Defining the Role of Hyperbaric Oxygen Therapy as an Adjunct to Reconstructive Surgery

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KEYWORDS

• Hyperbaric oxygen • Reconstructive surgery • Crush injuries
• Compartment syndrome • Compromised flap • Reperfusion injury • Burn

KEY POINTS

- Hyperbaric oxygen therapy is a useful but underutilized adjunct to wound care and reconstructive surgery.
- Surgical and nonsurgical indications for hyperbaric oxygen therapy follow 2 general patterns of ischemia, which are the trichotomy of perfusion and ischemia-reperfusion.
- The final common pathway for surgical and nonsurgical hyperbaric oxygen therapy is leukocyte adhesion to endothelium and the subsequent lipid peroxidation, both of which are ameliorated by hyperbaric oxygen therapy.

It is an academic error, as well as a transgression of common decency, for any plastic surgeon to discuss this topic without first acknowledging the contributions of William A. Zamboni, MD, FACS. His contributions to this subject are extensive yet underappreciated. Despite this body of work, HBOT has been slow to be accepted by reconstructive and wound care surgeons alike.

There are some obvious barriers to this acceptance, such as limited access to hyperbaric chambers and staff, especially during off hours, when these conditions need emergent/urgent attention; lack of institutional enthusiasm, because these treatments consume valuable diagnosis-related group revenue; possible lack of insurance reimbursement based on local coverage determinants, when these treatments are extended to the outpatient period; and surgeon bias and the view that HBOT is a technology searching for a purpose.

This article addresses only the surgeon bias in hopes that achieving increased acceptance from the surgical community will create the momentum to overcome the other barriers.

Author note: No declarations or conflicts of interest.
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Surg Clin N Am 100 (2020) 777–785
https://doi.org/10.1016/j.suc.2020.04.003 **surgical.theclinics.com**

The article begins by reviewing conditions where there is uniform acceptance of the role of HBOT in their treatment and then demonstrates that these conditions have similar pathophysiologic derangements as conditions commonly encountered by the reconstructive and wound care surgeon. Each section concludes with a brief review of some of the experimental and clinical data showing the benefit of HBOT in the treatment of these conditions.

INDICATIONS

Universally Accepted Indications

Among the indications for hyperbaric oxygen therapy (HBOT), as determined by the Undersea and Hyperbaric Medical Society (UHMS),[1] the indications discussed seem universally accepted. This is in no way to imply a complete absence of controversy.

Carbon monoxide poisoning

Treatment of carbon monoxide poisoning traditionally has focused on reducing the hypoxic stress brought about by the elevated carboxyhemaglobin level. Carbon monoxide is known to cause cardiac injury, motor weakness, peripheral neuropathies, hearing loss, and Parkinson-like syndrome.[2] The negative sequalae that carbon monoxide poisoning shares with the reconstructive surgical indications are the adhesion of leukocytes to injured microvasculature and the resultant lipid peroxidation[2] (**Fig. 1**).

If there is a period of syncope or even a brief episode of hypotension during an episode of carbon monoxide poisoning, lipid peroxidation can be initiated. Carbon monoxide can enhance the rate of release of nitric oxide from both platelets and endothelial cells. The resultant nitric oxide–mediated changes are necessary for leukocyte adherence to cerebral microvasculature. Once the leukocytes are adherent to the endothelial cells, leukocyte activation occurs. This activation results in the release of reactive oxygen species (ROS) that convert xanthine dehydrogenase to xanthine oxidase, which is required for lipid peroxidation to ensue.[3] Thom and colleagues[3] note that the mechanism of cerebral injury associated with carbon monoxide poisoning is similar to postanoxic encephalopathy, which is a form of ischemic reperfusion injury.

HBOT has been shown to prevent brain oxidative injury in animals by inhibiting β2 integrin–mediated leukocyte adherence to endothelial cells[3,4] and that HBOT at 2.8 atmospheres absolute (ATAs) to 3 ATAs inhibits the function of β2 integrin in human polymorphonuclear cells.[3–5]

Decompression illness

One of the earliest recognized and most frequently touted uses for HBOT is in the treatment of decompression illness (DCI), or the bends. DCI describes a spectrum of injuries ranging from the purely cutaneous cutis marmorata to air gas emboli. The underlying mechanism for DCI is the formation of inert gas bubbles (typically nitrogen) in blood and tissues due to supersaturation of the gas,[6] which can occur with scuba diving or anytime an individual is breathing air at increased atmospheric pressures (eg, caisson disease) followed by rapid ascent to altitude.

Despite DCI being one of the first known uses for HBOT, the exact pathology in humans is not fully known. This is because study has been hampered by the lack of reproducible animal models.[7] The primary mechanism by which bubbles are thought to exert their deleterious effects is by mechanical occlusion of blood flow. HBOT improves the condition by simply decreasing bubble size by mechanical means combined with nitrogen washout. Divers with low bubble production, however, have been shown to develop symptoms of DCI, and divers with high bubble production

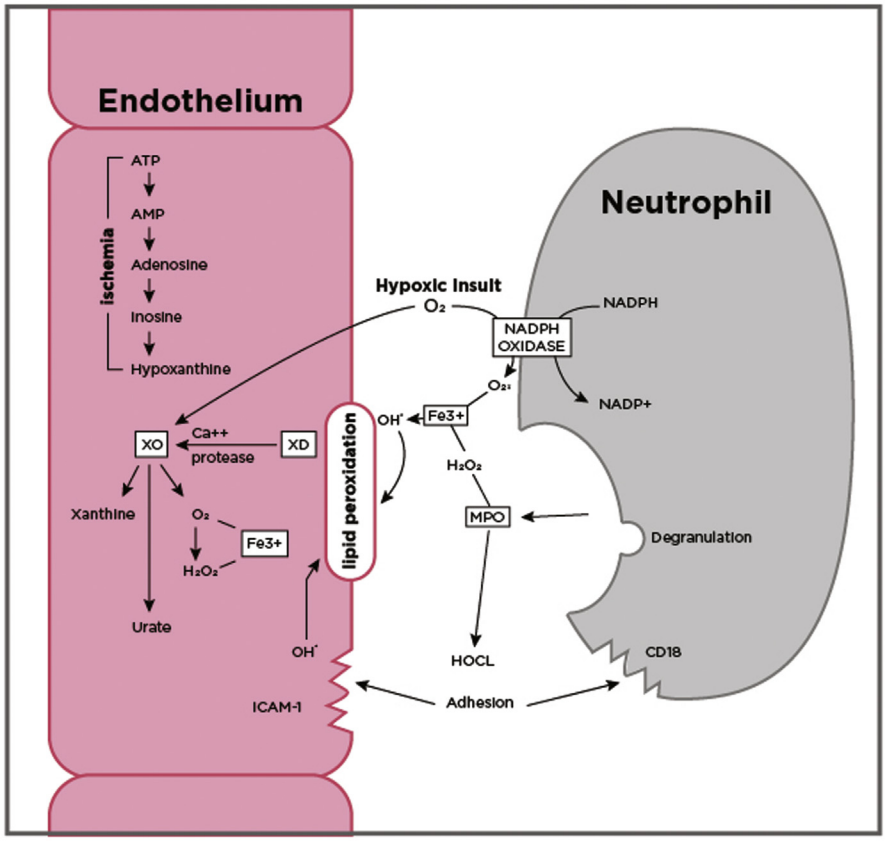

Fig. 1. Leukocyte adhesion to endothelium and the subsequent lipid peroxidation. AMP, adenosine monophosphate; HOCL, hypochlorous acid; MPO, myeloperoxidase; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, the reduced form of NADP; XD, xanthine dehydrogenase; XO, Xanthine Oxidase.

do not necessarily develope DCI.[8] Interestingly, bubbles have been shown to cause platelet activation[9] and to affect leukocyte-endothelial cell interaction.[10] Therefore, it is likely that the beneficial effects of HBOT extend beyond simple bubble mechanics.

Madden and colleagues[11] hypothesize that "gas bubbles are not the causative agent in progression of DCI, but rather an exacerbating factor." It has been demonstrated that β2 integrin–mediated leukocyte adhesion is associated with neurologic deterioration after decompression stress in rats and that prophylactic HBOT can improve outcomes.[12] Even so-called silent bubbles have been shown to impair endothelial-dependent vasoactive responses and to increase neutrophil infiltration.[13] Zamboni and colleagues[14] have demonstrated that HBOT produced sharp reduction in the adherence of leukocytes in the venules of postischemic muscle and that, by blocking leukocyte action, the no-reflow phenomenon may be abated.

Conditions Encountered by Reconstructive and Wound Care Surgeons

It often is said that the answer to almost every question in reconstructive surgery is blood flow. This can be translated more specifically to mean oxygen delivery. Many

of the problems encountered in reconstructive surgery, wound care, and medicine in general can be understood in terms of their specific aberration in oxygen delivery. The conditions that follow are those commonly encountered by reconstructive and wound care surgeons and are thought to benefit from the adjunctive use of HBOT. It is helpful to think of them as different manifestations of ischemia-reperfusion injury. Many of these conditions manifest the trichotomy of perfusion. That is to say that there will be an area with adequate perfusion, an area with no perfusion, and in-between these 2 areas a region of marginal perfusion. It is at this area of marginal perfusion, or penumbra, where HBOT exerts its greatest influence. Any injury state that has an element of ischemia-reperfusion or the trichotomy of perfusion (or both) likely will benefit from the timely administration of HBOT. The injury state that best exemplifies the ischemia-reperfusion model is crush injury/compartment syndrome, and the injury that best demonstrates the trichotomy of perfusion is burn.

Crush injury/compartment syndrome

At the cellular level, crush injury produces a vicious cycle of edema, hypoxia, and more edema. If this process occurs in an enclosed space, the microcirculation completely collapses and further contributes to the hypoxic insult until irreversible tissue damage has occurred. Eventually, a fasciotomy is required to restore blood flow. One way to arrest the progression of this process is to disrupt the vicious cycle early on with HBOT.[15] Once perfusion is temporarily interrupted, however, the endothelium becomes sensitized to the hypoxic insult, resulting in the activation of adhesion molecules, leading to the attachment of neutrophils to the endothelium and subsequent lipid peroxidation.[15] The deleterious cascade of events associated with ischemia-reperfusion injury from this point on resemble elements of carbon monoxide poisoning and DCI, as discussed previously, with ROS converting the dehydrogenase form to the oxidase form of xanthine oxidoreductase, which produces further ROS, which then stimulates neutrophil adhesion to endothelium, and which then produces more ROS.[16] In the normal physiologic state, there exist multiple free radical scavengers, such as superoxide dismutase, glutathione, and catalase. In ischemia-reperfusion injury, however, they are rapidly overwhelmed.[16]

HBOT has a unique, seemingly paradoxic, benefit in preventing compartment syndrome by reducing edema via vasoconstriction[17] while maintaining tissue oxygenation as a result of plasma hyperoxygenation.[18] Unfortunately, HBOT consultation rarely is obtained in the setting of impending compartment syndrome. Rather, if it is obtained, it is done after the compartment release, when threatened tissue loss is observed. HBOT potentially still is beneficial in this setting by mitigating the effects of ongoing ischemia-reperfusion injury by blocking the adhesion of neutrophils to the endothelium and stopping the release of ROS. Earlier use of HBOT, however, leads to a more significant reduction in tissue damage.[15]

Thermal burns

Classic teaching describes the burn wound as having 3 zones: a central zone of coagulation, surrounded by an area of stasis, which is surrounded by an area of erythema. At a tissue level, this represents an oxygen gradient. Most chronic wounds also have an oxygen gradient, and it has been shown that HBOT improves healing by increasing this gradient and stimulating neoangiogenesis.[19]

The zone of coagulation usually is not salvageable, and the zone of hyperemia almost always heals. So, any efforts to reduce the size of the burn and healing time typically focus on the zone of stasis (the penumbra); this is an attempt to prevent

the conversion of this burn from a partial-thickness burn to a full-thickness burn. These 3 zones represent the trichotomy of perfusion seen with most thermal burns.

One of the main factors affecting hypoxia in the zone of stasis is edema, and a decrease in edema has been shown to decrease burn conversion from partial thickness to full thickness.[20] Edema is most evident in the burned tissues but also develops in distant, unburned tissue. It has been demonstrated that this edema generation is from increased capillary permeability and is the result of more than just thermal injury. Changes have been demonstrated in the distant microvasculature, including red cell aggregation, white cell adhesion to venular walls, platelet microthrombi, and complement activation.[21,22] Also, failure of the sodium pump as a result of reduced intracellular adenosine triphosphate (ATP) is felt to be a major factor in the swelling of endothelial cells and the resultant edema.[21] Lastly, it has been demonstrated that there is an element of ischemia-reperfusion injury in the burn with activation of neutrophils, production of xanthine oxidase, release of ROS, and the resultant lipid peroxidation.[22] Ward and Till[22] speculate that the burn activates complement, which in turn activates neutrophils, causing them to adhere to the endothelium of the interstitial capillaries of the lung, leading to some of the pulmonary complications associated with burn injuries.

The effects on burn injury that are shared with the other indications for HBOT are the reduction of edema while increasing oxygenation via vasoconstriction and plasma hyperoxygenation, increasing intracellular ATP and decreasing endothelial cell swelling, and blocking neutrophil adhesion to endothelium, which blocks the release of ROS, thus preventing lipid peroxidation.

Cianci and colleagues[23] have demonstrated numerous beneficial effects of HBOT in the burn patient, which likely extend well beyond just treating the cutaneous injury. Their 2013 article leaves little room to debate the benefits of HBOT, yet most burn patients never see the inside of a hyperbaric chamber. This likely is because most burn units lack access to hyperbaric centers that are capable of diving a critically injured burn patient.

Compromised flaps

All flaps by their nature experience some degree of ischemic insult and this typically occurs at the time of transfer or transposition. Flaps are broadly placed into 1 of 2 categories. They are either a free flap, which has its blood supply divided and is transferred to a new, remote location using microsurgery, or are categorized as pedicled flaps, which are left attached to their blood supply and transposed to a nearby location. The ischemic insult experienced by free flaps is dominated by the ischemia-reperfusion model, whereas the pedicled flaps more clearly demonstrate the trichotomy of flow. Both have been shown to benefit from HBOT.

Zamboni and Baynosa[24] states that “HBOT is neither necessary nor recommended for the support of normal, uncompromised grafts or flaps. However, in tissue compromised by irradiation or in cases where there is decreased perfusion or hypoxia, HBOT has been shown to be extremely useful in flap salvage. Hyperbaric therapy can help maximize the viability of the compromised tissue thereby reducing the need for regrafting or repeat flap procedures.”

Using a skeletal muscle microcirculatory model of ischemia-reperfusion injury, Zamboni and colleagues[25] demonstrated that HBOT reduces neutrophil endothelial adherence in venules and suggests that HBOT is affecting the neutrophil CD18 adhesion molecule. In support of this, using a superior epigastric-based transverse rectus abdominis myocutaneous flap ischemia-reperfusion model in rats, Hong and

colleagues[26] demonstrated that HBOT decreases the expression of the adhesion molecule ICAM-1 on endothelial cells.

Clinical studies have shown improvement of ischemic flaps, especially if HBOT is initiated within 24 hours of the ischemic insult.[25,26] The key point is the recognition of the ischemic event before irreversible tissue damage has occurred. Intraoperative fluorescent angiography can demonstrate areas of poor perfusion and, in the author's experience, assuming mechanical causes have been excluded, then HBOT is

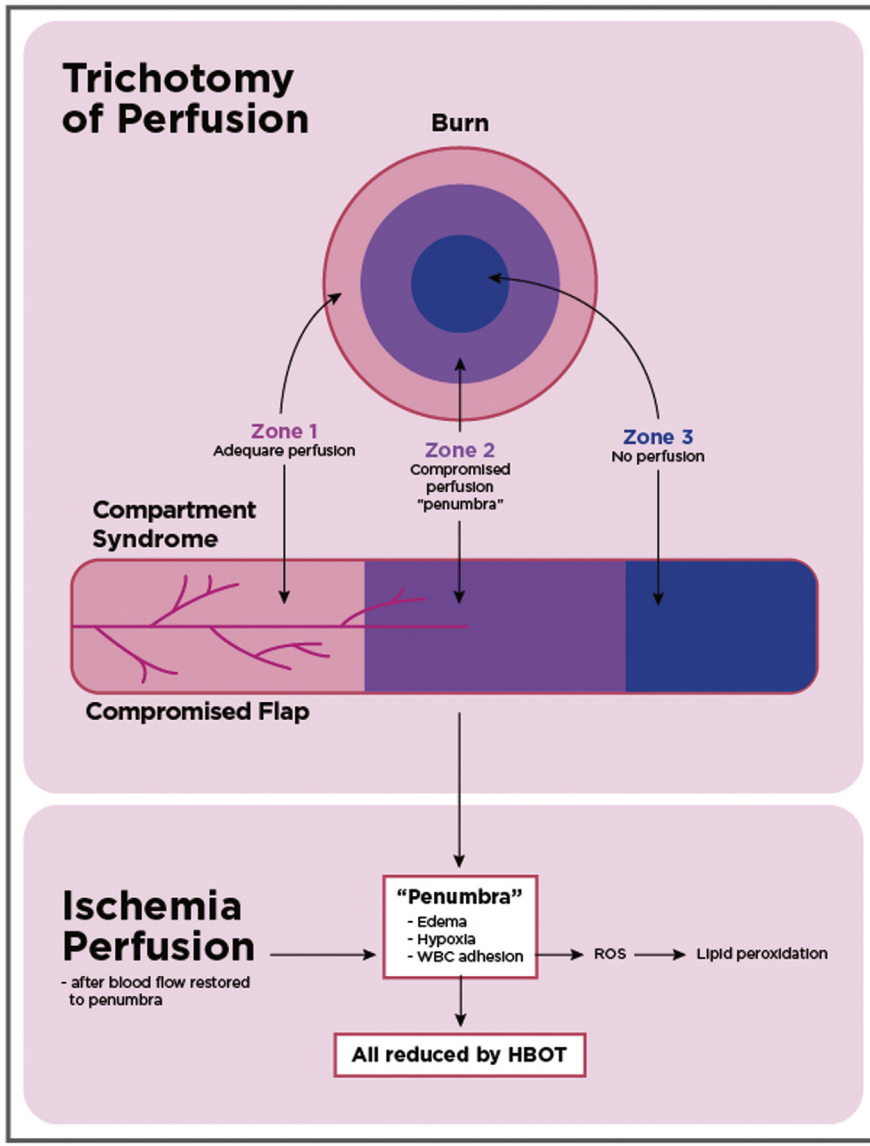

Fig. 2. The 2 patterns of ischemia. (*Top*) The trichotomy of perfusion. (*Bottom*) Ischemia-perfusion. WBC, white blood cell.

considered. Ideally, an intubated patient is taken directly from the operating room to the hyperbaric chamber for treatment. After the treatment, the patient would be taken to the intensive care unit for extubation and flap monitoring. At this time, logistical issues prevent this sequence from happening, so emphasis is made on the patient receiving the first treatment within 24 hours of surgery.

TREATMENT PROTOCOLS

Carbon Monoxide Poisoning

Two treatment protocols are listed by the UHMS. The first is the Weaver protocol, which consists of providing 3 ATAs of oxygen for 25 minutes, followed by a 5-minute air break, followed by another 3 ATAs of oxygen for 25 minutes, then a 5-minute air break, followed by chamber depressurization to 2 ATAs of oxygen for 30 minutes, 5-minute air break, 2 ATAs of oxygen for 30 minutes, and then depressurizing to barometric pressure.[2]

The Thom protocol is 2.8 ATAs of oxygen for 30 minutes, followed by 2 ATAs of oxygen for 90 minutes.[2] With either treatment protocol, patients should have electrocardiogram, serial troponins, and frequent neurologic examinations. Multiple treatments frequently are required, and cognitive and neurologic sequalae can occur weeks after the initial insult.

Decompression Illness

The treatment protocols for DCI are vast and vary depending on the inhaled gas and the depth/pressure at which the gas is inspired. The interested reader is referred to the US Navy and National Oceanic and Atmospheric Administration dive tables as well as current recommendations from the UHMS.

Crush Injuries and Compartment Syndromes

Strauss[15] recommends that HBOT be considered in patients with Gustilo types IIIB and IIIC fractures and in lesser Gustilo types in impaired hosts. The recommended treatment is 2 ATAs to 2.4 ATAs for 90 minutes for 2 treatments per day, or 120 minutes once a day.[15] HBOT is recommended after fasciotomy if significant residual problems remain. These include ischemic muscle, threatened flaps, residual neuropathy, massive edema, and ischemic time greater than 6 hours. HBOT protocols after fasciotomy are the same as for crush injuries.[15]

Thermal Burns

It is recommended that treatment with HBOT begin as early as possible, attempting 3 treatments within the first 24 hours and twice daily thereafter. This should be 100% oxygen at 2 ATAs to 2.4 ATAs for 90 minutes.[23]

Compromised Flaps

Current recommendations by the UHMS are to treat with HBOT at 2 ATAs to 2.5 ATAs for 90 minutes to 120 minutes. Initial treatments are given twice daily until the flap is stable; then the treatments can be reduced to daily.[24]

SUMMARY

This article is not intended to be an exhaustive defense for the use of hyperbaric oxygen as an adjunct to surgery. In truth, this has been done far better elsewhere by many of the investigators referenced in this article.[14,15,17,21,23–26,27,28] Instead, it is intended to provide a conceptual framework for the reconstructive and wound care

surgeon to better understand the role of HBOT in the treatment of their patients and hopefully stimulate the timely initiation of hyperbaric therapy so as to have the most favorable impact on patient outcomes. The 2 models used (trichotomy of perfusion and ischemia-reperfusion) also are manifest in conditions, such as traumatic brain injury, myocardial infarction, and stroke,[16] which begin as pure ischemic insults and manifest the trichotomy of perfusion and its associated penumbra. Once blood flow is restored, however, these conditions evolve to behave like ischemia-reperfusion injury. The role of HBOT for these conditions has yet to be elucidated, although some of these conditions are the subject of multicenter studies (**Fig. 2**).

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