FROM THE $HBO_2$ INDICATIONS MANUAL, 14TH EDITION:

CHAPTER 5

# The effect of hyperbaric oxygen on compromised grafts and flaps

Shawna Kleban, MD; Richard C. Baynosa, MD

Department of Plastic and Reconstructive Surgery, UNLV School of Medicine, Las Vegas, Nevada U.S.

CORRESPONDING AUTHOR: Richard Baynosa – *richard.baynosa@unlv.edu*

## ABSTRACT

The use of grafts and flaps serves as an integral tool in the armamentarium of the reconstructive surgeon. Proper planning and surgical judgment are critical in the ultimate success of these procedures.

However, there are situations when grafts and/or flaps can become compromised and require urgent intervention for salvage. These instances can include irradiated or otherwise hypoxic wound beds, excessively large harvested grafts, random flap ischemia, venous or arterial insufficiency, and ischemia-reperfusion injury. Alternatively, compromised grafts and flaps can be inadvertently created secondary to trauma. It is in these types of cases, hyperbaric oxygen ($HBO_2$) therapy can serve as a useful adjunct in the salvage of compromised flaps and grafts.

This review outlines the extensive basic science and clinical evidence available in support of the use of $HBO_2$ therapy for compromised grafts and flaps. The literature demonstrates the benefit of adjunctive $HBO_2$ therapy for multiple types of grafts and flaps with various etiologies of compromise. $HBO_2$ therapy can enhance graft and flap survival by several methods including decreasing the hypoxic insult, enhancing fibroblast function and collagen synthesis, stimulating angiogenesis and inhibiting ischemia-reperfusion injury. The expedient initiation of hyperbaric oxygen therapy as soon as flap or graft compromise is identified maximizes tissue viability and ultimately graft/flap salvage. ∎

## RATIONALE

Hyperbaric oxygen ($HBO_2$) therapy 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, as in traumatic amputations and degloving injuries, $HBO_2$ therapy 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 who are likely to benefit from adjunctive hyperbaric oxygen for graft or flap compromise are 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 $HBO_2$ therapy. A number of studies have shown the efficacy of $HBO_2$ therapy on enhancement of flap and graft survival in a variety of experimental and clinical situations.

## PATIENT SELECTION CRITERIA

As hyperbaric oxygen therapy is indicated only 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 solution for the compromised graft is prevention. By ensuring an appropriate recipient bed for a given graft size, a compromised graft can be avoided altogether. 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. Traumatic avulsions of the soft tissues of the nose, ear and fingertips or poor surgical planning/judgment can lead to excessively large composite grafts. These compromised grafts become hypoxic and

KEYWORDS: compromised flaps; compromised grafts

may be salvaged with prompt institution of $HBO_2$ therapy. Hyperbaric oxygen can help maximize the viability of the compromised graft while revascularization takes place, thereby reducing the need for repeat 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/occlusion, to arterial occlusion – even after meticulous harvest and inset. Similarly, traumatic accidents can result in significant avulsion of soft tissues, extensive degloving injuries, and open fractures with poorly perfused skin flaps.

In addition, free tissue transfers, flaps 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 some instances there is no correctable mechanical cause of decreased flap perfusion. Moreover, in skin flaps created by trauma, the compromised perfusion is typically the result of crush injury or the development of exceptionally large random flaps that do not follow the classic 3:1 length-to-width ratio, resulting in poor perfusion to the distal flap. In these cases, $HBO_2$ therapy can play an important role in flap salvage. The key to successful salvage is the prompt institution of $HBO_2$ therapy, which can help maximize tissue viability while perfusion is restored. Similar to its use in compromised grafts, $HBO_2$ therapy can reduce the need for repeat flap procedures, thus 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. A recent review of these topics was conducted by Francis and Baynosa [1]. Here we provide a more in-depth review of the current literature.

## ANIMAL STUDIES

Although basic science and animal studies are classified by the Oxford Centre for Evidence-Based Medicine (CEBM) as Level 5 evidence and are no longer valued as highly as they once were, they still present one of the best scientific methods to maintain complete control of the experimental study population. The main benefit in examining these studies that evaluate the use of $HBO_2$ therapy for compromised flaps and grafts is not only the sheer volume of controlled experiments that have been conducted, but also the overwhelmingly positive results of $HBO_2$ therapy in these studies. A recent review of the cellular mechanisms of hyperbaric oxygen pathways and ischemia reperfusion injury provides a summary of the basic science to support the use of $HBO_2$ therapy in compromised flaps and grafts [2].

The role of $HBO_2$ therapy in compromised wound beds vs. non-compromised wound beds has been examined experimentally in animal models. Kivisaari and Niinikoski [3] showed that $HBO_2$ therapy in rats 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, $HBO_2$ therapy significantly enhanced wound closure rates over control groups.

Shulman and Krohn [4], in a study of full-thickness and partial-thickness wounds in rats, found that $HBO_2$ therapy shortened healing time significantly. Further, the combination of repeated skin grafting and $HBO_2$ therapy reduced the healing time of partial-thickness wounds to one-half 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 $HBO_2$ therapy.

There are a number of experimental studies describing the effect of $HBO_2$ therapy on compromised skin grafts and composite grafts. Erdmann et al. [5-6] evaluated the effect of $HBO_2$ therapy as treatment for skin allograft rejection. Using a mouse skin allograft rejection model, these authors demonstrated that treatment with $HBO_2$ therapy alone [5] or in combination with cyclosporine [6] lengthened the time to allograft rejection. This effect was more profound in animals receiving more frequent $HBO_2$ therapy compared to animals receiving less frequent $HBO_2$ therapy.

Renner et al. [7] investigated the efficacy of $HBO_2$ therapy in improving survival of reattached auricular composite grafts. A prospective randomized double-blind study used 20 New Zealand albino rabbits randomized to a treatment or control group. Their study was a continuation of a pilot study suggesting some enhancement of composite graft survival with the use of $HBO_2$ therapy in the rabbit ear. Both experiments have demonstrated a slight survival benefit using $HBO_2$ therapy in auricular composite grafts in the rabbit model.

Rubin et al. [8] 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 $HBO_2$ therapy-treated animals demonstrated significantly greater survival than grafts in control animals. Similarly, Zhang et al. [9] examined the effects of $HBO_2$ therapy on composite skin grafts in the rabbit ear model. Experimental animals received $HBO_2$ therapy at 2 ATA daily for five days and demonstrated a significantly increased survival area compared to the control group, 82% versus 26.5%.

Li et al. [10] investigated the efficacy of $HBO_2$ therapy 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 $HBO_2$ therapy for 90 minutes at 2.4 ATA for five days. Three weeks post-operatively, the 2.0-cm composite grafts treated with $HBO_2$ therapy 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 $HBO_2$ therapy for the larger-size composite grafts, which could be considered compromised and hypoxic.

More recently, Fodor et al. [11] looked at the effect of $HBO_2$ therapy on the survival of relatively large 3.0 *x* 3.0cm composite grafts including skin, subcutaneous tissue and fascia harvested from the upper back of rats. The experimental group was treated with $HBO_2$ therapy for 90 minutes at 2.0 ATA daily for two weeks. After this time, they examined both the internal and external surfaces of the grafts, comparing the experimental group and controls. After two weeks of $HBO_2$ therapy, the internal surface of the experimental composite grafts had a mean survival rate of 62% compared to 41% survival rate in controls ($p=0.001$). The external surface of the $HBO_2$ therapy-treated grafts had a 31% survival rate compared to 25% survival in the control group, but this was not statistically significant. Although complete survival was not achieved, this study suggests that composite grafts that are harvested or traumatically created and much larger than the classically recommended size of 1.5cm can benefit from $HBO_2$ therapy, even if only to preserve the deep layer as a suitable bed for subsequent skin grafting.

Several early studies have demonstrated the benefits of $HBO_2$ therapy on experimental skin flaps [12-14]. The effects of $HBO_2$ therapy on compromised and ischemic random flaps have been studied experimentally as well. Niinikoski [15] found a 51% improvement in the length of the viable portion of tubed random skin flaps in rats treated with HBO2 therapy (2.5 ATA for two hours twice daily for two 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. [16] showed that in skin flaps in rats, $HBO_2$ therapy at 3 ATA raised mean tissue oxygen tensions to 600 mmHg, whereas 100% oxygen at sea level did not raise mean flap oxygen tension.

Pellitteri et al. [17] demonstrated the effect of $HBO_2$ therapy 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 $HBO_2$ therapy for 90 minutes 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 [18], 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 $HBO_2$ therapy had a significant improvement in flap survival over untreated controls ($p<0.05$). Other flap-enhancing agents were studied, and in some cases these agents enhanced flap survival. However, the best results were found in rats treated with $HBO_2$ therapy.

Similarly, Esclamado et al. [19] studied the effect of $HBO_2$ therapy 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, $HBO_2$ therapy only, and combined steroids plus $HBO_2$ therapy. $HBO_2$ therapy 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 $HBO_2$ therapy-only group, which showed a 36% improvement compared to controls.

Stewart et al. [20] demonstrated the positive effect of $HBO_2$ therapy in combination with free-radical scavengers in increased random skin flap survival. $HBO_2$ therapy 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 significantly greater flap survival ($p<0.05$) compared to controls.

Conversely, da Rocha et al. [21-22] suggested that the addition of the antioxidant N-acetylcysteine (NAC), a precursor to the potent free radical scavenger glutathione,

to $HBO_2$ therapy does not improve flap survival above $HBO_2$ therapy alone. Dorsal random skin flaps in rats were divided into four groups including sham, NAC, $HBO_2$ therapy, and $HBO_2$ therapy plus NAC. The group treated with $HBO_2$ therapy demonstrated significantly increased survival and decreased molecular markers for apoptosis in comparison to the NAC group and sham. However, the combination of $HBO_2$ plus NAC did not significantly improve on the results of the NAC group alone and the best results were seen in the $HBO_2$ therapy-only group.

Greenwood and Gilchrist [23] demonstrated the effectiveness of $HBO_2$ therapy 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 versus the $HBO_2$ therapy group.

A controlled, randomized study on the effects of $HBO_2$ therapy and irradiation on experimental random skin flaps has been performed by Nemiroff et al. [24-25]. One hundred eighty-five rats were randomly assigned to one of 15 conditions, including possible sequencing effects of $HBO_2$ therapy, irradiation and flap creation, as well as controls that included flap creation only, irradiation only and $HBO_2$ therapy groups. Results showed that all groups receiving $HBO_2$ therapy 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.

Other studies have also looked at the benefit of $HBO_2$ therapy in improving survival of random pattern skin flaps complicated by other factors known to compromise wound healing. Zhang et al. [26] demonstrated the beneficial effects of $HBO_2$ therapy in improving dorsal random skin flap survival in diabetic rats. They demonstrated a significant ($p<0.01$) reduction in necrosis in the diabetic rats treated with $HBO_2$ therapy for 90 minutes at 2.5 ATA daily for seven days compared to the untreated diabetic rats (50.5% vs. 38.5%).

Selcuk et al. [27] revealed a positive effect of $HBO_2$ therapy on random dorsal skin flap survival in nicotine-treated rats. While the $HBO_2$ therapy group demonstrated significantly better survival than the control group (63.80% vs. 56.98%, $p=0.007$) and the control group had significantly better survival than the nicotine group (56.98% vs. 36.15%, $p<0.01$), there was no significant difference between the control group and the nicotine group treated with $HBO_2$ therapy (56.98% vs. 54.08%). Similarly, Demirtas et al. [28] used a degloving injury model in the tails of nicotine-treated rats to demonstrate that $HBO_2$ therapy treatment could not only significantly improve the survival rate compared to controls and nicotine-treated rats, but also mitigate the detrimental effects in the nicotine-treated rats and increase survival rate to the level of controls. These studies suggest that HBO2 therapy may have a role in increasing random flap survival even in cases where there are multiple etiologies of flap compromise.

Further work by Nemiroff and Lungu [29] elucidated some of the mechanisms whereby $HBO_2$ therapy enhanced random flap survival. Skin flaps from animals treated with $HBO_2$ therapy versus 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 $HBO_2$ therapy groups when compared with that in controls ($p<0.01$). The mean surface area of vessels of the flap-$HBO_2$ therapy groups was also significantly greater than in controls in all but one group ($p<0.01$). The authors concluded that $HBO_2$ therapy significantly enhanced flap survival by increasing and/or maintaining the number – and possibly the size – of vessels within the microvasculature. The authors stated that to be most efficacious, $HBO_2$ therapy must be administered as soon as possible after surgery. Other investigators have shown that $HBO_2$ therapy can enhance healing and flap survival by promoting angiogenesis [30-33].

Manson and associates [30], in studies using histochemical staining with ATPase to visualize small blood vessels, demonstrated that capillaries grew distally almost three times further in pedicle flaps of pigs that were treated with $HBO_2$ therapy, compared with age-matched controls.

Further studies using pedicle flap models have also demonstrated a beneficial effect of $HBO_2$ therapy. Champion and colleagues [34], using a pedicle flap model in rabbits, were able to obtain 100% survival of $HBO_2$ therapy-treated flaps (2 ATA for two hours twice a day for five days), whereas all control flaps had significant areas of necrosis to greater than 40%. Similarly, work by McFarlane and Wermuth [35] concluded that $HBO_2$ therapy was of definite value in preventing necrosis in a pedicle flap in the rat and also had 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 $HBO_2$ therapy in preventing necrosis [35].

Using a cranially based pedicle flap in a rat Jurell and Kaijser [36] showed that rats treated with $HBO_2$ therapy had a significantly greater flap survival compared with controls ($p<0.001$). The surviving area of the $HBO_2$ therapy group was approximately twice that of the control group.

Even when the start of $HBO_2$ therapy was delayed for 24 hours after surgery, there was still a significantly greater survival area of $HBO_2$ therapy-treated flaps when compared with controls ($p<0.01$). However, the increase in surviving area was greater if the $HBO_2$ therapy was begun immediately after surgery. This emphasizes the importance of initiating $HBO_2$ therapy as soon as a flap problem is suspected.

Tan et al. [37] studied the effect of $HBO_2$ therapy 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 $HBO_2$ therapy treatment pressure) exhibited no improvement in skin survival. Skin flaps treated with 100% hyperbaric oxygen exhibited significant increases in survival.

Similarly, Ramon et al. [38] studied the effects of $HBO_2$ therapy 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 $HBO_2$ therapy showed a significant improvement compared to the control group ($p<0.05$).

Prada et al. [39] compared the effect of allopurinol, superoxide-dismutase, and 100% therapy on axial pattern skin flap survival after eight hours of warm ischemia. All treatments demonstrated significantly improved survival compared to controls, with mean survival percentages of 63.53%, 83.03% and 55.98% respectively for allopurinol, superoxide-dismutase and 100% therapy (2.8 ATA for 45 minutes every 12 hours for three days). Unfortunately, this study did not examine the potential benefit of combination therapy using these beneficial interventions.

Nemiroff and colleagues, in controlled animal studies using random and axial flap models, have clearly shown that $HBO_2$ therapy can significantly enhance flap survival [24-25,40]. Nemiroff's [40] study investigated the effects of pentoxifylline and $HBO_2$ therapy on skin flaps in rats under four conditions. Pentoxifylline is a rheologic agent that 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. $HBO_2$ therapy-treated group
4. a pentoxifylline plus $HBO_2$ therapy-treated group

Rats that were treated with $HBO_2$ therapy received a total of 14 two-hour treatments at 2.5 ATA in divided doses. Results indicated that the surviving length of flaps in the pentoxifylline or $HBO_2$ therapy-treated groups were significantly greater than those in the control group. However, animals treated with both pentoxifylline and $HBO_2$ therapy had significantly greater flap survival than animals in any of the other three groups ($p<0.001$). This reflected a 30-39% improvement over animals treated with pentoxifylline alone or $HBO_2$ therapy alone and an 86% improvement over control animals.

Other experiments combining $HBO_2$ therapy with other therapies in pedicle flap models have had positive results. Collins et al. [41] examined the effects of $HBO_2$ therapy and nicotinamide on 7 *x* 7cm inferior epigastric pedicle skin flaps in rats. The $HBO_2$ therapy groups had a mean survival of 76.7% in comparison to the control group survival of 45.7%. However, the combination of $HBO_2$ therapy 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. [42] evaluated the effect of $HBO_2$ therapy 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 (elevation of the flap only) demonstrated 99% survival, whereas the flaps in the venous occlusion-only group demonstrated 100% necrosis. The flaps in the occlusion with $HBO_2$ therapy, the occlusion with leeching, and the occlusion with $HBO_2$ therapy and leeching groups demonstrated 1%, 25% and 67% survival, respectively. This study demonstrated that $HBO_2$ therapy alone was not an effective treatment for skin flaps compromised by total venous occlusion. The combination of leeching and $HBO_2$ therapy treatment of total venous occlusion resulted in a significant increase in flap survival above that found with leeching alone.

Yucel and Bayramicli [43] investigated the effects of $HBO_2$ therapy 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 $HBO_2$ therapy 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. [44] evaluated the effect of $HBO_2$ therapy on pedicle flaps with arterial, venous and combined arteriovenous insufficiency. Their findings indicated that $HBO_2$ therapy 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 postoperatively. Several experimental studies have demonstrated the beneficial effects of $HBO_2$ therapy in ischemia-reperfusion injury of both skin and muscle flaps. Zamboni et al. [45] examined the effect of $HBO_2$ therapy administered during prolonged total ischemia and immediately followingischemia during reperfusion in axial pattern skin flaps in a rat model. The animals were divided into four experimental groups:

1. **Control Group:** exposed to eight-hour flap ischemia without $HBO_2$ therapy.
2. **Group 1:** treated with $HBO_2$ therapy during the ischemia.
3. **Group 2:** treated with $HBO_2$ therapy following the ischemia.
4. **Group 3:** treated with $HBO_2$ therapy 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 $HBO_2$ therapy 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 $HBO_2$ therapy 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 $HBO_2$ therapy groups. Thus, $HBO_2$ therapy 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 $HBO_2$ therapy would exacerbate reperfusion injury. In a follow-up study, the same skin flap model was used to show that $HBO_2$ therapy increased microvascular blood flow during reperfusion compared to untreated ischemic controls [46]. Kaelin et al. [47] have shown that $HBO_2$ therapy 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 [48]. $HBO_2$ therapy administered during and up to one hour following a four-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 $HBO_2$ therapy is affecting the neutrophil CD18 adhesion molecule. Subsequent studies by Jones et al. [49] have suggested that effects of $HBO_2$ therapy on CD18 neutrophil adherence are dependent on nitric oxide via a nitric oxide synthase (NOS) pathway. More recently, Baynosa et al. [50] have used this skeletal muscle model of ischemia-reperfusion injury to demonstrate that the benefits of $HBO_2$ therapy may result from an early increase in NOS activity followed by a delayed increase in NOS expression. In addition, the effects of $HBO_2$ therapy on CD18 polarization and neutrophil adhesion were found to be mediated by a vascular endothelial growth factor (VEGF) pathway involving the extracellular matrix plasminogen system [51].

Hong et al. [52] demonstrated the effects of $HBO_2$ therapy 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 $HBO_2$ therapy ($p<0.05$), which was similar whether the $HBO_2$ therapy 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 $HBO_2$ therapy.

Focusing on the role of free oxygen radicals on ischemia-reperfusion injury, Tomur et al. [53] studied the effects of $HBO_2$ therapy and/or an antioxidant vitamin combination (Vitamins E and C) in a rat epigastric island skin-flap model of ischemia-reperfusion injury. These authors demonstrated a significant increase in flap survival in the $HBO_2$ therapy, the antioxidant, and the combined therapy groups ($p<0.05$) after eight hours of ischemia and subsequent reperfusion.

A beneficial effect of $HBO_2$ therapy in situations of secondary flap ischemia has been demonstrated in

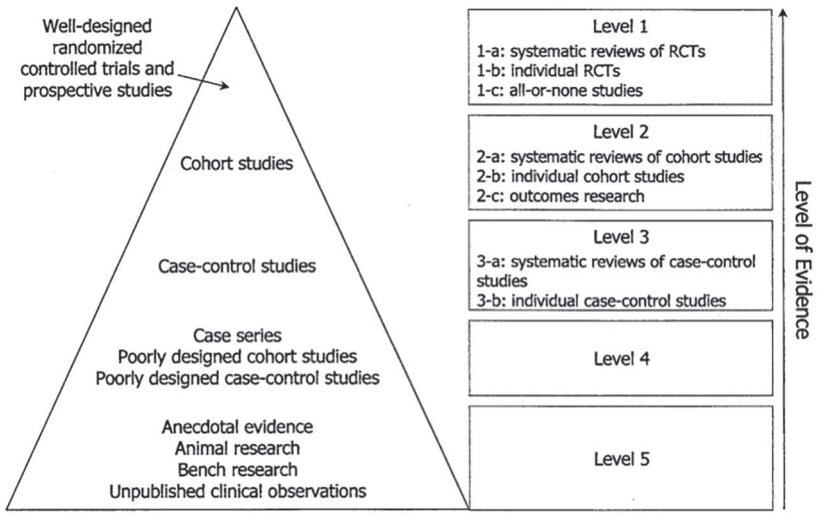



**FIGURE 1. The Levels of Clinical Evidence Based on Study Design**
*Adapted from the Oxford Centre for Evidence-Based Medicine (CEBM)*

experimental studies. Using a rat axial skin flap model Stevens et al. induced a primary ischemia of six hours followed by two hours of reperfusion and then a secondary ischemia time of six, 10 and 14 hours [54]. The secondary ischemic time at which 50% of the flaps survived (D50) in both air and 100% oxygen groups was six hours. The secondary ischemic time to D50 in the using a rat axial skin flap model, 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 two-hour primary ischemia was significantly reduced from 40% to 24% by $HBO_2$ therapy [ 55]. Adding a secondary two-hour ischemia time significantly increased necrosis in controls to 85%, which was significantly reduced in the $HBO_2$ therapy 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. [56] studied the beneficial effect of $HBO_2$ therapy on island flaps subjected to secondary venous ischemia in the rat superficial epigastric flap model. They concluded that $HBO_2$ therapy significantly increased the survival of flaps subjected to a secondary ischemia, even if administered before primary ischemia. The effect of administering $HBO_2$ therapy prior to secondary venous ischemia was marginal, which may be due to the effect of $HBO_2$ therapy not lasting longer than five hours.

## CLINICAL STUDIES

With the current emphasis on evidence-based medicine and practice, the clinical data available in the literature plays a tremendous role in the decision to recommend or institute a treatment. The levels of evidence according to the Oxford CEBM are outlined in Figure 1. A review of the literature examining the clinical evidence available for the use of $HBO_2$ therapy for compromised flaps and/or grafts reveals no less than 23 studies involving over 2,200 different flaps or grafts, with the available clinical evidence ranging from Level 1- to Level 4-type studies.

Perrins and colleagues were among the first clinicians to examine the benefit of $HBO_2$ therapy in compromised flaps and grafts. Their initial work [57] was first published in 1966 and demonstrated preliminary results of the value of $HBO_2$ therapy in ischemic skin flaps. Later, this group demonstrated the value of adjunctive $HBO_2$ therapy for compromised skin grafts in a controlled clinical study. In this blinded prospective, randomized controlled trial [58] involving 48 patients, half of the patients were treated with $HBO_2$ therapy and half served as controls. Experimental patients received $HBO_2$ therapy at 2.0 ATA for 120 minutes twice a day for three days. Complete graft take was defined as >95% total surface area survival. A significant 29% improvement in graft survival was seen in the $HBO_2$ therapy group compared to controls. Complete survival of grafts occurred in 64% of

the treated group as opposed to only 17% of the controls ($p<0.01$). 100% of the HBO2 therapy patients achieved >60% graft survival while only 64% of controls achieved at least 60% graft survival. Although the etiology of graft compromise in this study is not defined, the patients clearly manifest an etiology for graft compromise given the low success rates in the control population. Results of this study suggested that whole-body exposure of $HBO_2$ therapy significantly enhanced compromised graft healing. This remains the single Level I prospective, randomized controlled trial evaluating the use of $HBO_2$ therapy for compromised grafts to date.

Level II evidence is available in a study published by Roje et al. [59] in 2008. This retrospective, controlled cohort study evaluated the effect of adjunctive $HBO_2$ therapy on short-term complications for war injury reconstructions. They studied a total of 388 patients, with 289 patients in the control group and 99 patients in the $HBO_2$ therapy group. The $HBO_2$ group received treatments ranging from 2.2-2.8 ATA, with the frequency and number of sessions based on the clinical scenario. Outcome measures for this study included skin graft lyses and flap necrosis as well as soft tissue infection and osteomyelitis. The study revealed a significantly higher incidence of skin graft lyses in the control group (52%) compared to the $HBO_2$ therapy group (23%) ($p<0.001$). Similarly, flap necrosis was also significantly higher in the control group (51%) compared to the $HBO_2$ therapy group (15%) ($p<0.001$).

In order to determine if the beneficial effects seen in this study were related to injury severity, the authors scrutinized their data and further stratified the patients into four subgroups based on severity, with Group I patients having the most severe and complex injuries and Group IV patients having the least severe injuries. Compromising factors for injuries in Group IV included ischemia, compartment syndrome, complex soft tissue injury or open fracture while Group I injuries were further complicated by blood vessel injury, nerve injury, crush syndrome, and guillotine amputation of an extremity. Groups II and III injuries were further characterized by initial soft tissue infection, with Group II injuries having a neurovascular injury present while Group III injuries did not. This further substratification of the patients based on injury severity continued to demonstrate a statistically significant beneficial effect of $HBO_2$ therapy across each of the injury groups, which held true in the preservation and salvage of both compromised grafts and flaps.

Other favorable case series have been reported in the literature involving both compromised flaps and grafts. Gonnering et al. [60] used adjunctive $HBO_2$ therapy (2.0 ATA for 120 minutes twice a day for five days) in six patients undergoing periorbital reconstruction. This study demonstrated complete survival of two ischemic random flaps and four composite grafts ranging in size from 1.7-2.2cm. Similarly, Bowersox et al. [61] demonstrated a benefit to adjunctive $HBO_2$ therapy in their series of 105 patients with compromised grafts or ischemic skin flaps where 90% of patients had risk factors considered to be poor prognostic indicators of flap/graft survival. Adjunctive $HBO_2$ therapy was performed at 2.0 ATA for 90 minutes twice a day for five to seven days followed by 120 minutes daily once sustained clinical improvement was noted. Patients received an average of 16 + 4 treatments overall. Eighty-nine percent of compromised flaps and 91% of threatened skin grafts were salvaged using this protocol. Failed flaps and grafts were associated with two or more risk factors for poor wound healing. In addition, compromised flap failure was associated with a delay in the initiation of $HBO_2$ therapy of more than two weeks (19.8 days post-op for failed flaps vs. 4.6 days post-op for salvaged flaps, $p<0.01$).

Several other case series [62-65] have suggested a benefit of $HBO_2$ therapy for compromised grafts. These studies involved both skin grafts as well as composite grafts used in a wide variety of reconstructive scenarios including nasal reconstructions, chronic non-healing leg ulcers and periorbital reconstruction. Likewise, there have been several case series [66-68] that have demonstrated the benefit of $HBO_2$ therapy in the treatment and salvage of compromised flaps. Ueda et al. [66] studied 26 compromised flaps (23 axial and three random flaps) treated with $HBO_2$ therapy and noted an average improvement of 92.1%. Mathieu et al. [67] examined the use of $HBO_2$ therapy in 15 pedicle flaps where seven flaps survived and eight flaps failed. They noted a positive correlation between transcutaneous $PO_2$ (TCOM) readings and defined a value of 50mmHg at pressure as the critical cutoff for success when deciding whether to treat with $HBO_2$ therapy for compromised flaps. Waterhouse et al. [68] studied the value of $HBO_2$ therapy in 14 free flaps and two replantations compromised by prolonged ischemia, a secondary ischemia, or radiation history. This study demonstrated that the benefit of $HBO_2$ therapy was related to the time to initiation of treatment, with 89% of patients (eight of nine) treated within 24 hours having complete salvage, with partial necrosis (< 25%) occurring in one patient.

Of those treated between one to three days post-op, 25% (one of four) were salvaged, with the remaining three undergoing partial necrosis. All three patients treated after three days post-op resulted in complete loss. Necrosis of a free tissue transfer is a significant loss because the defect, which the free flap was used to close, is recreated along with the donor site morbidity. This study also underscored the rationale of initiating $HBO_2$ therapy as soon as signs of flap compromise appear, particularly in free flaps and replantations where the time to restoration of perfusion is even more critical, as the cutoff for salvage was much shorter in this study compared to the Bowersox et al. study evaluating skin flaps.

A more recent case series by Larson et al. [69] retrospectively reviewed 15 patients being treated with $HBO_2$ therapy for failing or threatened post-reconstructive flaps. Eleven of the 15 (73.3%) flaps survived, with four healing completely, and seven with substantial improvement. Average area of improvement was 68.3% of flap area. The authors noted that successful outcomes were associated with patient compliance with the treatment regimen and high pretreatment transcutaneous oxygen levels. Another case series from 2015 noted a 75.7% success rate when treating compromised free flaps with $HBO_2$ therapy for a median of 30 days [70].

There have been several favorable case reports [71-74] on the use of $HBO_2$ therapy in compromised composite grafts consisting of skin, subcutaneous tissue, and cartilage for nasal reconstruction after traumatic injuries. In addition, there have been reported cases [75-76] of successful salvage of compromised flaps following trauma, including a compromised facial flap avulsion from a severe dog bite and a complete scalp degloving injury both treated with adjunctive $HBO_2$ therapy. Several case reports have demonstrated the successful salvage of compromised mastectomy skin flaps [77-79]. Most recently, a 2016 case report by Copeland-Halperin et al. [79] described a patient with a history of breast irradiation who suffered mastectomy skin flap ischemia after nipple-sparing mastectomies and immediate reconstruction with tissue expanders. The patient received 15 treatments of $HBO_2$ therapy which resulted in complete mastectomy flap salvage and completion of her reconstruction.

Zhou et al. [80] performed the largest review of randomized controlled studies on the use of $HBO_2$ therapy in flaps and grafts to date. Twenty years of data from China were reviewed, including cases of 957 $HBO_2$ therapy patients, with 583 control patients from a total of 23 clinical trials. A survival rate of 62.5-100% was reported for $HBO_2$ therapy patients compared to a 35.0-86.5% rate reported in controls. There was heterogeneity in treatment time and regimen, and most studies had small sample sizes.

## SUMMARY

It can be noted that a variety of types of grafts and flaps has been investigated in animal and human studies. Baynosa and Zamboni provide a critical review of $HBO_2$ therapy and its applications to different types of compromised flaps and grafts in a recent book chapter [ 81]. Friedman et al. [82] have also presented an evidence-based appraisal of the use of $HBO_2$ therapy on compromised flaps and grafts. Results of the preponderance of work in the literature clearly show the efficacy of $HBO_2$ therapy 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 $HBO_2$ therapy through a reduction of the hypoxic insult. Other mechanisms of action whereby $HBO_2$ therapy enhances flap survival include the enhancement of fibroblasts and collagen synthesis, creation of neovascularity [40,83], the possibility of closing off arteriovenous shunts [84-85], and the favorable effects on the microcirculation [48].

A summary of the available clinical evidence is provided in Figure 2. The prospective randomized controlled trial evaluating 48 patients with compromised grafts by Perrins et al. [58] provides the best Level I evidence. Level II evidence is provided by Roje et al. [59] in a retrospective, controlled cohort evaluating 388 patients with compromised grafts and flaps used in the reconstruction of traumatic extremity war injuries. A second Level II study by Zhou et al. [80] reviewed 23 randomized controlled and controlled trials on $HBO_2$ therapy in grafts and flaps, encompassing a total of 957 $HBO_2$ therapy patients and 583 controls. A total of 1,928 patients provide Level II evidence to support the use of $HBO_2$ therapy for compromised grafts and flaps. Level IV evidence is represented by 11 case series [60-70] encompassing 109 skin grafts, 53 composite grafts, and 139 flaps as well as nine case studies [71-79] involving four composite grafts and five flaps. Given this available data, the use of $HBO_2$ therapy for the salvage of compromised grafts and flaps should be considered as a Class IB intervention

**FIGURE 2. Summary of the available clinical evidence evaluating $HBO_2$ therapy for compromised grafts and flaps**

**SUMMARY OF THE EVIDENCE**

| | |
|---|---|
| Level I Evidence One Study – 48 patients | (Compromised grafts) |
| Level II Evidence Two Studies – 1,928 patients | (Compromised grafts and flaps) |
| Level IV Evidence | 11 Case Series – 109 skin grafts,<br>53 composite grafts, 139 flaps<br>9 Case Studies – 4 composite grafts, 5 flaps |

according to the American Heart Association (AHA) Evidence Based Guidelines, as it is both useful and effective based on evidence from a single, randomized trial and non-randomized studies with the potential benefit far outweighing the risks.

## CLINICAL MANAGEMENT

The hyperbaric oxygen treatments are given at a pressure of 2.0-2.5 ATA and range from 90 to 120 minutes (depending on the type of $HBO_2$ therapy facility available, patient status, and other factors). Mechanical causes of flap compromise that can be treated surgically should be addressed prior to initiation of $HBO_2$ therapy. Currently there is no consensus as to the optimal $HBO_2$ therapy treatment regimen for compromised flaps and grafts. Weber et al. [86] used the rat random flap model to compare the efficacy of daily to twice-daily (BID) $HBO_2$ therapy. Results of this study suggest no additional benefit when performing BID $HBO_2$ therapy. Should the compromised graft of flap fail, daily $HBO_2$ therapy treatments may be continued to prepare the compromised wound bed for a salvage graft or flap reconstruction.

To be maximally effective, $HBO_2$ therapy should be started as soon as signs of flap or graft compromise appear. Flap viability can be assessed by clinical judgment as well as by a variety of non-invasive and invasive techniques, including transcutaneous oximetry and laser Doppler studies. The diagnosis of graft/flap compromise and evaluation of the subsequent response to $HBO_2$ therapy treatment should be a multidisciplinary effort between the hyperbaric physician and plastic surgeon. Objective measures should be used to assess and monitor the compromised flap or graft whenever possible.

## 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, although the indication for $HBO_2$ therapy may be better classified by the underlying cause of wound healing compromise (i.e., soft tissue radionecrosis, osteoradionecrosis, chronic osteomyelitis, diabetic foot ulcer) unless treatments are continued immediately following compromised graft or flap failure. Utilization review should also be employed following 20 treatments after a flap or graft has been placed into its recipient site.

## COST IMPACT

Failed flaps are extremely expensive and result in significant morbidity and distress for both the patient and the surgeon. Adjunctive $HBO_2$ therapy can help reduce these financial, physical and mental costs by salvaging skin grafts, pedicle flaps, random flaps, composite grafts, as well as free flaps and thus eliminating or minimizing the need for secondary surgeries and alternate donor sites.

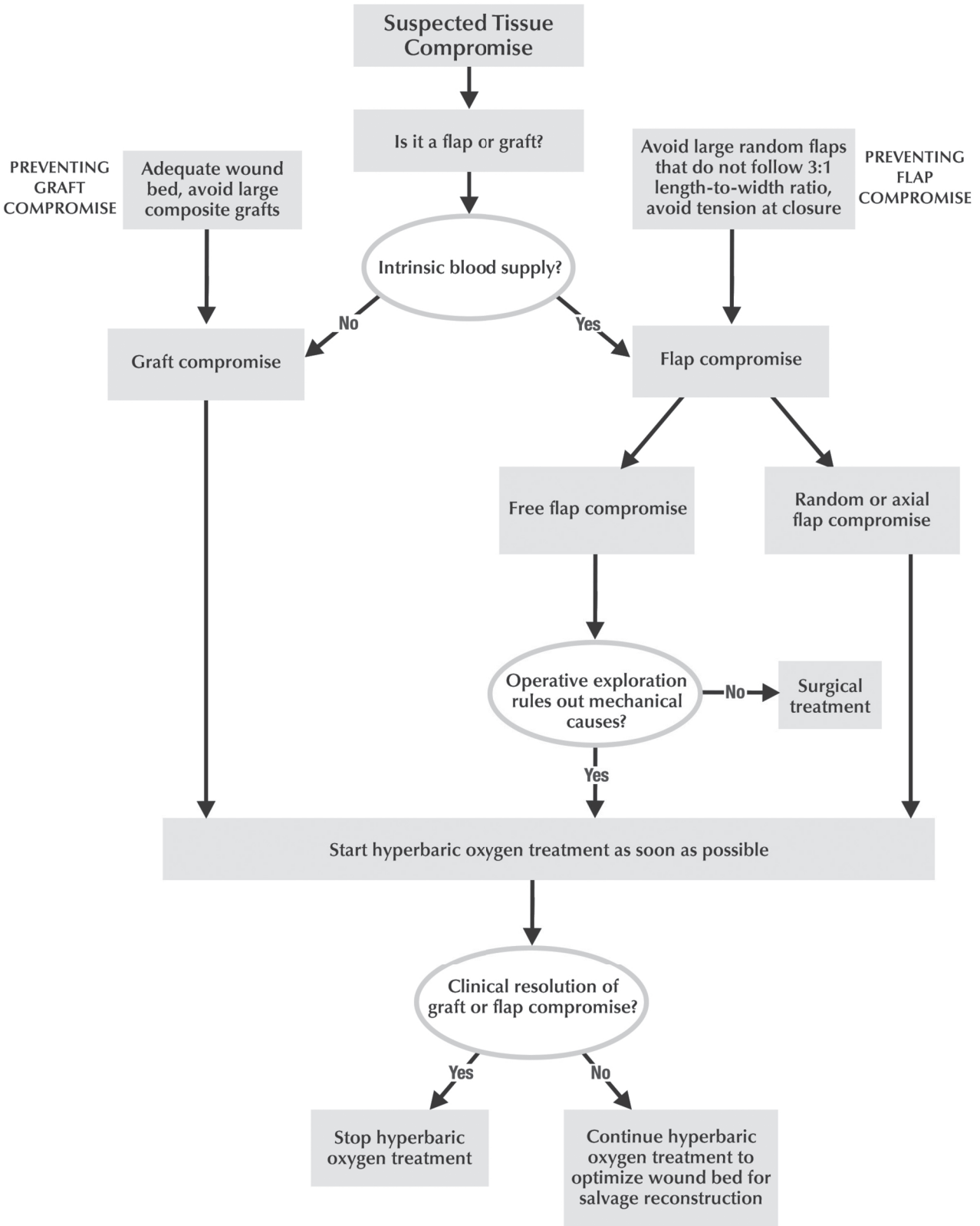
■

***Acknowledgment***

*William A. Zamboni MD, FACS, contributed to the earlier editions of this review.*

**FIGURE 3. Flowchart for compromised grafts and flaps**

*Details of management are described in the text.*



## REFERENCES


1. Francis A, Baynosa RC. Hyperbaric oxygen therapy for the compromised graft or flap. Adv Wound Care (New Rochelle). 2017 Jan 1;6(1):23-32.

2. Francis A, Baynosa RC. Ischaemia-reperfusion injury and hyperbaric oxygen pathways: a review of cellular mechanisms. Diving Hyperb Med. 2017 Jun;47(2):110-117.

3. Kivisaari J, Niinikoski J. Effects of hyperbaric oxygen and prolonged hypoxia on the healing of open wounds. Acta Chir Scand. 1975;141:14-19.

4. Shulman AG, Krohn HL. Influence of hyperbaric oxygen and multiple skin allografts on the healing of skin wounds. Surgery. 1967;62:1051-1058.

5. Erdmann D, Roth AC, Hussmann J, et al. Skin allograft rejection and hyperbaric oxygen treatment in immunohistocompatible mice. Undersea Hyperbaric Med. 1995;22: 395-399.

6. Erdmann D, Roth AC, Hussman J, et al. Hyperbaric oxygen and cyclosporine as a combined treatment regimen to prevent skin allograft rejection in immunohistocompatible mice. Ann Plast Surg. 1996;36:304-308.

7. Renner G, McClane SD, Early E, et al. Enhancement of auricular composite graft survival with hyperbaric oxygen therapy. Arch Facial Plast Surg. 2002;4:102-104.

8. Rubin JS, Marzella L, Myers RA, et al. Effects of hyperbaric oxygen on the take of composite skin grafts in rabbit ears. J Hyperbaric Med. 1988;3:79-88.

9. Zhang F, Cheng C, Gerlach T, et al. Effect of hyperbaric oxygen on survival of the composite ear graft in rats. Ann Plast Surg. 1998;41:530-534.

10. Li EN, Menon NG, Rodriguez ED, et al. The effect of hyperbaric oxygen therapy on composite graft survival. Ann Plast Surg. 2004; 53:141-145.

11. Fodor L, Ramon Y, Meilik B, et al. Effect of hyperbaric oxygen on survival of composite grafts in rats. Scand J Plast Reconstr Surg Hand Surg. 2006;40:257-260.

12. Kernahan KA, Zingg W, Kay CW. The effect of hyperbaric oxygen on the survival of experimental skin flaps. Plast Reconstr Surg. 1965;36:19-25.

13. McFarlane RM, DeYoung G, Henry RA. Prevention of necrosis in experimental pedicle flaps with hyperbaric oxygen. Surg Forum. 1965;6:481-482.

14. Wald HI, Georgiade NG, Angelillo J, et al. Effect of intensive hyperbaric oxygen therapy on the survival of experimental skin flaps in rats. Surg Forum. 1968;19:497-499.

15. Niinikoski J. Viability of ischemic skin in hyperbaric oxygen. Acta Chir Scand. 1970: 136: 567-568.

16. Gruber RP, Heitkamp DH, Lawrence JB. Skin permeability to oxygen and hyperbaric oxygen. Arch Surg. 1970;101:69-70.

17. Pellitteri PK, Kennedy TL, Youn BA. The influence of intensive hyperbaric oxygen therapy on skin flap survival in a swine model. Arch Otolaryngol Head Neck Surg. 1992;118:1050-1054.

18. Arturson GG, Khanna NN. The effects of hyperbaric oxygen, dimethyl sulfoxide and complamin on survival of experimental skin flaps. Scand J Plast Reconstr Surg. 1970;4:8-10.

19. Esclamado RM, Larrabee WF Jr, Zel GE. Efficacy of steroids and hyperbaric oxygen on survival of dorsal skin flapsin rats. Otolaryngol Head Neck Surg. 1990;102:41-44.

20. Stewart RJ, Moore T, Bennett B, et al. Effect of free-radical scavengers and hyperbaric oxygen on random-pattern skin flaps. Arch Surg. 1994;129:982-987.

21. Da Rocha FP, Fagundes DJ, Rivoire HC, et al. Immunohistochemical expression of apoptosis and VEGF expression on random skin flaps in rats treated with hyperbaric oxygen and N-acetylcysteine. Undersea Hyperbaric Med. 2011;38:167-174.

22. Da Rocha FP, Fagundes DJ, Pires JA, et al. Effects of hyperbaric oxygen and N-acetylcysteine in survival of random pattern skin flaps in rats. Indian J Plast Surg. 2012;45:453-458.

23. Greenwood TW, Gilchrist AG. The effect of HBO on wound healing following ionizing radiation. In: Trapp WC, et al., Eds. Proceedings of the fifth international congress on hyperbaric medicine, Vol I. Barnaby, Canada: Simon Fraser University. 1973;253-263.

24. Nemiroff PM, Merwin GE, Brant T, et al. HBO and irradiation on experimental skin flaps in rats. Surg Forum.1984;35:549-550.

25. Nemiroff PM, Merwin GE, Brant, et al. Effects of hyperbaric oxygen and irradiation on experimental flaps in rats.Otolaryngol Head Neck Surg. 1985;93: 485-491.

26. Zhang T, Gong W, Li Z, et al. Efficacy of hyperbaric oxygen on survival of random pattern skin flap in diabetic rats. Undersea Hyperbaric Med. 2007;335-339

27. Selcuk CT, Kuvat SV, Bozkurt M, et al. The effect of hyperbaric oxygen therapy on the survival of random pattern skin flaps in nicotine-treated rats. J Plast Reconstr Aesthet Surg. 2012; 65:489-493.

28. Demirtas A, Azbo I, Bulut M, et al. Effect of hyperbaric oxygen therapy on healing in an experimental model of degloving injury in tails of nicotine-treated rats. J Hand Surg Eur Vol. Epub ahead of print. 2012 Dec 7.

29. Nemiroff PM, Lungu AL. The influence of hyperbaric oxygen and irradiation on vascularity in skin flaps: a controlled study. Surg Forum. 1987;38:565-567.

30. Manson PN, Im MJ, Myers RA, et al. Improved capillaries by hyperbaric oxygen in skin flaps. Surg Forum. 1980;31: 564-566.

31. Hartwig J, Kohnlein HE. The influence of hyperbaric oxygen therapy and Dextran 40 on wound healing. Eur Surg Res. 5 (Suppl). 1973:109.

32. Meltzer T, Myers B. The effect of hyperbaric oxygen on the bursting strength and rate of vascularization of skin wounds in rats. Am Surg. 1986;52: 659-662.

33. Marx RE and Ames JR. The use of hyperbaric oxygen therapy in bony reconstruction of the irradiated and tissue deficient patient. J Oral Maxillofac Surg. 1982;40: 412-420.

34. Champion WM, McSherry CK, Goulian D. Effect of hyperbaric oxygen on survival of pedicled skin flaps. J Surg Res. 1967; 7:583-586.

35. McFarlane RM, Wermuth RE. The use of hyperbaric oxygen to prevent necrosis in experimental pedicle flaps and composite skin grafts. Plast Reconstr Surg. 1966;37:422-430.

36. Jurell G, Kaijser L. The influence of varying pressure and duration of treatment with hyperbaric oxygen on the survival of skin flaps: an experimental study. Scand J Plast Reconstr Surg. 1973;7:25-28.

37. Tan CM, Im MJ, Myers RA, et al. Effect of hyperbaric oxygen and hyperbaric air on survival of island skin flaps. Plast Reconstr Surg. 1974;73:27-30.

38. Ramon Y, Abramovich A, Shupak A, et al. Effect of hyperbaric oxygen on a rat transverse rectus abdominis myocutaneous flap model. Plast Reconstr Surg. 1998:102;416-422.

39. Prada FS, Arrunategui G, Alves MC, et al. Effect of allopurinol, superoxide-dismutase, and hyperbaric oxygen on flap survival. Microsurg. 2002;22;352-360.

40. Nemiroff PM. Synergistic effects of pentoxifylline and hyperbaric oxygen on skin flaps. Arch Otolaryngol Head Neck Surg. 1988;114:977-981.

41. Collins TM, Caimi R, Lynch PR, et al. The effects of nicotinamide and hyperbaric oxygen on skin flap survival. Scand J Plast Reconstr Surg Hand Surg. 1991;25:5-7.

42. Lozano DD, Stephenson LL, Zamboni WA. Effect of hyperbaric oxygen and medicinal leeching on survival of axial skin flaps subjected to total venous occlusion. Plast Reconstr Surg. 1999;104:1029-1032.

43. Yucel A, Bayramicli. Effects of hyperbaric oxygen treatment and heparin on the survival of unipedicled venous flaps: an experimental study in rats. Ann Plast Surg. 2000;295-303.

44. Ulkur E, Yuksel F, Acikel C, et al. Effect of hyperbaric oxygen on pedicle flaps with compromised circulation. Microsurg. 2002; 22: 16-20.

45. Zamboni WA, Roth AC, Russell RC, et al. The effect of acute hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. J Reconstr Microsurg. 1989;5:343-347.

46. Zamboni WA, Roth AC, Russell RC, et al. The effect of hyperbaric oxygen on reperfusion of ischemic axial skin flaps: a laser Doppler analysis. Ann Plast Surg. 1992;28:339-341.

47. Kaelin CM, Im MJ, Myers RA, et al. The effects of hyperbaric oxygen on free flaps in rats. Arch Surg. 1990;125:607-609.

48. Zamboni WA, Roth AC, Russell RC, et al. Morphological analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effect of hyperbaric oxygen. Plast Reconstr Surg. 91. 1993;1110-1123.

49. Jones SR, Carpin KM, Woodward SM, et al. Hyperbaric oxygen inhibits ischemia-reperfusion-induced CD18 neutrophil polarization by a nitric oxide mechanism. Plast Reconstr Surg. 2010:126:403-411.

50. Baynosa RC, Naig AL, Murphy PS, et al. The effect of hyperbaric oxygen on nitric oxide synthase activity and expression in ischemia-reperfusion injury. J Surg Res. Epub ahead of print. 2013 Feb 1.

51. Francis A, Kleban SR, Stephenson LL, et al. Hyperbaric oxygen inhibits reperfusion-induced neutrophil polarization and Adhesion Via Plasmin-mediated VEGF release. Plast Reconstr Surg Glob Open. 2017 Sep 25;5(9):e1497.

52. Hong JP, Kwon H, Chung YK, et al. The effect of hyperbaric oxygen on ischemia-reperfusion injury: an experimental study in a rat musculocutaneous flap. Ann Plast Surg. 2003;51:478-487.

53. Tomur A, Etlik O, Gundogan NU. Hyperbaric oxygenation and antioxidant vitamin combination reduces ischemiareperfusion injury in a rat epigastric island skin-flap model. J Basic Clin Physiol Pharmacol. 2005;16: 275-285.

54. Stevens DM, Weiss DD, Koller WA, et al. Survival of normothermic microvascular flaps after prolonged secondary ischemia: Effects of hyperbaric oxygen. Otolaryngol Head Neck Surg. 115: 360-364, 1996.

55. Wong HP, Zamboni WA, Stephenson LL. Effect of hyperbaric oxygen on skeletal muscle necrosis following primary and secondary ischemia in a rat model. Surg Forum. 1996;47:705-707.

56. Gampper TJ, Zhang F, Mofakhami NF, et al. Beneficial effect of hyperbaric oxygen on island flaps subjected to secondary venous ischemia. Microsurg. 2002;22:49-52.

57. Perrins DJD. Hyperbaric oxygenation of skin flaps. Br J Plast Surg. 1966;19:110-112.

58. Perrins DJD, Cantab MB. Influence of hyperbaric oxygen on the survival of split skin grafts. Lancet. 1967;1: 868-871.

59. Roje Z, Roje Z, Eterovic D et al. Influence of adjuvant hyperbaric oxygen therapy on short-term complications during surgical reconstruction of upper and lower extremity war injuries: retrospective cohort study. Croat Med J. 2008;49:224-232.

60. Gonnering RS, Kindwall EP, Goldmann RW. Adjunct hyperbaric oxygen therapy in periorbital reconstruction. Arch Opthalmol. 1986;104: 439-443.

61. Bowersox JC, Strauss MB, Hart GB. Clinical experience with hyperbaric oxygen therapy in salvage of ischemic skin flaps and grafts. J Hyperbaric Med. 1986; 141-149.

62. Friedman HI, Stonerock C, Brill A. Composite earlobe grafts to reconstruct the lateral nasal ala and sill. Ann Plast Surg. 2003; 3:275-281.

63. Qing Y, Cen Y, Chen J, Ke S. Reconstruction of a large through-and-through defect of the nasal tip using a modified auricular composite graft. J Craniofac Surg. 2015;26:382-383.

64. Saber AA, Yahya KZ, Rao A, et al. A new approach in the management of chronic nonhealing leg ulcers. J Invest Surg. 2005;18: 321-323.

65. Assaad NN, Chong R, Tat LT, et al. Adjuvant hyperbaric oxygen therapy to support limbal conjunctival graft in the management of recurrent pterygium. Cornea. 2011;30:7-10.

66. Ueda M, Kaneda T, Takahashi H, et al. Hyperbaric oxygen therapy of ischemic skin flaps: clinical and experimental study. Proceedings of 9th International Symposium on Underwater Hyperbaric Physiology. Undersea & Hyperbaric Medical Society. 1987;823.

67. Mathieu D, Neviere R, Pellerin P, et al. Pedicle musculocutaneous flap transplantation: Prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. Plast Reconstr Surg. 1993;91: 329-334.

68. Waterhouse MA, Zamboni WA, Brown RE, et al. The use of HBO in compromised free tissue transfer and replantation, a clinical review. Undersea Hyperbaric Med.1993; 20(Suppl):64.

69. Larson JV, Steensma EA, Flikkema RM, Norman EM. The application of hyperbaric oxygen therapy in the management of compromised flaps. Undersea Hyperb Med. 2013;40:499-504.

70. Skeik N, Porten BR, Isaacson E, et al. Hyperbaric oxygen treatment outcome for different indications from a single center. Ann Vasc Surg 2015; 29:206-214.

71. Nichter LS, Morwood DT, Williams GS, et al. Expanding the limits of composite grafting: a case report of successful nose replantation assisted by hyperbaric oxygen therapy. Plast Reconstr Surg. 1991;87: 337-340.

72. Rapley JH, Lawrence WT, Witt PD. Composite grafting and hyperbaric oxygen therapy in pediatric nasal tip reconstruction after avulsive dog-bite injury. Ann Plast Surg. 2001;46: 434-438.

73. Cantarella G, Mazzola RF and Pagani D. The fate of an amputated nose after replantation. Am J Otolaryngol. 2005;26: 344-347.

74. Pou JD, Graham HD. Pediatric nasal tip amputation successfully treated with nonmicrovascular replantation and hyperbaric oxygen therapy. Ochsner J. 2017 Summer;17(2):204-207.

75. McCrary BF. Hyperbaric oxygen treatment for a failing facial flap. Postgrad Med J. 2007;83: e1-e3.

76. Khandelwal S, Wall J, Kaide C, et al. Case report: successful use of hyperbaric oxygen therapy for a complete scalp degloving injury. Undersea Hyperbaric Med. 2008;35: 441-445.

77. Mermans JF, Tuinder S, von Meyenfeldt MF, et al. Hyperbaric oxygen treatment for skin flap necrosis after a mastectomy: a case study. Undersea Hyperbaric Med. 2012;39:719-723.

78. Fredman R, Wise I, Friedman T, Heller L, Kami T. Skin-sparing mastectomy flap ischemia salvage using urgent hyperbaric chamber oxygen therapy: a case report. Undersea Hyperb Med 2014;41:145-147.

79. Copeland-Halperin LR, Bruce SR, Mesbahi AN. Hyperbaric oxygen following bilateral skin-sparing mastectomies: a case report. Plast Reconstr Surg Glob Open. 2016;4:e680.

80. Zhou YY, Liu W, Yang YJ, Lu GD. Use of hyperbaric oxygen on flaps and grafts in China: analysis of studies in the past 20 years. Undersea Hyperb Med. 2014;41:209-216.

81. Baynosa RC and Zamboni WA. Compromised grafts and flaps. In: TS Neuman & SR Thom, Eds. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia, PA: Saunders/Elsevier. 2008; 373-395.

82. Friedman HI, Fitzmaurice M, Lefaivre JF, et al. An evidence-based appraisal of the use of hyperbaric oxygen on flaps and grafts. Plast Reconstr Surg. 2006;117 (Suppl):175S-190S.

83. Nemiroff PM, Rybak LP. Applications of hyperbaric oxygen for the otolaryngologist-head and neck surgeon. Am J Otolaryngol. 1988;9:52-57.

84. Reinisch JF. Pathophysiology of skin flap circulation: The delay phenomenon. Plast Reconstr Surg. 1974;54:585-598.

85. Reinisch JF. The role of arteriovenous anastomosis in skin flaps. In: Grabb WC, Myers MBG, Eds. Skin Flaps. Boston, MA: Little Brown & Co. 1975;81-92.

86. Weber R, Silver A, Williams SJ, et al. Random flap survival with hyperbaric oxygen: daily versus twice-daily treatments. Undersea Hyperb Med. 2018 Mar-Apr;45(2):157-164.

✦