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Hyperbaric Oxygen Therapy in the Treatment of Necrosis and Gangrene

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1. Introduction

Historically, hyperbaric oxygen therapy has been used for treatment of decompression sickness in deep-sea divers. Today, hyperbaric oxygen is commonly used for the treatment of wide variety of surgical and non-surgical conditions, and has persuasively proved its high clinical efficiency in many areas. Currently, established indications include different bacterial (mostly anaerobic) and fungal infections, arterial gas embolism, poorly healing diabetic wounds , osteomyelitis, radiation tissue injury, carbon monoxide poisoning, crush injuries, gangrene, brain abscesses, burns, skin grafts or skin flaps at risk of compromised tissue perfusion, severe anemia, and also conditions like long-standing neurologic deficit, cerebral palsy or autism, and many more. The existing trend of ever-expansion indications to previously untouched areas holds for decades.

The purpose of this review is to examine advantages and disadvantages of the hyperbaric oxygen therapy, and also to explore the underlying physiological mechanisms of the hyperbaric oxygen actions in the ischemic, necrotic and otherwise compromised tissues.

This review will mostly be focused on the discussion of clinical efficacy and practical approach to HBOT use in the treatment of different types of gangrene and necrotizing fasciitis. Role and place of hyperbaric oxygen therapy in the treatment of ischemic and diabetic chronic wounds and ulcers will also be explored.

With currently recommended clinically tested protocols and using contemporary equipment, administration of hyperbaric oxygen therapy is generally considered very safe. However, it is not absolutely innocuous, and certain contraindications, ranged from medical problems to physical abnormalities, while mostly relative, should be carefully considered in every case.

The only absolute contraindication for hyperbaric oxygen therapy is untreated tension pneumothorax. Other contraindications include:

1. Severe chronic obstructive pulmonary disease with carbon dioxide
2. retention, pulmonary blebs, and/or dyspnea with slight exertion; restrictive airway disease (possibility of air trapping with barotraumas ensued)
3. Optic neuritis
4. Acute viral infection
5. Congenital spherocytosis
6. Uncontrolled, acute seizures disorders
7. Upper respiratory tract infection
8. Uncontrolled high fever

9. Pregnancy (questionable)
10. Psychiatric problems
11. History of prior thoracic or ear surgery, which would make it impossible to equalize middle ear pressure or pulmonary pressure (Foster,1992)
12. Concomitant chemotherapy with cis-platinum and adriamycin. Cytotoxicity of these agents has been shown to be potentiated by hyperbaric oxygen (Leifer , 2001; Monstrey et al,1997)

Adverse effects of HBO treatment include reversible myopia (Leach et al, 1998), barotrauma of the ear, claustrophobia (only in small treatment chambers), seizures (1.3 per 10 000 patient treatments), and, very rare, pulmonary oxygen toxicity (Bakker, 1984).Vasoconstiction, that could be expected due to the increased oxygen levels, was not observed in ischaemic or hypoxic tissues (Sheffield, 1988). Worsening of diabetic retinopathy could theoretically occur during hyperbaric oxygen therapy, but up until now this complication has not been reported.

2. Hyperbaric oxygen: mechanisms of action

The principle effect of hyperbaric oxygen treatment is creating hyperoxia in blood and tissues. Hyperbaric oxygen therapy implies administration of 100% under pressure greater than atmospheric. By raising the ambient pressure of oxygen either in the chamber or by breathing 100% oxygen through tight fitting mask, it is possible to increase the inspired PO_2 up to 3.0 bar. The most commonly used levels of inspired oxygen range from 2.4 to 2.8 bar. At these levels, amount of dissolved oxygen in plasma could potentially meet oxygen consumption requirements of the whole body. Hemoglobin remains saturated even in the venous capillary blood (Ramaswami &Lo, 2000). At 3 atmospheres of pressure, which is commonly used in the modern hyperbaric oxygen treatment, the alveolar oxygen pressure is about 2,180 mm Hg, the arterial oxygen tension is at least 1,800 mmHg, and tissue oxygen concentration is approximately 500 mmHg. High tissue oxygen concentration remains elevated for variable period of time (likely up to a few hours) after removal from hyperbaric chamber, which depends on tissue density and perfusion. (Sheridan & Shank,1999).

It has been demonstrated, that inhalation of O2 at pressures greater than 1 ATA will increase production of reactive oxygen species, which is fundamental for physiological mechanisms of numerous effects and also therapeutic mechanisms. (Thom,2009). Reactive oxygen species, as well as reactive nitrogen species, play important roles as signaling molecules in transduction cascades, or pathways for a variety of growth factors, cytokines, and hormonal substances.

3. Hyperbaric oxygen for chronic diabetic wound and ulcer healing

Diabetes mellitus is increasing in incidence and currently presents one of the major health problems worldwide. The total number of diabetic patients has been projected to increase from 171 million in 2000 to 366 million in 2030 (Wild et al, 2004), with concomitant rise of the major complications rate, among which chronic non-healing leg diabetic wounds, associated with vascular insufficiency du e to accelerated atherosclerotic process, is within area of this review focus. With this trend, the requirements for efficient treatment are obviously expected to increase exponentially.

The most prevalent forms of chronic wounds in diabetic patients are leg and foot ulcerations.(Leung, 2007; Tam & Moschella ,1991). Typical chronic, non-healing ischemic

and diabetic wounds require prolonged time (more than 8 weeks) to heal, and sometimes do not heal or recur.

The pathophysiology of diabetic foot ulcer and its prolonged healing, however complex, has been extensively studied and is well described. Early development and accelerated progression of the lower extremity peripheral arterial atherosclerotic occlusive disease, with predilection to complete vascular blockade on the level distal to the knee, is a major causing factor. Other contributing factors include progressive development of sensory, vasomotor and autonomic neuropathy, alterations in autoregulation of dermal blood flow (Liu & Velazquez, 2008).It has been shown, that peripheral vascular disease (macroangiopathy), along with diabetic polyneuropathy, constitute the most important factors in the diabetic wound and ulcer development. About 20% of diabetic lower extremity ulcers have impaired arterial flow as primary ethiological factor, approximately 50 % associated with primary diabetic neuropathy, and up to 30% have both conditions (Reiber et al.,1999). Recently, microangiopathy has also been implicated in the pathogenesis of diabetic foot ulcers (La Fontaine et al.,2006; Ngo et al., 2005). Along with rapidly progressing atherosclerotic obstructive vascular disease, diabetic patients commonly exhibit an enhanced vascular responsiveness to vasoconstrictors, attenuated response to vasodilators and impaired regulation of blood flow in many different regions, from cerebral blood flow to local, dermal perfusion. Altered endothelial function of resistance vessels could contribute to altered regulation of regional blood flow and insufficient tissue perfusion in diabetes mellitus (Unfirer et al., 2008).

The fundamental role of oxygen in the physiology of wound healing is well documented (Brakora & Sheffield,1995; Hunt,1988). Measurement of the transcutaneous pressure of oxygen ($TcpO_2$) has been shown to be a valuable tool in predicting healing or non-healing in diabetic foot ulcers (Mathieu et al.,1990). It has been demonstrated, that patients with $TcpO_2$ values <20 mmHg, in comparison to patients with values >40 mmHg, have a 39-fold increase in failure of wound healing (Pecoraro, 1991, Bakker, 2000; Rollins et al., 2006). Hypoxia in the wound tissues promote the ulceration process, whereas a plentiful supply of oxygen is critically important for a variety of healing processes (Liu &Velazquez, 2008). Oxygen tension is positively correlated with key components of the healing process, such as angiogenesis (Knighton et al., 1983), collagen production (Hunt &Pai ,1972; Jonsson et al., 1991; Gurdol et al.,2010), bacterial elimination (Knighton et al., 1984;Cimsit et al.,2009) and epithelization (Uhl et al., 1994). In well-oxygenated wounds, all these components are greatly enhanced.

Of all other available oxygen delivery methods, hyperbaric oxygen therapy appears to be the most efficient option (Liu & Velazquez, 2008). Hyperbaric oxygen therapy has proved its efficiency in healing acceleration of ischemic and refractory diabetic wounds (Zamboni et al.,1997;Abidia et al., 2003; Hopf et al., 2005).

Despite the well-known beneficial effects of hyperbaric oxygen therapy on healing process of chronic ischemic and diabetic wounds and ulcers, its mechanisms of action are not completely understood. Restoring an adequate blood flow to the site of chronic wound is an essential prerequisite of successful healing response, which include modifying the altered vascular responsiveness to vasoactive substances and new vessel growth stimulation. It has been suggested, that hyperbaric oxygen is capable of induction of complex changes in the conducted vasomotor responses, thus modifying vascular sensitivity and reactivity to vasoactive substances (Drenjancević-Perić et al.,2009).It has also been hypothesized, that hyperbaric oxygen exerts beneficial effects on vascular function by affecting production or

vessel sensitivity to vasoconstrictor and vasodilator metabolites of arachidonic acid and nitric oxide in response to physiological stimuli, namely acetylcholine, hypoxia and flow-mediated dilation, thus effectively restoring vascular reactivity (Unfirer et al., 2008). Available data is quite scarce and almost exclusively experimental. To date, no published results of large-scale, controlled prospective studies could be found.

Angiogenesis, in form of neovascularisation, is one of the essential processes that occur in the course of chronic diabetic wound healing. In conditions of hyperoxia, created by applying the hyperbaric oxygen therapy either locally (isolated extremity treatment) or generally in hyperbaric chamber, neovascularisation in hypoxic tissues occurs by two processes. Regional angiogenic stimuli increase the efficiency of new blood vessel growth by proliferation of microvascular endothelial cells, and also the recruitment and differentiation of circulation stem/progenitor cells (SPCs) to form vessels de novo. In clinically relevant concentrations, hyperbaric oxygen has been shown to influence both these processes (Thom, 2009). It has been demonstrated, that hyperbaric oxygen induces a cytoprotective and angiogenic response in human microvascular endothelial cells by increasing expression of immediate early and cytoprotective genes, which corresponded with increase in cell proliferation and oxidative stress resistance (Godman et al.,2010a,2010b).

Hyperbaric oxygen reduces circulating levels of proinflammatory cytokines, and also increases synthesis of many growth factors. Oxidative stress at the sites of neovascularization stimulates growth factors synthesis by augmenting synthesis and stabilizing hypoxia-inducible factor (HIF)-1. (Hunt et al.,2004, 2007) Vascular endothelial growth factor (VEGF) , angiopoetin and also stromal-derived factor-1 influence stromal cells differentiation to endothelial cells. VEGF, the most specific growth factor for neovascularization, has been shown to be increased by hyperbaric oxygen(Sheikh et all.,2000;Thom,2011).

Diabetic foot ulceration is a major predisposing factor for local infections, whereas various immunological disturbances and peripheral polyneuropathy play secondary roles. Diabetic foot ulcers are frequently polymicrobial with a high incidence of anaerobic organisms. Anaerobic infections are especially frequently seen in tissues with low oxygen tensions. Anaerobes are found in about 33% of cases of diabetic foot infections (Calhoun et al.,1992; Calhoun et al.,2002). Among the frequently isolated anaerobic organisms are species of *Bacteroides* and *Clostridia* (Boulton, 1988). Aerobic Gram-positive cocci (especially Staphylococcus aureus) are also among the most common, sometimes predominant, pathogens in diabetic foot infections. Patients with chronic wounds who are already receiving antibiotics, may be also infected with gram-positive rods, and those with established foot ischemia or gangrene may have obligate anaerobic pathogens (Lipsky et al., 2006).Hyperbaric oxygen therapy is often combined with antibiotics as an adjunctive treatment for various wound infections. Hyperoxia and hyperbaric oxygen exert antimicrobial effects by increasing the intracellular flux of reactive oxygen species. Hyperbaric oxygen may be either bacreiostatic or bactericidal for microorganisms that lack defenses against oxidants. In bacteria, reactive oxygen species cause DNA strand breaks, degradation of RNA, inhibition of amino acid biosynthesis, and inactivation of membrane transport proteins. Oxygen tensions also affect the activity of antimicrobial agents. In general, hyperoxia potentiates while anaerobiosis decreases the activity of many antimicrobial drugs. With regard to host defenses, hypoxia can seriously impair leukocyte bacterial killing function (Rabkin &Hunt ,1988; LaVan & Hunt ,1990). Hyperoxia elevates oxygen tensions in infected tissues to levels that facilitate oxygen-dependent killing by

leukocytes. Prolonged hyperoxia inhibits DNA synthesis in lymphocytes and impairs chemotactic activity, adherence, phagocytic capacity, and generation of the oxidative burst in polymorphonuclear leukocytes and macrophages. (Park et al., 1992; Cimsit, 2009).

One of the suggested criteria for hyperbaric oxygen therapy use is transcutaneous oxygen measurement of less than 40 mm Hg at the tissues surrounding the wound, most precisely, at the wound edges. This baseline measurement should be followed by testing the patient's tissue response to administration of 100% via tight face mask. The trascutaneous oxygen level should increase by at least 10 mm Hg to justify starting of hyperbaric oxygen therapy. After an hyperbaric oxygen trial, the transcutaneaous measurement should be greater than 200 mm Hg (Attinger, 2006; Hunter et al, 2010). It has been also demonstrated, that a transcutaneous oxygen tension (TcPO2) of 200 mmHg, measured in the peri-wound tissues while in-chamber, was the most effective determinant of success or failure of the therapy. It has been found , that TcPO2 in peri-wound tissues at sea level air of less than 15 mm Hg, together with a TcPO2 less than 400 mm Hg, measured in the same tissues in-chamber, proved to be most accurate predictor of hyperbaric oxygen therapy failure (reliability 75.8%, positive predictive value 73.3%)(Fife et all, 2002, 2007).

The commonly used protocols for hyperbaric oxygen therapy administration vary among institutions. No consensus has been reached so far in respect to single session and whole treatment duration. Most commonly, hyperbaric oxygen for diabetic wounds is administered at pressure range of 2 to 2.8 ATA, 5 days a week, with typical session duration of 45 to 90 minutes.(Wang, 2003). Other authors have been using daily treatments of 1.5 to 2 hours duration, for 20 to 40 days (Thom,2010).

The effectiveness of hyperbaric oxygen for diabetic and ischemic wounds treatment may be evaluated from prospective of two most important clinical outcomes: expediting the wound healing and reduction the amputation rate. Clinical efficacy of hyperbaric oxygen therapy in healing of chronic diabetic and ischemic wounds has been demonstrated by many researchers (Hinchliffe et al., 2008). Another group reported 90% healing in the intervention group *versus* 28% controls (Heng et all, 2000). The wound area reduction has been reported to occur at 2 weeks: 42% in the intervention group *versus* 21% (p = 0.037) and at 4 weeks: 62% *versus* 55% (Kessler et al., 2003). Two groups reported a favorable outcome after hyperbaric oxygen therapy in respect to expedited diabetic ulceration healing. One of groups has conducted a double-blind randomized trial, the main outcome of which was completely healed wound by 12 month after commencement of the therapy (2.5 ATA for 85 min, 5 days a week, for 8 weeks)in 52% of patients that received hyperbaric oxygen versus 29% of those from control group (Duzgun et al., 2008; Londahi et al.,2010,2011) .

It has been well demonstrated, that use of hyperbaric oxygen therapy was associated with decrease in amputation rate in diabetic patients. A decrease by 30% of major amputations rate in Wagner grade 4 patients has been reported in large prospective study (Faglia et al., 1996). Another study demonstrated even more significant (almost in 71%, 2 amputations in the study group versus 7 in control, a total of 30 patients) decrease of amputation rate (Doctor et al., 1992).

4. Hyperbaric oxygen in the treatment of necrotizing fasciitis and Fournier's gangrene

Necrotizing fasciitis has been defined as rapidly progressing life-threatening bacterial infection, that primarily involves skin and secondary subcutaneous tissues (Jallali et al.,

2005). Incidence of necrotizing fasciitis has increased over two decades (1980-2000), yet the disease still remains quite rare. The possible explanation may include increased microbial virulence and resistance because of excessive use of powerful antibiotics, and also possibly disease reporting and statistical work improvement (Sarani et al., 2009).

There are three basic subtypes of necrotizing fasciitis described. Approximately 55 to 75 % of type I caused by combination of gram-positive cocci, gram-negative rods, and anaerobes; less commonly, by species of bacteroides or Clostridium (Childers et al.,2002; Wong et al., 2003;Anaya &Dellinger, 2007). This type of infection tend to occur in the trunk and perineal areas and include Fournier's gangrene. Type II of necrotizing fasciitis mostly caused by monomicrobial flora, that include group A Streptococcus (S. pyogenes) alone or in association with Staphylococcus aureus. This type may be associated with toxic shock syndrome. During last 5 years, an increasing incidence of methicillin-resistant S. aureus (MRSA) is being reported, especially in IV drug users. Today, MRSA is cultured in approximately 40% of necrotic wounds (Miller et al., 2005; Maltezou & Giamarellou,2006;Thulin et al.,2006). Some sources classified necrotizing infection caused by Vibrio vulnificus as type III, although consensus regarding such classification remains yet to be reached. The biggest risk factors for this, the rarest, type of necrotizing fasciitis include exposure to warm sea water and also moderate to severe liver disease, particularly chronic hepatitis B (Howard et al., 1985).

Bacterial agents, that invade subcutaneous tissues through disrupted viscus of colorectal or urogenital area or perforated skin, rapidly spread over the adjacent tissues, producing endo- and exotoxins, that cause deep tissue ischemia and liquefactive necrosis that eventually lead to systemic disease (Salcido, 2007). Some of the exotoxins, namely M-1 and M-3 surface proteins, produced by S.aureus and Staphyloocci, increase microbial virulence by enhancing their ability to adhere to tissues and resistance to phagocytosis. Other exotoxins, namely A and B exert a variety of ill effects, that include endothelium damage, loss of microvascular integrity, increase of capillary permeability , causing plasma capillary leak, which results in tissue edema and impairment of capillary blood flow. These toxins, along with streptolysin O, stimulate CD4 cells and macrophages to produce large amounts of tumor necrosis factor-a,interleukin1 and 6 (Hackett & Stevens, 1992). Release of these cytokines into the circulation causes systemic inflammatory response and may lead to septic shock, multiorgan failure and eventual death. Superantigenes directly stimulate T-cells, causing activation of complement, bardykinin-kallikrein system and coagulation cascade, with small vessel thrombosis and tissue ischemia ensued (Salcido,2007).

Early radical surgical debridement along with aggressive, wide-spectrum antibiotic therapy remains a mainstay of the necrotizing fasciitis treatment. Despite the certain progress, achieved in this field, unfavorable outcome remains quite common.

High mortality rate of 20 to 40% (McHenry et al. ,1995) have prompted a search for effective ancillary methods of treatment to improve patients outcome. Hyperbaric oxygen therapy has shown some promising results, which promoted its use as an adjuvant therapeutic modality in this category of patients. Although variety of protocols have been employed, the most common method includes administration of oxygen at 2 to 3 ATA with average duration of 60 to 120 minutes. However, no consensus has been reached so far regarding either duration, timing or number of sessions, and established protocols for HBO therapy in necrotizing fasciitis or Fournier's gangrene are absent.

Most of clinical evidences, supporting the use of hyperbaric oxygen therapy, are of only anecdotal value at best. Most authors have chosen a decrease of the overall mortality rate as

an universal index of HBO therapy efficacy, reporting improved patients survival rates in majority of studies. The reported mortality rates varied significantly, from 0 to 33% (Jallali et al., 2005).

The lowest mortality rate ever reported, essentially zero deaths after combined early surgical debridement and HBO therapy in small group of only 9 patients with Fournier's gangrene, was shown in the early clinical study of (Eltorai et al.,1986). In this study, however, no data was provided either in respect to details of the treatment protocol details (duration of the study, number of sessions, time intervals between hyperbaric oxygen therapy sessions and surgical debridments). Another study included two series of 32 patients with clostridial gas gangrene and 11 patients wit perineal necrotizing fasciitis, who underwent hyperbaric oxygen therapy at 2.5 ATA for 120 minutes of session duration , and 3 first treatments were administered during first 24 hours after admission, and then repeated twice daily. The overall mortality rate was reported as 28% in gas gangrene group. In the group of patients treated with hyperbaric oxygen, 94% of the survivors healed completely and were able to walk normally (Him, 1993).

In yet another study, 33 patients were treated for perineal necrotizing fasciitis. Their management included wide early surgical debridment and drainage, massive antibiotic therapy and hyperbaric oxygen therapy at 2.5 ATA, 2 to12 times. The reported mortality rate was quite low (9.1%, 3 patients died out of 33) (Korhonen, 2000). Same group of researchers had also managed a group of 53 patients with Clostridial gas gangrene, and protocol here was pretty much identical to that used in patients with Fournier's gangrene. The reported mortality rate was 22.6%. In this study, substantially higher levels of subcutaneous PO2 at the same O2 pressures of 2.5 ATA during hyperbaric oxygen therapy were found in the vicinity of infected areas than in healthy tissues. Authors concluded, that hyperbaric oxygen therapy appears to be life-, limb, and tissue saving, and that the hyperoxygenation of tissue zone surrounding the infected area may be of significance in preventing the expansion of microorganisms. (Korhonen at al., 1999, 2000).

Authors of another study administered hyperbaric oxygen shortly (about 7 hours) after surgical debridement, which resulted in achievement of only 12.5% mortality rate. However, no control group was mentioned in this study, which makes it difficult to draw a definite conclusion regarding the net effect of the hyperbaric oxygen therapy (Gozal et al., 1986) In the controlled study, included group of 17 patients that received hyperbaric oxygen along with surgical debridement and antibiotics versus that of 12 patients, whose treatment did not include hyperbaric oxygen therapy, use of this modality has allowed to decrease overall mortality from 66% to 23%. This result has been achieved despite the fact, that patients received hyperbaric oxygen, were more seriously ill (some of them were in septic shock), which makes the beneficial effect of the therapy in this study particularly noteworthy (Riseman et al., 1990). In larger, albeit without control group study, efficacy of including HBOT in the treatment protocol in 42 consecutive patients has been proved by decreasing of overall mortality from 34%(national reported rate) to 11.9%, with 0% amputations (vs.50% of national average) in hyperbaric oxygen-treated patients (Escobar et all, 2005)

A growing number of studies, in contrast with those reported positive results of hyperbaric oxygen therapy, have demonstrated lack of any advantages of the hyperbaric oxygen therapy. In the large controlled multicenter study, (Brown et al.,1994), hyperbaric oxygen therapy was not associated with statistically significant decrease in mortality (30% in HBO group vs. 42% in control), number of debridements (2.4 in hyperbaric oxygen

group vs 1.3 in control) was actually higher, and length of hospital stay was not different between groups(31.6 days in hyperbaric oxygen vs. 31.3 days in control). In this study, however, majority of the patients (66%) received less than 4 sessions, which potentially makes the impact of hyperbaric oxygen therapy substantially weaker. Also, patients who were selected for hyperbaric oxygen therapy, had more advanced stages of sepsis, which potentially may have introduce a bias factor in the results interpretation. Authors of another study found no differences in length of hospital stay, complications rate and mortality between groups of patients with necrotizing fasciitis, where one was treated with hyperbaric oxygen therapy, and another wasn't; however, 25% of non- hyperbaric oxygen therapy group required amputations, whereas patients from hyperbaric oxygen therapy group needed no such intervention (Hassan et al.,2010). Authors of the retrospective study, reviewing 10-year - long experience of using HBOT as an adjuvant treatment for necrotizing fasciitis, found no improvements from hyperbaric oxygen use, but rather worsening of results in respect to mortality rate (36% in hyperbaric oxygen therapy group vs. 25% in control), number of debridements (2.5 with hyperbaric oxygen therapy vs 1.5 in controls). Difference in length of hospital stay, which was, however, shorter in hyperbaric oxygen therapy group (15.9 vs 20 days in controls), was not statistically significant.

Another retrospective study revealed considerably higher mortality among the patients with Fournier's gangrene, treated with hyperbaric oxygen therapy, in comparison with those received no such treatment (26.9 vs 12.5%). The potential reason for this finding, again, may be attributed to the selection of the much sicker patients for hyperbaric oxygen therapy (Mindrup et al., 2005).

Absolute majority, if not all, of studies investigating the effects of hyperbaric oxygen therapy, are retrospective ones. Even the largest series include several dozen patients at best, with most common sample size around 20 patients, either in study or control groups. Such small numbers of subjects preclude the use of vigorous statistical methods in comparison studies, investigating mortality and morbidity rates, tissue- and limb- salvage efficacy of the hyperbaric oxygen therapy. These limitations substantially diminish the predictive value of quite scarce published studies.

To date, even after thorough literature research, we could not find any prospective, randomized comparison study investigating different effects of hyperbaric oxygen therapy. Regretfully, it appears that truly robust proof of either positive or negative effect of hyperbaric oxygen therapy, at least as an adjuvant therapy for necrotizing fasciitis and gangrene, is currently absent.

There are numerous reasons to this situation. Scarcity of the resources (many hospitals do not possess the hyperbaric oxygenation chambers), lack of established guidelines, differences on clinical protocols (outlining timing, number of sessions, time correlation with debridements , and more), clinicians' opinions and experience, and also tendency to reserve the hyperbaric oxygen therapy, a quite expensive method, for the sickest, critically ill, oftentimes frankly moribund patients, are among the important limiting factors, making it truly difficult to elucidate the genuine impact of hyperbaric oxygen therapy in practically every area of its use (Jallali et al., 2005). In its current status, based on existent level of pro— and contra- evidences, HBOT efficacy remains controversial at best, and may not be unanimously recommended as therapeutic modality in every case of necrotizing fasciitis or gangrene.

5. Conclusion

Diabetic foot chronic wounds and ulcerations adjuvant treatment with hyperbaric oxygen appears to be efficient with respect to promoted healing and also in decrease of major amputations rate.

Hyperbaric oxygen therapy may not replace the combination of early aggressive debridements and wide-spectrum antibiotic therapy, but rather remains an adjuvant, however sometimes efficient, method in the management of necrotizing fasciitis and gangrene.

6. References

Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA &McCollum PT. (2003)The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg*.25,6,((Jun 2003),pp.513-8

Anaya DA, Dellinger EP.(2007) Necrotizing soft-tissue infection: diagnosis and management. *Clin Infect Dis.* 44,5,(Mar 2007),pp.705-10

Attinger CE, Janis JE, Steinberg J, Schwartz J, Al-Attar A & Couch K.(2006) Clinical approach to wounds: débridement and wound bed preparation including the use of dressings and wound-healing adjuvants. *Plast Reconstr Surg.* 117, 7 Suppl, (Jan 2006),pp.72S-109S

Bakker DJ(1984). The use of hyperbaric oxygen in the treatment of certain infectious diseases especially gas gangrene and acute dermal gangrene (Dissertation). *University of Amsterdam: Wageningen, The Netherlands,* 1984.

Bakker DJ (2000)Hyperbaric oxygen therapy and the diabetic foot. *Diabetes Metab Res Rev.* 16 Suppl 1 (Sep-Oct 2000),pp.S55-8

Boulton AJ.(1988) The diabetic foot. *Med Clin North Am 72,6,(Nov 1988),pp.1513-30*

Brakora MJ, Sheffield PJ (1995). Hyperbaric oxygen therapy for diabetic wounds. *Clin Podiatr Med Surg* 12, (1995)*pp.* 105–117.

Brown DR, Davis NL, Lepawsky M, Cunningham J & Kortbeek J.(1994) A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. *Am J Surg*.167,5,(May 1994),pp.485-9

Calhoun JH, Mader JT & Sanford JP. (1992)Infection in the diabetic foot. *Hosp Pract (Off Ed)* 27,3A,(Mar 1992),pp.81-4,87-90,99 passim

Calhoun JH, Overgaard KA, Stevens CM, Dowling JP & Mader JT.(2009) Diabetic foot ulcers and infections: current concepts. *Adv Skin Wound Care.* 15,1,(Jan-Feb 2002),pp.31-42

Childers BJ, Potyondy LD, Nachreiner R, Rogers FR, Childers ER, Oberg KC, Hendricks DL &Hardesty RA.(2003) Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. *J Bone Joint Surg Am.* 85-A,8,(Aug 2003),pp.1454-60

Cimşit M, Uzun G & Yildiz S.(2009) Hyperbaric oxygen therapy as an anti-infective agent. *Expert Rev Anti Infect Ther7,8,(Oct 2009),pp.1015-26*

Doctor N, Pandya S& Supe A.(1992) Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Med.* 38,3,(Jul-Sep 1992),pp.112-4

Drenjancević-Perić I, Gros M & Kibel A.(2009) Influence of hyperbaric oxygen on blood vessel reactivity: concept of changes in conducted vasomotor response. *Coll Antropol 33,2,(Jun 2009),pp.681-5*

Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B &Coskun F.(2008) Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *J Foot Ankle Surg.* 47,6, (Nov-Dec 2008),pp.515-9

Eltorai IM, Hart GB, Strauss MB, Montroy R & Juler GL.(1986) The role of hyperbaric oxygen in the management of Fournier's gangrene. *Int Surg.* 71,1,(Jan-Mar 1986),pp.53-8

Escobar SJ, Slade JB Jr, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen therapy (HBO2)for treatment of necrotizing fasciitis reduces mortality and amputation rate. *Undersea Hyperb Med.* 32,6,(Nov-Dec 2005), pp.437-43

Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P & Morabito A.(1996) Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care.* 19,12,(Dec 1996),pp.1338-43

Fife CE, Buyukcakir C, Otto GH, Sheffield PJ, Warriner RA, Love TL & Mader J.(2002) The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. *Wound Repair Regen.* 10,4,(Jul-Aug 2002),pp.198-207

Fife CE, Buyukcakir C, Otto G, Sheffield P, Love T &Warriner R 3rd.(2007) Factors influencing the outcome of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy. *Wound Repair Regen.* 15,3,(May-Jun 2007),pp.322-31

Foster JH.(1992) Hyperbaric oxygen therapy: contraindications and complications. *J Oral Maxillofac Surg*.50 ,10,(Oct.1992),pp.1081-66

Godman CA, Joshi R, Giardina C, Perdrizet G &Hightower LE.(2009) Hyperbaric oxygen treatment induces antioxidant gene expression. *Ann N Y Acad Sci*.1197,(Jun 2009),pp.178-83

Godman CA, Chheda KP, Hightower LE, Perdrizet G, Shin DG &Giardina C.(2010) Hyperbaric oxygen induces a cytoprotective and angiogenic response in human microvascular endothelial cells. *Cell Stress Chaperones.* 15,4,(Jul 2010),pp.431-42

Gozal D, Ziser A, Shupak A, Ariel A & Melamed Y.(1986) Necrotizing fasciitis. *Arch Surg.* 121,2,(Feb 1986),pp.233-5

Gurdol F, Cimsit M, Oner-Iyidogan Y, Kocak H, Sengun S&Yalcinkaya-Demirsoz S.(2010) Collagen synthesis, nitric oxide and asymmetric dimethylarginine in diabetic subjects undergoing hyperbaric oxygen therapy. *Physiol Res 59,3,(Aug 2010),pp.423-9*

Hackett SP, Stevens DL. Streptococcal toxic shock syndrome: synthesis of tumor necrosis factor and interleukin-1 by monocytes stimulated with pyrogenic exotoxin A and streptolysin O. *J Infect Dis.* 165,5,(May 1992),pp.879-85

Hassan Z, Mullins RF, Friedman BC, Shaver JR, Brandigi C, Alam B & Mian MA.(2010) Treating necrotizing fasciitis with or without hyperbaric oxygen therapy. *Undersea Hyperb Med.* 37,2,(Mar-Apr 2010),pp.115-23

Heng MC, Harker J, Csathy G, Marshall C, Brazier J, Sumampong S & Paterno Gomez E.(2000) Angiogenesis in necrotic ulcers treated with hyperbaric oxygen. *Ostomy Wound Manage.* 46,9,(Sep 2000),p.18-28,30-2

Him M.(1993) Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotizing fasciitis. A clinical and experimental study. *Eur J Surg Suppl.* 570,(1993),pp.1-36

Hinchliffe RJ, Valk GD, Apelqvist J, Armstrong DG, Bakker K, Game FL, Hartemann-Heurtier A, Löndahl M, Price PE, van Houtum WH &Jeffcoate WJ.(2008) A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev 24 Suppl 1,(May-Jun 2008), pp.S119-44*

Hopf HW, Gibson JJ, Angeles AP, Constant JS, Feng JJ, Rollins MD, Zamirul Hussain M& Hunt TK. Hyperoxia and angiogenesis. *Wound Repair Regen 13,6,(Nov-Dec 2005),pp.558-64*

Howard RJ, Pessa ME, Brennaman BH & Ramphal R.(1985) Necrotizing soft-tissue infections caused by marine vibrios. *Surgery.* 98,1,(Jul 1985),pp.126-30

Hunt TK, Pai MP.(1972) The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. *Surg Gynecol Obstet.* 135,4,(Oct 1972),pp.561-7

Hunt TK, Ellison EC & Sen CK.(2004) Oxygen: at the foundation of wound healing--introduction. *World J Surg.*28,3,(Mar 2004),pp.291-3

Hunt TK, Aslam RS, Beckert S, Wagner S, Ghani QP, Hussain MZ, Roy S & Sen CK.(2007) Aerobically derived lactate stimulates revascularization and tissue repair via redox mechanisms. *Antioxid Redox Signal.*9,8,(Aug 2007),pp.1115-24

Hunt TK (2008) The physiology of wound healing. *Med Hypotheses 71,7, (Nov.2008),pp.776-80*

Hunter S, Langemo DK, Anderson J, Hanson D &Thompson P.(2010) Hyperbaric oxygen therapy for chronic wounds. *Adv Skin Wound Care.*23,3,(Mar 2010),p.116-9

Jallali N, Withey S & Butler PE.(2005) Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg.* 189,4,(Apr 2005),pp.462-6

Jonsson K, Jensen JA, Goodson WH 3rd, Scheuenstuhl H, West J, Hopf HW& Hunt TK.(1991) Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. *Ann Surg 214,5, (Nov 1991),pp.605-13*

Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D, Pinget M & Schneider F.(2003) Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care.* 26,8,(Aug 2003),pp.2378-82

Knighton DR, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z & Banda MJ(1983). Oxygen tension regulates the expression of angiogenesis factor by macrophages. *Science.*221,4617, (Sep 1983),pp.1283-5

Knighton DR, Halliday B & Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. *Arch Surg119,2,(Feb 1984),pp.199-204*

Korhonen K, Kuttila K & Niinikoski J.(1999) Subcutaneous tissue oxygen and carbon dioxide tensions during hyperbaric oxygenation: an experimental study in rats. *Eur J Surg.* 165,9,(Sep 1999),pp.885-90

Korhonen K.(2000) Hyperbaric oxygen therapy in acute necrotizing infections. With a special reference to the effects on tissue gas tensions. *Ann Chir Gynaecol.* 89 Suppl 214, (Mar 2000),pp.7-36

Korhonen K, Kuttila K &Niinikoski J.(2000) Tissue gas tensions in patients with necrotising fasciitis and healthy controls during treatment with hyperbaric oxygen: a clinical study. *Eur J Surg.* 166,7,(Jul 2000),pp.530-4

La Fontaine J, Harkless LB, Davis CE, Allen MA & Shireman PK.(1999) Current concepts in diabetic microvascular dysfunction. *Diabetes Care.*22,1,(Jan 1999),pp.157-62

LaVan FB, Hunt TK. Oxygen and wound healing. *Clin Plast Surg.* 17,3,(Jul 1990),pp.453-72

Leifer G (2001)Hyperbaric oxygen therapy. *Am J Nurs.* 101, 8, (Aug 2001),pp.26-34

Leach RM, Rees PJ & Wilmshurst P.(1998) Hyperbaric oxygen therapy. *BMJ* 317,(Oct 24 1998)pp-no data

Leung PC. (2004)Diabetic foot ulcers--a comprehensive review. *Diabetes Care.*27,5,(May 2004),pp.1047-53

Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, LeFrock JL, Lew DP, Mader JT, Norden C, Tan JS; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. *Plast Reconstr Surg.*117,7Suppl,(Jun 2006), pp.212S-238S

Liu ZJ, Velazquez OC.(1991) Hyperoxia, endothelial progenitor cell mobilization, and diabetic wound healing. *Cardiol Clin.*9,3,(Aug1991),pp.555-63

Löndahl M, Katzman P, Nilsson A & Hammarlund C.(2010)Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care.* 33,5,(May 2010),pp.998-1003

Löndahl M, Katzman P, Hammarlund C, Nilsson A & Landin-Olsson M.(2011) Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle-brachial index in patients with diabetes and chronic foot ulcers. *Diabetologia.* 65,8,(Jan 2011),pp.65-8

Maltezou HC, Giamarellou H.(2006) Community-acquired methicillin-resistant Staphylococcus aureus infections. *Int J Antimicrob Agents.* 27,2,(Feb 2006),pp.87-96

Mathieu D, Wattel F, Bouachour G, Billard V&Defoin JF.(1990) Post-traumatic limb ischemia: prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. *J Trauma.*30,3,(Mar 1990),pp.307-14

McHenry CR, Piotrowski JJ, Petrinic D& Malangoni MA.(1995) Determinants of mortality for necrotizing soft-tissue infections. *Ann Surg.* 221,5,(May 1995),pp.558-63, discussion 563-5

Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, Tang AW, Phung TO & Spellberg B.(2005)Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. *N Engl J Med.* 352,14,(Apr 7 2005),pp.1445-53

Mindrup SR, Kealey GP & Fallon B.(2005) Hyperbaric oxygen for the treatment of fournier's gangrene. *J Urol.* 173,6,(Jun 2005),pp.1975-7

Monstrey SJ, Mullick P, Narayanan K & Ramasastry SS. (1997)Hyperbaric oxygen therapy and free radical production: an experimental study in doxorubicin (Adriamycin) extravasation injuries. *Ann Plast Surg.*38,2,(Feb.1997),pp.163-8

Ngo BT, Hayes KD, DiMiao DJ, Srinivasan SK, Huerter CJ & Rendell MS.(2005) Manifestations of cutaneous diabetic microangiopathy. *Am J Clin Dermatol.* 6,4,(2005),pp.225-37

Park MK, Myers RA & Marzella L.(1992)Oxygen tensions and infections: modulation of microbial growth, activity of antimicrobial agents, and immunologic responses. *Clin Infect Dis.* 14,3,(Mar 1992),pp.720-40

Pecoraro RE.(1991) The nonhealing diabetic ulcer--a major cause for limb loss. *Prog Clin Biol Res.* 365,(1991),pp.27-43

Rabkin JM, Hunt TK. (1987)Local heat increases blood flow and oxygen tension in wounds. *Arch Surg.* 122,2,(Feb 1987),pp.221-5

Ramaswami RA, Lo WK.(2000)Use of hyperbaric oxygen therapy in Hong Kong *HKMJ*, 6,1,(2000)pp.108-112

Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA & Boulton AJ.(2006) Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *J Am Podiatr Med Assoc.* 96,3,(May-Jun 2006),pp.245-52

Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR & Ross DS.(1990) Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. *Surgery.* 108,5,(Nov 1990),pp.847-50

Rollins MD, Gibson JJ, Hunt TK &Hopf HW.(2006) Wound oxygen levels during hyperbaric oxygen treatment in healing wounds. *Undersea Hyperb Med.* 33,1,(Jan-Feb 2006),pp.17-25

Salcido RS. Necrotizing fasciitis: reviewing the causes and treatment strategies. *Adv Skin Wound Care.* 20,5,(May 2007),pp.288-93

Sarani B, Strong M, Pascual J & Schwab CW.(2002) Necrotizing fasciitis: current concepts and review of the literature. *Am Surg.*68,2,(Feb 2002),pp.109-16

Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z & Hunt TK.(2000) Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg.* 135,11,(Nov 2000),pp.1293-7

Sheffield PJ. *(1988)*Tissue oxygen measurements. *In: Problem Wounds: The Role of Oxygen, (*Davis JC, Hunt TK*). pp.*17–51,*Elsevier: (ISBN-no data)* New York and Amsterdam.

Sheridan RL, Shank ES.(1999) Hyperbaric oxygen treatment: a brief overview of a controversial topic. *The Journal of Trauma: Injury, Infection and Critical care* 47,2,(Aug 1999) pp.426-435

Tam M, Moschella SL.(1991) Vascular skin ulcers of limbs. *Cardiol Clin.* 9,3,(Aug 1991),pp.555-63

Thom SR.(2009) Oxidative stress is fundamental to hyperbaric oxygen therapy. *J Appl Physiol.* 106,3,(Mar 2009),pp.988-95

Thom SR.(2011) Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg* 127 Suppl 1,(Jan 2011),pp.131S-141S

Thulin P, Johansson L, Low DE, Gan BS, Kotb M, McGeer A & Norrby-Teglund A.(2006) Viable group A streptococci in macrophages during acute soft tissue infection. *PLoS Med.* 3,3,(Mar 2006),e53

Uhl E, Sirsjö A, Haapaniemi T, Nilsson G & Nylander G.(1994) Hyperbaric oxygen improves wound healing in normal and ischemic skin tissue. *Plast Reconstr Surg.* 93,4,(Apr 1994),pp.835-41

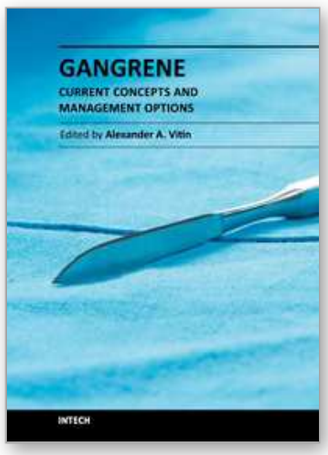
Unfirer S, Kibel A& Drenjancevic-Peric I.(2008) The effect of hyperbaric oxygen therapy on blood vessel function in diabetes mellitus. *Med Hypotheses.* 71,5,(Nov 2008), pp.776-80.

Wang C, Schwaitzberg S, Berliner E, Zarin DA& Lau J.(2003) Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg.* 138,3,(Mar 2003),pp.272-9

Wild S, Roglic G, Green A, Sicree R& King H.(2007) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Surgeon*.5,4,(Aug 2007)pp.219-31

Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL& Low CO.(2009) Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. *J Am Coll Surg*. 208,2,(Feb 2009),pp.279-88

Zamboni WA, Wong HP, Stephenson LL& Pfeifer MA.(1997) Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *Undersea Hyperb Med*.24,3,(Sep 1997),pp.175-9



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Gangrene is the term used to describe the necrosis or death of soft tissue due to obstructed circulation, usually followed by decomposition and putrefaction, a serious, potentially fatal complication. The presented book discusses different aspects of this condition, such as etiology, predisposing factors, demography, pathologic anatomy and mechanisms of development, molecular biology, immunology, microbiology and more. A variety of management strategies, including pharmacological treatment options, surgical and non-surgical solutions and auxiliary methods, are also extensively discussed in the bookâ€™s chapters. The purpose of the book is not only to provide a reader with an updated information on the discussed problem, but also to give an opportunity for expert opinions exchange and experience sharing. The book contains a collection of 13 articles, contributed by experts, who have conducted a research in the selected area, and also possesses a vast experience in practical management of gangrene and necrosis of different locations.

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