap survival. However, the best results were found in rats treated with HBOT. Similarly, Esclamado et al.[16] studied the effect of HBOT on survival of dorsal random skin flaps in rats in comparison to another adjunctive therapy – steroids. The random skin flaps were divided into four groups: control, steroids only, HBOT only, and combined steroids plus HBOT. HBOT consisted of 90 minute treatments at 2.4 ATA twice daily for three days. Each of the experimental groups showed a statistically significant ($P<0.01$) improvement in flap survival, however, the best results were seen in the HBOT only group which showed a 36% improvement compared to controls.

Stewart et al.[17] demonstrated the positive effectiveness of HBOT in combination with free-radical scavenger in increased random skin flap survival. HBOT for 90 minutes at 2.5 ATA daily was combined with one of several different free-radical scavengers including superoxide dismutase, catalase, and alpha-tocopherol acetate and each combination demonstrated a significantly greater flap survival ($P<0.05$) compared to controls.

Greenwood and Gilchrist[18] demonstrated the effectiveness of HBOT in reducing the extent of ischemic necrosis of skin flaps created in previously irradiated rats. Mean flap necrosis was significantly greater ($P<0.05$) in the control (air) group vs. the HBOT group.

A controlled, randomized study on the effects of HBOT and irradiation on experimental random skin flaps has been performed by Nemiroff et al.[19,20] One hundred eighty-five rats were randomly assigned to one of 15 conditions, including possible sequencing effects of HBOT, irradiation, and flap creation, as well as controls which included flap creation only, irradiation only, and HBOT groups. Results showed that all groups receiving HBOT within four hours after flap elevation had significantly greater flap survival time ($P<0.05$), with as much as a 22% increase in flap survival.

Further work by Nemiroff and Lungu[21] elucidated some of the mechanisms whereby HBOT enhanced random flap survival. Skin flaps from animals treated with HBOT vs. controls were analyzed in a controlled standardized method. The number and size of blood vessels in the microvasculature was significantly greater for all of the HBOT groups when compared with that in controls ($P<0.01$). The mean surface area of vessels of the flap-HBOT groups was also significantly greater than in controls in all but one group ($P<0.01$). The authors concluded that HBOT significantly enhanced flap survival by increasing and/or maintaining the number and possibly the size of vessels within the microvasculature. To be most efficacious, the authors stated that HBOT must be administered as soon after surgery as possible. Other investigators have shown that HBOT can enhance healing and flap survival by promoting angiogenesis.[22-25]

Manson and associates,[22] in studies using histochemical staining with ATPase to visualize small blood vessels, demonstrated that capillaries grew distally almost 3 times further in pedicle flaps of pigs that were treated with HBOT, compared with age-matched controls.

Further studies using pedicle flap models have also demonstrated a beneficial effect of HBOT. Champion and colleagues,[26] using a pedicle flap model in rabbits, were able to obtain 100% survival of HBOT treated flaps (2 ATA for 2 hours twice a day for 5 days) whereas all control flaps had significant areas of necrosis to greater than 40%. Similarly, work by McFarlane and Wermuth[27] concluded that HBOT was of definite value in preventing necrosis in a pedicle flap in the rat and also has limited the extent of necrosis in a free composite graft. The authors noted that their particular experimental design was a severe test of treatment and attests to the value of HBOT in preventing necrosis.[27]

Jurell and Kaijser,[28] using a cranially based pedicle flap in a rat, showed that rats treated with HBOT had a significantly greater flap survival compared with controls ($P<0.001$). The surviving area of the HBOT group was approximately twice that of the control group. Even when the start of HBOT was delayed for 24 hours after surgery, there was still a significantly greater survival area of HBOT treated flaps when compared with controls ($P<0.01$). However, the increase in surviving area was greater if the HBOT was begun immediately after surgery. This emphasizes the importance of initiating HBOT as soon as a flap problem is suspected.

Tan et al.[29] studied the effect of HBOT and air under pressure on skin survival in acute neurovascular island flaps in rats. Skin flaps treated with hyperbaric 8% oxygen (equivalent to

room air at standard HBOT treatment pressure) exhibited no improvement in skin survival. Skin flaps treated with hyperbaric 100% oxygen exhibited significant increases in survival.

Similarly, Ramon et al.[30] studied the effects of HBOT in a rat transverse rectus abdominis myocutaneous (TRAM) pedicle flap skin paddles in comparison to a control group, a normobaric 100% oxygen group, and a hyperbaric air-equivalent mixture in prevention of TRAM flap necrosis. The areas of surviving skin paddles in the rat TRAM flaps treated with HBOT showed a significant improvement compared to the control group ($P<0.05$).

Nemiroff and colleagues, in controlled animal studies using random and axial flap models, have clearly shown that HBOT can significantly enhance flap survival (19-21, 31). Nemiroff's[31] study investigated the effects of pentoxifylline and HBOT on skin flaps in rats under four conditions. Pentoxifylline is a rheologic agent, which enhances capillary circulation by increasing the flexibility of red blood cells. Sixty animals were randomly divided into one of four groups; 1) a control group, 2) pentoxifylline, 3) HBOT-treated group, and 4) a pentoxifylline plus HBOT-treated group. Rats that were treated with HBOT received a total of 14, 2-hour treatments at 2.5 ATA in divided doses. Results indicated that the surviving length of flaps in the pentoxifylline or HBOT treated groups were significantly greater than those in the control group. However, animals treated with both pentoxifylline and HBOT had significantly greater flap survival than animals in any of the other three groups ($P<0.001$). This reflected a 30-39% improvement over pentoxifylline alone or HBOT alone treated animals and an 86% improvement over control animals.

Other experiments combining HBOT with other therapies in pedicle flap models have had positive results. Collins et al.[32] examined the effects of HBOT and nicotinamide on 7 x 7 cm inferior epigastric pedicle skin flaps in rats. The HBOT groups had a mean survival of 76.7% in comparison to the control group survival of 45.7%. However, the combination of HBOT and nicotinamide demonstrated a mean survival of 90.9% with a statistical significance of $P<0.01$.

Total venous occlusion can occur in axial flaps secondary to mechanical obstruction or in free flaps secondary to venous anastomotic thrombosis. Lozano et al.[33] evaluated the effect of HBOT and medicinal leeching on axial skin flaps subjected to total venous occlusion. Hyperbaric oxygen protocol consisted of 90-minute treatments, twice daily, with 100% oxygen at 2.5 ATA for four days. The leeching protocol consisted of placing medicinal leeches on the congested flaps for 15 minutes, once daily, for four days. Laser Doppler measurements of flap perfusion and the percentage of flap necrosis were evaluated. The flaps in the sham group demonstrated 99% survival, whereas the flaps in the venous occlusion-only group demonstrated 100% necrosis. The flaps in the occlusion with HBOT, the occlusion with leeching, and the occlusion with HBOT and leeching groups demonstrated 1, 25, and 67 percent survival, respectively. This study demonstrated that HBOT alone was not an effective treatment for skin flaps compromised by total venous occlusion. The combination of leeching and HBOT treatment of total venous occlusion resulted in a significant increase in flap survival above that found with leeching alone. Yucel and Bayramicli[34] investigated the effects of HBOT and heparin on the survival of the rat inferior epigastric venous flap. They concluded that the rat inferior epigastric venous flap may be an ischemic flap with capillary circulation through a single venous pedicle, but it needs HBOT to survive, especially during the acute period. Heparin

treatment, reducing the flap size and the presence of a vascular wound bed also improve survival rates.

In addition to total venous occlusion, compromised pedicle flaps may suffer from partial venous congestion or arterial insufficiency. Ulkur et al.[35] evaluated the effect of HBOT on pedicle flaps with arterial, venous, and combined arteriovenous insufficiency. Their findings indicated that HBOT increased the percentage of survival length and mean laser Doppler flows of axial pattern skin flaps with all types of vascular insufficiency. This effect, however, was greatest in the arterial insufficiency flaps.

Ischemia-reperfusion injury can be a significant cause of compromise for free flaps or pedicle flaps subjected to prolonged ischemia either intraoperatively or post-operatively. Several experimental studies have demonstrated the beneficial effects of HBOT in ischemia-reperfusion injury of both skin and muscle flaps. Zamboni et al.[36] examined the effect of HBOT administered during prolonged total ischemia and immediately following ischemia during reperfusion in axial pattern skin flaps in a rat model. The animals were divided into four experimental groups: 1) a control group exposed to 8 hr flap ischemia without HBOT, 2) group 1 treated with HBOT during the ischemia, 3) group 2 treated with HBOT following the ischemia, and 4) group 3 treated with HBOT during ischemia but with the flap contained in a metal-coated Mylar bag to prevent oxygen diffusion. Mean flap necrosis for controls was 28% while HBOT during ischemia or during reperfusion significantly reduced this necrosis to 9 and 12%, respectively ($P<0.01$). The percentage of necrosis for group 3, with any local effect of HBOT on the flap being blocked by the diffusion barrier was 5%. This was also significantly better than the controls ($P<0.0005$) but no different from the other two HBOT groups. Thus, HBOT significantly increased the percentage of axial pattern skin flap survival when administered during or immediately after total flap ischemia. This beneficial effect was opposite to the author's original hypothesis that HBOT would exacerbate reperfusion injury. In a follow-up study, the same skin flap model was used to show that HBOT increased microvascular blood flow during reperfusion compared to untreated ischemic controls.[37] Kaelin et al.[38] have shown that HBOT during reperfusion significantly improved the survival of free skin flaps following microvascular reattachment and ischemia times of up to 24 hours. The skin flap studies have been corroborated by skeletal muscle experiments which are more important from a clinical standpoint since muscle is more sensitive to ischemia and reperfusion injury. An observation of a skeletal muscle microcirculatory flap model of ischemia-reperfusion injury has given some insight into potential mechanisms for this beneficial response.[39] HBOT administered during and up to 1 hour following a 4 hour global ischemia significantly reduced neutrophil endothelial adherence in venules and also blocked the progressive arteriolar vasoconstriction associated with reperfusion injury. The fact that neutrophil endothelial adherence is dependent on CD18 function in this model provides indirect evidence that HBOT is affecting the neutrophil CD18 adhesion molecule.

More recently, Hong et al.[40] demonstrated the effects of HBOT on ischemia-reperfusion injury of a superior epigastric-based TRAM flap in a rat model. These studies demonstrated a significant increase in survival in the groups treated with HBOT ($P<0.05$) which was similar whether the HBOT was initiated before or after reperfusion. The results of this study suggest a

possible decreased expression of the adhesion molecule ICAM-1 on endothelial cells secondary to HBOT.

Focusing on the role of free oxygen radicals on ischemia-reperfusion injury, Tomur et al.[41] studied the effects of HBOT and/or an antioxidant vitamin combination (Vitamins E & C) in a rat epigastric island skin-flap model of ischemia-reperfusion injury. These authors demonstrated a significant increase in flap survival in the HBOT, the antioxidant, and the combined therapy groups ($P<0.05$) after eight hours of ischemia and subsequent reperfusion.

A beneficial effect of HBOT in situations of secondary flap ischemia has been demonstrated in experimental studies. Stevens et al., using a rat axial skin flap model, induced a primary ischemia of 6 hours followed by 2 hours of reperfusion and then a secondary ischemia time of 6, 10, and 14 hours.[42] The secondary ischemic time at which 50% of the flaps survived (D50) in both air and 100% oxygen groups was 6 hours. The secondary ischemic time to D50 in the HBOT group was significantly increased to 10 hours. In a separate experiment, Wong et al. used an axial skeletal muscle flap model in rats. Percent necrosis following a 2 hour primary ischemia was significantly reduced from 40% to 24% by HBOT.[43] Adding a secondary 2 hour ischemia time significantly increased necrosis in controls to 85% which was significantly reduced in the HBOT group to 58%. These studies have important implications in free tissue transfer complicated by postoperative thrombosis with the thrombosis effectively acting as a secondary ischemia.

Gampper et al.[44] studied the beneficial effect of HBOT on island flaps subjected to secondary venous ischemia in the rat superficial epigastric flap model. They concluded that HBOT significantly increased the survival of flaps subjected to a secondary ischemia, even if administered before primary ischemia. The effect of administering HBOT prior to secondary venous ischemia was marginal, which may be due to the effect of HBOT not lasting longer than 5 hours.

Clinical Studies

Perrins and colleagues[45-48] demonstrated the value of adjunctive HBOT in skin grafts. This was first shown in some case studies[45] and later in controlled clinical trials.[46] In the latter study, 48 patients were studied. In this prospective, randomized clinical study, half of the patients were treated with HBOT and half served as controls. Complete survival of grafts occurred in 64% of the treated group as opposed to only 17% of the controls ($P<0.01$). Results of this study suggested that whole-body exposure of HBOT significantly enhanced flap healing. Similar positive results in the clinical situation have been described by Moines-Chass and Hashmonai.[49] In general, these cases represented failures of other available methods, after which HBOT was undertaken. Greenwood and Gilchrist[50] examined the effect of HBOT and wound healing in post-irradiated compromised wounds in laryngectomy patients. The authors conclude that healing was significantly improved by HBOT.

Other favorable case reports were noted by Barr et al.[51-52] Similarly, there have been several favorable case reports on the use of HBOT in compromised composite grafts consisting of skin, subcutaneous tissue, and cartilage for nasal reconstruction.[53-55] Bowersox et al.[56] reviewed

105 patients with ischemic skin flaps or grafts where 90% of the graft patients had risk factors that were considered to be poor prognostic indicators of graft or flap survival. They found that 89% of threatened flaps and 91% of threatened skin grafts were salvaged by HBOT. Thus, there was an average of approximately 10% failure rate. This observation compares favorably with other studies where failure rates with some complications can reach 67% in compromised tissues.[57]

HBOT also has been shown to improve the survival of ischemic skin flaps of the face as well as being an adjunct in periorbital reconstruction.[58] In another clinical study, the salvage of free flaps with secondary ischemia time was significantly enhanced by HBOT.[59] Necrosis of a free tissue transfer is a significant loss because the defect, which the free flap was used to close, is re-created along with the donor site morbidity. Free flaps compromised by prolonged primary or secondary ischemia in this study responded dramatically to HBOT with 100% viability, in most cases, if the time to the initiation of the treatment was less than 24 hours.

It can be noted that a variety of types of grafts and flaps have been investigated in animal and human studies. Zamboni provides a critical review of HBOT and its applications to different types of flaps in a previous book chapter.[60] More recently, Friedman et al.[61] has presented an evidence-based appraisal of the use of HBOT on compromised flaps and grafts. Results of the preponderance of work in the literature clearly show the efficacy of HBOT with respect to enhancement of skin graft and flap survival. Of importance is that different types of flaps have been analyzed in these studies including free skin grafts, pedicle flaps, random flaps, irradiated wounds and flaps, composite grafts, as well as free flaps. Although each flap problem is unique, a key factor to flap necrosis is tissue hypoxia. The results indicate that viability of flaps can be enhanced by HBOT through a reduction of the hypoxic insult. Other mechanisms of action whereby HBOT enhances flap survival include the enhancement of fibroblasts and collagen synthesis, creation of neovascularity,[31,62] the possibility of closing off arterio-venous shunts,[63-64] and the favorable effects on the microcirculation.[39]

Clinical Management

The hyperbaric oxygen treatments are given at a pressure of 2.0 – 2.5 atmospheres absolute (ATA) and range from 90 to 120 minutes (depending on the type of HBOT facility available, patient status, etc.). Mechanical causes of flap compromise that can be treated surgically should be addressed prior to initiation of HBOT. Initial treatment should be twice daily. Once the graft or flap appears more viable and stable, once-a-day treatments may suffice. To be maximally effective, HBOT should be started as soon as signs of flap compromise appear. Flap viability can be assessed by clinical judgment as well as by a variety of noninvasive and invasive techniques including transcutaneous oximetry and laser Doppler studies.

Utilization Review

Utilization review is required after 20 treatments when preparing a recipient site (such as a radiated tissue bed) for a flap or graft, and following 20 treatments after a flap or graft has been placed into its recipient site.

Cost Impact

Failed flaps are extremely expensive. Adjunctive HBOT can reduce these costs by salvaging free skin grafts, pedicle flaps, random flaps, irradiated wounds and flaps, composite grafts, as well as free flaps.

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