

Hyperbaric Oxygen Therapy in the Military Setting: Complications and Contraindications of HBOT Crush Injury / Soft Tissue Infections and HBO

Dietmar M. Fischer

German Armed Forces Hospital Ulm
Oberer Eselsberg 40 – 89081 Ulm
GERMANY

DietmarManfredFischer@bundeswehr.org

ABSTRACT

In the first of the two lectures we will have a closer look to the objectionable physiological changes under increased ambient pressure. Additionally we will discuss, what kind of side effects will occur when breathing pure oxygen under these conditions and therefore an extensive increase of oxygen partial pressure in blood will result.

As a chain of reasoning, these physiological changes will implicate contraindications against the use of hyperbaric oxygen.

The second lecture (Crush Injury and HBOT / Soft Tissue Infections and HBOT) will give a short overview about pathophysiology and common causes of these conditions. It will also explain the theoretically benefits of Hyperbaric Oxygen Therapy and its role in the treatment complex of these injuries/diseases.

1.0 COMPLICATIONS AND CONTRAINDICATIONS OF HBOT

The effects of HBOT are direct results of physical laws (e.g. higher ambient pressure) and of physiological changes due to higher partial pressure of the gases in the human body.

These physical and physiological changes do not lead to positive effects in the treatment of a variety of diseases/trauma and poisoning. They also bear an amount of specific risks.

These specific physical and physiological effects on the human body are also the cause for the various side effects of HBOT.

1.1 Complications of HBOT

Complications can be divided into three different groups / causes:

- stay in an enclosed surrounding (the hyperbaric chamber with limited space)
- the effects of an altered (higher) ambient pressure
- the effects of higher partial pressure of oxygen

HBOT In The Military Setting: Complications and Contraindications / Crush Injury / Soft Tissue Infections and HBOT

1.1.1 Stay in an enclosed surrounding

As the patient/staff is kept in an enclosed environment there are some severe problems that can occur:

a) Risk of combustion / fire:

Several fires in hyperbaric chambers with casualties and fatalities have been reported. There is a significant risk for fire in hyperbaric chambers when the oxygen fraction of the ambient air in the chamber exceeds 23%.

b) Psychological reactions:

Not only due to the limited space in the chamber but also due to the necessity to wear a tight fitting mask or helmet can cause severe effects in the patient:

Studies have shown that up to four percent of the patient's complaints were caused by such psychological phenomena rather than somatic problems:

dizziness, anxiety, vertigo, hyperventilation

1.1.2 Changes due to altered ambient pressure

Barotrauma of ear, sinuses, teeth

In a study of Plafki et al. (1997) with 694 patient and 9998 chamber-treatments, two percent of the patients complained about severe equalization problems resulting in modifications in the therapy protocol/therapeutic regimen.

About twelve percent of the patients reported equalization problems without the need to change the treatment protocol.

Three percent of the patients showed signs of middle ear barotrauma (ear drum injection, tympanic effusion), one patient suffered from an ear drum rupture. Half of these patients required a paracentesis before continuing their treatment

State of the art literature showed no evidence for inner ear barotrauma or barotrauma of the teeth.

Barotrauma of the lung

This is a general risk when exposed to a higher ambient pressure. Especially in the decompression phase lung areas with low ventilation (so called trapped air) are at risk to develop pulmonary barotrauma. This can lead to tension pneumothorax and/or arterial gas embolism.

There is no statistical evaluation of the specific risk to develop pulmonary barotrauma. This can be explained by the moderate pressure changes during the treatment. HBOT requires an 100% oxygen breathing for the patient. Thus, even in the rare case of a pulmonary barotrauma, there would be no harm for the patient - as the oxygen is metabolized in the body very rapidly.

Long term effects of repeated compression

Repeated exposure to high ambient pressure can lead to dysbaric osteonecrosis. The pathomechanism still remains unclear. This clinical entity affects hyperbaric staff only.

1.1.3 Acute side effects due to higher nitrogen partial pressure:

When the absolute pressure exceeds 4 bar, nitrogen narcosis will set in. It is characterized by euphoria, illusions and can lead to a loss of consciousness. During an HBOT this may only affect the HBO staff (as the patient breathes 100% oxygen).

1.1.4 Effects of increased oxygen partial pressure:

Side effects can be divided in acute and chronic effects.

Acute side effects:

The most important side effect (1,3 out of 10 000 treatments) is the so-called oxygen seizure (Paul-Bert effect). The risk for this seizures starts when oxygen partial pressure reaches 1,2 bar or higher. It increases exponentially with rising pressure. Patients with a fever, hypothermia, CNS trauma, history of seizures are at an even higher risk.

Acute pulmonary toxicity is also caused by oxygen. Typical symptoms are coughing, dyspnea, retrosternal sensations. This syndrome was first described by the end of the 19th century (Lorraine Smith effect).

Alterations of the ocular lens (e.g. cataract and visual impairment) as an effect of HBOT were reported by some patients.

Chronic Side Effects

Pulmonary fibrosis can be a longterm effect of repeated HBOT. To quantify the damage to the lung tissue the UPTD (Units of Pulmonary Toxicity Dose) was defined.

One UPTD equals breathing 1bar oxygen for 1 minute.

-> Therefore a treatment according to US-Navy table 6 equals 645 UPTDs.

615 UPTDs lead to a deterioration of the lung's vital capacity by two percent. 1425 UPTDs even by ten percent.

Experimental exposition to HBOT has shown DNA damage. Clinical effects of this phenomenon require further investigation as they may affect both, patient and HBO staff.

1.2 Contraindications of HBOT

Possible contraindications must always be considered as to the patient's individual risk and profit of HBOT. Especially the patient's prognosis with or without HBOT and alternative therapeutic regimens have to be considered.

Contraindications are always directly related to the individual case and therefore dependent on the severity of indication. In case of a life-threatening entity, e.g. severe CO-poisoning, there exists nearly none contraindication.

HBOT In The Military Setting: Complications and Contraindications / Crush Injury / Soft Tissue Infections and HBOT

The only absolute contraindication for HBOT is an untreated pneumothorax.

Table 1: Contraindications of HBOT

<p>Absolute Contraindication for HBOT</p> <ul style="list-style-type: none"> • untreated (unevacuated) Pneumothorax
<p>Relative Contraindications for HBOT</p> <ul style="list-style-type: none"> • History or current therapy with certain zytostatics (Bleomycin, Doxorubicine) • Current therapy with disulfiram (A drug used in the treatment of alcohol addiction: Rat experiments have shown a 30% letality when used simultaneously with HBOT at 2,5bar for 12(!) hours) • Severe cardiorespiratory insufficiency • Epilepsy • Severe emphysema with CO₂ retention • Ear or thoracic surgery in the past • Pacemakers/ defibrillators not suitable for hyperbaric exposure • uncontrolled high fever • Pregnancy • Claustrophobia

2.0 CRUSH INJURY AND HBOT

2.1 Pathophysiology of Crush Injury

The term crush injury summarizes traumatic tissue and/or vascular injuries that cause severe tissue damage and make tissue survival questionable.

The broad definition of soft tissue injury (non-bony, non-organ injury) accounts for the vast majority of traumatic injuries. Crush injuries are only a small portion of this category, but they result from a wide range of mechanisms:

Direct Force

Direct force crush injuries are the most common types of crush injuries. In this case, an object (or objects) applies force and destroys tissue by direct compression or force to the tissue is applied by high energy (e.g. blast wave). Examples of this include injuries caused by falling objects, blunt trauma distributed over larger areas and blast injury.

Entrapment / Weight-Based Compression

In this situation, compression of tissue is caused by the patient's position. This damage typically manifests over hours and sometimes days. The inability of a patient to shift position causes compression and restricts blood flow. Cells are deprived of oxygen, and waste products build up. Dramatic examples of this include victims trapped and pinned by earthquakes and bomb blasts, but more common examples occur in patients who fall and are unable to get up; their weight causes the crushing force on dependent structures.

These mechanism are falling in the specified class of blunt trauma. Blunt trauma damages by applying force and stretching tissues beyond their normal tolerances. A crush injury - a particular type of blunt trauma - damages tissues by compressive force. This force is generally applied over larger areas and damages more tissue, either through direct compression (direct, crushing force) or by compressing tissues and limiting blood flow (perfusion) to the cells in that area. Crush injuries can occur over a relatively small area, such as striking the thumb with a hammer, or over a large area.

The injuries result in local hypoxia (and possible systemic effects, e.g. shock).

Ischemia leads to edema and vice versa. Ischemia is caused by direct vascular trauma, fluid leakage or compartment syndrome. All these changes lead to tissue hypoxia.

Edema is either vasogenic or zytogenic and it enhances the diffusion distance from oxygen to the cells. Edema also leads to capillary collapse and thus extends the degree of hypoxia.

If reperfusion can be established this leads to excessive production of oxygen radicals that cause vasoconstriction and finally even more hypoxia.

**HBOT In The Military Setting: Complications and Contraindications /
Crush Injury / Soft Tissue Infections and HBOT**

**Table 2: Clinical stages: Gustilo classification
Evaluation of host status**

Factors	Scoring Criteria			Comments
	2 Points	1 Point	0 Point	
Age	<40	40-60	>60	1. use ½ point if severity of involvement is between two scoring criteria 2. for ambulation scoring criteria subtract ½ point if walking aids 3. when two factors such as “smoking/steroid use” are listed, use the scoring criteria which reflects the more severe involvement
Ambulation	Community	Houshold	none	
Smoking / Steroid Use	none	> 5 years ago	current	
Cardiac / Renal	normal	compensated with medications	decompensated even with medications	
Neuropathy/Deformity	none	mild to moderate	severe	

Table 3: host status score and severity of compromise

Score	Severity of compromise
8-10	normal Host
4-7	impaired Host
3 or less	severely compromised Host

Table 4: Use of HBOT for open fractures – crush injuries (Gustilo Classification)

Type	Mechanism	expected Outcome	Use of HBOT and Host Status		
			normal Host Score 8-10	impaired Host Score 4-7	severely compromised Host Score 3 or less
I	small (<1cm) laceration from inside to outside	usually not different from a closed fracture	NO	NO	YES
II	large laceration but minimal soft tissue damage	usually not different from a closed fracture	NO	YES	YES
III	Crush injuries:				
	A Sufficient soft tissue to close wound (primary or delayed)	infections and/or nonunion rates < 10%	NO	YES	YES
	B Flaps or grafts required to obtain soft tissue coverage	about 50% incidence of complications (infections/nonunion)	YES	YES	YES^b
	C Major (macrovascular) vessel injury	about 50% incidence of complications (infections/nonunion)	YES	YES	YES^b
b) consider primary amputation with adjunctive HBOT for wound healing and flap survival					

2.2 Rationale for HBO therapy

Main goal of hyperbaric oxygenation in crush injuries is to establish tissue hyperoxygenation. When pressurized to more than 2,4 bar almost all oxygen becomes dissolved in plasma. Thus tissue can remain alive without any other oxygen carriers.

Second effect of HBO is vasoconstriction that leads to significant reduction of edema (more than 20%).

Third, hyperoxygenation improves the work of fibroblasts, influences neutrophils and is toxic to anaerobic microorganisms.

Last HBO protects from reperfusion injuries due to antagonism of lipid peroxidation and other cellular or humoral reactions. Some authors postulate a promotion of neurogenesis or even angiogenesis due to HBO. It may improve the outcome of skin graftings.

In animal models (rodents, dogs) of crush injury, studies proved significant effects of HBO therapy: reduction of muscle necrosis, improved wound healing, fewer amputations, improvement of osteogenesis, improvement of microvascular blood flow, less muscular edema and better neutrophil adherence to vascular walls. It has no effect on myogenic transcription factors. HBO also regulates inflammatory gene expression in endothelial cells and can lead to decrease in apoptosis expression.

HBOT In The Military Setting: Complications and Contraindications / Crush Injury / Soft Tissue Infections and HBOT

Clinical scientific evidence:

We did a medline search for the items HBO and crush injury back until 1969. There are well established animal models of crush injury, data on human casualties are rare. There are only 28 hits for both items (HBO and crush injury) in the medline. Most of the data result from case reports of up to 35 patients. There is only one RCT that compares crush injuries with and without HBO therapy (Bouachour et al.)

HBO improved healing and reduced surgical procedures significantly. Especially patients over 40 could profite from the treatment.

Several clinical scales have been used to select patients suitable for HBO treatment. The items included age, limb ischemia, shock, skeletal and soft tissue injury.

For best results on human crush injuries the following recommendations exist:

- Gustilo grades IIIb and IIIc
- Begin as soon as possible
- If surgery is delayed more than one hour: HBO first
- 3-4 HBO sessions/day for 3days, then 2 sessions/day for 2 days, 1 session /day for 3 more days.

Management is two-fold: first direct interventions are required (surgical), second part is management of all indirect effects of the injury (fluid replacement, antibiotics, adequate oxygenation). Data are rare, levels of evidence are low. There is a need for more studies. From the existing data the experts conclude that the adjunctive use of HBO in crush injuries may result in a favorable outcome for selected patients.

3.0 HBOT AND GAS GANGRENE

3.1 Pathophysiology of the condition

Gas gangrene is mostly caused by *Clostridium perfringens* (80-90%).

30 % of all wounds are contaminated with *C. perfringens*, but only a few patients develop gas gangrene. Additionally a decreased oxygen-reduction potential in the wound is required. This is mostly caused by circulatory failure. Most tissue destruction can be found in „high velocity“- wounds, e.g. bullet and blast wounds and vehicle accidents. Mechanisms responsible for the rapid tissue destruction in gas gangrene are not well understood. The most important factor for this is tissue hypoxia.

C. perfringens grows freely in oxygen tensions under 30mm Hg. It produces 6 toxins. Alphatoxin is the most important one. It causes tissue necrosis. Thetatoxin leads to hemolysis, necrosis and cardiotoxicity. Clinical features are: Pain, tachycardia, crepitus, hemolysis, low grade fever, bronzing of the skin, bullae formation, obtunded sensation.

3.2 Rationale for HBO therapy

There are only a few studies as to the effects of HBO on gas gangrene. Animal models have not been established- except for one mouse model. Studies on isolated bacteria have shown suppression of clostridial growth when oxygen pressure of 40mmHg or more is applied. Oxygen pressure of 80mmHg inhibits toxin synthesis. Spore formation is also suppressed. On the mouse model HBO did not improve the survival rate of patients with gas gangrene.

Clinical scientific evidence:

Most data results from case reports, a lot from eastern Europe and Russia. They are mostly on the scientific levels of case reports or retrospective studies. When established within 24 hours after symptom onset HBO reduces the fatality of gas gangrene to about 5%. Therapeutic regimen is the Boerema table: 20m, 2x45minutes. HBO can be recommended on the basis of sound experimental evidence and favorable clinical experience. Additionally the therapy includes antibiotics, surgical debridements and intensive care therapy.

4.0 HBOT AND SOFT TISSUE INFECTIONS

4.1 Pathophysiology of the condition

Soft-tissue infections are common, generally of mild to modest severity, and are easily treated with a variety of agents. An etiologic diagnosis of simple cellulitis is frequently difficult and generally unnecessary for patients with mild signs and symptoms of illness. Clinical assessment of the severity of infection is crucial, and several classification schemes and algorithms have been proposed to guide the clinician

Nevertheless soft tissue infections are an increasing medical problem. They occur after trauma, invasive medical procedures, around foreign bodies and even spontaneously. Patients who present to the hospital with severe infection or whose infection is progressing despite empirical antibiotic therapy should be treated more aggressively

Clinical pictures vary widely (necrotizing fasciitis, Fournier gangrene, non-clostridial myonecrosis,...) and their etiology is multifactorial. These infections are mostly caused by gram negative bacteria and anaerobic microorganisms. Streptococci play an important role. Gram positive bacteria and even mycosis should also be considered.



Picture 1: Mucormycosis of leg (from: N Engl J Med 367;23)

Due to varying causes of infection the pathophysiology is not easy to describe. Common factor is tissue hypoxia that suppresses immunologic defense mechanisms. Additionally there are host factors (reduced defense, vascular insufficiency, vein thrombosis). Bacteroidaceae have been proven to interfere with the host's interferon production and influence phagocytic activity.

4.2 Rationale for HBO therapy

Oxygen is an important factor in wound healing:

- Hypoxia interferes with many components of wound healing. Many of these can be modelled or expressed numerically.
- There is in vitro, in vivo and clinical evidence of a relationship between the available amount of oxygen in the wound to healing processes. Oxygen is specially needed in the inflammatory phase.
- The presence of oxygen reduces wound oedema.
- Bacterial killing is oxygen dependent. It is maximal at several hundred mm Hg pO₂, and goes almost to zero in hypoxic patients. There is evidence for the relationship between hypoxia to wound infection at the cellular, animal, and human level. Questions remain on the type of bacteria most sensitive to hypoxia and which clinical parameters are involved (CRP, fibrin, procollagen, leukocytes, neutrophils).
- Angiogenesis, although previously thought to be induced by hypoxia, seems to be directly sensitive to oxygen as a function of local lactate delivery. Angiogenesis is reduced to zero at tissue tensions of 10 mm Hg. In clinically oxygen deficient situations, the granulation tissue is not formed. There is evidence for an effect of oxygen on angiogenesis in basic studies and for animals and humans.
- Collagen production is maximal at 250 mm Hg and falls to almost zero in severe clinical hypoxia (K_m= 25 mm Hg pO₂). Cell motility falls with loss of cell energy production that occurs at or below 10 mm Hg pO₂. There is evidence for the need of oxygen in collagen synthesis and strength in basic, animal and human wounds.

In vitro HBO showed several effects on soft tissue infections:

- Bacteriostatic effects on anaerobic microorganisms (due to their inability to fight oxygen radicals), bactericidal effects (injury by free radicals)
- Improvement of tissue oxygenation
- Preventing extension of invading microorganisms
- Improvement of phagocytic killing activity
- Edema reduction
- Increased function of capillaries
- Increased efficacy of antibiotics (e.g. aminoglycosides, linezolid)

HBOT In The Military Setting: Complications and Contraindications / Crush Injury / Soft Tissue Infections and HBOT

In animal models (mouse, rat, rabbit) the mortality rates were significantly lower when treated with antibiotics and HBO. But (depending on the specific type of bacteria) there were also some harmful effects to be seen: streptococci infections worsen under high oxygen tensions.

Clinical scientific evidence:

The level of evidence on soft tissue infections and HBO is low. There are only case reports and retrospective studies, no RCT. All most all study patients were compromised hosts.

HBO is one part of a multimodal therapy and is only to be used for certain patients. The main therapeutic interventions for these patients are surgery, antimicrobial drugs and intensive care therapy. Data are contradictory. Risemann and lots of other authors found significantly reduced fatality and improved outcome, less number of debridements. They recommend HBO should be used routinely in the treatment of necrotizing fasciitis. Some recent studies however showed no benefits for patients treated with HBO (no difference in survival, length of hospital stay or duration of antibiotic therapy). This is supported by three studies from the early 1980s. Further studies are required.

4.0 REFERENCES

- (1) Alvis, HJ: Hyperbaric oxygen therapy of gas gangrene. JAMA 1971 (128). 445
- (2) Bartlett, RL: Rabbit model of the use of fasciotomy and hyperbaric oxygenation in the treatment of compartment syndrome. UHM 1998 suppl 25
- (3) Boerema: life without blood. A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood. J Cardiovasc Surg 1960 (1): 133-146
- (4) Bouachour, G: Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. J Trauma 1996 (41): 333-339
- (5) Brown, DR: A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. Am J Surg 1994(167): 485-489
- (6) Brummelkamp, WK: Treatment of anaerobic infections (clostridial myonecrosis) by drenching the tissue with oxygen under high atmospheric pressure. Surgery 1961 (49): 299-302
- (7) Bryant, AE: Clostridial gas gangrene, Cellular and molecular mechanisms of microvascular dysfunction induced by eotoxins of *C. perfringens*. J Infect Dis 2000 (182): 799-807
- (8) Clark, LA: Hyperbaric oxygen in the treatment of life-threatening soft tissue infections. Resp. clin north america 1999 (5): 203-219
- (9) ECHM ETRS Ravenna 2006 Jury recommendations
- (10) Escobar, SJ: Adjuvant hyperbaric oxygen therapy for treatment of necrotizing fasciitis reduces mortality and amputation rate
- (11) Eskes, A: Hyperbaric oxygen therapy for treating acute surcial and traumatic wounds. Cochrane review 2010

- (12) George, ME: Hyperbaric oxygen does not improve outcome in patients with necrotizing soft tissue infections. *Surg infections* 2009 (10): 21-28
- (13) Gustilo, RB: Problems in the management of type III open fractures, A new classification of type III open fractures. *J Trauma* 1984 (24): 742
- (14) Hart, GB: Clostridial myonecrosis. The constant menace. *Milit Med* 1975 (140): 461-463
- (15) Hart, GB: Gas gangrene. *J Trauma* 1983 (23): 991-1000
- (16) Herr, M: Nekrotisierende Faszitis. Update 2011. *Unfallchirurg* 2011 (114): 197-216
- (17) Hirn, M: Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotizing fasciitis. A clinical and experimental study. *Eur J Surg* 1993 (570): 1-36
- (18) Holland, JA: Experimental and clinical experience with hyperbaric oxygen in the treatment of clostridial myonecrosis. *Surgery* 1975 (77): 75-85
- (19) Jallali, N: Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg* 2005 (198): 462-466
- (20) Johnson, JT: Hyperbaric oxygen therapy for gas gangrene in war wounds. *Am J Surg* 1969 (118): 839-843
- (21) Kaye, D: Effect of hyperbaric oxygen on clostridia in vitro and in vivo. *Proc Soc Exp Biol med.* 1967 (124): 360-366
- (22) Kindwall, EP, Whelan, HAT: *Hyperbaric medicine practice* 2004, Best Publishing Company, pp.169-245; 549-574; 575-603; 753-779
- (23) Koomanachai, p: Linezolid penetration into wound tissue of two diabetic patients before and after hyperbaric oxygen therapy. *Unders Hyperb med* 2011 (38): 11-16
- (24) Korhonen, K: Hyperbaric oxygen therapy in acute necrotizing fasciitis with a special reference to tissue gas tensions. *Ann chir et gyn* 2000, suppl 214, 7-36
- (25) Korhonen, K: Management of clostridial gas gangrene and the role of hyperbaric oxygen. *Ann chir et gyn* 1999 (88): 139-142
- (26) Lampl, L: Hyperbare Oxygenation-Stellenwert in der Intensivtherapie. *AINS* 2009 (44): 652-658
- (27) Legbo, JN: necrotizing fasciitis: a comparative analysis of 56 cases. *J Nat med Ass* 2005 (97): 1692-1697
- (28) Muhvich, KH: Evaluation of antimicrobials combined with hyperbaric oxygen in a mouse model of clostridial myonecrosis. *J Trauma* 1994 (36): 7-10
- (29) Murata, I: Characterization of systemic and histologic injury after crush syndrome and intervals of reperfusion in a small animal model. *J Trauma* 2011 (70): 1453-1463

HBOT In The Military Setting: Complications and Contraindications / Crush Injury / Soft Tissue Infections and HBOT

- (30) Myers, RA: Hyperbaric oxygen therapy for trauma: crush injury, compartment syndrome and other traumatic peripheral ischemias. *Intern Anaesth Clin* 2000 (38): 139-151
- (31) Risemann, JA: Hyperbaric oxygen therapy for necrotizing fasciitis and the need for debridements. *Surgery* 1990 (108): 847-850
- (32) Roje, Z: Necrotizing fasciitis: literature review of contemporary strategies for diagnosing and management with three case reports. *WJES* 2011 (6): 46
- (33) Stevens, DL: The role of clostridial toxins in the pathogenesis of gas gangrene. *Clin Infect Dis* 2002 (35, suppl 1): 93-100
- (34) Stevens, DL: Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. *CID* 2005;41, 1373-1406
- (35) Sugihara, A: The effect of hyperbaric oxygen therapy on the duration of treatment for soft tissue infections. *J Infection* 2004 (48): 330-333
- (36) Wagner, S: Is intensive multimodality therapy the best treatment for Fournier gangrene? Evaluation of clinical outcome and survival rate of 41 patients. *Surg Infect* 2011 (12): 379-383
- (37) Weaver, LK: Hyperbaric oxygen in the critically ill. *Crit Care Med* 2011 (39): 1784-1791
- (38) Wilkinson, D: Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. *Arch Surg* 2004 (139): 1339-1345
- (39) Zamboi, WA: management of Fournier's gangrene and the role of hyperbaric oxygen. *J Hyp med* 1990 (5): 177-186
- (40) Zamboni: Morphological analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effect of hyperbaric oxygen. *Plast Reconstr Surg* 1993 (91): 1110-1123
- (41) Ziser, A: Hyperbaric oxygen therapy for Fournier's gangrene. *Crit Care Med* 1985 (13): 773-774