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INFECTIONS AND HYPERBARIC OXYGEN: NEW METHODS FOR HIGH-DOSE PROTOCOLS AND NON-INVASIVE MEASUREMENTS

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ABSTRACT

The scientific evidence of Hyperbaric Oxygen Treatment is despite the fact that the hyperbaric method has been in use since 1662 still under debate. At Karolinska University Hospital the method has been under the supervision of the department of anesthesia and intensive care since 1990. The number of treatments increased slowly and reached a total of approximately 3000 /year in 2008 (fig 1) although evidence of the efficacy slowly developed. The facility develops towards HBO for intensive care patients, a real challenge because of the demand for high technology in high-pressure and fire hazard surroundings. Infectious disorders such as severe soft tissue infections or postoperative neurosurgical infections have slowly developed to make a large part of the patients (fig 1). In 2005 a committee from Karolinska Institutet inspected the facility and identified among other things the lack of clinical research projects.
My thesis was therefore started first with a description of one of our large patient groups (paper I) and with the aim to perform clinical research projects for severe soft tissue and neurosurgical infectious patients using prospective randomized protocols. The lack of evidence for the correct dosage of HBOT and the lack of non-invasive methods to measure oxygen content in tissues during treatment soon became evident. These issues made the efforts to construct conclusive prospective protocols seem premature and the focus of the thesis changed to help providing a solid basis for future HBO studies. We tested 2 non-invasive methods to monitor oxygen content in target tissues, NIRS and PPG, and developed a new method (HOPAN) to make it possible to treat intensive care patients according to patients' demands without risk of DCS for attendants. NIRS measurements provided focus on soft tissues and PPG on bone tissues. NIRS (paper II) and PPG (paper III) have been tested with healthy subjects during NBO and HBO. NIRS was found to follow the inhaled oxygen within minutes. Using PPG technique we found individual changes in blood flow following the inhaled oxygen also within minutes. NIRS is a commercially available method though not yet approved for use in hyperbaric chambers. PPG equipments for clinical use are not yet available.
To make it possible to test HBO doses with the focus on patient need instead of the conventional compromise between the attendants safety and patient need we constructed a protocol with nitrox breathing for attendants (HOPAN, study IV). In our retrospective evaluation the method we found the method to be safe for both patients and attendants.

Both the tested non-invasive oxygen monitoring methods and the new HBO method will hopefully make a contribution to the development of good clinical prospective randomized research protocols.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I. 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 and
Neurosurgery 2008 Feb;62:562-571

II. Larsson A, Uusijärvi J, Eksborg S, Lindholm P.
Tissue oxygenation measured with near-infrared spectroscopy during normobaric and hyperbaric oxygen breathing in healthy subjects.
Eur J Appl Physiol 2010 Jul; 109(4):757-61. Epub 2010 Mar 10

III. Larsson Agneta, Uusijärvi J, Näslund J, Lund I, Lindholm P.
Patellar blood flow during normobaric (NBO) and hyperbaric oxygen (HBO) breathing in healthy subjects.
Manuscript

IV. Larsson A, Uusijärvi J, Frånberg O, Eksborg S, Lindholm P.
Nitrox permits direct exit for attendants during extended hyperbaric oxygen treatment.
UHM 2012, Vol. 39, No. 1; 605-612. Epub 2012 Jan

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LIST OF ABBREVIATIONS

ATA	Atmospheres absolute
CNF	Cervical Necrotizing Fasciitis
DCS	Decompression Sickness
FDA	Food and Health Administration
EUBS	European Underwater and Baromedical Society
HBO	Hyperbaric Oxygen
HBOT	Hyperbaric Oxygen Treatment
HOPAN	Hyperbaric Oxygen Protocol Attendants Nitrox
kPa	Kilo Pascal
MPA/LMV	Medical Procedure Agency/Läkemedelsverket
LTP	Local Treatment Protocol (HBO)
NBO	Normobaric Oxygen, 101 kPa, 100% Oxygen at sea level
NIRS	Near-infrared Spectroscopy
NOAA	National Oceanic and Atmospheric Administration
PPG	Photoplethysmography
SD	Standard Deviation
SSTI	Severe Soft Tissue Infection
StO2	Tissue Oxygenation
UHMS	Undersea and Hyperbaric Medical Society
UPTD	Unit Pulmonary Toxicity Dose

1 INTRODUCTION

Hyperbaric Treatment has been suggested as early as 1662 [1]. The method started as treatment of diving related symptoms in the 19th century [2] and has been developed by military marine forces and by civilians. The two lines, though using the same drug – Oxygen – and the same pressure and method (hyperbaric chambers) have over the years separated into diving (diving and submarine rescue) and hyperbaric medicine. The protocols used for hyperbaric oxygen treatment are originally designed for healthy divers or for submarine rescue (also healthy soldiers).
Oxygen was discovered in the 1770 ties (Scheele 1772 and Priestly 1775) and the use of HBO for different disorders spread starting in France and then to the large cities of Europe during the 19th century [3] . HBO came into clinical routine use in the 1960 ties by the Dutch surgeon Boerema. During the same decade (1967) UHMS was formed to further science in this field.

Oxygen was, in Sweden, registered as a drug as late as 2004 [4], although it had already been clinically available and in use since world war I. As the drug was not scientifically evaluated or registered through the normal procedure by the medical procedure agency (MPA) or the Food and Drug Administration (FDA) before it was taken into use it has never been submitted to all of the tests modern drugs are submitted to. The pharmacokinetics and pharmaceutical knowledge of the drug is not fully understood although almost every medically trained person has personal experience of this drug. As with many others drugs different pharmaceutical effects are produced with different doses, and the use of oxygen has conventionally been divided into two different levels with totally different pharmacology. Normobaric Oxygen (NBO) = Oxygen breathing at sea level, i. a maximum dose is 100%=101kPa and Hyperbaric Oxygen (HBO) = oxygen (usually 100%) breathing at a pressure higher than sea level (> 101 kPa, > 1 ATA) (HBO definition from UHMS[5]). This thesis is focused on HBO.

HBOT has been under debate for many decades and how, where and when to use the treatment, evidence-based, has not yet come to a conclusion. Several studies with a high level of evidence have recently been performed, showing results in diabetic foot [6], carbon-monoxide poisoning [7], radio-induced proctitis [8]. Cochrane reports have been published showing favorable result for the use of HBOT in late radiation tissue injury [9] One of the most commonly internationally accepted list of indications is published by Undersea &Hyperbaric Medical Society (UHMS) since 1977 and revised every 2nd-4th year [5]. There is also a European list of indications from a Consensus Conference on HBO 2004 [10] where an evidence-based approach was applied. The lists of indications consists of, among others, a number of infectious conditions such as gas gangrene, intracranial abscess, necrotizing soft tissue infections and refractory osteomyelitis. In a Cochrane progress report [11], an evaluation of HBO treatment of severe soft tissue infections is made. The report is inconclusive and points at a number of difficulties i.e. definitions of the disease, dose of HBOT (i.e. treatment pressure, duration, number of treatments). To these difficulties can be added the lack of valid, non-invasive monitoring methods of the oxygen content in tissues to verify that a correct dose of the drug really reaches the target.

At the HBO unit of Karolinska University Hospital we have treated a number of infectious diseases during 2005-2010 (fig 1). Severe soft tissue infections (SSTI) are relatively rare [12], although the HBO unit has seen 288 adult patients with SSTI requiring intensive care during 1995-2010 (fig 2).

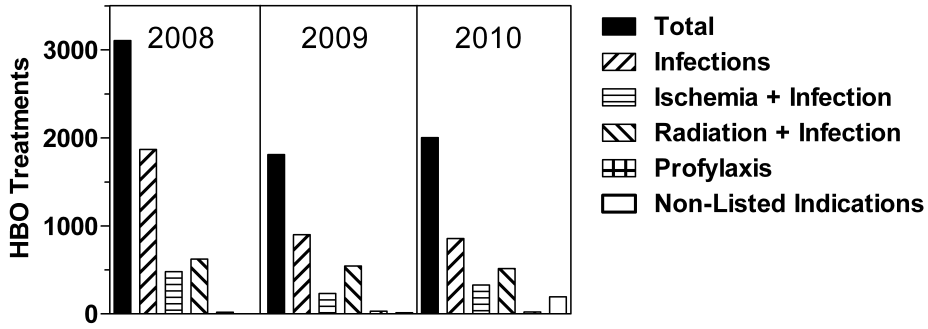

Fig. 1
HBO Treatments of infectious disorders at the Hyperbaric unit of Karolinska University Hospital

Our mortality (57% 1996 -7,7% 2010) during 1995-2010 for severe soft tissue infections compared to the expected mortality by APACHE II score (median APACHE II of CNF =16, 1998-2008 [13] -> expected mortality 26%, median APACHE II of SSTI= 23, 2005-2010 ->expected mortality 30-40%) suggests improved and good results. Other HBO-units have reported similar results [14].

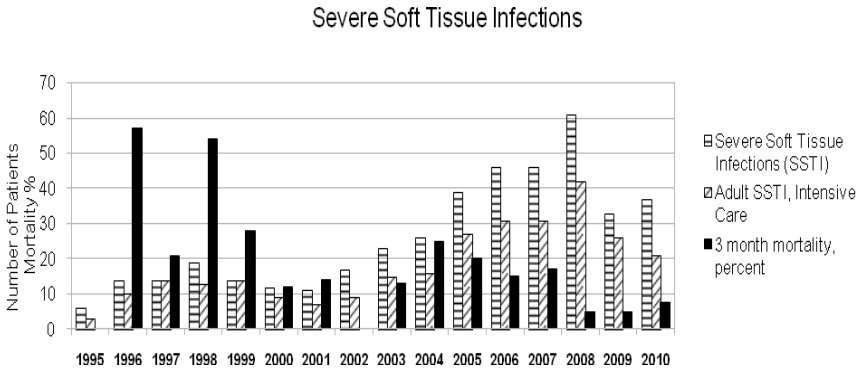

Fig. 2
Patients with SSTI at treated at the HBO unit of Karolinska University Hospital, 1995-2010.

In 2005 a committee from Karolinska Institutet inspected the facility and pointed, among other things, at the lack of clinical research projects.

The author have reported retrospective clinical results from the unit as case-reports, abstracts, posters at international, european and national conferences at 17 occasions during 2000-2010, with very little or no response [13, 15-21]. The report and the response from the multiple abstracts made several colleagues including me realize the need for scientific evidence of HBO rather than the routine of retrospectively reporting clinical experience. A research schedule was planned with a prospective randomized study of intensive care patients with severe soft tissue infections (SSTI). While planning the protocol of the study it became evident that the basics for an evidence-based HBO protocol was lacking and the research schedule was gradually changed to studies of monitoring methods and dose of HBOT.

As tissue hypoxia is intrinsic to the problem in severe soft tissue infections and osteomyelitis as well as many of the other indications for HBOT, the lack of reliable and suitable monitoring methods of the oxygen content in target tissues makes evaluation and dosage of the method difficult. Inadequate tissue oxygenation may exist while vital signs, such as blood pressure, heart rate and arterial oxygen saturation as measured with pulse oximetry (SpO_2) appear normal. Near-infrared spectroscopy (NIRS), like pulse oximetry, measures the changes in blood oxygen saturation non-invasively [22]. The difference between the two methods is that while pulse oximetry monitors the **systemic** oxygen saturation, tissue oxygen saturation (StO_2), as measured with NIRS, monitors changes in the **regional** oxygen saturation. This makes NIRS an interesting method to evaluate oxygen content in the tissues during both NBO and HBO administration, whereas SpO_2 quickly reaches the maximum value of 100% when the oxygen content in the breathing gas is elevated.

At our unit we started treatment of cranial osteomyelitis as a result of a discussion with professor Mathiesen (department of neurosurgery) on the subject of lack of available operation theatres for surgery. It was suggested that by using HBOT as an adjunct to antibiotics for postoperative neurosurgical infections some of the removal of infected bone cranioplasties could be inhibited thus making more room for other surgical interventions. The results were published 2002 [23] (paper I) and reprinted 2008 because of the originality of the study. Infectious conditions in bone are difficult to monitor and the knowledge of HBO mechanisms and dosage are as a consequence small.

Hemodynamic changes to hyperoxia in other tissues than bone have been extensively studied but the underlying mechanisms are still far from completely understood [24]. There is at present no non-invasive clinically available method to evaluate oxygen content in bones, which makes it very difficult to follow clinical progress of HBO treatment in these tissues. We tested (paper III) a newly developed non-invasive method, photoplethysmography (PPG), where changes in pulsatile blood flow within the patellar bone and overlying skin were recorded continuously. PPG has been used to

monitor blood flow in skin and muscles [25-27], and hemodynamic sensing in implanted devices [28]. It has also been shown that experimental induced changes in pulsatile blood flow within the patellar bone are possible to study using the PPG technique [29-31]. Monitoring changes in bone blood flow during oxygen treatment could be of value in the study of physiological reactions related to HBOT, although the method has not yet been evaluated for hyperbaric use.

In a multiplace chamber (pressurized with air), patients breathe oxygen via a ventilator, hood or a mask, usually assisted by chamber attendant(s) breathing the chamber air. Decompression Sickness (DCS) is therefore a possible complication for HBO attendants [32-34]. To reduce this risk, decompression protocols are calculated using algorithms developed and originally tested for diving [35]. A monoplace chamber (pressurized with 100% oxygen) where the patient breathes oxygen without a mask or hood, is most commonly used for conscious and communicable patients. Usually there is neither space nor need for chamber attendants inside a monoplace chamber, and the treatment protocol can be designed according to the patient's needs exclusively.

As the HBO patients breathe 100% oxygen, they will not accumulate nitrogen and thus not be at risk of DCS. Apart from oxygen toxicity risk, duration of HBOT for the critical care patient is limited by other essential treatments and examinations (e.g., imaging, surgery and dialysis). All protocols are therefore a balance between oxygen treatment for the patient, oxygen toxicity and chamber attendants' risk of DCS.

Historically, protocols were aimed at treatment of divers suffering from DCS [32-33]. For most infectious patients, a reduction or absorption of gas bubbles is irrelevant; instead, the increased delivery of oxygen to target tissues is paramount. A protocol with a flexible duration, ability to adapt to time constraints in the clinical program and shift balance towards optimal care of the patient (while keeping the safety of the attendants well within accepted limits) would be ideal.

We developed an HBOT protocol (HOPAN, paper IV) that enables the critical care patients in multiplace chambers to receive at least the same dose as the patients in monoplace chambers still with a minimal risk for attendants and keeping the option of a direct ascent to surface at all times. In this protocol attendants breathe nitrox (oxygen enriched air), a method known to divers to prolong time at depth since the1950ties [2]. Attendants breathing nitrox have been in routine use in other HBO facilities, but the experiences have not yet been published.

Oxygen constitutes a basic need for all cells in the human body, which means there are many physiological mechanisms including protective mechanisms involved in the metabolism of this drug. It is difficult to find the interest and economics to investigate an already widespread drug, that a wide majority of users already have a very definite opinion on how and why to use. It is therefore easy to understand why the scientific evidence of HBO and NBO is lacking. It is also easy to understand why there is a really huge need to investigate the evidence base for the wide use of oxygen both as NBO and HBO.

Combining the two non-invasive oxygen monitoring methods and the new HBOT protocol we think there are increased possibilities to plan good prospective randomized studies to answer some of the issues regarding dosage and indications of HBO. This may include monitoring oxygen in target tissues - making the dosage for each patient individual.

2 AIMS OF THE PRESENT STUDY

The general aim was to find monitoring methods and flexible HBOT protocols, based on the patients' need of oxygen, to investigate the possibility to use of HBOT in severe infectious conditions.

Our specific aims were:

1. To retrospectively report the additional use of hyperbaric oxygen (HBO) therapy for infections after craniotomy or laminectomy during 1996-2000 at the HBO unit of Karolinska University Hospital.

2. To examine if near-infrared spectroscopy (NIRS) would make it possible to monitor oxygen changes in target tissues (StO2) in healthy subjects during NBO and HBO administration.

3. To investigate, if photoplethysmographic technique (PPG), can be used to monitor individual changes in pulsatile blood flow in bone and in skin in healthy subjects during NBO and HBO administration.

4. Evaluate the newly designed HBOT protocol (HOPAN) in use in out unit during 2008- march 2009. The protocol's aimed at enabling an equal or higher dose of Oxygen to critically ill patients compared to other patients while maintaining a low risk of decompression sickness (DCS) for attendants.

3 MATERIALS AND METHODS

3.1 STUDY I: HYPERBARIC OXYGEN TREATMENT OF POSTOPERATIVE NEUROSURGICAL INFECTIONS

Retrospective non-randomised clinical study
HBOT was used, in a pilot study, as an alternative to standard surgical intervention for postoperative infections in the neurosurgical department at Karolinska University Hospital. 39 consecutive patients referred for HBOT with a clinical diagnosis of postoperative neurosurgical infection during 1996 to 2000 were included.
The study involved review of medical records, office visits, and telephone interviews. Infection control and healing without removal of cranioplasties or foreign material were considered a successful result.
Medical records were followed for a minimum of 6 months (mean 27, range 6-58) after completed HBOT or until failure.

The study has expanded to 72 patientens, 1996-2003 after publication. These results have been reported as abstract at scientific meetings [20].

3.2 STUDY II: NEAR-INFRARED SPECTROSCOPY DURING NORMOBARIC AND HYPERBARIC OXYGEN BREATHING IN HEALTHY SUBJECTS

Semi-Blinded test using healthy volunteers: Validation of near-infrared spectroscopy (NIRS) as a non-invasive monitor of tissue saturation (StO_2) during HBO
Tests were performed in a hyperbaric multi-place chamber (Kockums, Sweden) using hoods (CASTAR, STARMed) supplied with either air or oxygen during the experiment. Subjects were positioned in a semi-recumbent position; test protocol was started after 10 minutes of rest.

Subjects (9 healthy volunteers), were blinded as to whether they breathed air or oxygen. Different O_2 partial pressures were administered in the following 10 minute intervals:
NBO: 21 kPa (air), 101 kPa (100% O_2), 21 kPa.
HBO: 59 kPa (air), 280 kPa (100% O_2), 59 kPa.

Tissue oxygenation was monitored with an InspectraTM StO2 monitor (Hutchinson Technology, MN, USA) inside the chamber using a probe placed on the thenar eminence (thumb). The monitor was tested for use under hyperbaric conditions (maximum 3.5 bars) according to a risk analysis protocol in cooperation with the local medical technical department.

Heart rate and blood pressure were monitored with a Propaque monitor 106 EL (Protocol Systems Inc, Beaverton Oregon, USA), also inside the chamber.
Data were averaged over last 5 minutes at each pressure.
The volunteers were all recreational divers; eight males and one female.

3.3 STUDY III: BONE AND SOFT TISSUE BLOOD FLOW DURING NORMOBARIC AND HYPERBARIC OXYGEN BREATHING IN HEALTHY SUBJECTS

Semi-Blinded test using healthy volunteers: Validation of a new photoplethysmographic (PPG) method as a non-invasive monitor of bone and soft tissue blood flow during HBO
Tests and protocols were performed exactly as in study II, above. All performed in the afternoon or evening. The chamber was ventilated to hold an environmental temperature of 20 - 25 ºC.

Subjects (11 healthy volunteers, 2 female) all recreational divers, were blinded as to whether they breathed air or oxygen during NBO and HBO. Different O_2 partial pressures were administered in the same 10 minute intervals as in study II, above.
A two channel PPG instrument (Department of Biomedical Engineering, Linköping University, Sweden) and a PPG probe were used to continuously record blood flow changes in the patellar bone and in the skin overlying the patella. The probe was connected to the PPG instrument outside the chamber using a pass-through in the chamber wall.

The pulse-by-pulse amplitude of the AC component of the PPG signal was subsequently extracted with dedicated software (Daquhura 1.3, Linköpings Tekniska Högskola 1995). The PPG signal was later analyzed using software (MATLAB, R2006b). A base-line, pre-oxygen value was calculated from 30-60 seconds peak-to-peak recordings, both during NBO and HBO. When the bone blood flow was at its lowest level, ~ after 2 min, a 30 second peak-to-peak recording was used as oxygen breathing value.

Differences in individual data on assessments of pulsatile blood flow in bone and skin were expressed as percentage of changes between air breathing and NBO/HBO respectively.

3.4 STUDY IV: NITROX PERMITS DIRECT EXIT FOR ATTENDANTS DURING EXTENDED HYPERBARIC OXYGEN TREATMENT

Retrospective study of patient medical records and a questionnaire to attendant. Experiences from attendants and patients of a new protocol, HOPAN, for HBOT.

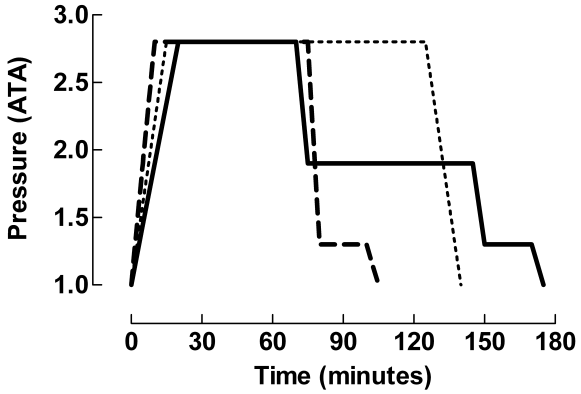

Fig 3.
LTP (local treatment protocols) and maximum HOPAN.
Thick line = 175 minutes multiplace LTP. Large interrupted line = 105 minutes multiplace LTP. Small interrupted line = maximum 200 minutes HOPAN. Thin line = 100 minutes monoplace LTP.

All treatments were performed in a multiplace chamber (HAUX Qaudro 3200). A minimum of two attendants inside and two outside the chamber were present throughout each protocol. Information regarding patients and attendants having participated in HOPANs were collected from the hospital patient and HBO unit documentation systems and medical records.

HOPAN
HOPANs were used occasionally during 2008-march 2009 under the supervision of at least one of the authors of the study. HOPAN were calculated using both the Bühlmann mathematical model (Bühlmann ZHL16B) and the variable permeability model (VPM). Both calculations were made using a commercially available program (Decoplanner version 3.1.4).

Attendants: breathed nitrox (using a HAUX mask) or chamber air (off mask), they were allowed to participate in one chamber “dive” per 24 hours. Cycles of 15 minutes of nitrox breathing followed by 10 minutes of chamber air were administered, using the hospital supply of medical oxygen and air, mixed continuously at a ratio of 1:1 (60.5% O_2). Treatment duration of up to a maximum of 200 minutes at 2.8 ATA was allowed; no randomization was carried out.

Expired oxygen was measured intermittently with a mobile oxygen detector though not documented.

An anonymous questionnaire was sent to attendants (n = 59; with study directors excluded n = 56) having participated inside or outside chambers during an HOPAN once the study period was finished. The questionnaire included one part with questions regarding LTP and a second repeating the questions for HOPAN. The questions included earlier experience of HBO/diving, DCS symptoms, comfort and safety. All symptoms or complaints were subjectively graded (1-10). The answers and separate written approval to participate in the study were sent to a study collator with no knowledge of the HBO unit or attendants. The answers were then transformed into a data file (with no participant identifiers) and sent to the study directors for further analyses.

Patients: breathed cycles of pure oxygen for 20 minutes interrupted by 5 minutes of air through a ventilator, hood (CASTAR, STARMed) or mask (HAUX). They were monitored according to clinical routine. Patients received local treatment protocols (LTP) as well as HOPANs in their HBOT series.

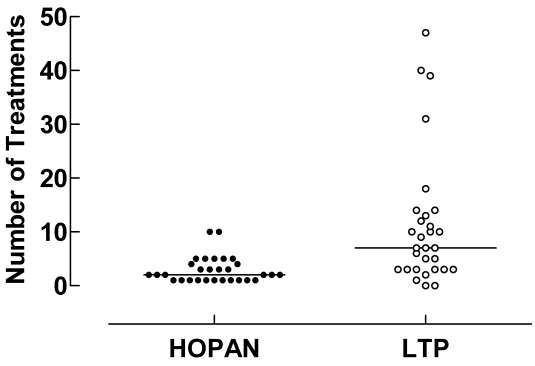

Fig.4
Number of HOPANs and of LTP for patients in the study (n=30).

Patients' medical records were followed for six months after the HBOT series was finished.

4 RESULTS

4.1 STUDY I: HYPERBARIC OXYGEN TREATMENT OF POSTOPERATIVE NEUROSURGICAL INFECTIONS

Successful results were achieved for 27 of 36 patients (n=39), with a mean follow-up period of 27 months (range 6–58). One patient discontinued HBOT because of claustrophobia, and two could not be evaluated because of death prior to the 6 month minimum follow-up time. There were no major side effects of HBO treatment. Patients were divided into 3 different groups according to their neurosurgical disorder.

Group 1 (uncomplicated cranial wound infections, n=15), 12 of 15 patients healed succefully with retentained autologous cranioplasties.

Group 2 (complicated cranial wound infections, with risk factors such as malignancy, radiation injury, repeated surgery, or implants, n=16), all except one infection resolved; three of four autologous and three of six acrylic cranioplasties could be retained.

Group 3 (spinal wound infections, n=7), all infections resolved, five of seven without removal of implants.

Additional data (fig 5) describes the cultures found in the 3 groups, this was not included in the original publication.

The study concludes that HBO treatment is an alternative to standard surgical removal of infected cranioplasties and implants.

Additional data was also published as an abstract at the annual scientific meeting of UHMS 2004 [20]. 72 consecutive patients (including the patients in the published study) treated during 1996-2003.

Group I: 19/24 healed with retained autologous cranioplasties.

Group II: 12/25 healed with retained cranioplasties.

Group III: 12/14 healed with retained implants/cerebral shunts.

Group IV brain abscesses/empyemas: 9/9 healed.

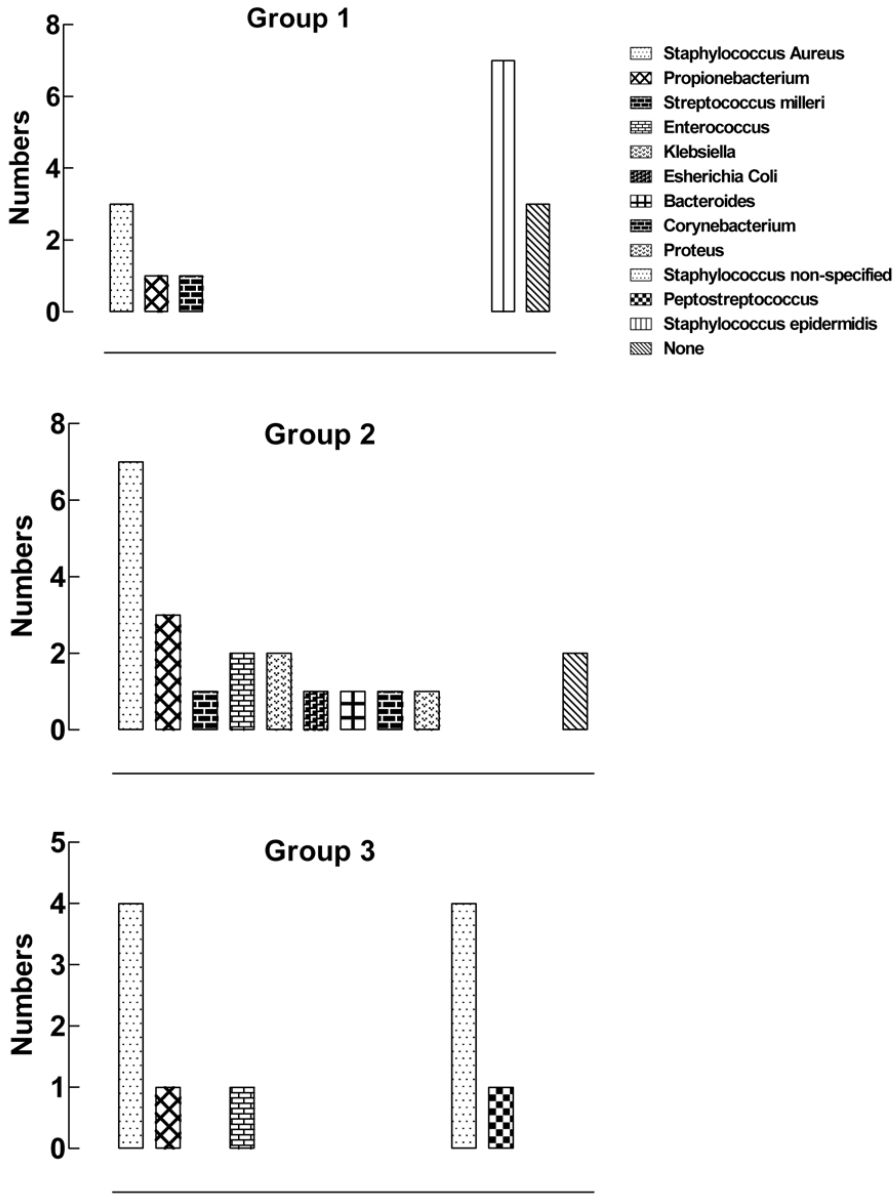

Fig. 5
Results from cultures of wounds in the 3 original groups (n=39).

4.2 STUDY II: TISSUE OXYGENATION MEASURED WITH NEAR-INFRARED SPECTROSCOPY DURING NORMOBARIC AND HYPERBARIC OXYGEN BREATHING IN HEALTHY SUBJECTS

When switching from air to NBO StO_2 increased from 83% (82-85%, median and interquartile range) to 85% (84-87%) (P\0.01), and when switching from air at pressure (59 kPa O_2) to HBO (280 kPa), StO_2 increased from 85% (85-86%) to 88% (87-89%) (P\0.001). There was no difference between baseline StO_2 while air breathing before NBO or after decompression.
The main finding of the study was that tissue oxygen saturation (as measured by NIRS) increased significantly, but did not reach 100% during both NBO and HBO. The results suggest that this method could be used to monitor changes in tissue saturation during HBOT.

Statistical analysis: Nonparametric statistical procedures were performed throughout the study unless otherwise stated. Median values of NIRS (%) during the last 5 min of the different pressure periods were compared for the different subjects. The Friedman test (nonparametric repeated measures ANOVA) was applied with Dunn's multiple comparison test.

4.3 STUDY III: BONE AND SOFT TISSUE BLOOD FLOW DURING NORMOBARIC AND HYPERBARIC OXYGEN BREATHING IN HEALTHY SUBJECTS

Pulsatile patellar- and skin- blood flow decreased during the first 2-3 minutes of NBO and HBO.
The decrease in blood flow was:
NBO: 32% ±15 in bone and 36% ±18 (mean SD, $p<0.0001$) in skin.
HBO: 22% ±18 in bone and 21% ±25 (mean SD, $p< 0.0344$) in skin.
Blood flow returned to base-line levels within 5-8 minutes.
The results suggest that PPG could be used to monitor individual changes in bone and skin blood flow during HBOT.

Statistical analysis: Blood flow changes were expressed as percentage of the pre-oxygen level and presented as mean (95% confidence interval). T-test for dependent samples was used analyzing blood flow changes. The level of significance was set at $P <0.05$.

4.4 STUDY IV: NITROX PERMITS DIRECT EXIT FOR ATTENDANTS DURING EXTENDED HYPERBARIC OXYGEN TREATMENT

HOPAN treatment protocols (n=88) were used during 2008-march 2009, 64 attendants (including three of the study directors) breathed nitrox on 142 occasions. Thirty patients were treated with a combination of LTP (n = 336)/multiplace LTP (n = 125) and HOPANs.

HOPAN:
duration:139.5 minutes (median, range 55-167 minutes).
time at treatment pressure (2.8 ATA): 110 minutes (median, range 45-145).
UPTD for attendants: 174 (median, range 130-232).
UPTD for patients: 403 (range 163-520).

LTP/multiplace LTP:
duration: 100 minutes/105 minutes (median, range 100 – 175/105 – 175).
time at treatment pressure (2.8 ATA): 60 minutes/65 minutes (median, range 0 - 90/60 - 65).
UPTD for attendants: 90.3/20.
UPTD for patients: 266 /423.
UPTD for LTP in monoplace chambers: 266.9 (2.8 ATA) resp. 238.2 (2.5 ATA).

ATTENDANTS:
5 were excluded (3 had participated in other experimental tables, 2 could not be reached). There were 35 physicians, 19 nurses and 5 others; ages 25 to 60-plus, 26 females. Total number of exposures in multiplace chambers (LTP and HOPAN) of the attendants (n = 59), historically and during study period, was 1808 (median 20, range 1-162).). The median number of HOPANs (inside the chamber) each attendant participated in was 2 (range 1-24). 56/64 attendants (study directors excluded) received an invitation to participate in the study and a questionnaire, 31 responded.

LTP:
24/31 minor symptoms, 10/31 (paresthesias, tingling of skin) 14/31 (tiredness, headache, slight dizziness).
5/31 joint pain (two severe -5 and 8/10).

HOPAN:
1/31 minor symptoms (tiredness).
1/31 mild joint pain (3/10).

There were no complications (DCS or symptoms of oxygen toxicity) reported or treated among attendants. Study of the HBO unit’s archive showed no recorded symptoms or complaints from any attendant, neither historically nor during the study period.

PATIENTS:
30 patients were treated with HOPANs in combination with LTP. Each patient received a median of 11 (range 1-51) HBOT sessions, of which the median number of HOPANs were 2.0 (range 1-10). No complications were documented. Six-month follow-up showed that mortality for critical care patients having received at least one HOPAN was 1/20, study period 2008-march 2009. The number of adult critical care patients treated with HBOT (including HOPAN) in Karolinska University Hospital during 2008-2009 was 64, with a mortality rate of 4/64 (fig 2 in introduction).

It is suggested that nitrox breathing for chamber attendants provide flexible HBOT for patients at 2.8 ATA for up to 200 minutes, facilitating future studies of HBOT dosage.

5 GENERAL DISCUSSION

Oxygen as a drug

The use of oxygen in medicine started long before it was recognized as a drug [36]. The process of bringing oxygen into clinical practice can rather be described as empirical although based on sound physiological principled and a logical rationale [36]. In Sweden oxygen was recognized by MPA/LMV as late as 2004 [4]. A lot of documentation is lacking such as maximum dose, optimal/correct dose for many of the different conditions the drug is used in and the indications have not been subjected to the modern evidence-based procedures of randomized studies before it was taken into a widespread use. Despite the lack of knowledge there are some facts known and there is a lot of experience of the use of oxygen.

The effects of HBO (defined as oxygen breathing at a higher than ambient pressure approximately 1.0 ATA at sea level, commonly an increase of 0.5-1.8 ATA for therapeutical use [5] is vastly different from those when the drug is used as NBO. The use of small quantities of supplementary oxygen (even as low as 2 liters of oxygen/minute at 1 ATA nasally) have been questioned in a recent study [37-38].

The physiologic effects of HBO include [5, 39] :

- intravascular and tissue gas bubble reduction
- improved tissue oxygenation
- vasoconstriction
- increased antimicrobial activity[40]
- modulation of inflammation and immune function[39, 41]
- promotion of angiogenesis[42-43]
- increased bone turnover [44]
- improved osseointegration and reduction of implant [45-46].

The immediate reactions of HBO on bone blood flow have not been studied (to our knowledge) or published prior to our study.

HBO-dose

An international standard for documentation of oxygen dose the patient is scheduled for or has received does not exist yet. National Board of Health and Welfare and Medical Procedure Agency in Sweden produce guidelines on the safe use of drugs, one of their important issues is how to properly document a drug and the dose given to a specific patient. The guidelines regarding oxygen are scarce and non-specific especially if you include HBO doses [4]. Some of the units conventionally used include added liters/minute to ambient air, % oxygen (usually mask breathing at sea level), bars, ATA, kPa and sometimes HBO-protocols are referred to i.e. USN table 6, HOPAN, LTP. The correct protocols of HBO to be used are very scarcely evaluated [47].

Lack of reliable and suitable methods for monitoring the oxygen content in the target tissues makes evaluation and dose determination of HBO difficult. Many questions remain to be answered: For example, is pressure or duration of HBO of greatest importance, or perhaps both combined? It is also not clear how often the treatment should be repeated [35, 47]. HBO dose varies between different treatment centers; and the appropriate dose of oxygen for the patient is not always the main issue, since logistics and staff safety have to be considered.

During our retrospective studies of HBO treated patients and the preparation of a prospective randomized protocol we found that the intensive care patients consequently received a lower dose of oxygen during HBO than other patients (fig 6, monoplace LTP contra multiplace LTP). Until further studies verify optimal pressure and duration of HBO we consider it rational to treat critical care patients with similar tables as monoplace patients and not less duration at treatment pressure.

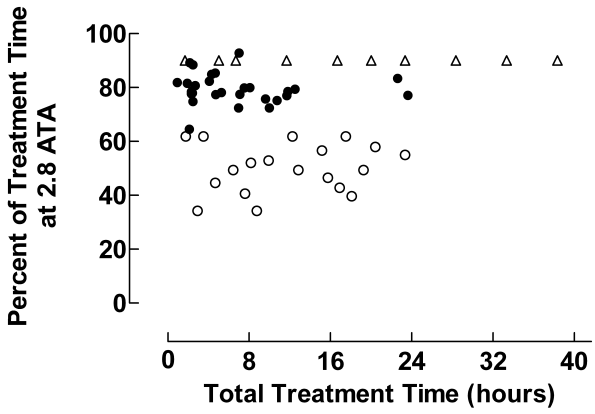

Fig.6.
Percent time (total HBO2T series) at treatment pressure (2.8 ATA) for each patient in study IV (n=30), separated into the different protocols used. Black dots denote HOPAN; transparent dots = multiplace LTP; and triangles = monoplace LTP.

At the UHMS annual scientific meeting 2010, dr Neil Hampson addressed this problem and suggested the use of ATA-hours of oxygen to describe the total dose of HBO the patient has received [47]. ATA-hours is calculated using the very simple formula “time of pure oxygen breathing at treatment pressure (hours) x treatment pressure (ATA)” (personal communication with dr Hampson, august 2010).

Below is dr Hampson's suggested ATA-hours applied on the patients in paper IV, SSTI adult patients in Intensive Care (fig 6, 7, 8).

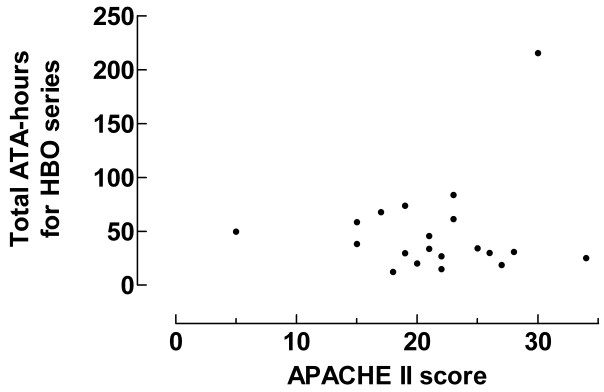

Fig. 6.
Total ATA-hours compared to APACHE II score for patients (20/30) in paper IV. For some of the patients APACHE II score has not been documented, they are not described in this figure. We cannot, from these data, establish any correlation between severities of disease to received HBO-dose.

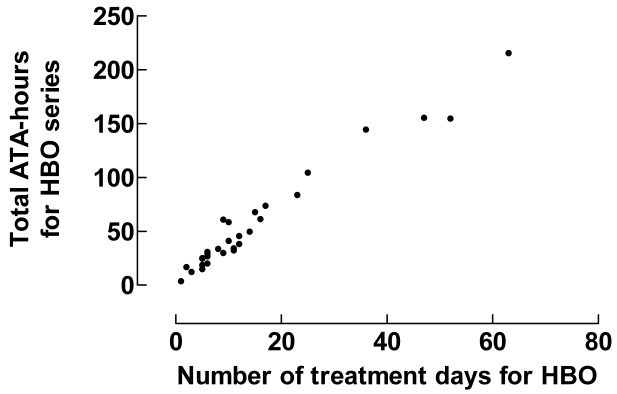

Fig. 7.
Total ATA-hours compared to the number of treatment days for the patients (n=30) in paper IV.

Our clinical experience (Study I, IV) regarding HBOT dose indicates that infection control and establishment of the healing process can be quite rapid and that many

patients continue to exhibit improvement after cessation of HBOT. For other patients a longer treatment period might have been beneficial, future refinements could include individual monitoring of HBO response to make a tailor-customized dose possible.

Many HBOT facilities have reported their experiences with HBOT as an addition to modern intensive care, extensive (although tissue-saving surgery) and antibiotics for SSTI patients[14]. The indication has been analyzed in a Cochrane report [11]. Some of the difficulties in comparing the publications were found to be definition of the disease, different HBOT doses, non-standardized surgical procedures and standards for when to stop the HBO series. The possibility of monitoring oxygen changes in target tissues may help to solve some of these issues namely HBO dose and indicate when to stop HBOT.

At Karolinska University Hospital we have used the triad of CRP below 100, no necessity of drugs to maintain MAP and the surgeons report there are no more production of necrotic tissue to define "infection control". When the patient reaches infection control we stop HBOT unless there is a need to support the wound healing.

If a scientific evaluation on the efficacy of oxygen is to be made there is a need for a standardized dose. Are studies of oxygen, not using an evidence-based dose, of any value? In some studies and a Cochrane report [37-38, 48-49] administration of oxygen has even been suggested to be negative for the patient rather than beneficial, can this be due to the low dose used?

HBO side effects

Patients breathing oxygen are exposed mainly to risk of central nervous system (CNS) and pulmonary oxygen toxicity [50]. Oxygen seizures may occur, especially when therapy is administered at high pressures to patients with fever or when hypercapnia, often attributable to hypoventilation, is present. An incidence of 1/10,000 treatments is often cited. Seizures are self-limiting, and sequelae are uncommon. A partial pressure of O2 of 170 kPa (1.7 ATA), as found in the nitrox mix (60.5% O2) used in the present study is higher than that recommended for use in commercial diving in water [51]; NOAA recommends a maximum of 1.6 ATA , while the US NAVY recommends 1.3 ATA. However, it is lower than the 190 kPa used for attendants in U.S. Navy Table 6 [52], one of our LTPs (study IV). The risk of CNS toxicity for attendants using nitrox, with intermittent air breaks at the proposed level in HOPAN (study IV) is considered very low [50, 53-54].

When breathing oxygen at a higher pressure than in ambient air for an extended period of time, pulmonary oxygen toxicity has to be considered [50], [55-56]. The toxicity to the lungs can be seen as a decrease in vital capacity and calculated as unit pulmonary toxicity dose (UPTD). The accumulative risk is limited by air breaks, common in most HBOT protocols. All HOPANs (study IV) were well within the Statute book of the Swedish National Board of Occupational Safety and Health regulations of UPTD for both patients and attendants (limit maximum 850 UPTD/day) [57-58].

Methodological considerations

Study I

A retrospective study although consecutive as to patients referred for HBOT because of a specific medical disorder (infections following neurosurgery) will never produce conclusive evidence of the usefulness of the intervention but can give valuable information to forthcoming study designs. This study started with one interested neurosurgeon, specialized in meningeomas, making the material deviate towards patients with meningeomas instead of a generalized neurosurgical population (Study I Table 1,2,3).

At the time of the study the hyperbaric chamber location was very far from the neurosurgical clinic making the transport of critically ill patients a hazard. As the indication for HBO was additional and not earlier described we decided to exclude all critically ill patients.

As experience of HBOT for these infections grew, a few more neurosurgeons took interest in the method and more complicated cases were referred. This made the material change during the study period from cleancut infections following surgery of meningeomas to infections in complicated cases following surgery of a diversity of disorders and including infections after spinal surgery. Diagnosis of an infection in bone tissue can also present a problem for cranial infections it is often based on the clinical presentation. X-ray or other forms of diagnostic imaging can rarely picture the infection until in the later stages [59-60] and blood samples are rarely conclusive. In order to find the correct pathogen for osteomyelitis a small sample of bone tissue to culture is required.

A bone sample is accompanied with a risk of complications and is therefore not included as a routine procedure, none of the patients in this study had such a sample taken.

We can therefore not be sure that the bacterias in the cultures taken from the wound in the soft tissues of the scull or spinally (fig 5, in methods), mostly after onset of antibiotic therapy, are the tue pathogens. In several of the cases we found no bacteria in the cultures although the clinical symtoms of infection were convincing.

It is a clinical challenge to decide, on the clinical symtoms only, whether a superficial infection of skin and soft tissues or a deeper infection of bone is present. Endpoints are also difficult since there are no clinically available monitoring methods to decide whether the bone tissue is infected or not. In this study we continued HBOT initially up to 40 sessions and later until the wound was healed + 5 days. A method to monitor the status of the bone tissue could have made it possible to individualize the number of HBOT as it is our opinion that the soft tissues would have healed without the addition of HBOT once the infection in the bone was under control.

The material has after the publication increased in volume, grown to include brain abscesses and infections following insertion of implants. Although this has been presented as abstracts [16, 20, 61] and a publication [62] there is still a need for randomised, controlled studies to make the use of HBOT evidence-based.

Study II and III.
Using technical equipment under hyperbaric conditions can put both the equipment and persons inside and outside the chambers at hazard. Most clinically available equipment have not been tested for hyperbaric use, the procedures for such tests are regulated by MPA/LMV in Sweden. The NIRS and PPG equipments used in our tests were not tested for hyperbaric use. The equipments were, prior to our use, tested in hyperbaric protocols by the medical technical department of Karolinska University Hospital. NIRS equipments are commercially available and in clinical use mostly in intensive care units [63-64].
We used the Inspectra equipment in our study but we also tested Somanetics equipment (with a pass-through in the chamber wall). The Inspectra NIRS monitor has been evaluated for use on the thenar eminence only; however, there are other NIRS monitors available with probes evaluated for use in other parts of the body. Our choice of monitor was made because it could be used safely inside the hyperbaric chamber. The Somanetics equipment was only tested on a few subjects to evaluate its feasibility for future studies. This equipment has a 4-channel parallel capacity making it possible to compare a healthy tissue on one side of a patient with infected target tissue on the other side.

None of the equipments are, as of yet, commercially available for hyperbaric use.
The protocol used with subjects first breathing NBO and then HBO at the same occasion may have influenced the results although we still have a reliable compliance between the monitored changes in StO_2 and inhaled oxygen.

The PPG method is quite new, not commercially available yet and its validation under further discussions [31, 65]. Blood flow in most tissues is influenced by activity. In our study we used a 10 minute resting period before exposure [66], the correct resting time to down-regulate bone blood flow to base-line values is not known, the 10 minutes used by us may have been too short. A period covering at least 30-60 heartbeats has been suggested to improve confidence in PPG pulse measurements [27], the 10 minute period used in our study is well over this limit.
The similar results in many studies using different measuring methods indicate that decreased blood flow is a valid immediate reaction in skin to increased oxygen tissue content in healthy subjects; it is not validated for oxygen content in bone.

Study IV
The new protocol was taken into clinical practise according to local routine, which at that time was that the protocol chosen was under the supervision of each senior hyperbaric specialist. There were several protocols in routine use.
The HOPAN protocol was only used under the direction and presence of one of the authors, the selection of when and what patients to treat was therefore not according to severity or disorder. The evaluation was done retrospectively after HOPAN had been in use for a little more than one year.
It is difficult to be conclusive when the patients have received an HBOT series which was random but not randomised with a variety of LTPs and HOPANs (fig 4 in methods). HOPAN could randomly be any (or all) of the treatments in a patients' series of HBOT.

It was found to be comfortable and safe to breathe nitrox intermittently and perform patient care during air breaks, as the attendants are not used to mask breathing as the most often-used LTP does not use mask breathing at all. During the most common LTP (local treatment protocol) in our unit, attendants breathe chamber air throughout the protocol. Oxygen breathing for attendants is used during safety stops in the more rarely used 175-minute LT P and U.S. Navy treatment table 6.

The questionnaire sent to attendants was sent after the study period was finished. This meant for some attendants that they received the questions within weeks of the HOPAN and for others a little more than a year after the HOPAN.
As there was no documented symtoms or complications, in the HBO units records, to any of the LTPs it was presumed that these protocols never caused any problems. The questionnaire was contructed under this presumtion which unfortunately proved to be questionable.
One of the difficulties is that there is no possibility to separate the different LTP protocols. Symptoms for attendants inside chamber, both minor (24/31) and severe (5/31 joint pain, VAS/NRS 1-8), were reported in connection with LTP, while no minor and one severe occurrence (1/31 joint pain, VAS/NRS 3) was reported in connection with HOPAN.
It is very difficult to retrospectively evaluate possible symtoms of DCS that has not been documented or examamined.

NIRS
Lack of reliable and suitable monitoring methods of the oxygen content in the target tissues makes evaluation and dosage of HBOT difficult.
To verify that HBOT does allow oxygen to reach the target tissues and also to evaluate at what dose it reverses tissue hypoxia, an efficacious measure of oxygen content in tissues is needed. As oxygen levels in tissues can change very quickly, in the order of minutes, monitoring should preferably be carried out during HBO administration.

In a previous study, Litscher et al. [67] evaluated NIRS using a different type of monitor (INVOS 3100 cerebral oximeter) than the one we used (Inspectra) measuring cerebral oxygenation during HBO. They used a pass-through penetrator in the chamber wall, situating the monitor outside the chamber with the probe attached to the subjects inside chamber. Although the results of the Litscher study are similar to those of the present study, one difference is that on returning to ground level (21 kPa oxygen) following the period of HBO, at 15 min the NIRS values had still not returned to the baseline levels recorded prior to the increase in pressure. A possible explanation for this finding is that the StO2 measurements were made in two very different tissues—cerebrally in the Litscher study and in our study (study II), in peripheral muscle (thenar muscle); the difference in delay of return to baseline StO2 levels after HBO exposure presents an interesting issue for further tests.

NIRS has not yet been evaluated for use under hyperbaric conditions.

PPG

PPG is a non-invasive optical technique that measures changes in pulsatile blood flow and PPG has been used to monitor blood flow in skin and muscles [25-27], and to monitor hemodynamic sensing in implanted devices [28].

It has been shown that experimental induced changes in pulsatile blood flow within the patellar bone are possible to study using the PPG technique [29-31]. Meiroviths et al [68] showed that microcirculatory brain blood flow in rats decreased significantly in the first few minutes after HBO but returned to baseline levels within a variable period, still under HBO.

Our results (study III) show similar results with a decreased blood flow initially. The effect of HBO on cerebral blood flow was though found to be highly dependent on the monitoring method, since other studies revealed no such systematic changes [69].

An important limitation of the present PPG technique is the lack of a gold standard for calibration. PPG measurements can at present therefore only be reported as changes from one point in time to another.

Hyperoxia-mediated vasoconstriction and, as a result, decreased blood flow has been shown to occur in most healthy vascular beds in animals and man [70]. Studies have shown that exposure to HBO causes a general quick vasoconstriction and blood flow reduction in various organs in rats and humans [24]. Vucetic et al [71] reports an overall reduction in human retina arterioles diameter of 10% after 10 min HBO (2.5 ATA), which corresponds with a 40% fall in blood flow.

The immediate reactions of HBO on bone blood flow have not been studied (to our knowledge) prior to our study (III).

6 CONCLUSIONS AND FURTHER PERSPECTIVES

We conclude that HBOT can be an alternative/adjunct to standard surgical procedures for many complicated cranial and spinal infectious problems. Prospective trials are needed to assess the appropriate doses, the medical and economic implications of this new treatment regime.

We found that the two non-invasive methods (NIRS and PPG) could be promising technologies to monitor oxygen changes in target tissues during NBO and HBO. Prior to the use of NIRS and PPG in clinical HBO practice, further test are necessary to ensure the correct safe and accurate use inside hyperbaric chambers.

HOPAN protocols for HBOT enables long and flexible treatments to patients in multiplace chambers, similar to the protocols used for monoplace chambers, while maintaining the possibility of a direct decompression and exit.
It appears that the HOPAN protocols did not cause any severe increases in side effects for patients or attendants.

Prospective study
We plan, as a post-doctoral study, to investigate the possible clinical benefits of the prolonged HBOT afforded by HOPAN.

Ethical permission: Dnr 2008/2074-31/4.

A prospective study of SSTI patients treated according to the Karolinska University Hospital protocol (approximately 15-20 patients/year). Patients are randomized to different HBOT protocols and monitored with NIRS and PPG to follow oxygen changes in target tissues.

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