Annex A – SCIENTIFIC BACKGROUND AND RATIONALE FOR THE USE OF HYPERBARIC OXYGEN THERAPY IN DISCUSSED DISEASES AND CONDITIONS

A.1 ACOUSTIC TRAUMA

A.1.1 Pathophysiology of the Condition

Acoustic trauma is defined as injury to the "hearing structures" in the inner ear due to very loud noise.

Damage to the hearing mechanisms may be caused by an explosion near the ear, gunshots, or by long-term exposure to loud noises. Symptoms are hearing loss (usually partial and involving high-pitched sounds) and noises, ringing in the ear (tinnitus). The higher the intensity of the sound, the greater its potential to cause hearing damage. The sound pressure levels capable of causing acoustic trauma vary among individuals on the average around 130 – 140 dB. Single exposures to impulse noises above 140 decibels have the potential to cause permanent damage. A gunner on a 105 mm towed howitzer experiences an impulse noise of 183 dB [1]. A service member who shoots a rifle is exposed to 157 – 163 dB and a gunner with a machine gun, 145 dB. Military men suffering from an improvised explosive device are exposed to impulse noise in excess of 180 dB.

Exposure to noise from firearm use during military service is probably the most frequent etiology of acute acoustic trauma worldwide; it is most commonly regarded as a professional disease in military populations. The hearing loss is sudden, sometimes painful, and is often followed by a (newly) onset of tinnitus. Soldiers sent to battle zones are over 50 times more likely to suffer hearing loss and/or tinnitus than soldiers who do not deploy. As a result of ongoing combat operations, one in three post-deploying soldiers report acute acoustic trauma and one in four reports on hearing loss and/or hearing complaints, including tinnitus.

The number of US service members on disability because of hearing damage is expected to grow up by 18% per year, with disability payments totaling $1.1 billion annually in 2011. Hearing loss is the fourth leading reason for medical referral for combatants routinely returning from their deployments [2]. From more than 5,000 post-deployment soldiers from Iraq and Afghanistan who were referred to audiologists, 1,550 reported exposure to acute acoustic blast trauma. Of those, 72% had resulting hearing loss. Among all post-deploying personnel who received hearing evaluations, 28% have some degree of hearing loss. More than two-thirds of British troops returning from Afghanistan are suffering severe and permanent hearing damage [3].

A.1.2 Rationale for HBO Therapy

A.1.2.1 Theoretical Benefit of HBO Therapy

Direct mechanical injury to the sensory cells of the cochlea is thought to be the main mechanism of injury in acoustic trauma. The cochlear activity is dependent on energy supply which is itself directed by oxygen metabolism [4]. The stria vascularis and the organ of Corti, as well as organs with high metabolic activity, have high oxygen consumption. Arterial oxygen diffuses from the capillary into the inner ear fluids; and increased partial oxygen saturation influences the oxygen tension of the inner ear. The use of Hyperbaric Oxygen Therapy (HBO) has long been proposed as a good way of increasing perilymphatic oxygen pressure: the vastly increased arterial and capillary oxygen tension increases the oxygen tension of the perilymphatic fluid by more than 400% of its initial value, and this state persists for one hour after termination of HBO. This high partial oxygen pressure restores oxygenation to the hypoxic areas of the cochlea and accelerates the biological mechanisms involved in functional recovery. Furthermore, oxygen diffusion from the middle

ear through the round window exerts its rheological effects in the cochlear region independently of haematocrit and blood viscosity.

The rationale in treating acoustic trauma with HBO is not only based on its general effects (massive increase in dissolved oxygen, vasoconstriction leading to oedema reduction, restoration of blood flow, deformability of red blood cells), but also on the potential for specific local effects. HBO may have an effect in restoration of oxidative metabolism in the stria vascularis and in protection of neurosensory cells whose metabolism has slowed down and thus secondarily initiate the recovery of physiological energy metabolism. In improving oxygenation in the inner ear, HBO increases transmembrane potential and ATP synthesis, and activates cell metabolism and the Na+/K+ pump, leading to a restoration of ionic balance and of electrophysiological function in the labyrinth.

A.1.2.2 Animal Experiments

Using animal experiments, it was established that HBO leads to an important increase in the oxygen partial pressure of the perilymph of the guinea pig cochlea [5]. It was shown that 60 hours after damage by acoustic trauma, the number of inner ear sensory cells that had suffered morphological damage in the animal was lower in those treated with HBO than without it. Cochlear blood flow, perilymphatic partial pressure of oxygen, cochlear microphonics, compound action potentials of the auditory nerve, and auditory brainstem responses were studied in noise-exposed guinea pigs during and after the additional treatments [6]. The best therapeutic effect on noise-induced hearing loss was achieved with a combination of HBO and prednisolone. All other therapies were significantly less effective or did not improve noise-induced reduction of auditory evoked potentials. The actual efficiency of the present medical treatments of acoustic trauma of guinea pigs indicated that in some animals the recovery of the threshold shifts are complete despite the fact that significant areas of hair cells are damaged [7]. Results indicated that pure oxygen and carbogen seem ineffective, and corticoids and combined treatment with corticoid/hyperbaric oxygen improve functional and morphological recovery.

After the exposure of Wistar rats to 60 impulses of 162 dB from a 7.62 mm assault rifle, animals were exposed to HBO for 90 min daily for 10 consecutive days at 0.25 MPa [8]. After 4 weeks, auditory brainstem responses were measured and cochleae were processed by light microscopy. The impulse noise caused permanent damage to the cochlea, but a significantly smaller number of hair cells were missing in the HBO group. The morphological damage was also reflected in function, as measured by auditory brainstem responses. Signal-to-noise ratios of rats were significantly decreased after the acoustic trauma [9]. HBO was started at different time after noise exposure. The evaluation on the third day showed that recovery had begun in all groups except the group in which the HBO was started 1 hour after exposure.

The influence of HBO on regeneration processes which take place in the inner ear of chickens after exposure to wide-band noise at the level 120 dB for 48 hours was found [10]. HBO applied once a day after exposure to the noise restricted extent of damage and decreased the dynamics of hair cells injury. The effects of HBO on guinea pigs exposed to noise in the 4 kHz range with intensity of 110 dB sound level pressure for 72 h showed significant difference in the signal-to-noise ratio of the distortion product otoacoustic emission and the scanning electron microscopy findings revealed damaged outer hair cells after exposure to noise, with recovery after HBO [11].

A.1.2.3 Human Data

Victims of acoustic traumata occurring in military service were treated with HBO [12]. A statistically significant amelioration of this hearing-loss was found. The results are more convincing when HBO could be started as soon as possible. The effect of HBO on 122 soldiers suffering from acute acoustic trauma showed that HBO shortened the course of healing with respect to high-pitch perception dysacusis [13]. The results of treatment after an observation period of 6 weeks were also more favourable when patients were treated with

HBO in comparison to patients given only infusions or vasoactive substances. Similarly, the use of HBO also reduces the frequency of relapse following discharge from hospital. In contrast, the vasoactive substance chosen (betahistine) failed to have a favourable effect on the course of healing. No method could be compared with HBO in eliminating tinnitus following acoustic trauma.

Therapeutic results confirmed that 65% of miscellaneous treated patients demonstrated a hearing improvement [14]. In the cases with no hearing improvement, HBO was administered after unsuccessful conventional therapy. If HBO had started from 2 to 6 weeks since acoustic trauma, one half of the cases showed a marked hearing gain, one-third of patients showed a moderate improvement. 4% of patients no longer experienced tinnitus, 81% observed a significant decrease and only 1% an intensity increase of their tinnitus. If HBO was administered at a later stage, but still within 3 months following a trauma, 13% of patients showed a definite improvement in hearing and 25% a moderate improvement. 7% of them no longer suffered from tinnitus, 44% reported an intensity decrease. If HBO was started longer than 3 months up to several years, no hearing improvement was found in the majority of patients; however, one third of the cases reported an intensity decrease of tinnitus. It may be deduced that HBO is recommended and warranted within 3 months after onset of disorder.

Significant difference in audiometry results obtained before and after HBO was noted in 4 kHz when considering all damaging factors that caused acoustic trauma and in 6 kHz only for damage resulting from shooting [15]. 4 days was the mean time interval between acoustic trauma and starting the pharmacological treatment, 7 days was the mean time interval for the HBO commencement. Statistically significant difference was noted in 4, 6, 8 kHz when HBO was started within 5 days since the acoustic trauma. HBO combined with steroids was an effective method of sensorineural hearing loss treatment following acute acoustic trauma.

The average recovery of hearing and cessation of tinnitus was significantly better after HBO than after normobaric oxygen therapy [16]. The recovery from hearing impairment and tinnitus treated with HBO was compared with ears treated with normobaric oxygen. Both were applied daily for 1 – 8 days. The average recovery of hearing both at high and speech frequencies was significantly better and tinnitus persisted less commonly after HBO.

A comparative review of three different treatment regimens in Belgian military personnel suffering from acute acoustic trauma was reported in 2011. Patients were unique in that a baseline audiometry result was available often less than one year old. Depending on the possibility and timing of HBO treatment, patients were treated with high-dose cortisone and piracetam (a rheological agent), either alone (Group 1) , associated with one standard HBO session per day for 10 days (Group 2) or with two HBO sessions and intravenous cortisone therapy (Group 3). Both treatment Groups 2 and 3 showed significantly better hearing gain than when no HBO was associated [17].

There is evidence that the prompt use of HBO in patients, who have lost their hearing suddenly (ISSHL – Idiopathic Sudden Sensorineural Hearing Loss), may reduce the duration and extent of hearing loss. This is the subject of current research [18]. There is a general consensus that the sooner any treatment is started, the better is the prognosis. HBO implies the administration of oxygen under pressures not lower than 0.2 MPa and for durations not less than 60 min [19]. HBO must be seen as part of a therapeutic continuum, without any interruption of the chain of treatment. It cannot be considered as an isolated treatment modality. In accord with the opinion of experts and with the assistance of literature reviewers, the 7th European Consensus Conference on Hyperbaric Medicine has graded HBO in sudden deafness to Level C of evidence (Consensus opinion of experts).

A.2 ARTERIAL GAS EMBOLISM

A.2.1 Pathophysiology of the Condition

Arterial gas embolism, the presence of air or another gas in the arteries, can occur as a result of pulmonary overpressure (usually as a result of uncontrolled ascent, even possible from very shallow depths, as little as 1 meter depth), [20] but also as a result of blast injury (in an out of water) [21], penetrating chest trauma [22], lacerating liver trauma [23], and passive entry of air into wounds that are elevated above the heart level [24]. Intravenous air entry may be asymptomatic unless a Patent Foramen Ovale (PFO) or Atrial Septal Defect (ASD) is present [25] or when massive amounts of air enter the vessels [26], as the lungs act as a very efficient bubble filter [27].

There are several possible mechanisms of injury. Massive venous air embolism may cause an intracardiac "vapour lock" when the right heart chambers are completely filled with gas. Large quantities of gas cause direct arterial occlusion. However, animal studies have shown that even if no vessel occlusion existed, bubbles cause a progressive decline in cerebral blood flow [28], by neutrophil activation subsequent to endothelial damage by the bubble. In many cases of cerebral gas embolism there is clinical improvement after the initial symptoms, followed by a delayed deterioration a few hours later [29].

Venous gas embolism manifests as hypotension, tachypnea, hypocapnia, pulmonary oedema or cardiac arrest. Arterial gas embolism presents as brutal loss of consciousness, confusion, focal neurological deficits, cardiac arrhythmias or ischemia (due to coronary embolisation of gas). The diagnosis is mainly clinical, with possible evidence of intravascular gas using ultrasound or by direct venous aspiration of gas. Brain imaging, even in the presence of severe neurological abnormalities, may be demonstrating no gas in the cerebral vessels, as these gas bubbles are usually quickly fragmented by the pulse waves and the reactive hypertension [30].

A.2.2 Theoretical Benefit of HBO

Application of hyperbaric pressure reduces the volume of the gas embolus (Boyle's Law); it enables gas removal by denitrogenation (effect of the hyperoxygenation) [31]; it maintains oxygenation in the ischemic tissues and it decreases intracranial pressure and cerebral oedema formation [32].

A.2.3 Clinical Scientific Evidence

Recompression treatment with oxygen has been considered the standard of care since the early 1960's [33],[34]. Human randomised prospective trials obviously are lacking, although retrospective reviews have been conducted, revealing significantly better outcomes with the use of recompression treatment versus non-recompression therapy only [35],[36],[37],[38]. Retrospective data published in 1964 showed a decrease in mortality from 93% with no treatment to 33% with conventional aggressive treatment (left lateral decubitus position, vasopressors, and oxygen by positive pressure). A later study showed a mortality rate of only 7% in 30 patients treated when hyperbaric oxygen was utilized [39]. Animal studies document the superiority of HBO above conventional treatment [40],[42].

As the pathophysiology of the condition involves tissue ischemia, treatment should be started as soon as possible after the clinical diagnosis has been made [44]. However, hyperbaric oxygen therapy has been reported successful in persistent symptoms even after a significant delay [36]. HBO therapy is indicated even if the patient appears to have recovered completely, because of the risk of secondary deterioration [29].

Repeat hyperbaric treatment, usually two or three but occasionally up to 10 sessions, can be performed as long as there is stepwise improvement after each session [43]. As patients can be hemodynamically highly unstable, appropriate medical intensive care and monitoring is mandatory [36],[45]. Adjunctive therapies

include adequate fluid management (in case of concomitant decompression sickness there may be significant hemoconcentration), along with possibly lidocaine [40],[41], NSAID and Low-Molecular Weight Heparin in case of immobilisation for more than 24 hours [46].

A.3 BURN INJURY – LIFE-THREATENING (HIGH TBSA OR RESPIRATORY BURNS)

See Section A.4.

A.4 BURN INJURY – NON-LIFE-THREATENING

A.4.1 Introduction

When soft tissues (such as skin and muscle) are damaged by burning, the blood flow in the damaged area is sharply reduced. This causes an area of swelling which radiates away from the area of damage, in all directions. The swelling may extend deep into muscles, and over the surrounding skin, and cause more damage than the initial injury.

HBO can help to reduce this swelling. The extra oxygen slows down the leak of fluid out of the damaged blood vessels. It also reaches tissues in the damaged area, allowing them to recover. The extent of tissue removal, and the need for amputation, is therefore reduced. In order to work, however, HBO must be used as early as possible.

A.4.2 Pathophysiology of the Condition

Thermal energy transfer to cutaneous cells cause cell and tissue destruction by direct coagulation and cell lysis. In the area surrounding the burn injury, interstitial oedema occurs, causing a microvascular compromise, with red blood cell sludging and finally capillary stasis [84]. The maximum of this microvascular compromise has been shown to occur within 24 hours [54],[55],[56].

Tissular hypoxia and ischemia occurs as a result of this stasis [82], which increase oedema by loss of integrity of the capillary wall (endothelial cell contraction). This fluid loss, by changing the oncotic pressure gradient across the capillary vessel wall, further decreases the intracapillary fluid pressure and thus increases stasis [57],[58],[59].

As a result, areas of burnt tissue that were initially second degree (partial thickness burn), are observed to progress within the first 24 hours after the burn, into deep second degree or third degree (full thickness) burns, needing early excision and grafting in order to heal. This happens even with optimal fluid resuscitation protocols [50],[53].

The tissue lesion caused by thermal energy induces a massive inflammatory reaction, with leucocyte stimulation, margination and activation. The resultant production of oxygen free radicals is further enhanced in the second (reperfusion) stage of the burn wound evolution [83]. This phenomenon is partly responsible for the generalized inflammatory reactions occurring in the bowel and lungs of severely burnt patients. This may lead to multi-organ failure and semi-delayed death [63],[64],[65],[66].

The third cause of death in burn patients is related to systemic infection during their hospital stay. Not only is there a large possible port of entry by loss of the epithelial barrier, also the immunologic state of a severely burnt patient is depressed, making him/her much more susceptible to infections [60],[61],[62],[90].

The mainstay of treatment of deep partial thickness or full thickness burns is the excision of the affected skin and coverage with a temporary (cadaver skin, synthetic skin equivalent) or permanent (autograft) epithelial

layer [48],[49]. In order for such a skin graft to "take" the underlying wound bed must be well perfused and "healthy". In cases where the oxygenation of the avascular skin graft cannot be ensured by diffusion of underlying wound bed (either by insufficient vascularisation or by utilisation of molecular oxygen by infectious microorganisms) the skin graft will fail, necessitating a renewed surgical intervention, possibly after a delay of approximately 10 – 14 days, needed for healing of the donor site. This increases the risk of infection and systemic complications [47],[51].

In all of these pathophysiological mechanisms, hypoxia plays a pivotal role. Oxygenation of ischemic tissues must be done in a rapid and massive way, in order to decrease paradoxical tissue damage by ischemia-reperfusion phenomena. Hyperbaric oxygenation is the only therapeutic means capable of ensuring this [98],[99].

A.4.3 Theoretical Benefit of HBO

A.4.3.1 In Vitro Studies

Antibacterial effect:

- Oxygen pressures as high as 200 mmHg have been shown to effectively inhibit growth and proliferation of anaerobic and facultative aerobic bacteria [86].
- A synergistic effect of oxygen and antibiotics has been demonstrated for clindamycin, aminoglycosids, amoxycillin/clavulanate and quinolones; this effect is not apparent for metronidazol, an antibiotic specifically developed for anaerobic infections [87].
- The bactericidal activity of polynuclear leukocytes is severely impaired in case of low surrounding oxygen tensions, limiting the capacity for "oxidative burst" of those cells. In fact, it has been shown that at "normal" tissue tensions of 40 – 50 mmHg, polynuclear leukocytes only function at half-maximal oxidant killing capacity, and that this capacity is maximal at around 300 mmHg [88],[89].

A.4.3.2 In Vivo (Animal – Human)

A.4.3.2.1 Fluid Loss

In a canine burn model of 40% TBSA, a reduction of the plasma loss of about 40% has been observed when HBO was administered in the early phase after injury (3.0 ATA, twice daily) [68]. A similar effect has been observed in a human – prospective, randomized – study, illustrating not only the pre-capillary vasoconstriction induced by HBO but even more importantly, the preservation of the integrity of the capillary vessel wall: in the first 24 hours after the burn, HBO-treated patients needed an average volume resuscitation of 2.2 ml/kg per %TBSA, whereas the control group needed 3.4 ml/kg % – a reduction of 35% [69]. A retrospective human study of 21 patients, of which 10 received HBO (2.0 ATA, 90 minutes, twice daily) in the acute phase, confirmed this reduction in necessary perfusion volumes [70].

A.4.3.2.2 Preservation of Dermal Elements [72],[76],[79]

In study in 1996, a "deep partial thickness" burn of 5% TBSA was created in rats which progressed, in a reproducible way, towards "full thickness" after 24 hours. Comparing two groups of animals, one who received a "classic" burn treatment and the other who received the same treatment plus two sessions of HBO (2.0 ATA, 60 minutes) per day, a preservation of deep dermal elements was observed, classifying the burn still as "second degree" at day 5 in the HBO-treated animals [73]. Very recently, a similar study report was published, confirming the effects of HBO on the preservation of regeneratory active follicles ($p = 0.009$) and on the rapidity of epithelial regeneration ($p = 0.048$) [74].

A.4.3.2.3 Antibacterial Effects

The antibacterial effects of HBO which have been known by its use in other pathologies have been confirmed in an animal burn wound model, even though its effect was less than that of silver sulfadiazine [75],[85]. This is not surprising, since molecular oxygen does not have a direct antibacterial effect at the pressures obtained in tissues under HBO. However, HBO restores the oxido-reduction potential in the (burned) tissues, thereby maintaining the leukocyte killing capacity of PMN and preserving the natural resistance against infection [102],[103].

A.4.3.2.4 Reduction of Ischemia-Reperfusion Effects

Several animal studies have demonstrated the reduction of inflammatory (leukocyte) infiltration in the burnt tissues as well as in distant tissues (lung and bowel) [96].

Oxidative damage has been evaluated in HBO-treated animals compared to classically treated animals, showing a reduction in free radical end products, TNFa and complement activation. In humans, this has been further confirmed with a reduction in soluble IL-2 receptor and preservation of fibronectin in burn patients [100].

Considerable attention has been given to the use of HBO in inhalation injury. There is currently a fear that it may cause worsening of pulmonary damage, particularly in those patients maintained on high levels of inspired O_2 [52]. Grim and colleagues from the University of Chicago Burn Center [101] reported no evidence of oxidative stress in HBO treated burn patients, using exhaled products of lipid peroxidation as a marker. Ray and colleagues [110] have analyzed serious burns being treated for concurrent inhalation injury, thermal injury, and adult respiratory distress syndrome, and noted no deleterious effect in those patients on continuously high-inspired oxygen. More rapid weaning from the ventilator was possible in the HBO treated group ($p < 0.05$). A significant savings in cost of care was achieved through the use of hyperbaric oxygen in this study ($p < 0.05$). There is presently no evidence to controvert these data [104],[105].

A.4.4 Clinical Scientific Evidence

Although a number of very convincing prospective and retrospective studies have been published [80],[81],[94],[95], demonstrating a reduced need for surgical interventions, a reduced mortality, a reduced duration of hospital stay, and reduced cost of treatment when systematically using HBO therapy adjunctive to classical therapy, to date no randomized controlled prospective, placebo-controlled trial has been published to unequivocally prove the effect of HBO therapy [77],[78],[106],[107]. Therefore, the acceptance of HBO as a valuable adjunctive treatment remains limited to those burn centers that are capable of providing early, intensive care HBO treatments, without adding supplementary (infectious, hemodynamic) risks to the patient's condition [67],[71],[108].

Over the past 20 years, the pendulum swung to an aggressive surgical management of the burn wound, i.e. tangential excision and early grafting of the deep second-degree, probable third-degree burns, especially to functionally important parts of the body. Hyperbaric oxygen, as adjunctive therapy, offers the surgeon yet another modality of treatment for these deep second-degree burns to the hands and fingers, face and ears, and other areas where the surgical technique of excision and coverage is often imprecise. These wounds, not obvious third degree, are then best treated with topical antimicrobial agents, bedside debridement, and adjunctive HBO, allowing the surgeon more time for healing to take place and to better define the extent and depth of injury. Adjunctive HBO can drastically reduce the healing time in the major burn injury, especially if the wounds are deep second degree [91],[92],[93],[94],[95].

There is some theoretical benefit of hyperbaric oxygen therapy for obviously less well-defined third-degree burns. Fourth-degree burns, most commonly seen in high voltage electrical injuries, benefit from several

processes, including reduced fascial compartmental pressures, reduced swelling of injured muscle due to preservation of aerobic glycolysis, and greatly reduced anaerobic infection.

Finally, reconstruction utilizing flaps and composite grafts, e.g. ear to nose grafts, can be greatly facilitated with HBO [97]. Often the decision to use HBO will be made intraoperatively because a surgeon is concerned about a compromised cutaneous or musculocutaneous flap.

In summary, HBO should be used in life-threatening burn injuries only when it can be applied early and aggressively, in order to limit the secondary tissue destruction caused by the thermal injury and its consequences.

In non-life-threatening burn injuries, especially to "difficult" areas such as ears, nose, hand, perineum, HBO should also be applied early in order to limit the early debridements and progressive tissue destruction [111].

A.5 CARBON MONOXIDE POISONING

A.5.1 Introduction

Carbon monoxide (CO) is a colorless, odorless and tasteless gas produced by the incomplete combustion of carbon-based compounds. While the heme catabolism is an endogenous source of CO, most frequent exogenous sources are house fires, poorly functioning heaters, chimneys, gas–powered electrical generators, automobile and cigarette smoke. Several occupational groups such as fire fighters and miners tend to be most at risk for CO poisoning. Some age groups and particular conditions such as the elderly, unborn babies, infants, children and pregnant women are also more susceptible to poisoning [112],[113]. Additionally, individuals with chronic heart disease or respiratory insufficiency and patients with decreased oxygen-carrying capacity (i.e. anemia, blood cancer) are more prone to suffer severe poisoning.

Cardiac and brain tissues are the most vulnerable tissues in CO poisoning [114]. Signs and symptoms associated with cardiotoxicity or brain injury are usually observed in the severely poisoned patient. While cardiotoxicity is usually responsible for acute death, brain injury is mostly responsible for delayed signs and symptoms. Pathologies implicated with cardiotoxicity are tissue hypoxia causing cellular damage, CO binding to cytochrome-c oxidase leading to impaired cellular metabolism, ROS mediated lipid peroxidation and cellular death. CO induced cardiotoxicity causes decreased myocardial function (pump failure) due to myocardial ischemia. Additionally, CO cardiotoxicity may lead to several cardiac rhythm abnormalities [115]. The central nervous system is particularly sensitive to the toxic effects of CO poisoning. While petechial hemorrhage associated with severe CO poisoning may cause death in the acute phase, brain edema accounts for the majority of CO related deaths in the sub-acute phase. The most common clinical scenario affecting the central nervous system in CO poisoning, however, is Delayed Neurologic Sequelae (DNS). CO poisoning may cause demyelination of the nerves and may lead to necrosis of the globus pallidus, susbstantia nigra, thalamus or putamen, namely the basal ganglia [116]. The more severe the acute state the higher the risk of DNS development. Neurological deterioration may occur over a wide span of time, but commonly occurs within 2 to 40 days. The prevalence varies from 1 to 47%. Older people are more susceptible. While complete resolution usually occurs within 2 months in patients with mild CO poisoning, it may take up to one year in patients with severe poisoning [117].

A.5.2 Pathophysiology of the Condition

There are 3 main pathways implicated with carbon monoxide poisoning:

- Hypoxia;

- Perivascular injury; and
- Excitotoxicity.

A.5.2.1 Hypoxia

CO rapidly binds to hemoglobin and forms carboxyhemoglobin (CO-Hb). Compared with oxygen, CO binds to hemoglobin with a 200 fold higher affinity. As the level of CO-Hb increases the oxygen hemoglobin dissociation curve shifts to the left and increases its affinity for oxygen ultimately causing tissue hypoxia. CO causes hypoxia through several mechanisms, as detailed in the sub-sections below.

A.5.2.1.1 Anemic Hypoxia

Anemic hypoxia is the earliest and most frequent consequence of CO poisoning. Following the binding of CO, hemoglobins are almost non-functional and can neither bind nor release oxygen. Although this condition is termed as anemic hypoxia, it significantly differs in that in carbon monoxide poisoning, in contrast to anemia, the oxygen dissociation curve displays a leftward shift and therefore the affinity of hemoglobin for oxygen is increased, further limiting oxygen delivery to the tissues.

A.5.2.1.2 Histotoxic Hypoxia

Carbon monoxide does not merely bind to hemoglobin but also to a critical enzyme functioning normally in the electron transport chain, i.e. cytochrome a,a3 enzyme. This binding incapacitates oxidative phosphorylation and thereby deprives body systems of their energy source.

A.5.2.1.3 Oligemic Hypoxia

Oligemic hypoxia occurs due to the binding of carbon monoxide to myoglobin. The resulting non-functioning compound is termed as carboxymyoglobin (Mb-CO). Mb-CO is, in great part, responsible for carbon monoxide induced cardiotoxicity. Severe poisoning with Mb-CO may cause ischemic myocardial damage and impair cardiac output thereby leading to oligemic hypoxia. Additionally arrhythmias are frequently observed in patients with Mb-CO induced cardiotoxicity.

A.5.2.2 Perivascular Injury

CO binds to the heme proteins in platelets. This binding activates platelets, which release Nitric Oxide (NO) to plasma [118]. NO reacts with neutrophil derived superoxide and form the peroxynitrite ($ONOO^-$) molecule, which is a potent nitrating and oxidizing agent. Peroxynitrite activates platelet adhesion molecules and causes platelet-neutrophil aggregation [119]. Neutrophil interaction with platelets or with the endothelium is a strong stimulus for degranulation. While primary granules of neutrophils comprise several deleterious enzymes such as elastase, Myeloperoxidase (MPO) and lipase, secondary or tertiary granules involve metalloproteinases and ß2 integrins. MPO release promotes endothelial oxidative stress and induces the synthesis of adhesion molecules for neutrophils, which lead to additional neutrophil aggregation. Neutrophil-derived proteases react with Xanthine Dehydrogenase (XDH) to form Xanthine Oxidase (XO), which is the major source of Reactive Oxygen Species (ROS), particularly superoxide, in the sub-acute phase.

A.5.2.3 Excitotoxicity

CO poisoning causes neutrophil diapedesis and brain lipid peroxidation by activating neutrophils [120]. Endogenous protective mechanisms against oxidative stress are impaired due to XO activation and lipid peroxidation occurs within the brain tissue. Lipid peroxidation products such as malondialdehyde interact

with Myelin Basic Protein (MBP) and change its three-dimensional structure and stimulate lymphatic immune reaction, which in turn induces microglia expression and activation, eventually starting an inflammatory process. Lipid peroxidation products cause injury to neural membranes and are believed to be responsible for neurologic symptoms and sequelae.

Glutamate is an important neurotransmitter implicated with neural toxicity [121]. Glutamate induces N-Methyl D Aspartate (NMDA) activation and Ca^{+2} influx into the cell cytoplasm. Ca^{+2} activates several deleterious enzymes such as protease, phospholipase and endonuclease, which together cause cellular membrane damage and DNA injury.

A.5.3 Theoretical Benefit of HBO

While the half-life of oxygen is around 320 minutes in room air (21% oxygen), it is approximately 60 minutes while inspiring 100% oxygen from a non-rebreather mask and only about 23 minutes while inspiring 100% oxygen inside a hyperbaric chamber at 3 atm abs. The effects of HBO on hypoxia associated with CO poisoning is well established.

Given the fact that lipid peroxidation is an important aspect of CO-induced neurological injury, the inhibition of Beta-2 integrins on the cell surfaces of neutrophils by HBO treatment is recognized as a significant benefit of HBO treatment. HBO treatment at 3.0 atm abs has been shown to prevent the adherence of neutrophils to the endothelium and thereby blocked leukocyte-mediated inflammatory changes and alleviated Reactive Oxygen Species (ROS)-related oxidative stress [124].

CO binds to the cytochrome a,a3 enzyme of the electron transport chain in the outer membrane of the mitochondria and impairs electron transport, thus oxidative phosphorylation and ATP production. This causes histotoxic hypoxia as well as an increase in ROS formation. HBO has been shown to improve mitochondrial function and increase adenosine triphosphate production [122].

Last, but not least, HBO resolves cerebral edema through vasoconstriction [123]. Indeed, HBO treatment is unique in increasing oxygenation while causing vasoconstriction.

A.5.4 Literature

Experimental studies have shown that in addition to resolving tissue hypoxia, HBO treatment restores mitochondrial oxidative metabolism [122] prevents lipid peroxidation [124] and impedes leukocyte-endothelium adhesion [125].

The majority of clinical studies with HBO have demonstrated favorable outcomes as compared to treatment protocols without HBO. Weaver et al. in a randomized, double-blinded, placebo-controlled study conducted on 152 patients, administered either HBO or normobaric oxygen to patients with CO poisoning. Almost half of the patients had a history of loss of consciousness 8% of whom were intubated. Of note, patients in the HBO group received 3 sessions within 24 h of which the first comprised treatment at 3.0 atm abs pressure for 50 min and treatment at 2.0 atm abs for 60 min, followed by two additional sessions at 2.0 atm abs for 90 min oxygen breathing, each. At 6-weeks follow-up, neurologic examinations revealed that 25% of patients who received HBO versus 46.1% who did not had still signs of neurologic sequelae [odds ratio: 0.39; 95% CI 0.20 to 0.78] [117].

In another randomized controlled study, 65 patients with CO poisoning received either HBO or normobaric oxygen. Patients with a history of loss of consciousness were excluded and hence the study assessed merely patients with mild to moderate CO poisoning. Patients in the HBO group received only 1 HBO session with a maximum pressure at 2.8 atm abs. While none of the HBO treated patients experienced neurologic sequelae at follow-up, 23% of those who did not receive HBO suffered various symptoms related to neurologic deterioration [126] .

Gorman et al. [127] in a non-randomized longitudinal study reported their results from 100 patients with CO poisoning. Of these 8 received normobaric oxygen alone, 24 one HBO session and 68 two or more HBO sessions. At study completion data analysis revealed that while patients who received NBO or a single HBO displayed similar rates of neurologic sequelae at both discharge (63 and 46 %) and one month follow-up (67 and 50 %); a significantly lower rate of neurologic sequelae, at discharge and one month follow-up, was observed in patients who received 2 or more HBO sessions (13 and 18 %, respectively).

In contrast to these trials, several others failed to demonstrate a benefit of HBO in CO poisoning. Rapahel et al. [128] in an unblinded study randomized a total of 343 patients to receive either NBO or 1 session of HBO administered at 2.0 atm abs. None of the patients had a history of loss of consciousness. Outcome results assessed at one month follow-up revealed similar rates of persisting neurologic symptoms (32.1% vs. 33.8%, respectively) for both groups. Patients received additional HBO sessions, up to 6, until neurological recovery.

Scheinkestel et al. [129] enrolled a total of 191 patients, 73% of whom suffered severe CO poisoning, and almost half were comatose. Patients were randomly assigned into either HBO or sham HBO groups and received continuous oxygen by face mask for 3 days between the sessions. Outcomes were assessed at completion of study and at one month follow-up. While 74% of the patients in the HBO group displayed persistent neurologic sequelae at treatment completion, 68% in the sham HBO group displayed similar symptoms. Unfortunately a large number of the patients were lost to follow-up at 1 month (54%), rendering reported results controversial. Nonetheless, study results revealed similar outcomes for each treatment arms at one month follow-up. This study was criticized on the basis that patients in the control arm received high oxygen doses and hence results could not be generalized.

Annane et al. [130] recently conducted two randomized single blind controlled trials. While the first trial included 179 patients who suffered a transient loss of consciousness (malaise, syncope) the second included 206 patients with coma. In the first trial patients were treated with 6 h of NBO or with 4 h of NBO plus one HBO session. In the second, patients received either 4 h of NBO plus one or two HBO sessions. Of note HBO sessions were administered at 2 atm abs. In summary, the authors failed to demonstrate a significant benefit of one session HBO therapy over NBO therapy in patients with transient loss of consciousness. Similarly, two sessions of HBO therapy did not yield any benefit over one HBO session in comatose patients.

A.6 CRUSH INJURY (COMBINED TRAUMA TO BONES, SOFT TISSUE, VESSELS, OR NERVES)

A.6.1 Pathophysiology

The term crush injury summarizes traumatic vascular injuries that cause severe tissue damage and make tissue survival questionable. 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 cytogenic 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 [159],[170].

Table A-1: Patient Assessment and Recommendations for HBO.

Patient Assessment (from Kindwall, pp. 508-509) [152]				
Factors	**Scoring Criteria (0 → 10 scale)**			**Comments**
	2 points	1 point	0 points	
Age	< 40 yrs	40 – 60 yrs	> 60 yrs	1) Use ½ points when the severity of involvement is between two scoring criteria. 2) For ambulation scoring criteria subtract ½ point if walking aids (e.g. walkerette or crutches) are required. 3) Where two factors such as 'smoking/steroid use' are listed, use the scoring criteria, which reflects the more severe involvement.
Ambulation	Community	Household	None	
Smoking / Steroid Use	None	Over 5 years ago	Current	
Cardiac / Renal	Normal	Compensated with medications	Decompensated even with medications	
Neuropathy / Deformity	None	Mild-to-moderate	Severe	

Recommendations for HBO after patient assessment		
Score	**Severity of Compromise**	**HBO Indication**
8 – 10	Normal Host	No
4 – 7	Impaired Host	Yes
3 or Less	Severely Compromised Host	Yes

Clinical stages: the most used classification for crush injury is the Gustilo classification [143].

Table A-2: Gustilo Classification and Recommendations for HBO.

Use of HBO for Open Fractures – Crush Injuries (Gustilo Classification)					
Type	**Mechanism**	**Expected Outcome**	**Use of HBO and Host Status (see Table A-1)**		
			Normal Host (score 8 – 10)	Impaired Host (score 4 – 7)	Severely Compromised Host (score 3 or less)
I	Small (< 1 cm) laceration from inside to outside	Usually no different from a closed fracture	No	No	Yes
II	Large laceration, but minimal soft tissue damage	Usually no 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

Use of HBO for Open Fractures – Crush Injuries (Gustilo Classification)					
Type	**Mechanism**	**Expected Outcome**	**Use of HBO and Host Status (see Table A-1)**		
	b) Flaps or grafts required to obtain soft tissue coverage	About 50% incidence of complications (infections, nonunion)	Yes	Yes	Yes*
	c) Major (macrovascular) vessel injury	About 50% incidence of complications (infections, nonunion)	Yes	Yes	Yes*
* Consider primary amputation with adjunctive HBO for wound healing and flap survival.					

A.6.2 Theoretical Benefit of HBO

The 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 cells could remain alive without any other oxygen carriers (reduced hemoglobin and/or reduced perfusion) [133].

Secondly, an important effect of HBO is vasoconstriction, which leads to significant **reduction of edema** (more than 20%).

Third, hyperoxygenation improves the anti-bacterial action of neutrophils and is inhibitory to anaerobic microorganisms [160].

Fourth, HBO protects from **reperfusion** injuries due to the antagonism of lipid peroxidation and other cellular or humoral reactions [170].

Fifth, HBO improves the work of fibroblasts, some authors postulate a promotion of neurogenesis or even angiogenesis due to HBO. It may improve the outcome of skin grafts.

A.6.2.1 In Vivo

Animal models (rodents, dogs) of crush injury studies have shown 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 [132].

A.6.2.2 In Vitro

HBO also regulates inflammatory gene expression in endothelial cells and can lead to decrease in apoptosis expression.

A.6.3 Clinical Scientific Evidence

A Medline search was performed for the items “HBO and crush injury” back until 1969. There are well-established animal models of crush injury; however data on human casualties are rare. There only 28 hits for both items (HBO and crush injury) in Medline. Most of the data result from case reports or series of up to 35 patients. There is only one RCT that compares crush injuries with and without HBO therapy [134], where HBO improved healing and reduced surgical procedures significantly. Especially patients over 40 profited from HBO treatment.

Several clinical scales have been proposed 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;
- HBO should be administered "as soon as possible";
- If surgery is delayed for more than one hour, HBO could/should be administered first; and
- 3 – 4 HBO sessions/day for 3 days, then 2 sessions/day for 2 days, 1 session/day for 3 more days [139],[152].

Management is two-fold:

- Firstly, direct interventions are required (surgical); and
- Secondly, management of all indirect effects of the injury (fluid replacement, antibiotics, adequate oxygenation) is needed.

Data are rare, levels of evidence are low ("Expert Opinion"). There is an obvious need for more studies [141]. 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 [139],[141].

A.7 DECOMPRESSION SICKNESS – LIFE-THREATENING

See Section A.8.

A.8 DECOMPRESSION SICKNESS – NON-LIFE-THREATENING

A.8.1 Introduction

Decompression Sickness (DCS) is a clinical entity caused by the rapid desaturation of tissues due to a reduction in surrounding (atmospheric) pressure. The formation of inert gas bubbles in tissues and or in the blood stream causes mechanical damage (compression of tissue structures) and biochemical effects by the inflammatory responses between the blood – tissue fluids and the gas phase interface. This may cause pain or organ dysfunction which is essentially ischemic in nature [172]. Usually, symptoms arise within 24 hours after the pressure reduction – this may be after surfacing from a dive or after rapid pressure reduction while at altitude (e.g. loss of pressurisation in an aircraft). Cases have been described of DCS after repetitive deep breath-hold diving, but usually, DCS only arises when compressed gas has been breathed while at depth.

In underwater diving, decompression procedures have been developed since over a century ago [173], designed to allow divers to exit the water after a dive as quickly as possible with low risk of developing symptoms of DCS. However, these "dive tables" were calculated on the basis of a number of theoretical assumptions, derived from animal experiments, and are thus not completely physiologically accurate. Although they have been refined over the years, allowing more flexibility while maintaining a similar safety profile, it is generally accepted that they have a "failure rate" of approximately 0.5%. This of course depends not only on the actual profile of the dive, but also on the time and depth of the previous dive(s) as desaturation is not complete upon surfacing and residual inert gas is present in the tissues for as long as 12 hours after the dive. Decompression obligation calculations for repetitive dives and multi-day diving are less reliable than those for a single dive, and incidences as high as 1/1000 have been recorded in a cohort of live-aboard dive instructors [174].

Symptoms of DCS depend on the territory where decompression gas bubbles are lodged. They are typically classified as "mild" or "Type I" DCS – joint pains, cutaneous rashes, lymphatic obstruction, general fatigue; and "serious" or "Type II" DCS – neurological dysfunction (paralysis, paresthesias, bladder dysfunction), inner ear symptoms (vertigo, hearing loss), cardiorespiratory symptoms (the "chokes") and shock [175].

A.8.2 Theoretical Benefit of HBO

Emergency first aid of DCS consists of general cardiorespiratory support, with adequate fluid resuscitation, as well as the administration of 100% oxygen. In some cases, especially mild or equivocal DCS, and in altitude induced DCS, this may be sufficient and constitute the definite treatment [176],[177].

A return to increased pressure has been observed to alleviate the symptoms of DCS and has been used as a treatment since the mid-19th century. However, recompression with pure oxygen breathing has only been advocated since 1937 [178]. Whereas initially, recompression depth was considered the most important factor, and oxygen use was limited by its toxicity at the commonly used pressures, in 1965 lower pressure, pure oxygen tables were proposed that have been since considered the most efficient treatment for the majority of cases [179].

Hyperbaric oxygen treatment of DCS is now considered the standard of care [180]. A rapid return to elevated atmospheric pressure not only reduces the size of gas bubbles in the body, but the high partial pressure of oxygen increases desaturation and nitrogen wash-out, increases the oxygen diffusion in the tissues and thus reduces the ischemic effects of trapped gas emboli. It is likely that other effects of hyperbaric oxygen therapy play a role in the therapeutic effects, such as a reduction of oedema and of neutrophil adhesion to the capillary endothelium with subsequent extravasation and inflammation [181].

A.8.3 Scientific Evidence

Whereas animal experiments confirm that rapid recompression with oxygen results in prompt cure of DCS, it is by no means easy to extrapolate animal data to humans, as no single animal has been proven to be a perfect model. In humans, no prospective, randomised studies have been performed to compare recompression with expectant management; however, non-randomised outcome studies comparing the "historical" US Navy recompression treatment tables (the US Navy Recompression Tables 3 and 4) tested and recommended since 1945 with "minimal pressure oxygen-breathing" tables in 1965 showed a reduction in failure rate of over 50% [179]. Epidemiological data indicate, as expected, that early hyperbaric treatment yield more likely a complete resolution of symptoms [182],[183]. Current recommendations indicate that, unless recompression can be done within a few minutes, a time frame within 6 hours yields is a reasonable objective [182],[187],[188]. Current data have not established a maximum time after which recompression would be ineffective [184],[185],[186]. US Navy oxygen recompression tables (and similar Royal Navy – UK and Comex – FR tables) are most widely used and have achieved a high degree of success in the treatment of DCS [189],[190],[191],[192]. Higher pressure mixed-gas tables (such as the Comex 30 Heliox treatment table) present some theoretical and (animal-)experimental benefits over oxygen-only tables [193],[194], but necessitate more complex logistics and are thus reserved for facilities and personnel with the appropriate experience, expertise and hardware [195].

Repetitive treatments may be necessary in divers who do not respond satisfactorily to a single hyperbaric recompression treatment, although the efficacy of more than 5 – 10 additional (typically shorter, classical HBO treatments) has not been documented statistically in large series [196].

Adjunctive treatments, except for adequate fluid resuscitation and prophylaxis of venous thrombo-embolism for patients with leg immobility, have not been proven substantially contributing to a better outcome [197],[198],[199].

A.9 FROSTBITE

A.9.1 Introduction

Like thermal burns, frostbite has a profound impact on the local microcirculation. It can be defined either as a hyper-acute cold injury or a prolonged exposure. It has been shown that after thawing, a protracted injury phase occurs, which bears striking resemblance to ischemia-reperfusion injury as has been seen in thermal burns. Theoretically at least, hyperbaric oxygen therapy could represent the following benefits in frostbite injury:

- Reduction of secondary cell death and tissue damage by reducing ischemia-reperfusion injury;
- Early demarcation of viable versus non-viable tissue, allowing for early definite surgical intervention and more rapid rehabilitation; and
- Prevention of secondary infection of vulnerable frostbitten tissues.

These potential benefits of HBO are not unique to frostbite or burns, in fact, most acute traumatic peripheral ischemia injuries (crush, compartment syndrome, flaps and grafts, re-implantations) share pathophysiological elements with these two.

A.9.2 Literature Review

The first case report of the use of HBO in frostbite dates back from 1963 [200], but in the period 1963 – 1974, only 14 more cases have been reported in the literature. Some animal experiments were performed between 1968 and 1972, but since then, no more cases were reported until 2001 [201],[202].

Okuboye et al. [203] demonstrated in the rabbit model (rabbit foot, slow freezing in ethylene bath, rapid thawing) that the use of HBO (3.0 ATA) could reduce tissue loss from 75% in control animals to 25%. On the other hand, Gage et al., [204] using a rapid freezing model to -30°C, also in the rabbit's foot, with active and passive rewarming, could show no effect from HBO. A similarly very cold (-30°C) mouse model (Hardenbergh, 1972), demonstrated a limited benefit of HBO [205].

These differing results indicate that rapid, profound freezing injury may represent some important differences in pathogenesis and tissue injury from slow, moderately cold freezing. In fact, frostbite probably comprises a range of tissue injury from Freezing Cold Injury (FCI) to Non-Freezing Cold Injury (NFCI) to normal but cold tissue. Based on these animal data, HBO would probably only be of use in NFCI.

These animal experiments used early application of HBO, during or immediately after rewarming. Some scattered case reports seem to hint that even a long time after rewarming, HBO may be of some benefit – although, since these are uncontrolled and single reports, the evidence backing these claims is not very strong. In 2001, von Heimburg reported on a case where HBO was only applied after 4 days in a young boy whose both hands were frozen, saving all fingers [206]. Similarly, cases were reported 12 and 22 days after cold injury, where the microcirculation clinically improved dramatically after application of HBO, and this treatment was considered a key factor in the preservation of all toes and fingers [207],[208].

A.9.3 Mechanism of Action of HBO

Based on these animal experiments and human case reports, elements of beneficial action can be defined in all stadia of the injury and recovery:

- Tissue survival (capillary stasis);
- Oedema reduction;
- Infection prevention;

- Necrotic tissue demarcation; and
- Faster granulation and epithelialisation.

It follows that, at least from a pathophysiological point of view, HBO should be initiated as soon as possible, even during rewarming, to limit the ischemia-reperfusion time. However, as impairment of microcirculation persists for many days after thawing [209],[210], and as it has been shown that the accompanying inflammatory cascade effects can be mitigated by HBO (as demonstrated in several models of ischemia-reperfusion injury [211]), the effects of delayed HBO can be considered "logical", even so that it is not possible to define a time period where HBO is to be considered "beyond utility" [212],[213].

A.9.4 Clinical Experience

Our own experience is relatively limited, as HBO is not generally recognised as a standard adjunctive treatment for frostbite. Over the past 15 years, only 8 cases were treated. All of them presented late, and had already advanced demarcation and sloughing of necrotic tissue. Cases referred to our hospital are primarily Belgian soldiers suffering injury during (sub) arctic training exercises, with a typical delay of 3 – 5 days, and civilian mountaineers who suffered injury either in the Himalayas or the Alps – with similar or longer delays to HBO. Our own therapeutic results are thus not any more significant than what has been reported before. However, we can confirm that HBO, when applied "lege artis", is a low-risk, well-tolerated treatment; a conservative treatment attitude (wait and see, amputate late) is still warranted. Early HBO clinically seems to provide a good and rapid separation of viable versus non-viable tissue. Magnetic resonance angiography one week after onset of injury seems promising in estimating the possibility of recovery of fingers or toes [109]. No randomised controlled human trials are available, and probably never will be.

A.10 SOFT TISSUE INFECTIONS – LIFE-THREATENING

A.10.1 Gas Gangrene

Gas gangrene is mostly caused by C. 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 [144],[145],[146],[150]. Mechanisms responsible for the rapid tissue destruction in gas gangrene are not well understood. The most important factor for this is tissue hypoxia [137].

C. perfringens grows freely in oxygen tensions under 30mmHg. It produces 6 toxins. Alphatoxin is the most important one. It causes tissue necrosis. Thetatoxin leads to hemolysis, necrosis and cardiotoxicity [163],[164]. Clinical features are: pain, tachycardia, crepitus, hemolysis, low grade fever, bronzing of the skin, bullae formation, obtunded sensation [164].

A.10.1.1 Benefit of HBO

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 [158]. Studies on isolated bacteria have shown suppression of clostridial growth when oxygen pressure of 40 mmHg or more is applied. Oxygen pressure of 80 mmHg inhibits toxin synthesis. Spore formation is also suppressed [148],[151]. On the mouse model HBO did not improve the survival rate of patients with gas gangrene.

A.10.1.2 Clinical Scientific Evidence

Most data results from case reports, a lot from Eastern Europe and Russia. They are mostly on the scientific level of case reports or retrospective studies [131],[152]. When established within 24 hours after symptom onset HBO reduces the fatality of gas gangrene to about 5% [156]. Therapeutic regimen is the Boerema table: 20 m, 2 x 45 minutes [136]. HBO can be recommended on the basis of sound experimental evidence and favorable clinical experience [139],[147]. Additionally the therapy includes antibiotics, surgical debridements and intensive care therapy [155],[156].

A.10.2 Soft Tissue Infections and HBO

Soft tissue infections are an increasing medical problem. They occur after trauma, around foreign bodies and even spontaneously [162]. Clinical pictures vary widely (necrotizing fasciitis, Fournier gangrene, non-clostridial myonecrosis, etc.) and their etiology is multi-factorial. These infections are mostly caused by gram negative bacteria and anaerobic microorganisms. Streptococci play an important role [157].

Due to varying causes of infection the pathophysiology is not easy to describe. A common factor is tissue hypoxia that suppresses immunologic defence mechanisms [154]. Additionally there are host factors (reduced defence, vascular insufficiency, vein thrombosis). Bacteroidaceae have been shown to interfere with the host's interferon production and influence phagocytic activity.

A.10.2.1 Theoretical Benefit of HBO

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) [151];
- Improvement of tissue oxygenation [154];
- Preventing extension of invading microorganisms [147];
- Improvement of phagocytic killing activity [154];
- Edema reduction [169];
- Increased function of capillaries [170]; and
- Increased efficacy of antibiotics (e.g. aminogylcosides, linezolid) [153].

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 [146].

A.10.2.2 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 [165],[166],[167],[168],[135].

HBO is one part of a multi-modal 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 [138],[140],[161]. 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) [142],[149]. This is supported by three studies from the early 1980's [171]. Further studies are required [141].

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