Contraindications to Hyperbaric Oxygen Therapy

A review of literature from 1946-2015

International consensus meeting Lille, France
April 14th-16th, 2016
held by
Professor Daniel Mathieu

Authors:

Beatrice Ratzenhofer–Komenda[1], Freyja Maria Smolle-Juettner[2]
[1]Dept. of Cardiovascular Thoracic Anaesthesia and Intensive Care Medicine
[2] Dept. of Thoracic Surgery and Hyperbaric Medicine
University Hospital, Landeskrankenhaus-Univ. Klinikum, A-8036 Graz, Austria

Correspondence address: Email: beatrice.ratzenhofer@medunigraz.at
Phone 0043 (0)316 385 81923

I. Introduction and background

Hyperbaric oxygen therapy is considered a safe treatment modality when applied by trained personnel. Lessons learned from adverse events with sudden or delayed sequelae lead to a list of contraindications. Some of them are based on physics, like the evolution of barotrauma, others on the interaction of oxygen as a drug with other agents or pre-existing diseases.

In the course of time, conditions formerly thought to be absolute contraindications turned out to be treatable by hyperbaric oxygen. The authors performed a literature search widely sticking to the table of contraindications listed by Professor Mathieu in a chapter of Thom's book on "Physiology and Medicine of Hyperbaric Oxygen Therapy" (book ref.). These are the conditions mostly addressed by the hyperbaric societies throughout the world. There remain, of course, very rare conditions which are not discussed in this context.

Literature search comprised the following issues:

1. Absolute contraindications
1.1 unvented pneumothorax/ history of pneumothorax
1.2 acute severe bronchospasm
1.3 unvented cavities
1.4 Drugs: Doxorubicin (Adriamycin), Bleomycin, etc.
2. Relative contraindications
2.1 upper airway infection (laryngitis, sinusitis, bronchitis)
2.2 allergic rhinitis
2.3 chronic otitis
2.4 chronic obstructive pulmonary disease (COPD)
2.5 history of thoracic surgery
2.6 history of ENT surgery
2.7 epilepsy
2.8 optic neuritis
2.9 hypertension
2.10 heart failure
2.11 pacemakers
2.12 pregnancy
2.13 claustrophobia
2.14 tumor growth

Our search was done in Medline, Embase and Ovid databases from 1946 to 2015. Using mainly the above-mentioned terms as keywords we found 1310 articles related to HBOT. With more complex keywords we reduced the number of abstracts to 700. After removing duplicates and analyzing the content 74 out of 700 abstracts remained eligible. In contrast to exactly defined research fields, contraindications were empirically established based on anecdotal reports more than on prospective controlled trials. Therefore literature provides a lot of case reports which do not generate a high level of evidence but a high level of information and caveats for good hyperbaric medicine practice.

II. Literature survey of each contraindication

Literature is indicated in the reference list under each section, the books are separately listed. A selection of most informative contents is shortly summarized within tables corresponding to form 8. Those references not shown in form 8 are marked with a star in the reference list.

1. Absolute contraindications

1.1 Unvented pneumothorax (PTX) / history of PTX

If a patient with a pre-existing pneumothorax is exposed to pure oxygen under pressure used in clinical HBO setting, the volume of the pneumothorax will be smaller in the isopression phase, also due to nitrogen wash-out by oxygen. Nevertheless, as an example, a pneumothorax of 1 litre will expand to 2.5 litre volume after decompression from 2.5 ATA. It is therefore advisable to insert a chest tube prior to the session. For safety reasons a thoracic drainage set has to be ready for use in the chamber. Insertion of central venous lines shortly before the sessions have to be controlled by chest X ray with the tender being aware of a possible time delay until the patient presents with PTX that may extend to the life-threatening condition of tension pneumothorax (Kindwall, 1999, book ref.).

The most impressive case reports published between 1989 and 2008 showed that some of the patients presented with PTX during or immediately after the hyperbaric session, some of them at repeated sessions. Trauma patients and patients after CPR require increased vigilance, and patients undergoing emergency HBOT are highly suspicious for developing PTX (Kot, 2008; Cakmak, 2015; Inoue, 2013; Murphy, 1991). Over a period of 10 years, Sloan et al. ((1989) retrospectively evaluated the incidence of complications in patients with carbon monoxide intoxication requiring HBOT. A tension pneumothorax occurred in 3 out of 297 pts (1%).
In 2013, the Chinese Medical Association released a new list of contraindications where the untreated pneumothorax is considered the *only* absolute contraindication to HBOT (Ling Yan, 2015).

1.2 Acute severe bronchospasm

Apart from clinical use, Jammes et al. (1988) performed an observational study in rabbits and in 3 healthy volunteers breathing cold air or helium-oxygen at high ambient pressures between 2 and 8 ATA. Cold-induced bronchospasm was observed in 38-95% of the individuals. The incidence of bronchospasm induced by cold gas mixture inhalation is interesting but not applicable to clinical HBOT.
In 2011, Harch evaluated the safety and efficacy of HBOT in a military cohort of 16 subjects with concussion syndrome or posttraumatic stress disorder exposed to 1.5 ATA for 40 sessions. One subject experienced reversible bronchospasm.
Keenan et al. (1998) found an incidence of bronchospasm of 34% in mechanically ventilated critically ill children in a retrospective observational study. Nevertheless, the authors concluded that HBO is a safe treatment tool if the hyperbaric staff is well trained in intensive care so that most complications can be managed easily in the hyperbaric environment.
In 2008, Toklu and colleagues worked out a questionnaire to screen how hyperbaric centres dealt with these patients and how they were diagnosed . 66 out of 98 centres replied. Although not very reliable in diagnosis, but at low costs, chest X ray was

mostly used for diagnosis, and only one centre out of 66 denied HBOT to these patients. Prevalence of barotrauma was calculated at 0.00045 percent.
Residual cavities after *mandibular cyst extraction* seem to be no contraindication to HBOT as, according to the investigation of Tripathi et al.(2011), the residual size of the cavities was significantly smaller in the HBO-treated group compared to previous controls without HBO exposure.

1.3 Unvented cavities
Air trapping in *air cysts or bullae* may pose the patient at risk of pulmonary barotrauma
In 2013, Wang et al. compared 80 patients diagnosed with *otic and sinus barotrauma after HBOT* for carbon monoxide poisoning to 88 patients with acute otitis media and effusion on MRI. According to NMRI findings, rates of middle ear and mastoid cavity abnormalities were higher in the barotrauma group. Also the rate of sinus abnormalities was increased in the barotrauma group in comparison to the controls. Most abnormalities were seen in the mastoid cavity in both groups.

Irreversible spastic quadriparesis appeared in a patient with *lung bullae* suffering cerebral arterial gas embolism during decompression (Rivalland, 2010), another patient presented with tension *pneumocephalus* after HBOT for brain edema. He had a history of multiple bone fractures, untreated skull base fracture, and cerebrospinal fluid leakage. He was discharged in a vegetative state (Lee, 2008)

1.4 Drugs: Doxorubicin (Adriamycin), Bleomycin, etc.
Extravasation of Doxorubicin can cause severe tissue damage so that the application of HBO for wound healing seems reasonable. But combining Doxorubicin treatment with HBO ended up in 87% mortality in a rat model due to cardiotoxicity (Upton, 1986). Therefore a delay of 2 to 3 days is recommended between the last administration of Doxorubicin and the beginning of HBOT as the drug is likely to be eliminated from the body within 24 hours (Kindwall,1999, book ref.).

Controversial discussion arose about the impact of additional HBOT on the healing of Doxorubicin-induced skin lesions: in an animal experiment published by Aktas and co-workers (2000), 95 rats underwent subcutaneous injection of Adriamycin solution into the upper hind leg. 43 animals received HBOT, the controls did not. Lesion size was equal in both groups on day 7 but was siginificantly smaller in the HBO group on days 21 ($P= 0.025$) and 28 ($P=0.0001$) .
Contrary to these findings, another rat extravasation model with HBOT administered 3 days before and 7 days after injection showed that Doxorubicin-induced cytotoxicity was potentiated by hyperbaric oxygen. Alopecia size and markers of lipid peroxidation were determined (Monstrey, 1997).
To evaluate cardiotoxicity of HBO during doxorubicin treatment Karagoz and co-workers (2008) made an experiment in female Wistar rats. They allocated the animals to 3 treatment groups: to either HBO or Doxorubicin, or to both, i.e., Doxorubicin and HBO simultaneously for 4 weeks. The extent of cardiomyopathy was determined by echocardiography and by histopathological investigation at 8 weeks from the beginning of treatment. Doxorubicin and concomitant HBOT significantly reduced ejection fraction and fractional shortening ($P<0.001$) and caused adverse histopathological changes but significantly less than in the group treated with Doxorubicin alone ($P<0.05$). The authors conclude that HBOT does not aggravate doxorubicin-induced cardiotoxicity in rats.

HBO may also be beneficial to improve liver regeneration after chemotherapy and embolization (Firat, 2009) and to potentiate antineoplastic agents (Wheeler) but pre-treatment with HBO does not induce angiogenesis in the malign tissue to render chemotherapy more effective (Heys, 2006).

Even a long interval between bleomycin therapy and HBOT should be considered a contraindication to exposure to increased fractions of even normobaric (e.g., during anaesthesia) or hyperbaric oxygen potentially causing interstitial pneumonitis or lung failure. Lung damage is likely to be attenuated or withheld by an adequate perioperative fluid management (Kindwall, 1999, book ref.).
Interestingly, Torp and co-workers (2012) conducted a retrospective uncontrolled observational study in patients undergoing HBOT for mixed indications who were formerly treated with vinblastine, methotrexate, cisplatinum, dacarbazine, and vincristine, on average 34 months before the hyperbaric session. There were no changes in spirometry, arterial blood gases, and chest radiograph findings after exposure.

2 Relative contraindications

2.1 Upper airway infection

There are mainly case studies reported with severe affections of the upper respiratory tract like acute bacterial submucosal laryngitis and phlegmone of the neck (Jordan, 1996), cervical necrotizing fasciitis (Ye et al.), orbital osteomyelitis due to sinusitis (El-Toukhi, 1997), or the very rare manifestation of orbital osteomyelitis after hypobaric exposure (Steigleman, 2003). All authors estimate HBO a highly valuable and even life-saving adjunct to immediate surgical debridement and initially broad-spectrum and then targeted antimicrobial therapy.
There is wide agreement in the hyperbaric community to treat these severe conditions although they constitute relative contraindications to do so. On the other hand, a subject suffering from upper airway infection should avoid the hyperbaric environment unless there is a sharp indication. A fracture of the maxillary bone based on sinusitis is reported in a chamber technician (Liu, 2008).
A patient treated for diabetic foot ulcer got confused and hemiplegic after the session. On recompression her neurologic condition improved briefly but then she fell comatous and died. Autopsy showed an emphysema with a high amount of intrabronchial mucus and multifocal cortical lesions. Air embolism is likely to have caused this fatal event suggesting a potential risk of HBOT in patients with a history of pulmonary disease (Wolf, 1990).

2.2 allergic rhinitis

no articles found

2.3 chronic otitis

no articles found

2.4 Chronic obstructive pulmonary disease (COPD)

Patients with COPD are prone to air trapping in overinflated lung areas which may provoke a dangerous condition with ambient pressure changes.
Reports about patients with COPD undergoing HBOT are scarce. In 2004, Verna et al. reported 2 cases of Fournier`s gangrene, one of them had pre-existing COPD and

was treated without complications. In the authors' opinion, it is likely that many elder people with unrecognized COPD have been treated without complications so far. As compression and decompression usually are smoothly done in the clinical setting, alveoli and lung tissue are allowed to adapt slowly to pressure changes and adequate venting will be maintained.

2.5 History of thoracic surgery

According to literature, HBOT was applied due to emergency events after pulmonary resection: Togo and co-workers (2012) reported a case of air embolism that happened after pleurodesis 4 months after right lower lobectomy. She had had repetitive postoperative episodes of pneumothorax, air embolism was successfully treated in the hyperbaric chamber.
Another manifestation of cerebral arterial gas embolism occurred after diagnostic bronchoscopy in a patient who had had a lobectomy 3 months ago. Although he was treated with a delay of about 2 days with U.S. Navy Treatment Table 6 he regained consciousness and recovered without sequelae (Wherret, 2002).
Postoperative ischemia of an anastomosis after central airway resection could be preserved by HBO (Dickhoff, 2015).
Kindwall reports to have successfully treated post-pneumonectomy patients shortly after surgery and advises, of course, to leave the chest tube inserted to avoid distortion of the thorax during compression (1999, book ref.).

2.6 History of ENT Surgery

Among the surgical disciplines, ENT specialists seem to belong to those who are the most aware of the beneficial effect of HBO. As the Italian authors Farri et al. (2002) describe in their review, HBOT is widely used in otorhinolaryngology with radiation lesions, chronic osteomyelitis of the mandible, infections of the neck, malignant external otitis, mucormycosis, sudden deafness, and cervicoencephalic traumas whereas the role of HBO as a chemo- or radiosensitizer is a still under investigation.

A randomized controlled trial was conducted in China in 83 patients with impaired wound healing after pharyngolaryngectomy. 48 patients out of the collective received HBOT additionally to standard wound care. The authors compared the average healing time of the wound with necrosectomy of the myocutaneous flap or forearm flap, of the pharyngeal fistula, and of the infected or fluid-filled wound between the groups. The healing time of all these ailments was significantly shorter in the HBO-treated group ($P<0.01$, Jiang, 2011).
Ear surgery for otosclerosis predisposes for ear barotrauma that can be avoided by performing myringotomy or inserting a transtympanic tube prior to the session (Mathieu, 2008, book ref.).

2.7 Epilepsy

Masserini (1986) showed in Swiss albino mice that HBO was an appropriate agent to provoke seizures with an age-dependent trend. The young animals had a much longer convulsion latency time than the adult ones. The authors consider HBO an interesting model for studying the neurochemical mechanism of convulsions and of brain aging.

A team of Zheijiang University in Hangzhou conducted a randomized controlled trial in 320 patients with traumatic brain injury. Half of them received two to four courses of HBOT in addition to their conventional drug therapy. The neural status and SPECT

were assessed before and after therapy. HBOT turned out to be superior to medication treatment alone with regard to control of epilepsy, neurological condition, and resolution of hydrocephalus ($P<0.01$, Shi, 2003).

Neuropediatric and neurophysiologic improvement was reported in 14 Cuban children with epilepsy and cerebral palsy when they were offered HBO within 12 months from the injury (Cordoba-Cabeza, 1998).

Seidel et al. (2013) investigated whether patients having experienced oxygen toxicity-induced seizures had had other underlying factors that may have lowered seizure threshold. A chart review in the Wisconsin area detected 5 patients who had had 7 seizures, and all of them had risk factors that might have triggered them. On the other hand, there are cases of seizures in the chamber without risk factors except carbon monoxide poisoning (Sanders, 2012). Furthermore, seizures after post-radiation brain necrosis were reported (Doherty, 2005).

Numerous retrospective studies and chart reviews were made in about 85700 patients receiving HBOT for manifold indications, the incidence ranging from 2.4 per 100000 treatments to 6 per 10000 patients treated (Yildiz, 2004; Banham, 2011; Heyboer, 2014). Interestingly, Hampson et al. (1996) found a significant relationship between treatment pressures and the number of seizures in a collective of 300 patients treated for carbon monoxide poisoning.

A very recently published retrospective analysis of 62614 treatment sessions administered to 2334 patients revealed an overall incidence of 0.011% occurring in 7 patients of whom only one had a seizure absolutely related to oxygen toxicity (Hadanny, 2016). They estimated HBO to be a safe treatment modality for patients with chronic neurological disorders except for uncontrolled epilepsy.
The patient with epilepsy should not be rejected from HBOT if epilepsy is well controlled, if other supporting conditions like hypercapnia, hypoglycaemia and fever are treated before the session (Mathieu, 2008, book ref).

2.8 Optic neuritis

Optic neuritis is an autoimmune disease probably triggered by a previous viral infection. Furthermore, the eye is one of the main targets of oxygen toxicity. Twitching of the eyelids, blurred vision, constriction of the visual field, myopia and cataract may occur.
The case of a 21-year-old male who was diagnosed with recrudescence of retrobulbar neuritis after exposure to HBO laid the basis to consider optic neuritis a strong relative contraindication in the hyperbaric community over decades (Nichols, 1969). This young man had had a history of optic neuritis 10 years ago and participated in a study on pulmonary oxygen toxicity with exposure to HBO for 6 hours, i.e., an unusual profile in the clinical setting.
42 years later, in 2011, Register et al. published a case of a female patient with optic neuritis and infection after breast surgery who received 40 uneventful treatments at 2.4 ATA under close ophthalmologic control. The author suggested that "… the medical literature may not support an automatic exclusion of a patient with a history of optic neuritis if there is an indication for HBOT". He also pointed out that optic neuritis is often associated with multiple sclerosis. This article was followed by a comment on the use of HBO with optic neuritis where Heather-Murphy Lavoie (2011) stated that 14000 cases of multiple sclerosis had been treated in the chamber

without a report related to optic neuritis; therefore he claimed to drop optic neuritis off the list of relative contraindications.
Nevertheless, manifestation of a reversible central scotoma after HBOT in a patient with multiple sclerosis (Lambrou, 1987) and a successful treatment in a patient with malignant otitis externa and optic neuritis were reported (Bath, 1998).

2.9 Hypertension
Wolf and co-workers (2012) compared the side effects of HBO in a randomized clinical trial in military service members with mild traumatic brain injury. 48 subjects completed 30 exposures allocated either to HBO at 2.4 ATA or to sham treatment. Apart from ear barotrauma with the highest rate of events, hypertension occurred in one subject (0.07%). Blood pressure was slightly elevated at the beginning of the study and increased throughout the study period up to 162/106. Blood pressure medication was initiated.

Marie-Ludivine Chateau-Degat and colleagues (2012) analysed the data from 93 patients with chronic wounds who had 40 sessions at 2.5 ATA for 90 minutes. The age- and sex-adjusted models showed a siginificant decrease of noninvasive systolic blood pressures after 20 sessions. Mean diastolic blood pressures remained unchanged. The decline of heart rate was predominant during the first 20 sessions. The authors hypothesize that repetitive exposure to HBO might stimulate the elimination of reactive oxygen species responsible for activation of the sympathetic nervous system so that blood pressure declines after multiple exposures.
Al Weili and colleagues (2006) investigated the influence of HBO on blood pressures, heart rates and blood glucose levels in patients with diabetes mellitus and hypertension. HBO lowered blood glucose levels and increased systolic and diastolic blood pessures when the baseline value exceeded 140 mmHg; critical values were observed when systolic blood pressure was more than 160 mmHg. Blood pressures were still more elevated in patients on beta blockers medication. The authors recommend to pause the beta receptor blocking agents during the course of HBOT (an issue that has to be discussed with cardiologists), they also postulate a “cumulative” HBO effect on the autonomous nervous system and on the vessel tone.

2.10 Heart failure
Hemodynamic parameters were measured in instrumented dogs breathing hyperbaric air at 3 ATA, 100% oxygen and hyperbaric oxygen (Abel, 2000). HBO resulted in decreased heart rate, cardiac output and cardiac work. All left ventricular performance indices decreased without a change in preload or afterload whereas right ventricular performance indices remained stable, only right ventricular-dp/dt decreased. The authors derived from these data that HBO may act in a different way on the autonomic innervation of both ventricles. In the clinical setting, patients with congestive heart failure could be susceptible to pulmonary edema under hyperbaric conditions.

One year later, in 2001, Weaver and co-workers published 3 case reports about the manifestation of pulmonary edema after HBOT. All patients had reduced left ventricular ejection fractions, one of them severe aortic stenosis. The authors advised caution in patients with heart failure or reduced ejection fractions undergoing HBOT but, on the other hand, a prediction of who will develop pulmonary edema will not be possible.

In 2015, Obiagwu reported another case of reversible pulmonary edema in an 80-year-old male with a history of ischemic heart disease without manifestation of heart failure before the hyperbaric treatment.

2.11 Implanted pacemakers

Former pacemaker models were shown to function properly under elevated ambient pressure with tests performed between 10 to 60 fsw (Kratz, 1983; Wilmshurst, 1998). As an example, concerning the Medtronic 1(800)328-2518 type, rate responsive pacing began to diminish at pressures over 60 fsw with a decrease of the pacing rate. At pressures of 132 fsw, deformation of the case became visible (Kindwall, 1999, book ref.).

Trigano and colleagues (2006) tested activity-based rate-adaptive pacemakers in a miniaturized hyperbaric chamber. The pacemakers were commonly used models from 4 manufacturers (Ela, Guidant, Medtronic, St. Jude Medical). They were tested at 30 msw and at 60 msw, with a brief shaking of the device during pressurization and afterwards to test the response, i.e., the rate increase. Group I pacemakers were exposed to 30 msw and after a 1- month waiting period to 60 msw. Group II pacemakers were only exposed to 60 msw. A total of 45 tests was made. A transient rate increase was noticed in 18 out of 45 tests at both pressure levels just after inflation of the chamber with the rate increase ranging from 8 to 35 bpm. No pacing dysfunction or lack of sensor response was shown afterwards or at 1 month after testing. Case distortion was observed in 15 out of 29 devices at 60 msw whereas there was no change of thickness measurements at 30 msw.

The authors concluded that diving should not be allowed at depths greater than 20 msw. in subjects with implanted devices.

2.12 Pregnancy

The use of HBO in pregnancy has raised some concern on triggering retrolental fibroplasia or closure of the patent ductus arteriosus. Profound knowledge in this field was gathered in Eastern countries: research in Russia with reports on about 700 pregnant women during all stages of gestation mostly published in the eighties did not reveal HBO-related detrimental side effects to mother or foetuses (Mathieu, 2008, book ref.).

Moreover, HBO was successfully applied in cases of delayed fetal growth due to placental insufficiency. Initially 11 in the first, and 21 pregnant women in the 2nd group received repetitive HBO cycles with each of them consisting of 10 hyperbaric sessions at 1.5 ATA for 60 min; after birth, the neonates had satisfactory maturation indices, the placentas were normal although volume-reduced. HBO succeeded in correcting the fetal growth defect (Sparacia, 1996).

Animal studies also aimed at investigating the effect of diving on pregnancy. Consequently, the experimental design does not always address problems associated with clinical HBO, and differences in placental circulation between humans and other animals question the applicability of the animal model to human pregnancy.

Interestingly, however, in an experiment in 11 pregnant sheep exposed to 31 HBO sessions at 165 fsw. Bubbles were detected in two thirds of the ewes but in none of the foetuses. 9 ewes gave birth to normal lambs (Nemiroff, 1981).

Western literature mainly focusses on evaluating the outcome of children exposed to HBO before birth. Most exposures reported were attributed to carbon monoxide poisoning (Silverman, 1997; Elkharat, 1991; Koren, 1991). There is common

agreement that HBO may be applied in pregnant women with acute intoxication and that a severe degree of poisoning puts the foetus at high risk of intrauterine death oralsy.
A recent study of Wattel and Mathieu (2013) looked at the psychomotor development of 412 children with intrauterine carbon monoxide poisoning compared to local controls. They found no significant differences between the groups and concluded that further assessments would not be compulsory when the neonatal status is normal.

2.13 Claustrophobia

Confinement anxiety may pose a serious problem if untreated. Bennett (2015) reported an incidence of 15% in a collective of 665 patients when treated in a monoplace chamber. Most authors mention it as unplanned events in the course of studies not dealing with claustrophobia. Taking the reports from several authors together, confinement anxiety occurred in 6 out of 149 patients during the course of HBOT (Saxby, 2010; Larsson, 2008; Corman, 2003; Nighogossian, 1995). One patient out of 12 developed transient claustrophobia in a Gamov bag which disappeared after inflation (Jay, 1995).
Confinement anxiety rarely leads to interruption of the therapy within the chamber, and prophylactic treatment, e.g., a mild sedation, may be advisable if the patient has a history of claustrophobia. It may also be helpful if the tender accompanies the patient throughout the session talking to him or practicing medical hypnosis as it was already demonstrated in patients hardly tolerating magnetic resonance imaging (Friday, 1990)

2.14 Tumor growth

There is still an ongoing discussion about whether HBO will promote tumor growth or not. Animal experiments disclose controversial findings. In the mouse model of Braks et al. HBO triggered tumor growth but the overall survival rate was improved. On the other hand, in the breast cancer mouse model of Pande and co-workers (2012) HBOT did not stimulate cancer growth but there was a progression of the tumor observed afterwards. Nevertheless, there is broad agreement about the observation that HBO enhances the effect of chemo- or radiotherapy. According to the review published by Moen and co-authors (2012) who analysed the data on HBO and cancer between 2004 and 2012, they found no evidence and stated that “ HBO neither acts as a stimulator of tumor growth nor as an enhancer of recurrence”. Tumor oxygenation plays a crucial role in inhibiting tumor growth in certain cancer types and needs further investigation.

2.15 Acute lung injury

HBO was shown to transiently decrease arterial oxygen tension by 19-22% from baseline in mechanically ventilated critically ill patients (Ratzenhofer-Komenda, 2007; Bingham, 2011). This decrease is hypothesized to happen due to atelectasis formation with subsequent ventilation-perfusion mismatch. A promising strategy to rule out this effect might be a change of the ventilation mode in order to antagonize atelectasis formation by using pressure controlled ventilation throughout the session *and* starting nitrogen wash-in phase by reducing the inspired fraction of oxygen (FiO_2) prior to decompression. Nevertheless, a decrease by 19-22% after treatment is likely not to be tolerated by the patient suffering from acute lung injury.

Historically, hyperoxia-induced lung injury was observed in subjects exposed to elevated ambient pressure but is also nowadays of growing interest in intensive care as high concentrations of oxygen may be delivered with modern ventilators.
Prolonged exposure to hyperoxia leads to inflammation and acute lung injury.
Multiple therapeutic strategies aim at attenuating or abolishing the pulmonary damage by targeting oxidative stress and inflammation, cytokines, cytochrome P450, renin-angiotensin system, glutamate and glutamin, iron, and surfactants.
Most therapeutic steps were evaluated in animal experiments and were not yet introduced into clinical practice (Runxiao, 2014).

III. Comment and recommendations

It is interesting to look at the guidelines of other countries disposing of a considerable amount of hyperbaric chambers like China.
In 2004, HBOT was absolutely prohibited in patients suffering from untreated pneumothorax or pneumomediastinum, lung bullae, active bleeding or hemorrhagic disease, tuberculous cavity or hemptysis, In 2013, however, the guidelines were updated and only one absolute contraindication was left: the unvented pneumothorax.
According to the Chinese Medical Association the relative contraindications are as follows:

- Intraventricular external drainage
- Fracture of the skull base with cerebrospinal fluid leakage
- Birth weight < 2000 g in premature and low birth weight infants
- Serious infection of the upper respiratory tract
- High blood pressure (systolic >180 mmHg, diastolic > 110 mmHg)
- Patients with chronic obstructive pulmonary disease with CO_2 retention

(Ling Yan, 2015, chapter 1.1)

Reviewing the former contraindications listed in chapter I, some of them could be dropped due to advances in pharmacy and technical and monitoring equipment. Nevertheless, when looking for clear data to do so, it turns out that the number of anecdotal reports exceeds the number of prospective clinical trials by far. Thus this report can hardly follow the general scheme. Furthermore, many contraindications were overruled by emergency situations where HBO seemed to be more beneficial than harmful and more promising to the outcome of the patient.

There is no doubt considering the *untreated pneumothorax* an absolute contraindication but also other *unvented cavities* may become life-threatening under hyperbaric conditions.
A patient presenting with *acute severe bronchospasm* is not taken into the chamber; if it occurs unexpectedly during the session, it may be successfully treated.

Combining HBOT with *Doxorubicin or Bleomycin* is likely to enhance cytotoxicity and cardiotoxicity in the animal experiment. The sequelae after hyperbaric exposure are controversially discussed so that HBOT should be administered only in an emergency situation where there is no alternative to save the patient`s life, and with a time delay to chemotherapy until the agent is eliminated from the body. It is worthwhile to discuss how to decide if this time delay is not possible .

Patients with *upper airway infections* and/or *COPD* are prone to mucus retention and air trapping but have been treated under special emergency situations without serious side effects. A slow descent supports the venting of the small airways. Our search did not reveal data on *allergic rhinitis* and *chronic otitis* associated with a high risk of barotrauma during pressurization.

The *history of thoracic surgery* is no more an obstacle to HBOT; data on patients with a *history of ENT surgery* undergoing HBOT are scarce because HBO was only given in severe cases as an ultima ratio measure for wound healing without undesirable hyperbaria-related events during or after the session.

Epilepsy and hypertension should finally be deleted from the list because both conditions can be well controlled and managed by an experienced therapist.

Based on a single case report, *optic neuritis* was regarded as a relative contraindication. Patients with optic neuritis shall not be rejected from HBOT but closely monitored by an ophthalmologist. This diagnosis should be removed from the list.

The condition of a patient with *heart failure* will become better or worse in the hyperbaric environment. Close hemodynamic monitoring and experienced personnel trained in cardiac intensive care is required for the patient`s safety.
Implanted pacemakers constitute basically no contraindication to HBOT – but the tender is advised to be informed about the type of pacemaker and potentially to contact the manufacturer. He/she should be aware that heart rate may increase up to 30 beats per minute. It is also useful to know whether the patient is completely dependent on the pacemaker's activity or not.

HBOT can be done in *pregnancy* if the foetus is at risk of intrauterine death or cerebral damage, e.g., in carbon monoxide poisoning.

Confinement anxiety is a relative contraindication and can end up with psychotic behaviour unless treated in advance.

Research on the pro- and anticarcinogenic properties of HBO and its impact on *tumor growth* is a challenge for the future.

Last not least, a cut-off value of the inspired fraction of oxygen (FiO_2) or other respiratory parameters in *acute lung injury* would be desirable to select the patients fit for HBOT in the critical care setting.

Contraindications to HBOT

1. **Absolute Contraindications**

1.1 Unvented Pneumo-thorax	**Type**	**No. pts.**	**Aims Evaluation criteria**	**Inclusion/ Exclusion Criteria**	**HBO Protocol**	**Results**	**Conclusion/ Comment**
Kot J; 2008	Case report	1 pt	Girl, 13a, CO poisoning + near-drowning		4	Pt. died of ARDS and repeated CPR Trained anaesthesiologist in the chamber is obligatory	Case report
Lin Yang, Ting Liang, 2015	Review		HBO in China CMA: List of indications, contra-indications			Before 2013: untreated pneumothorax/ pneumomediastinum; pulmonary bulla; active haemorrhage; tuberculous cavity; hemoptysis. After 2013: Only 1 absolute contra-indication: untreated pneumothorax	
Cakmak T, Battal B, Kara K, 2015	Case report	1 pt.	28 yr, male, earth quake survivor: crush injury, ARDS	Mechanical ventilation. 6 sessions uneventful.		On the 7th HBOT, presentation of pneumothorax near the end of decompression – CPR – immediate chest tube insertion outside the chamber.	The symptoms improved; trauma pts. require an increased vigilance.
Inoue Y, Yoshida S, Hirose S, 2013	Case report	1 pt.	86 yr, male: HBOT for adhesive intestinal obstruction	1st session uneventful		Severe dyspnea and backache after decompression – CPR – immediate thoracic drainage	It is essential to manage pneumo-thorax prior to HBOT.
Murphy DG, Sloan EP, Hart R, 1989	Case report	3 pts.	Intubated pts. receiving HBOT due to CO poisoning.			All pts. needed closed chest compression for cardiac arrest before HBOT. Despite the absence of PTX prior to the session, it developed after decompression.	A high index of suspicion for PTX is recommended with emergency HBOT.

1.1 Unvented Pneumo-thorax	Type	No. pts.	Aims Evaluation criteria	Inclusion/ Exclusion Criteria	HBO Protocol	Results	Conclusion/ Comment
Sloan EP, Murphy DG, Hart R, 1989	Retro-spective study without controls	297 pts.	E: occurrence, type, timing and incidence of complications, observation period: 10 yr.	Emergency pts. due to CO poisoning receiving HBOT		Before HBOT: cardiac arrest (8%), respiratory arrest (3%). During HBOT: emesis (6%), seizures (5%), agitation (2%), cardiac arrest/ dysrhythmias (2%), arterial hypotension (2%), tension PTX in 3 pts. (1%).	

1.2 Acute severe broncho-spasm	Type	No. pts.	Aims Evaluation Criteria	Inclusion/ Exclusion Criteria (I/E)	HBO Protocol	Results	Conclusion/ Comment
Jammes Y, Burnet H, Cosson P, 1988	Obser-vational Animal Exp.	3 volun-teers. + rabbits	Effect of cold air/ He-O2-breathing			Increase of lung resistance at 2.0/3.5 ATA Manifestation of bronchospasm (38-95%) at 25 ATA	
Harch PG, Andrews SR, Fogarty EF, Amen D, et al. 2012	Prospect. obser-vational study (broncho-spasm)	16 pts.	Safety and efficacy of HBOT in military subjects E: SPECT neuro-psychological testing	I: Pts. with blast-induced concussion syndrome (PCS) and posttrauma tic stress disorder(P TSD).	1.5 ATA 60 min; 40 sess. 30 days	Post-treatment testing demonstrated significant improvement in, e.g., full-scale IQ (P<0.01), delayed memory (P=0.026), working memory (P=0.03), PTSD symptoms (P<0.01), depression (P<0.001), anxiety (P= 0.007), and quality of life (P=0.003)…SPECT: diffuse improvements in regional cerebral blood flow. 1 Subject experienced reversible bronchospasm, 5 reversible middle ear barotrauma, 4 transient deterioration of symptoms.	The authors concluded that HBOT was safely applied in a military cohort with PCS and PTSD.
Keenan HT, Bratton SL, Norkool DM, Brogan TV, Hampson NB, 1998	Retro-spect. Observat. (broncho-spasm)	32 children	Purpose: (1) to describe the method of mechanical ventilation during HBOT; (2) to review the complications during HBOT	I: mechani-cally ventilated critically ill children age: 3d - 11 yr		Complications: hypotension (63%), bronchospasm (34%) hematotympanum (13%), progressive hypoxemia (6%).	HBO can be administered safely to most critically ill children in a multi-place chamber under close monitoring. Most complications can be managed easily by a skilled team.

1.3 Unvented cavities	Type	No. Pts.	Aims Evaluation Criteria (E)	Inclusion/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Toklu AS, Korpinar S, Erelel M, 2008	Question-naire to HBO centres	66/98 centres re-sponded	How are bullae/plebs diagnosed? Pre-valence of pulmonary barotrauma?			X-ray is the mostly used tool for diagnosis. 65 centres accept pts. with air cysts for HBOT. Prevalence of pulmonary barotrauma was calculated at 0.00045% being very low.	
Tripathi K, Moorthy A, Karai RC, Rao G, 2011		14 treated pts. Com-pared to 27 pre-vious controls	Effect of HBOT on healing after mandibular cysts extraction. E:1 rate of filling of the residual cavity. 2 bone density Treatment vs control group	I: healthy pts., no modifiers of wound healing	20 sessions	Group with HBO: reduction of residual size of cavity: 55±9% vs. 12±4% in controls (P=1.21E-11x(10-11)). Bone density: increase of 55 ± 17% vs. 37±23% in controls (P=0.029).	HBO is a useful adjunct No randomization Control group is retrospectively evaluated. Residual cavity is no contraindication to HBOT
Wang P, Zhang XM, Zhai ZH, Li PL, 2013		80 pts.with CO poiso-ning and HBOT 88 Pts. as controls.	Discrepancies of otic and sinus abnormalities on MRI between barotrauma and acute otitis media	I: pts. diagnosed with otic and sinus barotrauma after HBOT.E: Abnormalities of middle ear and paranasal sinuses Controls: acute otitis media with effusion on NMRI		Barotrauma group: bilateral middle ear abnormalities (92%), worsening in 7 pts. 60% had middle ear cavity and mastoid cavity abnormalities. In both groups, most abnormalities were observed in the mastoid cavity. Sinus abnormalities: barotrauma group (66.3%), controls (50%, P= 0.033).	MRI is useful for detecting abnormalities and differentiating between barotraumas and acute otitis with effusion.

1.3 Unvented cavities	Type	No. Pts.	Aims Evaluation criteria (E)	Inclusion/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ comment
Rivalland G, Mitchell SJ, van Schalk-wyk JM, 2010	Case report	1 pt.	Pulmonary baro-trauma and cerebral arterial gas embolism (CAGE) during decompression.	Unexpected lung bullae		Irreversible spastic quadriparesis during decompression from HBOT.	A paradox: HBOT is the cause of CAGE but also the treatment of choice.
Lee CH, Chen WC, Wu CI, 2009	Case report	1 pt.	Male with multiple bone fractures, cerebrospinal fluid (CSF) leak	HBOT for brain edema		Tension pneumocephalus developed after HBOT. Emergency Bur hole drainage, cranioplasty and repair of skull base fractures. Discharge in a vegetative state.	Pneumocephalus, untreated skull base fracture, CSF leak-> contraindications

1.4 Drugs: Doxorubi-cin (D)/ Adriamy-cin(A)/ Bleomycin (B), etc.	Type	No. pts.	Aims Evaluation criteria (E)	Inclusion/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ comment
Karagoz B, Suleyma-noglu S, 2008	Prospective random. animal exp.	Rats	Cardiotoxicity of HBOT during DR treatment E: Ejection fraction (EF) Fractional shortening Histopathology (HP)	Groups: HBOT (n=10) D (n=8); D+HBOT (n= 10) 4 weeks; follow-up after 8 weeks		D: Reduction of EF and fractional shortening (P<0.001) HP: severe injury (P<0.05) D+HBOT: Reduction of EF and fractional shortening (P<0.001), but less than reduction in D (P<0.05). HBO attenuated D-induced HP changes (P<0.05).	"HBO does not potentiate D-induced cardiotoxicity in rats. Cardioprotection warrants further studies."
Firat O, Kirdok O, Makay O, 2009	Prospective random. animal exp.	Rats	Right portal vein ligation (RPVL) -> E: Can HBO alleviate D-induced hepatotoxicity ? Liver regeneration by ALT, AST, Albumin, mitotic index (MI)	Groups: I: RPVL II: D before RPVL III: D before RPVL+HBO IV: sham-operated. Sacrifice d 7.		AST and ALT equal in III to those in I; Albumin in groups II and III not significantly different to those of groups I or IV. MI significantly higher in group III compared to group I. AST/ALT II>I	"HBO has the potential to diminish D-related hepatotoxicity and improve liver regen." Good design Animal experiment
Aktas S, Toklu AS, Olgac V, 2000	Prospective random. animal exp.	95 Rats	Does HBO favour healing of A-induced skin lesions? Injection of 0.7 ml A into the upper hind leg. E: lesion size measurement for 4 weeks	I: HBO (n=43) II: controls (n=42) without HBOT	2.5 ATA 80 min BID, 28 d	No lesion size difference on d 7 and 14 but significant reduction of lesion size on day 21 (p=0.021) and on d 28 (P=0.0001) in the HBO group. Complete wound healing on day 40 in 16 animals, no complete wound healing in the control group.	HBO has a beneficial effect in A-induced skin lesions. Prospektive random. trial, clear design, animal experiment.

1.4 Drugs	Type	No. pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Monstrey SJ, Mullick P Naraya-nan K, et al. 1997	Prospective animal exp.	rats	D extravasation model: 0.3 ml D 0,2% intradermally on both flanks. E: ulcer & alopecia size; malondialdehyde (MDA)	**I**: HBOT (n= 28) at 3 d before injection + 7d postinjection **II**: no HBOT (n=26)	2 ATA, 120 min	Ulcer size (mm2) 112.2 (I) vs. 42.8 (II) (P<0.01). Alopecia (mm2): 1132.2 (I) vs. 364.8 (II) (P< 0.005). MDA (ng/min/mg protein): 36.58 (I) vs. 5.84 (II)	Cytotoxicity of D is potentiated by HBOT. MDA increase reflects membrane lipid peroxidation. HBOT deleterious with D-Extravasation.
Heys SD, Smith IC, Ross JA, et al. 2006	Random. prospect. Controlled	32 pts. With breast carci-noma > 5 cm	Does pre-treatment with HBO improve tumor vascularity rendering chemotherapy more effective?	**I:** (n=11): chemo-therapy (vincristine, D, cyclophospha-mide + HBOT **II:** controls (n=17): without HBOT	2.4/ 2.0 atm abs, 10 sessions before chemoth.	No reduction in tumor cell volume and no increased vascularity on NMRI. No evidence of neovascularization by HBO. Five year survival did not differ between the groups.	Clinical and pathological responses to chemotherapy were the same in both groups. HBOT did not improve the effects of chemotherapy.
Wheeler RH, Dirks JW, Lunardi I, Nemiroff MJ, 1979	Prospective Random. controlled	Burkitt's lympho ma cells (PJ3)	Effect of HBO exposure on the cytotoxicity of A (0.15 mcg/mL) and nitrogen mustard (NSC 762, 0.15 and 0.25 mcg/mL) in P3J cells in vitro	PJ3 exposed to: **I:** HBO alone **II**: HBO and A concomitantl y **III**: A given 2-8 hr before or after HBO	3.0 atm abs, 3 hr	I: Inhibition of DNA synthesis and mitosis II: decreased cytotoxicity III: increased drug effect Increased cytotoxicity with exposure to HBO before, during or after exposure to NSC 762. Lower concentrations of A or NSC 762 are not potentiated.	HBO potentiation of antineoplastic agents appears to depend on the agent, its concentration and the scheduling of drug and HBO exposure.

1.4 Drugs	Type	No. pts.	Aims Evaluation Criteria	In-/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Torp K, Carraway MS, Ott MC, Stolp BW, Moon RE, et al. 2012	Retrosp. Uncontr. Obser- vational	14 pts.	Safe administration of HBO after bleomycin? Pts. also received A (1), vinblastine (11), methotrexate (11), cisplatinum (7), dacarbazin (2), vincristine (1)	Cancer pts. Treated with A and others Mixed HBO indications Median bleomycin HBOT Latency: 34 months	2.0 atm abs, 120 min	Range after bleomycin exposure: < 6 months (3 pts.), < 2 yr (7 pts.); No adverse pre-to-post HBO-related changes in arterial blood gases, spirometry, chest radiograph findings or clinical reports.	Long-term susceptibility after bleomycin may be overstated. Case series, post-HBO data missing to some extent.

2. Relative Contraindications

2.1 upper airway infection	Type	No. pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ comment
Jordan J, Piotrowski G, Kwiatek M, 1996	Case study (laryngitis)	1pt.	Pt. with acute laryngits and phlegmon of the neck due to streptococci		2.5 ATA 60 min q.d., 6-9 d	The pt. received NBO via the tracheostomy tube for 5 d + debridement surgery. The pt. recovered.	The authors assume HBO to be responsible for the pt.'s survival in addition to surgery and antibiotic therapy.
Ye X, Liang X, Ji W, 1998	Literature review + case study (pharyngo-laryngitis)	1pt.	Cervical necrotizing fasciitis treatment E: bacteriology Diagnosis Antibiotic regimen Surgery				The key to successful management is early recognition, antibiotics and prompt surgical intervention and HBOT.
Wolf HK, Moon RE, Mitchell PR, Burger PC, 1990	Case report (bronchitis)	1 pt.	Pt. with nonhealing ulcer of her foot.			The pt. presented with hemiplegia and confusion after HBOT. Recompression resulted in short-term neurologic improvement, then she became comatous and died. History of chronic bronchitis and intrabronchial mucus. Autopsy findings strongly support the diagnosis of air embolism.	There is a potential risk of HBOT in pts. with pre-existing pulmonary disease.
Liu YH, Hsia TC, Liu JC, Chen W, 2008	Case report (sinusitis)	1 pt.				A chamber technician experienced a fracture of the maxillary bone during HBOT based on sinusitis.	

2.1 upper airway infection	Type	No. pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ Comment
Steigle-man A, Butler F, Chhoeu A, 2003	Case report (sinusitis)	2 pt	Pt. with orbital osteomyelitis after hypobaric exposure		USNTT VI	Improvement after the 1st session	
El-Toukhi E, Szal M, Levine MR, 1997	Case report (sinusitis)	2 pts.	Orbital osteomyelitis due to sinusitis	1 pt. HBO 1 pt. without HBO		1 patient declined, the pt. receiving HBOT survived after multiple surgical procedures. On time of publication HBOT was still given.	

2.2 allerg. rhinitis	No items found

2.3 chron. otitis	No items found

2.4 COPD	Type	No. pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ comment
Verna G, Fava F, Baglioni E, 2004	Case report	2 pts.	Fournier's gangrene + pre-existing COPD + hypertension		14 d of treatment	Full recovery by antibiotics, debridement and HBOT; split-thickness skin grafts on the scrotum.	

2.5 Thoracic surgery							
Togo T, Ota S, Hirose M, 2012	Case report	1 pt. 61 yr, f	E: PTX after right lower lobectomy			POD7: development of PTX, pleurodesis after the 3rd event – sudden loss of consciousness –NMRI: air in the carotids and right parietal lobe: successful HBOT.	

2.6 ENT Surgery	Type	No. pts.	Aims Evaluation Criteria	In-/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Farri A, Pecorari GC, Enrico A, 2002	Review		E: application of HBOT in otorhino-laryngology and head and neck surgery			Most widely accepted indications: post-radiation injury, osteomyelitis, infection, malignant external otitis, hypoacusia, chronic tinnitus, cervicoencephalic traumas	Still undecided issue: Role of HBO as radio-chemosensitizer. HBO -> ↓hospital stay, faster recovery.
Jiang W, Liang D, Zhang H, 2011	Random. Controlled trial	83 pts	E: Effect of HBO on impaired wound healing after pha-ryngolaryngectomy	HBO group (n=48); Controls: no HBOT (n=35)	2 x 10(5) Pa, 110 min/d 5-10 d	Average healing time : HBO group vs. controls : 27.5/45 d (P<0.01) in necros-ectomy of myocutaneous flap; 8.5/ 14.09 d (P<0.01) in pharyngeal fistula; 5.9/ 8.6 d (P<0.001) in the infected wound.	HBOT is a powerful treatment for late healed wounds in la-ryngeal and pharyn-geal carcinoma surg.

2.7 Epilepsy	Type	No. pts.	Aims Evaluation Criteria	In-/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Masserini C, Rosina E, Morosini F, 1986	Journal article	Albino mice	E: Comparison of 2 methods of arousing convulsions by: pentylentetrazole (P) HBO/ age factor			P induced convulsions without variation by age, HBO showed an age-dependent trend.	HBO is an interesting model for studying the neurochemistry of convulsions and of membrane changes.
Shi XY, Tang ZQ, Xiong B, 2003	Random. Controlled trial.	320 pts.	To evaluate the effect of HBOT on pts. with postbrain injury neural status	HBO/ non-HBO group. E: SPECT before/ after therapy		HBO was superior to medication treatment alone in the recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus (P<0.01).	HBOT has specific curative effects, and SPECT could be useful for monitoring.
Cordoba-Cabeza T, Perez-Fonseca R, 1998	Clinical trial prospective	14 children	Effects of HBO on children with CNS lesions due to asphyxia, infections, brain/ vessel trauma	Age: 4.8 $\pm$ 3 yr Symptoms: cerebral paralysis, epilepsy		Satisfactory response was observed in the children when treated within the 1st year of the lesion, with better and faster results.	HBO seems to be beneficial Comment: small sample sizt
Seidel R, Carroll C, Thompson D, 2013	Case reports	7 pts.	Chart review at several facilities to explore threshold-lowering medication or comorbidity	I: 7 pts. experiencing seizures in the chamber		Each pt. had risk factors: hypercapnia due to COPD, narcotic withdrawal, alcohol addiction, antidepressant, tramadol, or cephalosporin medication.	Pts. presenting with oxygen toxicity seizures may have other contributing factors.
Sanders RW, Katz D, Suyama J, 2012	Case reports	2 pts.	E: seizure frequency during HBOT for CO poisoning, survey over 5 years	I: pts. treated for CO poisoning		Although both pts. had no predisposing factors like fever, hypothermia, previous seizure, brain injury they presented with convulsions during HBO.	

2.7 Epilepsy	Type	No. Pts.	Aims Evaluation Criteria	In-/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Yildiz S, Aktas S, Cimsit M, 2004	Retrospect. study	80679 pts.	E: Incidence of seizures in 2 falcilities affiliated to the university	I: 80679 pts. treated for 9 indications	Various HBO protocols	Only 2 seizures were documented with 2.4 ATA , mask oxygen breathing 3 x 30 min, 5 min air breaks. Incidence of 2.4 per 100000 patient treatments.	CNS Oxygen toxicity during HBOT is very low.
Banham ND, 2011	Obser-vational retrospect. study	3737 pts.	Incidence of oxygen toxicity seizures (OTS) during HBOT ovoTer 20 yr.	Review of 41273 sessions	Various protocols	Incidences: all sessions: 6 OTS/ 10000 pts. Dysbarism (USNTT6): 0.56% CO poisoning: 0.18%, 1st session: 0.49%. OTS increased with increasing pressure.	
Doherty M.	Case report	1 pt.	HBOT due to brain radionecrosis			The pt. presented with tonic-clonic convul-sions after brain irradiation due to anaplastic sarcoma.	
Hampson NB, Simonson SG, Kramer CC, 1996	Obser-vational retrospect.	300 pts.	E: CNS toxicity during HBOT for carbon monoxide (CO) poisoning	I: CO-poisoned pts. at 3 treat-ment pressures	2.45 atm 2.80 atm 3.0 atm abs.	No. of seizures: 1 at 2.45 atm (0.3 %), 9 at 2.8 atm (2.0%), 6 at 3.00 atm abs (P=0.032; Fisher's exact test).	The difference in seizure risk should be considered when selecting the treat-ment pressure.
Heyboer M 3rd, Jen-nings S, GrantWD , 2014	Retrospect. Chart review	931 pts. 23328 session s	Incidence of oxygen toxicity seizures (OTS) and dependence on pressure	I: 23328 treat-ments at 3 pressure levels	2.0 atm 2.4/2.5 atm 2.8 atm abs.	Incidence of seizures per10000 treatments: Overall: 5 At 2.0 atm: 0; at 2.4/2.5 atm: 15 At 2.8 atm: 51. (Chi^2 (2.23,540) = 31.38, P<.001)	Statistically significant increased risk of OTS with in-creasing treatment pressure.

2.8 Optic neuritis	Type	No. pts.	Aims/ Evaluation criteria	In-/Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Register SD, Aaron ME, Gelly HB, 2011	Case report review	1 pt.	Consideration about whether optic neuritis (ON) is a strong contraindication for HBOT or not	Case of a female with OT receiving HBOT for bad wound healing	2..4 ATA 3x30 min 40 sessions	ON was present 10 yr prior to HBOT in this patient. No visual deficits occur. The contraindication for HBOT is originally based on one subject exposed to 6 hr of HBO at 2.0 ATA for research reasons. ON may precede MS occ. treated with HBO	Automatic exclusion of pts. with a history of ON is not justified. Checking MS pts. for associated ON is recommended.
Bath AP, Rowe JR, Innes AJ, 1998	Case report	1 pt.	Pt. with malignant otitis externa and optic neuritis and adjuvant HBOT			The pt. was refractory to conventional treatment but was cured by additional HBOT. The only reported case that survived this disease with optic neuritis.	

2.9Hyper-tension	Type	No. pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ comment
Wolf EG, Prye J, Michael-son R, 2012	Single-blinded random. controlled study	50 pts.	To catalog the side effects of 2.4 atm abs HBO vs. sham (1.3 atm abs air-breathing) treatment	I: 50 pts. with post-con-cussion or mild traumatic brain injury	2.4 am abs 90 min 30 sessions	Beside other side effects (ear barotrauma, sinus squeeze, confinement anxiety, headache, etc.) hypertension occurred in 1 subject and persisted in the 6-week follow-up (sham exposure group).	
Chateau-Degat ML, Belley R, 2012	Observatio-nal retros-pective	93 pts.	To evaluate the impact of 20-40 sessions on blood pressure (BP)	I: Pts treated for wound healing	2.5 atm abs 90 min 25 sess.	BP before HBOT: 145/78 mmHg. HR: 69 Age- and sex-adjusted models showed a decrease in HR and systolic BP ($P<0.0001$) during the last 20 sessions.	
Al-Waili NS, Butler GJ, Beale J, 2006	Observatio-nal prospective	41 pts.	The influence of HBO on diabetes mellitus (DM), systolic (SBP) and diastolic blood pressure (DBP), blood glucose (BGL)	SBP/ DBP and BGL before and after the session.: pts with hypertension (HTN), DM, HTN + DM	15-40 sess.	Elevation in SBP (11%), DBP (12%), decrease in HR (18%) ($P<0.001$). DM+HTN pts. showed higher elevation in SBP/DBP. BGL decreased by 23% ($p<0.001$). Marked elevation in SBP and DBP when basal SBP>140 mmHg, critical rise with SBP>160 mmHg. Beta blockers caused significant elevation of BP while HR was reduced.	HBO causes an increase of BP which is enhanced in the presence of HTN, DM or medication with beta-blocking agents

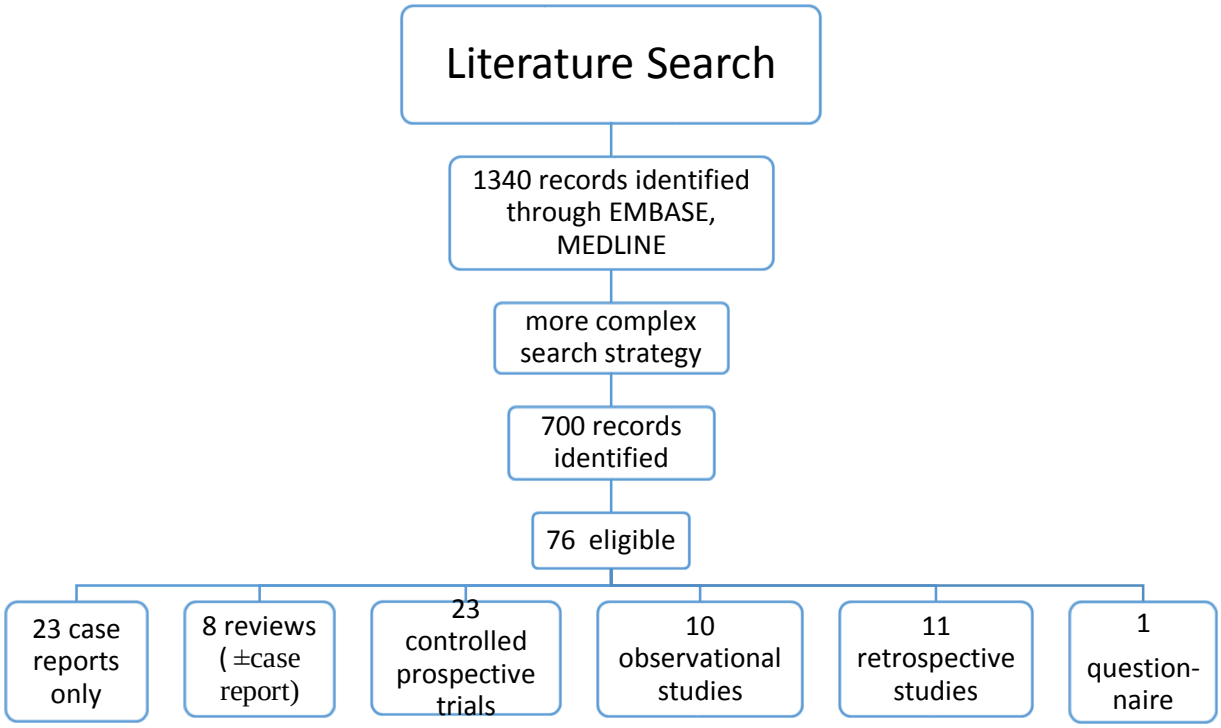
2.10 Heart Failure	Type	No. pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ comment
Abel FL, Mc Namee JR, Cone DL, 2000	Observ. Prospective study	13 dogs	The cardiovascular effects of oxygen	Animals breathing hyperbaric air(3atm abs), NBO, HBO		HBO (3atm abs) caused a decrease in heart rate, cardiac output. Left ventricular performance indices decreased, no change in preload or afterload. Systemic vascular resistance increased, pulmonary vascular resistance remained constant.	HBO may act different on the right and left ventricles.
Weaver L, Churchill S, 2001	Case report	3 pts.	Evidence of pulmonary edema after HBOT		2.4 atm abs. 90 min	All pts. had a history of cardiac disease, reduced left ventricular ejection fraction, one had severe aortic stenosis. This pt. died .	Caution is re-commended with HBOT in heart failure pts. No cut-off value.
Obiagwu C, Paul V, Chadha S, 2015	Case report	1 pt.	80 yr old man	Male, 80 yr, undergoing HBOT for diabetic foot		Acute event of pulmonary edema after HBOT. He had a history of stable systolic heart failure. Emergency intubation-intensive care treatment – successful extubation after 3 days.	Attention with HBOT in pts. with pre-existing cardiac disease.

2.11 Pace-makers	Type	No. Pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ comment
Trigano A, Lafay V, Blandeau O, 2006	Device-related experiment	Pace-maker reliabili-ty under pressur e	E: Pacing stimuli by ECG and event marker telemetry and measurements of case distortion	Group **I**: 4 ATA + after 30 d at 7 ATA. Group **II**: once at 7 ATA	4 ATA 7 ATA I: 2 sess. II: 1 sess.	Pacing rate unchanged in 27 tests. Return to baseline in 18 tests after transient sensor-driven rate. Sensor rate response to manual brief shaking. Case distortion in 15/29 tests at 60 m.	No pacing dysfunction despite a high case distortion. Diving depth to keep below 3 ATA.

2.12 Pregnancy	Type	No. Pts.	Aims Evaluation Criteria	In-/ Exclusion Criteria (E/I)	HBO Protocol	Results	Conclusion/ Comment
Nemiroff MJ, Willson JR, 1981	Prospective observat. study	11 sheep	HBO at days 112th to 165th of pregnancy Bubble detection by Doppler		165 fsw 31 sessions	Bubbles occurred in 8/12 ewes but in none of the foetuses. 9 ewes were delivered of normal lambs, in 1, twin foetuses died due to abnormal labor. Cesarean section in 1.	
Silverman RK , Montano J, 1997	Case report	1 pt	Female, 22 yr, pregnant	CO poisoning when repairing the heating		Resolution of the symptoms (tachycardia, tachypnea, mild fetal decelerations) after HBOT. Delivery at term of a healthy baby.	No sequelae of CO poisoning
Elkharat D, Raphael JC, et al. 1991	Prospective observat.	44 pts.	CO poisoned women with various severity at different ages of pregnancy. Follow-up		2 ATA 120 min + NBO 240 min	All women underwent the same treatment. 6 pts. lost to obstetric follow-up. 2 pts. had spontaneous abortion shortly after intoxication. 34 women: normal newborns, one Down`s syndrome, 1 elected abortion.	HBO may be carried out in pregnant women with acute CO intoxication
Wattel F, Mathieu D, Mathieu-Nolf M, 2013	Prospective single-centre cohort study	406 women, 412 children	Psychomotor development assessment of children with intrauterine CO intoxication and HBOT (1983-2008)	Assessment within 8 days, in years 2 and 6 after birth. Local control group	2.5 ATA 90 min	Comparison of the 2 groups by compulsory health&development assessments. Up to day 8: 388, year 2: 276, year 6: 232 cases evaluated. No significant differences (P>0.05) in psychomotoric skills, weight, hight. No malformations after exposure.	The data support the use of HBOT in pregnancy in CO intoxication. No follow-up with normal neonatal status necessary.
Koren G, Sharav T, Pastusak A, 1991	Prospective multicentre study		CO poisoning in pregnancy (1985-1989). Physical and neurobehavioural development	Mild and moderate, and severe CO intoxication		Mild to moderate CO poisoning: normal outcome in 31 babies. 5 pregnancies with severe toxicity: 2 normal outcomes in those treated with HBO, 2 stillbirths, 1 cerebral palsy.	Severe poisoning poses serious fetal risk, mild exposure is likely to result in normal fetal outcome.

2.13 Claustro-phobia	Type	No. Pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ Comment
Bennett MH, Lehm JP, 2015	Review	665 pts. 6 trials	HBO for acute coronary syndrome			Side effects: Incidence of claustrophobia in monoplace chambers: 15%	
Saxby A, Barakate M, 2010	Retrosp.	17 pts.	HBOT for malignant otitis externa			1 pt. had claustrophobia	
Larsson A, Engström M, et al. 2008	Retrosp. study	39 pts.	HBOT for postop. neurosurgical infections	36 pts. included		1 pt. presented with claustrophobia and stopped HBO therapy.	
Corman JM, McClure D, 2003	Retrosp. study	62 pts.	HBOT for hemorrhagic cystitis	62 pts. included after radiation		2 pts. developed claustrophobia	
Jay GD Tetz DJ 1995	Double cross-over prospective	12	HBOT with Gamov bag	12 volunteers		1 subject had claustrophobia which abated after inflation of the Gamov bag	
Nigho-ghossian N, Trouillas P, 1995	Prospective random. controlled	34 pts	HBOT for acute ischemic stroke	HBO-group: 17 pts Controls: 17 pts		3 pts. in the HBO-group discontinued, 1 of them had claustrophobia	

2.14 Tumor growth	Type	No. Pts.	Aims Evaluation criteria	In-/ Exclusion Criteria (E/I)	HBO protocol	Results	Conclusion/ Comment
Ding JB, Chen JR, Xu HZ, 2015	Random. controlled animal experiment	Sprague Dawley rats	Glioma cell inoculation: follow-up for 16 d: HBOT – group (n=20) vs. non- HBOT-group (n=20)	E: bilat. Forelimb function test, head NMRI		VEGF and intratumoral micorvessel density were was significantly higher, apoptosis sign. lower in HBO-treated rats.	HBO *alone* may promote tumor growth in glioma pts. Combination with radio-/chemo-therapy is advisable.
Moen I, Stuhr LE, 2012	Review		Summary of work on HBO and cancer between 2004-2012			No evidence indicating that HBO neither acts as a stimulator of tumor growth nor as an enhancer of recurrence	HBO might act tumor-inhibitory in some cancer subtypes
Braks JA, Spiegel-berg L, Koljeno-vic S, 2015	Animal model with neck squamous cell carcin-oma(SCLC)	Mice undergo ing irrad.	Tumors were established in mice near infrared fluorescence imaging to assess tumor vas-cular permeability			HBOT resulted in accelerated growth of non-irradiated tumors, but mouse survival was improved.	SCLC responds to HBOT with regard to tumor growth, vascular permeabi-lity and hypoxia.
Pande S, Sengupta A, Srivastav a A, 2012	C3H mouse model for breast cancer		E: tumor growth, body weight, survival time, metastasis formation	Mice with and without HBOT for 7/ 21 d at 1.1 (n=10)/1.2 bar (n=5)	1.1 /1.2 bar 120 min 7d/21d	No cancer enhancing effect was observed during HBOT but afterwards there was an accelerated progression of tumor. HBO-treated mice lived shorter. Obstacle: differential growth pattern in each animal.	Asymmetry of tumor growth requires a symmetrical model for reproducing the results in man.


Literature Search
1340 records identified through EMBASE, MEDLINE
more complex search strategy
700 records identified
76 eligible
23 case reports only
8 reviews (±case report)
23 controlled prospective trials
10 observational studies
11 retrospective studies
1 question-naire

Consensus Conference on Hyperbaric Medicine, Lille, 2016: Contraindications to HBOT:

References

Those references not shown in form 8 are marked with a star (*) in the reference list.

1. Absolute contraindications

1.1 Unvented pneumothorax

1. Cakmak T, Battal B, Kara K, Metin S, Demirbas S, Yildiz S, Uzun G. **A case of tension pneumothorax during hyperbaric oxygen therapy in an earthquake survivor with crush injury complicated by ARDS (adult respiratory distress syndrome).** Undersea Hyperb Med. 2015 Jan-Feb; 42(1):9-13

2. Inoue Y[1], Yoshida S, Hirose Y, Nishimaki H, Nomoto Y. **Tension pneumothorax during hyperbaric oxygen therapy.** Masui. 2013 Feb;62(2):175-7

3. Kot J[1], Michałkiewicz M, Sićko Z. **Pneumothorax during hyperbaric oxygenation.** Anestezjol Intens Ter. 2008 Jan-Mar;40(1):35-8. Published online 2015 Feb 18. doi: 10.1186/s13618-015-0024-4

4. Ling Yan, Ting Liang, and Oumei Cheng. **Hyperbaric oxygen therapy in China.** PMCID: PMC4341238. Med Gas Res. 2015 Feb 18;5:3. doi: 10.1186/s13618-015-0024-4. eCollection 2015.

5. Murphy DG[1], Sloan EP, Hart RG, Narasimhan K, Barreca RS. **Tension pneumothorax associated with hyperbaric oxygen therapy.** Am J Emerg Med. 1991 Mar;9(2):176-9

6. Sloan EP[1], Murphy DG, Hart R, Cooper MA, Turnbull T, Barreca RS, Ellerson B. **Complications and protocol considerations in carbon monoxide-poisoned patients who require hyperbaric oxygen therapy: report from a ten-year experience.** Ann Emerg Med. 1989 Jun;18(6):629-34

.

1.2 Acute severe bronchospasm

1. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, Aubrey C, Taylor DV, Staab PK, Van Meter KW. **A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder.** J Neurotrauma. 2012 Jan 1; 29(1):168-85. doi: 10.1089/neu.2011.1895. Epub 2011 Nov 22

2. Jammes Y, Burnet H, Cosson P, Lucciano M.[1]Laboratoire de Physiologie Hyperbare GS 15-CNRS, Faculté de Médecine, Marseille, France. **Bronchomotor response to cold air or helium-oxygen at normal and high ambient pressures.** Undersea Biomed Res. 1988 May;15(3):179-92

3. Keenan HT, Bratton SL, Norkool DM, Brogan TV, Hampson NB **Delivery of hyperbaric oxygen therapy to critically ill, mechanically ventilated children.** J Crit Care. 1998 Mar;13(1):7-12

1.3 Unvented cavities

1. Lee CH[1], Chen WC, Wu CI, Hsia TC. **Tension pneumocephalus: a rare complication after hyperbaric oxygen therapy.** Am J Emerg Med. 2009 Feb;27(2):257.e1-3. doi: 10.1016/j.ajem.2008.06.036.

2. Rivalland G, Mitchell SJ, van Schalkwyk JM. **Pulmonary barotrauma and cerebral arterial gas embolism during hyperbaric oxygen therapy.** Aviat Space Environ Med. 2010 Sep;81(9):888-90.

3. Toklu AS, Korpinar S, Erelel M, Uzun G, Yildiz S**. Are pulmonary bleb and bullae a contraindication for hyperbaric oxygen treatment?** Respiratory Medicine. 102(8). 1145-7, 2008 Aug.

4. Tripathi KK, Moorthy A, Karai KC, Rao G, Ghosh PC. **Effect of hyperbaric oxygen on bone healing after enucleation of mandibular cysts: a modified case control study.** Diving & Hyperbaric Medicine. 41(4):195-201, 2011 Dec.

5. Wang P; Zhang XM; Zhai ZH; Li PL. . **MRI findings of otic and sinus barotrauma in patients with carbon monoxide poisoning during hyperbaric oxygen therapy.** PLoS ONE [Electronic Resource]. 8(6):e65672, 2013. Other ID: Source: NLM. PMC3680481

1.4 Concomitant treatment with Doxorubicin (Adriamycin), Bleomycin, etc.

1. Aktas, S; Toklu, A S; Olgac, V. **Hyperbaric oxygen therapy in adriamycin extravasation: an experimental animal study**. Annals of Plastic Surgery. 45(2):167-71, 2000 Aug.10949345.

2. Firat O, Kirdok O, Makay O, Caliskan C, Yilmaz F, Ilgezedi S, Karabulut B, Coker A, Zeytunlu M. **Can hyperbaric oxygenation decrease doxorubicin hepatotoxicity and improve regeneration in the injured liver?** Journal of Hepato-Biliary-Pancreatic Surgery. 16(3): 346-52, 2009

3. Heys SD; Smith IC; Ross JAS; Gilbert FJ; Brooks J; Semple S; Miller, ID; Hutcheon A; Sarkar T; Eremin O. **A pilot study with long term follow up of hyperbaric oxygen pretreatment in patients with locally advanced breast cancer undergoing neo-adjuvant chemotherapy.** Undersea & Hyperbaric Medicine. 33(1):33-43, 2006 Jan-Feb.

4. Karagoz B; Suleymanoglu S; Uzun G; Bilgi O; Aydinoz S; Haholu A; Turken O; Onem Y; Kandemir EG. **Hyperbaric oxygen therapy does not potentiate doxorubicin-induced cardiotoxicity in rats.** Basic & Clinical Pharmacology & Toxicology. 102(3):287-92, 2008 Mar.

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

6. Torp K, Carraway MS, Ott MC, Stolp BW, Moon RE, Piantadosi CA, Freiberger JJ. **Safe administration of hyperbaric oxygen after bleomycin: a case series of 15 patients**. Undersea & Hyperbaric Medicine. 39(5):873-9, 2012 Sep-Oct.

7. Upton PG, Yamaguchi KT, Myers S, Kidwell TF, Anderson RJ. **Effects of antioxidants and hyperbaric oxygen in ameliorating experimental doxorubicin skin toxicity in the rat.** Cancer Treat Rep 1986 Apr; 70(4): 503-7.

8. Wheeler RH, Dirks JW, Lunardi I, Nemiroff MJ. **Effect of hyperbaric oxygen on the cytotoxicity of adriamycin and nitrogen mustard in cultured Burkitt's lymphoma cells.** Cancer Research. 39(2 Pt 1):370-5, 1979

2. Relative contraindications

2.1 Upper airway infection

1. El-Toukhy E[1], Szal M, Levine MR, Levine HL. **Osteomyelitis of the orbit.** Ophthal Plast Reconstr Surg. 1997 Mar;13(1):68-71

2. Jordan J[1], Piotrowski S, Piotrowski G, Kwiatek M. **Hyperbaric oxygen therapy in case of the neck diffuse phlegmon with very hard clinical course.** Otolaryngol Pol. 1996;50(1):8-16

3. Liu YH, Hsia TC, Liu JC, Chen W. **Fracture of the maxillary bone during hyperbaric oxygen therapy.** CMAJ 2008 Dec 2; 179 (12). 1351 doi: 10.1503/cmaj.0880713

4. Steigleman A[1], Butler F, Chhoeu A, O'Malley T, Bower E, Giebner S. **Optic neuropathy following an altitude exposure.** Aviat Space Environ Med. 2003 Sep;74(9):985-9

5. Wolf HK, Moon RE, Mitchell PR, Burger PC. **Barotrauma and air embolism in hyperbaric oxygen therapy.** Am J Forensic Med Pathol. 1990 Jun 11(2): 149-53

6. Ye X[1], Liang X, Ji W. **Cervical necrotizing fasciitis].** [Article in Chinese]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 1998 Oct;12(10):460-2

2.2 allergic Rhinitis: no items found

2.3 chronic Otitis: no items found

2.4 Chronic obstructive pulmonary disease (COPD)

1. Verna G[1], Fava F, Baglioni E, Cannatà M, Devalle L, Fraccalvieri M. **Fournier's gangrene: remarks on two clinical cases.** [Article in French]. Ann Chir Plast Esthet. 2004 Feb; 49(1):37-42

2.5 History of thoracic surgery

1. *Dickhoff C, Daniels JM, van den Brink A, Paul MA, Verhagen AF. **Does hyperbaric oxygen therapy prevent airway anastomosis from breakdown?** Ann Thorac Surg. 2015 Feb; 99(2):682-5. doi: 10.1016/j.athoracsur.2014.03.055.

2. Togo T, Ota S, Hirose M, Arima D, Maruhama S. **Air embolism at the pleurodesis for air leakage after pulmonary resection.** Kyobu Geka. 2012 Mar; 65(3):201-4

3. *Wherrett CG, Mehran RJ, Beaulieu MA. **Cerebral arterial gas embolism following diagnostic bronchoscopy: delayed treatment with hyperbaric oxygen.** Can J Anaesth. 2002 Jan; 49(1):96-9.

2.6 History of ENT surgery

1. Farri A; Pecorari GC; Enrico A; Sartoris A. **Hyperbaric oxygen therapy application in otorhinolaryngology and head and neck surgery: state of the art and review of literature**. Acta Otorhinolaryngologica Italica. 22(4):227-34, 2002 Aug.

2. Jiang W; Liang D; Zhang H; Shang W; Wang P; Li W. **The effect of hyperbaric oxygen therapy on treatment of late healed wounds after pharyngeal and laryngeal surgery.** [Chinese]. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi = Journal of Clinical Otorhinolaryngology, Head, & Neck Surgery. 25(1):14-5, 19, 2011 Jan.

2.7 Epilepsy

1. Banham ND. **Oxygen toxicity seizures: 20 years' experience from a single hyperbaric unit.** Diving & Hyperbaric Medicine. 41(4):202-10, 2011 Dec**.**

2. Cordoba-Cabeza T; Perez-Fonseca R; Morales-Vargas D; Lopez A. **Hyperbaric oxygenation and neurological recovery in children with organic brain damage.** [Spanish]. Revista de Neurologia. 27(158):571-4, 1998 Oct.

3. Doherty, Michael J, Hampson, Neil B. **Partial seizure provoked by hyperbaric oxygen therapy: possible mechanisms and implications.** Epilepsia. 2005 Jun;46(6):974-6

4. Hadanny, A, Meir O, Bechor Y, Fishlev G. Bergan J, Efrati S. **Seizures during hyperbaric oxygen therapy: retrospective analysis of 62614 treatment sessions.** UHM 2016, Vol 43, no. 1, 21-28

5. Hampson NB, Simonson SG, Kramer CC, Piantadosi CA. **Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning**. Undersea & Hyperbaric Medicine. 23(4):215-9, 1996 Dec.

6. Heyboer M 3rd, Jennings S, Grant WD, Ojevwe C, Byrne J, Wojcik SM. **Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy**. Undersea & Hyperbaric Medicine. 41(5):379-85, 2014 Sep-Oct.

7. Masserini C, Rosina E, Morosini F, Altamura AC, Cazzullo CL, Torcello L. **Hyperbaric oxygen induced experimental epilepsy: the age factor.** Ital J Neurol Sci. 1986 Jun;7(3):343-8

8. Sanders RW, Katz KD, Suyama J, Akhtar J, O'Toole KS, Corll D, Ladenburger RN. **Seizure during hyperbaric oxygen therapy for carbon monoxide toxicity: a case series and five-year experience. [Review].** Journal of Emergency Medicine. 42(4):e69-72, 2012 Apr**.**

9. Seidel R; Carroll C; Thompson D; Diem RG; Yeboah K; Hayes AJ; Hall B; Whelan HT. **Risk factors for oxygen toxicity seizures in hyperbaric oxygen therapy: case reports from multiple institutions**. Undersea & Hyperbaric Medicine. 40(6):515-9, 2013 Nov-Dec.

10. Shi XY; Tang ZQ; Xiong B; Bao JX; Sun D; Zhang YQ; Yao Y. **Cerebral perfusion SPECT imaging for assessment of the effect of hyperbaric oxygen therapy on patients with postbrain injury neural status**. Chinese Journal of Traumatology. 6(6):346-9, 2003 Dec.

11. Yildiz S, Aktas S, Cimsit M, Ay H, Togrol E. **Seizure incidence in 80,000 patient treatments with hyperbaric oxygen.** Aviation Space & Environmental Medicine. 75(11):992-4, 2004 Nov.

2.8 Optic neuritis

1. Bath AP; Rowe JR; Innes AJ. **Malignant otitis externa with optic neuritis.** [Review]. Journal of Laryngology & Otology. 112(3):274-7, 1998 Mar.

2. *Heather Murphy-Lavoie. **Notes on the use of HBO_2 with optic neuritis**. J Undersea Hyperbaric Med, Vol 38, No. 6: 561, 2011

3. *Lambrou, G N; Kopferschmitt, J; Jaeger, A; Brini, A. **Slowly reversible central scotoma: iatrogenic effect of hyperbaric oxygenation in the treatment of multiple sclerosis.** [French]. Journal Francais d Opthalmologie. 10(1):51-9, 1987

4. *Nichols CW, Lambertsein CJ, Clark JM. **Transient unilateral loss of vision associated with oxygen at high pressure.** Arch Opthal 1969; 81: 548-552

5. Register SD, Aaron ME, Gelly HB. **Hyperbaric oxygen therapy and optic neuritis: case report and literature review.** Undersea & Hyperbaric Medicine. 38(6):557-9, 2011 Nov-Dec.

2.9 Hypertension

1. Al-Waili NS[1], Butler GJ, Beale J, Abdullah MS, Finkelstein M, Merrow M, Rivera R, Petrillo R, Carrey Z, Lee B, Allen M. **Influences of hyperbaric oxygen on blood pressure, heart rate and blood glucose levels in patients with diabetes mellitus and hypertension.** Arch Med Res. 2006 Nov;37(8):991-7

2. Chateau-Degat ML[1], Belley R. **Hyperbaric oxygen therapy decreases blood pressure in patients with chronic wounds.** Undersea Hyperb Med. 2012 Sep-Oct; 39(5):881-9.

3. Wolf EG[1], Prye J, Michaelson R, Brower G,Profenna LBoneta O**. Hyperbaric side effects in a traumatic brain injury randomized clinical trial.** Undersea Hyperb Med. 2012 Nov-Dec;39(6):1075-82.

2.10 Heart failure

1. Abel FL[1], McNamee JE, Cone DL, Clarke D, Tao J. **Effects of hyperbaric oxygen on ventricular performance, pulmonary blood volume, and systemic and pulmonary vascular resistance**. Undersea Hyperb Med. 2000 Summer;27(2):67-73

2. Obiagwu C[1], Paul V[2], Chadha S[3], Hollander G[3], Shani J[3]. **Acute pulmonary edema secondary to hyperbaric oxygen therapy.** Oxf Med Case Reports. 2015 Feb 4; 2015(2):183-4. doi: 10.1093/omcr/omv002. eCollection 2015.

3. Weaver LK, Churchill S. **Pulmonary edema associated with hyperbaric oxygen therapy.** Chest. 2001 Oct;120(4):1407-9

2.11 Pacemakers

1. *Kratz JM, Blackburn JG, Leman RB, Crawford F. **Cardiac pacing under hyperbaric conditions.** Annals of Thoracic Surgery 36: 66-68, 1983

2. *Wilmshurst P. **Cardiovascular problems in divers**. Heart 80: 537-538, 1998

3. Trigano A[1], Lafay V, Blandeau O, Levy S, Gardette B, Micoli C. **Activity-based rate-adaptive pacemakers under hyperbaric conditions.** J Interv Card Electrophysiol. 2006 Apr; 15(3):179-83. Epub 2006 Aug 10.

2.12 Pregnancy

1. Elkharrat D, Raphael JC, Korach JM, Jars-Guincestre MC, Chastang C, Harboun C, Gajdos P. **Acute carbon monoxide intoxication and hyperbaric oxygen in pregnancy**. Intensive Care Medicine. 17(5):289-92, 1991.

2. Koren G, Sharav T, Pastuszak A, Garrettson LK, Hill K; Samson I, Rorem M, King A, Dolgin JE. **A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy**. Reproductive Toxicology. 5(5):397-403, 1991.

3. Nemiroff M J, Willson J R, Kirschbaum TH. **Multiple hyperbaric exposures during pregnancy in sheep.** American Journal of Obstetrics & Gynecology. 140(6):651-5, 1981 Jul 15.

4. *Sparacia B. **New Frontiers: HBO in treatment of fetal growth deficiencies**. In: Oriani G, Marroni A, Wattel F (Eds.). Handbook on Hyperbaric Medicine. Springer Verlag Italia, Milano, 1996, 791-7

5. Silverman RK, Montano J. **Hyperbaric oxygen treatment during pregnancy in acute carbon monoxide poisoning. A case report.** Journal of Reproductive Medicine. 42(5):309-11, 1997 May.

6. Wattel F, Mathieu D, Mathieu-Nolf M**. A 25-year study (1983-2008) of children's health outcomes after hyperbaric oxygen therapy for carbon monoxide poisoning in utero**. Bulletin de l Academie Nationale de Medecine. 197(3):677-94; discussion 695-7, 2013 Mar.

2.13 Claustrophobia

1. Bennett MH, Lehm JP, Jepson N. **Hyperbaric oxygen therapy for acute coronary syndrome.**Cochrane Database Syst Rev. 2015 Jul 23;7:CD004818. doi: 10.1002/14651858.CD004818.pub4. Review.

2. Camporesi EM. **Side effects of hyperbaric oxygen therapy**. Undersea Hyperb Med. 2014 May-Jun; 41(3):253-7. Review.

3. Corman JM, McClure D, Pritchett R, Kozlowski P, Hampson NB. **Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen.** J Urol. 2003 Jun;169(6):2200-2.

4. *Friday PJ, Kubal WS. **Magnetic tolerance imaging: improved patient tolerance utilizing medical hypnosis.** Am J Clin Hypn 1990 Oct: 33(2): 80-4

5. *Hadanny A, Meir O, Bechor Y, Fishley G, Bergan J, Efrati S. **Seizures during hyperbaric oxygen therapy: retrospective analysis of 62614 treatment sessions.** UHM 2016, Vol 43 (1): 21-28

1. Health Quality Ontario. Hyperbaric oxygen therapy for non-healing ulcers in diabetes mellitus: an evidence-based analysis. Ont Health Technol Assess Ser. 2005; 5(11):1-28. Epub 2005 Sep 1.

2. Jay GD, Tetz DJ, Hartigan CF, Lane LL, Aghababian RV. **Portable hyperbaric oxygen therapy in the emergency department with the modified Gamow bag.** Ann Emerg Med. 1995 Dec; 26(6):707-11.

3. Larsson A, Engström M, Uusijärvi J, Kihlström L, Lind F, Mathiesen T. **Hyperbaric oxygen treatment of postoperative neurosurgical infections.** Neurosurgery. 2002 Feb;50(2):287-95; discussion 295-6.

4. Larsson A, Engström M, Uusijärvi J, Kihlström L, Lind F, Mathiesen T. **Hyperbaric oxygen treatment of postoperative neurosurgical infections. Neurosurgery**. 2008 Feb; 62 Suppl 2:652-71. doi: 10.1227/01.neu.0000316260.67220.cf.

5. Nighoghossian N, Trouillas P, Adeleine P, Salord F. **Hyperbaric oxygen in the treatment of acute ischemic stroke. A double-blind pilot study.** Stroke. 1995 Aug; 26(8):1369-72.

6. Saxby A, Barakate M, Kertesz T, James J, Bennett M. **Malignant otitis externa: experience with hyperbaric oxygen therapy.** Diving Hyperb Med. 2010 Dec; 40(4):195-200.

2.14 Tumor growth

1. Braks JA[1], Spiegelberg L[2], Koljenovic S[3], Ridwan Y[4], Keereweer S[5], Kanaar R[4,6], Wolvius EB[2], Essers J[7,8,9]. **Optical Imaging of Tumor Response to Hyperbaric Oxygen Treatment and Irradiation in an Orthotopic Mouse Model of Head and Neck Squamous Cell Carcinoma.** Mol Imaging Biol. 2015 Oct; 17(5):633-42. doi: 10.1007/s11307-015-0834-8.

2. Ding JB, Chen JR, Xu HZ, Qin ZY**. Effect of Hyperbaric Oxygen on the Growth of Intracranial Glioma in Rats.** Chin Med J (Engl). 2015 5th Dec; 128(23):3197-3203. doi: 10.4103/0366-6999.170278.

3. Moen I, Stuhr LE. **Hyperbaric oxygen therapy and cancer--a review**. Target Oncol. 2012 Dec;7(4):233-42. doi: 10.1007/s11523-012-0233-x. Epub 2012 Oct 2. Review.

4. Pande S[1], Sengupta A, Srivastava A, Gude RP, Ingle A. **Re-evaluate the effect of hyperbaric oxygen therapy in cancer - a preclinical therapeutic small animal model study.** PLoS One. 2012 ;7(11):e48432. doi: 10.1371/journal.pone.0048432. Epub 2012 Nov 7.

2.15 Acute lung injury

1. *Ratzenhofer-Komenda B, Offner A, Ofner P, Klemen H, Prause G, Smolle-Jüttner FM, Toller W. **Arterial oxygen tension increase 2-3 h after hyperbaric oxygen therapy: a prospective observational study**. Acta Anaesthesiol Scand. 2007Jan: 51(1): 68-73

2. *Bingham G, Millar J, Koch S, Paul E, Varma D, Pilcher D. **Changes in oxygenation in mechanically ventilated critically ill patients following hyperbaric treatment**. Diving Hyperb Med 2011 Jun; 41(2): 59-63

3. *Runxiao L, Juan Zheng, Zhouheng Ye, Xuejun Sun, Hengyi Tao, Kan Liu, Runping Li, Weigang Xu, Wenwu Liu, Rongjia Zhang. **Advances in the therapy of hyperoxia- induced lung injury: findings from animal models.** UHM 2014, Vol 41, No3: 183-202.

Books

Kindwall E (1999). **Contraindications and side effects to hyperbaric oxygen treatment**. In: Eric. P. Kindwall & Harry T. Whelan (eds.). Hyperbaric Medicine Practice, 2nd ed, Best Publishing Company, Flagstaff AZ 86003-0100, USA, 1999, 83-98. ISBN0-941332-78-0.

Mathieu D. **Contraindications to Hyperbaric Oxygen Therapy**. In: Tom. S. Neuman & Stephen R. Thom (eds.). Physiology and Medicine of Hyperbaric Oxygen Therapy. Saunders Elsevier Inc., Philadelphia, PA 19103-2899, USA, 2008, 587-598. ISBN 978-1-4160-346-3.