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ONLINE REGISTRATION available at: www.uhms.org REV 7/01/2011
Hyperbaric oxygen therapy (HBO₂T) is widely used in basic research and clinical studies, and has been a field of increasing scientific publications in the past 10 years. A bibliometric analysis of the number of citations in HBO₂T-related publications would be helpful for researchers to identify the research focus in this field. The review paper entitled “Top-cited articles on hyperbaric oxygen therapy published from 2000 to 2010” by Drs. Ching-Hsing Lee, Lan Lee, Kun-Ju Yang and Teng-Fu Lin) in this issue of Undersea & Hyperbaric Medicine [1] offers researchers a terrific chance to see the 100 top-cited papers about HBO₂T.

The authors reviewed all published HBO₂T-related articles to find citation classics for the period 2000-2010. The review summarizes the major information of the top 100 most-cited articles on HBO₂T, including title, first author, country, journal, published year and number of times cited. This information helps the readers to select the HBO₂T-related articles by their interests, and may save a great deal of time in exploring HBO₂T-related articles. This review is helpful for researchers in this field to understand the major research directions of HBO₂T.

Clinical and mechanistic data support use of HBO₂T for a variety of diseases or disorders including stroke, radiation injury, carbon monoxide, wounds, brain injury, diabetic mellitus foot, ischemia/reperfusion injury, necrotizing fasciitis, genotoxicity, air embolism, calciphylaxis, atherosclerosis, avascular necrosis, cerebral palsy, myocardial infarction, osteonecrosis, pancreatitis and subarachnoid hemorrhage [1].

As suggested in this review, stroke, radiation injury, carbon monoxide and wounds comprised the main focus of the HBO₂T study fields which accounted for 50% of the top-cited articles and 55.4% of citations of the top-cited articles [1]. Most of the studies included in the review mainly emphasized the positive aspects of HBO₂T, but there is clearly a potential negative effect for HBO₂T. Oxygen toxicity, grand mal seizure, progressive myopia and development of nuclear cataracts have been reported in patients who undergo prolonged daily therapy [2]. Further studies are required to maximize its positive effects and minimize its side effects. In addition, the ideal “dose” (determined by pressure and duration) and timing of HBO₂T are needed to be further evaluated. Furthermore, the research field of HBO₂T is still expanding. Recent studies have documented that HBO₂T could alleviate neuropathic pain in both animals [3,4] and patients [3] and ameliorate anxious behavior and cognitive impairments in stressed rats [5]. I believe that with the development of HBO₂T-related research, HBO₂T should be used more widely in the clinic.

It is generally accepted that HBO₂T exerts its effects largely through controlled and brief increases in reactive oxygen species (ROS) and reactive nitrogen species (RNS) [2]. However, how the reactive species mediate the therapeutic responses of HBO₂ needs further investigation, for the biological effects of HBO₂T are rather more complicated than we already know. Elevation of reactive species triggers a series of expressive or functional changes of many endogenous molecules, such as monocyte chemokine, hemoxygenase-1, heat shock proteins, hypoxia-inducible factor-1, proinflammatory cytokines, growth factors, vascular endothelial growth factor and angiopoietin.

However, many downstream effects of these molecules are only partially understood. Since its initial application in neuroprotection as a preconditioning approach [6], the underlying mechanisms of HBO₂ preconditioning in neuroprotection has been an active research field. A recent study reported that peroxisome proliferator-activated receptor-gamma has potent neuroprotective effects through regulation of apoptosis [7]. Another report proposed that HBO₂ preconditioning elevates autophagic activity, which elicits a neuroprotective effect against ischemic injury in the brain [8].

Although there has been substantial progress in the HBO₂T research field in the past decade, more work is required to investigate fundamental mechanisms and its clinical application.
REFERENCES


Effects of hyperbaric oxygenation on vascular reactivity to angiotensin II and angiotensin-(1-7) in rats

Aleksandar Kibel¹, Ana Cavka¹, Anita Cosic¹, John R. Falck², Ines Drenjancevic¹

¹ Department of Physiology and Immunology, Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Croatia
² Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

CORRESPONDING AUTHOR: Ines Drenjancevic M.D., Ph.D. – ines.drenjancevic@mefos.hr

ABSTRACT

Objective: To assess and elucidate the mechanisms of hyperbaric oxygenation (HBO₂) effects on vascular reactivity to angiotensin-(1-7) [ANG-(1-7)] and angiotensin II (ANG II).

Methods: Rat aortic rings (HBO₂ vs. control group) were used to test responses to ANG II, ANG II+ ANG-(1-7) or ANG-(1-7) after noradrenaline precontraction in the presence/absence of MS-PPOH, a specific CYP 450-epoxygenase inhibitor, and glibenclamide, a Kₐtp channels inhibitor. mRNA expression studies of specific CYP isozymes have been conducted as well.

Results: The mean contraction (expressed as percent of maximal contraction) for ANG II was similar between groups. Contraction for ANG II + ANG-(1-7) was 15% ± 10 (HBO₂) and 20% ± 9 (control). There was a significant decrease between the contraction response to ANG II (HBO₂) and the response to ANG II + ANG-(1-7) in the HBO₂ group, without such a difference within the control group. Mean percentage of noradrenaline precontraction decrease after ANG-(1-7) addition was significantly different [10% ± 9 (control) and 19% ± 11 (HBO₂)]. The epoxygenase inhibitor MS-PPOH in HBO₂ animals reversed these changes. Glibenclamide had no effect on relaxation in response to ANG-(1-7). Expression of CYP4A2, CYP4A3 and CYP2J3 mRNA was not significantly altered with HBO, whereas CYP4A1 was significantly upregulated.

Conclusions: Our results suggest a role for epoxygenase in modulating relaxation response to ANG-(1-7) with HBO₂ that is conducted via potassium channels other than Kₐtp channels. HBO₂ increased the responses to ANG-(1-7) after precontraction with noradrenaline. The difference between the response to ANG II in the HBO₂ group and ANG II + ANG-(1-7) in the HBO₂ group (the contraction force of the peptide combination being lower), without such difference in the control group, suggests an influence of HBO₂ on vascular reactivity.

INTRODUCTION

Hyperbaric oxygenation (HBO₂) is an adjunctive therapy used in many conditions where tissue oxygenation or perfusion is reduced (states of hypoxia and ischemia). The mechanisms by which HBO₂ mediates its observed effects are still not completely elucidated [1,2,3] and cannot be simply explained by a compensation of the oxygen deficit. Conclusive studies on the effect of HBO₂ on vascular function and structure are lacking. We previously hypothesized that HBO₂ will have a beneficial effect on vascular function by modulating mechanisms of vascular responses to various dilator and constrictor agonists, leading to restored vascular reactivity [3]. Under this hypothesis, HBO₂ would affect production or vessel sensitivity to vasoconstrictor and vasodilator metabolites of arachidonic acid and NO in response to physiological stimuli [3]. Both HBO₂ as a treatment and in vitro hyperbaric oxygenation have been shown to change reactivity of rat thoracic aortic ring preparations to certain compounds [4,5].

The involvement of the renin-angiotensin system in regulation of blood pressure, vascular function, extracellular fluid volume and sodium balance is widely recognized [6,7,8,9]. Angiotensin-(1-7) [ANG-(1-7)], a metabolite of ANG II, has dilating activity, in contrast to ANG II [10,11,12,13]. Another ANG II metabolite,
angiotensin-(1-9) [ANG-(1-9)] has by some accounts been described as a weak vasoconstrictor in isolated rat aortas and might potentiate ANG II-mediated vasoconstriction in isolated rat aortic rings. However, the original reference presenting this information [14] only cites unpublished data and no details are given.

Interestingly, there has been research reporting that environmental factors can affect components of the renin-angiotensin system. A recent study determining the human serum proteomic profile under conditions of hyperbaric oxygen-nitrogen-argon exposure detected an increase in ANG II, besides other serum proteins, as a result of such exposure [15]. ANG II might also play a role in cardiac changes induced by repeated hyperbaric exposures in rats [16]. Acute hyperbaric oxygenation has been found to worsen myocardial low flow ischemia-reperfusion injury in isolated rat hearts, and the vasopressor activity of ANG II on coronary perfusion pressure was significantly changed [17]. An influence of hyperbaric oxygenation on renin release has been documented as well in experiments with conscious dogs, where hyperoxia was found to suppress renin release [18].

In this paper, we aimed to assess whether there are effects of HBO₂ on vascular reactivity to ANG II and its metabolites – especially the vasodilating ANG-(1-7) – and if there are, to evaluate a possible role of specific metabolites of arachidonic acid as mediators of such effects. Namely, changes in oxygen tension (reduction of tissue pO₂) have previously been linked to changes (inhibition) in the synthesis of arachidonic acid metabolites [19,20]. It is well known that changes in oxygen availability are crucial in control of vascular tone, leading to changes in production of, or vessel sensitivity to, vasoconstrictor and vasodilator metabolites of arachidonic acid and nitric oxide (NO) [19,20,7]. For example, previous studies demonstrated the important role of a normally functioning renin-angiotensin system in maintaining vascular reactivity to hypoxia [7]. In the present study we tested the hypothesis that HBO₂ will increase aortic reactivity to ANG II and its metabolites. It would thus facilitate contraction in response to ANG II or ANG-(1-9) and accentuate an expected potentiating effect of ANG-(1-9) on ANG II contraction. Considering the vasodilator properties of ANG-(1-7), under this hypothesis HBO₂ would facilitate relaxation in response to ANG-(1-7) and increase an expected inhibitory effect of ANG-(1-7) on ANG II contraction. A possible modulation of vascular reactivity to these important physiological stimuli by HBO₂, with the resulting change in vascular function, could form part of the explanation of observed effects of HBO₂ in certain medical conditions.

The additional aim was to evaluate the role of cytochrome P450 epoxyenase metabolites of arachidonic acid, the epoxyeicosatrienoic acids (EETs), in HBO₂-induced changes of vascular responses to ANGs. The production of EETs is known to be reduced with a decrease in pO₂ [19]. EETs have been recognized to induce vasorelaxation and enhance K⁺ current in smooth muscle cells, in addition to other (including pro-angiogenic, anti-inflammatory and pro-fibrinolytic) effects [21,22,23,24].

The investigation of HBO₂ effects on vascular reactivity to ANG II and its metabolites is not only important for possibly gaining more insight into the role of oxygen in vascular function in health and disease, but it may also have relevant clinical implications. A better knowledge of this specific issue is a prerequisite for a more efficient use of HBO₂ in medical conditions and for more targeted use with clearer indications. It is also crucial for a better understanding of possible adverse and toxic effects of HBO₂ and interactions with drugs (for example, with medications that modify components of the renin-angiotensin system or arachidonic acid metabolism – medications which are often prescribed in patients with chronic/metabolic diseases such as diabetes where the use of HBO₂ is important [1,2,3] and can be expected to increase).

MATERIALS AND METHODS

Animals and surgery

Healthy male Sprague-Dawley rats (14-16 weeks of age, 350-400 g) were housed doubly in shoebox-style cages with free access to standard rat chow and tap water, maintained on a 12:12 hour light : dark cycle. The animals were divided into a control group and an HBO₂ group which underwent the HBO₂ protocol. The number of animals used in the specific experiments is listed in the results section.

Under the HBO₂ protocol, rats from the HBO₂ group were treated in a hyperbaric chamber (containing CO₂ adsorbent) with 100% oxygen (using a pressure of 2 bar) for two hours a day (with the addition of 15 minutes for the compression phase and 15 minutes for the decompression phase) during four consecutive days. On the fifth day, the aortic ring experiments were conducted. For that purpose, the rats were anesthetized with a combination of ketamine (75 mg/kg) and midazolam.
(2.5 mg/kg) and afterwards decapitated with a guillotine. The abdomen and thorax were surgically opened and the lungs, heart, esophagus and adjacent tissue removed. The thoracic aorta was carefully and promptly isolated, placed into an oxygenated Krebs-Henseleit solution and cleaned of adherent tissue. The procurement of animals, the husbandry and the experiments conformed to the “European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes” (Council of Europe No 123, Strasbourg 1985).

Reagents
ANG II and ANG-(1-7), noradrenaline and acetylcholine were purchased from Sigma Aldrich, ANG-(1-9) from Phoenix Pharmaceuticals, Inc., USA. Ketamine and midazolam were obtained from Pfizer.

The Krebs-Henseleit solution (composition: 113 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4 · 7H2O, 22 mM NaHCO3, 1.2 mM KH2PO4, 11 mM glucose, 2.5 mM CaCl2 · 2H2O, 0.026 mM EDTA; pH 7.4) was prepared from EDTA purchased on the basis of previous studies where such concentrations were effective [10,12,25]. In one chamber 10-6 M ANG II was applied. A second ring was treated with 10-6 M ANG II + 10-6 M ANG-(1-7) in order to test the inhibitory effect of ANG-(1-7) on ANG II contraction.

One ring was precontracted with noradrenaline for five minutes, after which 10-6 M ANG-(1-7) was added and the tension read after three minutes. In another chamber a ring was treated with 10-6 M ANG II + 10-6 M ANG-(1-7) and afterwards decapitated with a guillotine. If the vessel ring failed to relax, it was not used for further studies. If the vessel ring relaxed, it was washed three times with a fresh solution and allowed to equilibrate for 30 minutes, with washing at 10-minute intervals. After the rings were stabilized, maximal contraction was induced with 60 mM KCl + 10-7 noradrenaline. When plateau was reached, the rings were washed three times with a fresh solution and allowed to equilibrate for 30 minutes, washing at 10-minute intervals.

After this period, aortic ring responses to ANG II and its metabolites were tested, by treating every ring of a certain animal with a different peptide/protocol and only once. The concentrations for the peptides were chosen on the basis of previous studies where such concentrations were effective [10,12,25]. In one chamber 10-6 M ANG II was applied. A second ring was treated with 10-6 M ANG II + 10-6 M ANG-(1-7) in order to test the inhibitory effect of ANG-(1-7) on ANG II contraction.

Ring responses to ANG II or response to ANG II + ANG-(1-7) – the number ‘n’ corresponds simultaneously to the number of animals and to the number of rings (because every aortic ring tested for this substance is from a different animal). The peak contraction force of the responses to ANG II and ANG II + ANG-(1-7) was expressed as percentage of maximal contraction of the particular ring, and thereby the contractile responses for a certain substance were normalized to the maximal contraction of that ring. The responses to ANG-(1-7) were expressed as percent of the decrease of the noradrenaline-induced precontraction measured three minutes after adding ANG-(1-7). Aortic responses to noradrenaline were also evaluated.

To explore the role of EETs in mediating relaxation in response to ANG-(1-7) the specific inhibitor of the epoxygenation reactions (catalyzed by specific CYP450 isozymes CYP4A2 and CYP4A3), N-methylsulfonyl-6-(2-propargyloxyphenyl)-hexanamide (MS-PPOH) was used. To test whether ATP-sensitive K+ channels (KATP channels) would be involved in a potential facilitation of vasodilator effects of ANG-(1-7) by the HBO2 protocol, since these channels participate in vasodilation to hypoxia

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and ischemia (states of changed oxygen tension) and are present in a variety of tissues [26,27], a specific K_{ATP} inhibitor, glibenclamide, was used to analyze this possibility. In a series of experiments with HBO₂ rats, the CYP450 inhibitor MS-PPOH (10^{-5} M final concentration) was added 15 minutes before application of ANG II or ANG II + ANG-(1-7) or precontraction with noradrenaline – and subsequent addition of ANG-(1-7).

Likewise, in another series of HBO₂ rat experiments, glibenclamide (10^{-6} M final concentration) was added 15 minutes before application of either ANG II + ANG-(1-7) or precontraction with noradrenaline – and subsequent addition of ANG-(1-7).

CYP expression studies – RNA isolation, construction of cDNA and Q-PCR analysis

Quantitative real-time PCR was used to detect the expression levels of CYP4A2 and CYP4A3 (which are inhibited by MS-PPOH), as well as CYP2J3 and CYP4A1 in HBO₂ and control samples. Aorta samples were collected and stored in RNA later (Qiagen) at -80° C until RNA isolation. Total RNA was extracted using TRI Reagent (Molecular Research Center, Inc.) according to the manufacturer’s instructions. RNA concentration and purity was assessed using NanoDrop (Thermo Scientific). Using a Deoxyribonuclease kit (Sigma), total RNA was additionally purified from gDNA. Reverse transcription was performed with High Capacity cDNA Reverse Transcription kit (Applied Biosystems) according to manufacturer’s instruction on MyCycler thermal cycler (BioRad). Quantitative real-time polymerase chain reaction (Q-PCR) was performed on a AB7500 (Applied Biosystems) platform. Expression of messenger RNA (mRNA) for CYP4A1, CYP4A2 and CYP4A3 was measured in aorta specimens of healthy HBO₂ and control rats using real-time PCR (with TaqMan Gene Expression Assay products Rn04224034_s1, Rn0147068_g1 and Rn00598412_m1 on Applied Biosystems 7500 Real-Time PCR System). CYP2J3 mRNA expression was determined with the use of custom-made primers designed on Primer Express (Applied Biosystems) using ABSolute QPCR SYBR Green Low ROX Master Mix (Thermo scientific) - also on the Applied Biosystems 7500 Real-Time PCR System. Gene expression (CYP mRNA expression) was normalized to the expression of two housekeeping genes – HPRT and 18S.

Blood pressure and oxidative stress

Additionally, we analyzed potential changes in blood pressure and oxidative stress in animals in regard to treatment with hyperbaric oxygen, to test whether such changes could explain HBO₂ effects on vascular reactivity. Because it is known from earlier work that both blood pressure changes and oxidative stress can affect vascular reactivity [28,29,30,31,32,33], it is important to observe the roles of these factors in analyzing the effects of HBO₂.

A separate batch of healthy male Sprague-Dawley rats was divided into HBO₂ and control animals. After the HBO₂ rats were subjected to the hyperbaric oxygen protocol, all rats were anesthetized with a combination of ketamine (75 mg/kg) and midazolam (2.5 mg/kg). A catheter made of PE-50 tubing had been surgically inserted into the left femoral artery. Body temperature was maintained constant, and the mean blood pressure was measured with a Spacelabs Medical monitor system (Spacelabs Medical, Inc., Redmond, WA, USA). After 10 minutes of stabilization, the blood pressure was determined as the average blood pressure during a period of one minute.

As indicators of oxidative stress, ferric reducing ability of plasma (FRAP) [34] and thiobarbituric acid reactive substances (TBARS) [35] were determined from arterial blood samples. The FRAP assay offers an index of antioxidant, or reducing, potential and uses Trolox as a standard, whereas the TBARS assay is used to detect byproducts of lipid peroxidation (malondialdehyde (MDA) is used as standard).

Statistical analysis

Statistics were performed with the use of SigmaPlot 11.2 (Systat Software, Inc.). Contraction to ANG II (mean percentage of maximal contraction) was compared between the HBO₂ and the control group. Similarly, in experiments measuring contraction to ANG II + ANG-(1-7) the mean percentage of maximal contraction was compared between the two groups; likewise, experiments determining the mean percentage of precontraction decrease after ANG-(1-7) addition were analyzed as well. Within the control and within the HBO₂ group, the difference between contraction to ANG II and ANG II + ANG-(1-7) was tested (since every peptide was applied to a distinct aortic ring). The Shapiro-Wilk test was used as normality test. If passed, Student’s t-test was used with significance set at \( p<0.05 \). If the normality test was not passed, the non-parametric Mann-Whitney U test was used with significance set at \( p<0.05 \). Results from the
HBO₂ group where MS-PPOH was added before application of the peptides were compared with HBO₂ animals where no MS-PPOH was applied in a similar manner. Results are expressed as mean ± STDEV. Comparison of aortic responses of the HBO₂ group, HBO₂/MS-PPOH group and the HBO₂/glibenclamide group (to addition of ANG II + ANG-(1-7) or ANG-(1-7) after noradrenaline precontraction) was performed with one-way ANOVA analysis.

Statistical analysis of CYP expression levels, blood pressure values and indicators of oxidative stress (FRAP and TBARS), compared between the HBO₂- and control groups, was done with the use of Student’s t-test or Mann-Whitney U test, respective of the outcome of the Shapiro-Wilk normality test, with significance set at p<0.05.

RESULTS
No contraction responses to ANG-(1-9) (at concentrations 10⁻⁶ M and 10⁻⁵ M) could be measured on several aortic rings/animals, including no potentiating effect of ANG-(1-9) on ANG II contraction. As a result, the experiments with ANG-(1-9) were discontinued.

ANG II response experiments
Contraction in response to ANG II (expressed as percent of maximal contraction) was 20% ± 9 in the control group (median = 17.0%) and 21% ± 11 in the HBO₂ group (median = 18.7%), n [control] = 16, n [HBO₂] = 17. There was no statistically significant difference between the two groups.

Experiments with ANG II + ANG-(1-7)
Figure 1a (above left) compares contraction responses to ANG II vs. the combination of ANG II and ANG-(1-7). Contractile force in rings treated with ANGII + ANG-(1-7) (n [control] = 17, n [HBO₂] = 14) tended to be lower in the HBO₂ group (15% ± 10) compared to control (20% ± 9), but this was not statistically significant (p=0.054, Mann-Whitney U test).

Contraction to ANG II + ANG-(1-7) in the HBO₂ group was significantly less than that to ANG II alone in the HBO₂ group. There was no such significant difference between the contraction responses of ANG II + ANG-(1-7) and ANG II within the control group.

Noradrenaline precontraction + ANG-(1-7)
Mean percentage decrease of the noradrenaline precontraction three minutes after ANG-(1-7) addition of rat aortic rings, n [control] = 17, n [HBO₂] = 12; the asterisk (*) marks statistically significant difference (p<0.05).
MS-PPOH experiments
In the presence of MS-PPOH, contraction to ANG II in the HBO2 group (18% ± 7, n = 7) was similar to ANG II contraction of HBO2 rings when no MS-PPOH was applied. Contraction to ANG II + ANG-(1-7) was similar in the presence of MS-PPOH (15% ±5, n = 7). MS-PPOH eliminated the significant difference between the responses to ANG II and to the combination (ANG II + ANG-(1-7)) within the HBO2 group (Figure 3a, above right). MS-PPOH caused a significant reduction in the relaxation to ANG-(1-7) in the HBO2 group (4% ± 5, n =7) (Figure 3b, right).

Experiments with glibenclamide
The effect of the KATP inhibitor on responses mediated by ANG-(1-7) in the HBO2 group was of interest. The mean contractile force in response to ANG II + ANG-(1-7) was 21% ± 4 (n = 8). The mean relaxation (% NA precontraction decrease) in response to ANG-(1-7) was 15% ± 7 (n = 8). Mean contraction after ANG II + ANG-(1-7) addition was similar between HBO2, HBO2/glibenclamide and HBO2/MS-PPOH groups (Figure 4a, facing page). The mean relaxation after ANG-(1-7) addition was less in the HBO2/MS-PPOH group compared to the HBO2/glibenclamide and the HBO2 group, and glibenclamide alone had no effect on ANG (1-7) relaxation in the HBO2 group (Figure 4b, facing page). Contractions to noradrenaline alone between the HBO2, HBO2/MS-PPOH and HBO2/glibenclamide groups were not statistically significantly different (Figure 5, facing page).

CYP expression studies
CYP4A2 and CYP4A3 mRNA expression measured by Q-PCR in aorta of control SD rats and rats treated with hyperbaric oxygenation is shown in Figures 6a and 6b (n [control] = 8, n [HBO2] = 8) – (Page 1060). Although expression of both CYP isoymes (with both housekeeping genes – 18s and HPRT) is higher in HBO2 rats, the difference is not statistically significant.
Expression of CYP2J3 mRNA is given in Figure 7 ($n$ [control] = 8, $n$ [HBO$_2$] = 9, Page 1060). The expression is similar between groups. The expression of CYP4A1 mRNA is shown in Figure 8 (Page 1060). ($n$ [control] = 8, $n$ [HBO$_2$] = 7) and is statistically significantly higher for CYP4A1/18s in the HBO$_2$ group vs. control. CYP4A1/HPRT is higher in the HBO$_2$ group, but without statistical significance.

Blood pressure and oxidative stress after HBO$_2$

The values of mean arterial pressure, body mass, TBA$_{RS}$ and FRAP for HBO$_2$ and control animals are listed in Table 1 ($n$ [HBO$_2$] = 6, $n$ [control] = 6; Page 1061). The results are expressed as mean ± STDEV. There was no statistically significant difference of the TBARS and FRAP values between HBO$_2$ and control rats. Mean arterial pressure between the two groups was similar as well.

DISCUSSION

In the context of our research, it is important to notice that HBO$_2$ should be viewed as a factor for increased availability of oxygen as an active molecule in changing vascular function. To investigate the effects of HBO$_2$ on ANG-(1-7) alone we analyzed its effects on ANG-(1-7) actions after noradrenaline precontraction (such pre-contraction with noradrenaline was used to study ANG-(1-7) effects in various earlier work [10,12]). Additionally, the responses to a combination of ANG II + ANG-(1-7) were measured because ANG-(1-7) was found to counteract ANG II-induced contractions and might also behave differently in the presence of ANG II (as discussed later). The impact of HBO$_2$ on ANG II contractions alone was analyzed as well.

The results of this study demonstrate for the first time that HBO$_2$ does not seem to alter reactivity of rat aortic rings to ANG II; the responses were similar between groups (Figure 1a), contrary to our initial hypothesis, where we predicted an increase in vascular reactiv-
ity in general – to physiological stimuli of both dilating and constricting activity. There was, however, a significant increase in relaxation to ANG-(1-7) in HBO$_2$ rats (Figure 1b). The peak contraction force for the ANG II + ANG-(1-7) combination was lower in the HBO$_2$ group compared to control, but only on the border of statistical significance ($p=0.054$, Mann-Whitney U test). The much higher potency of ANG II compared to ANG-(1-7) might explain that effects seen with ANG-(1-7) alone (after noradrenaline precontraction) might not be measurable when ANG II is present. Interestingly, when we compared the responses to ANG II with the responses to the ANG II + ANG-(1-7) combination within the HBO$_2$ group, the contraction to the combination of the peptides (ANG II + ANG-(1-7)) was significantly lower than the ANG II contraction. Such a difference was, however, not present in the control group. This suggests that HBO$_2$ does exert some effects on vascular reactivity to ANG-(1-7), and it is possible to speculate that HBO$_2$ brings to light or potentiates the counteractive effects of ANG-(1-7) on ANG II contraction that are not readily detectable in control rats at the given
peptide concentrations. ANG-(1-7) may act both as an angiotensin AT1 receptor agonist and antagonist, depending upon the presence of ANG II [11], as well as a ligand for the Mas receptor – releasing NO and prostaglandins [36,37,38]. Taking that into account, it is clear that its actions are complex and that an interaction with ANG II could result in different and less predictable outcomes than, for instance, when the actions of ANG-(1-7) are viewed independently of ANG II (e.g., after precontraction with noradrenaline, as was carried out in our experiments).

The exact role of HBO2 in the observed changes is not yet clear, and possible (and probably multiple) mechanisms have yet to be discovered and explained. A first step towards this goal might be provided with our experiments using the epoxygenation inhibitor MS-PPOH. Cytochrome P450 epoxygenase metabolites of arachidonic acid, the EETs, have long been recognized to induce vasorelaxation, in addition to other effects [22,24], and the role of arachidonic acid metabolites in the regulation of vascular function during changes in oxygen tension has received much attention [20].

When MS-PPOH was applied in HBO2 rats, the response to ANG II was again similar to that of the HBO2 group rats. However, the relaxation after ANG-(1-7) addition of aortic rings treated with MS-PPOH was significantly lower compared to aortic rings of HBO2 animals when no MS-PPOH was applied (Figure 3b). In contrast, the values were similar to control, whereas the relaxation in HBO2 rings without MS-PPOH addition was accentuated compared to control.

It seems, therefore, that inhibition of EETs formation reverses the actions of HBO2 on vascular reactivity, implying that HBO2 might be increasing the reactivity to ANG-(1-7) at least partially by influencing EETs synthesis. Furthermore, the difference between ANG II contraction and contraction to ANG II + ANG-(1-7) was no longer visible when MS-PPOH was used in HBO2 rats, eliminating an implied facilitating effect of HBO2 on ANG-(1-7) counteraction of ANG II-induced contraction (Figure 3a). This impressive reversal of observed HBO2 effects with MS-PPOH certainly speaks strongly in favor of a mechanism that includes metabolites of arachidonic acid and is in concordance with our earlier hypothesis [3]. Some other enzymes of the CYP450 4A family have already been characterized as oxygen sensors in the microcirculation [19,20], which makes this even more plausible. In these previous studies, a decrease of pO2 led to an inhibition of EET formation (and also inhibition of 20-hydroxyicosatetraenoic acid formation), showing the dependence of CYP450 4A activity on the oxygen tension [19]. More recently, CYP P450 3A13 was found to be involved in oxygen sensing, mediating ductus arteriosus constriction to oxygen, together with endothelin-1 [39]. Considering this, along with the interaction of arachidonic acid pathways with nitric oxide pathways in oxygen sensitivity [20], regional differences of arachidonic acid metabolite roles, and various conflicting evidence [20], it is clear that the role of CYP 450 enzymes in oxygen homeostasis is very complex and may be a significant factor in mediating the responses to HBO2.

We performed measurements of mRNA expression for the CYP isozymes inhibited by MS-PPOH (CYP4A2 and CYP4A3), as well as for CYP2J3 and CYP4A1. Since we were not able to measure an HBO2-induced statistically significant elevation of CYP4A2, CYP4A3 and CYP2J3 expression, isozymes that produce EETs, the results suggest that HBO2 might increase vascular sensitivity to EETs, instead of significantly increasing EETs synthesis. Namely, if MS-PPOH diminishes the effects of HBO2 (on ANG-(1-7) induced relaxation) by inhibiting EETs synthesis, and EETs synthesis was not significantly increased by HBO2, then this suggests that HBO2 increases the vascular sensitivity to EETs.

Of course, there is no definite proof, based on our data, that the possibility of CYP4A2 and CYP4A3 up-regulation induced by HBO2 does not exist. Therefore,
both pathways are plausible – it is possible that the effects of HBO₂ are partly explained by CYP upregulation and partly by increase of vascular sensitivity to EETs. A final verdict may come from future research in resistance arteries (such as the gracilis or mesenteric arteries) and in microcirculation, where the effects may be much more pronounced than in the aorta. It is also very interesting that CYP4A1 expression was significantly elevated in the HBO₂ group. This isozyme, which produces 20-hydroxyeicosatetraenoic acid, belongs to the enzymes already characterized as oxygen sensors in the microcirculation, as explained above [19, 20]. Since earlier findings demonstrated inhibition of both EET and 20-hydroxyeicosatetraenoic acid synthesis when pO₂ is decreased [19], our results fit very well into this model, because hyperbaric oxygenation increased at least the expression of CYP4A1 (and thereby 20-hydroxyeicosatetraenoic acid synthesis), although EET synthesis remains in question. Moreover, the inhibition of EET synthesis described previously was only readily apparent after larger reductions of pO₂, whereas changes in 20-hydroxyeicosatetraenoic acid synthesis were more easily measurable and statistically significantly different already with minor pO₂ reduction [19]. Our results obviously accentuate the vast complexity of the roles of CYP 450 enzymes in circulation and oxygen homeostasis.

Numerous studies about the mechanisms of ANG-(1-7) and its receptor function are being conducted and links to other factors such as oxidative stress [40], inflammation or ischemia/reperfusion injury [41,42] might all provide possible interconnecting points for potential HBO₂ influence. More research on these topics is necessary as well. For instance, it is interesting that recently ANG-(1-7) has been demonstrated to reduce vascular superoxide levels and restored the nitric oxide-dependent dilation to acetylcholine that was lost in middle cerebral arteries after rats were fed a high-salt diet [43]. The positive effect of ANG-(1-7) was blocked by a Mas receptor antagonist. This link with endothelial dysfunction, vascular reactivity and salt load could be important in the pathogenesis of hypertension.

Taking into account that ATP-sensitive K⁺ channels are a part of the bond between cellular metabolism and membrane excitability [26], and are important in vasodilation to hypoxia and ischemia (being responsive to a number of vasoconstrictors and vasodilators) [44,26,27], the question arises as to whether these channels may have a role in the observed influence of HBO₂ on the vasodilator actions of ANG-(1-7). Preliminary results showed the role of K_ATP channels in mediating vasodilation in response to hypoxia in middle cerebral arteries [45]. Blocking of K_ATP channels can lead to vasoconstriction, or impaired vasodilation or impaired autoregulation in some vascular beds [26]. Our results show that glibenclamide does not seem to alter the changes in aortic ring reactivity to ANG-(1-7) induced by HBO₂. The responses to ANG-(1-7) after glibenclamide addition are similar to responses of the HBO₂ group and statistically significantly higher than in the HBO₂/MS-PPOH group. Since glibenclamide inhibits K_ATP channels, and glibenclamide addition did not reverse the facilitating effects of HBO₂ on ANG-(1-7) responses of aortic rings, it appears that K_ATP channels are not involved in mediating the influence of HBO₂ on vessel reactivity to this dilating peptide, and ANG-(1-7) probably acts through different signaling pathways (Figures 4a and 4b). This is an interesting finding, since, EETs potently activate K_ATP channels in vasculature [46] but can also act through Ca²⁺-activated K⁺ channels [47]. Our findings suggest the involvement of EETs as mediators of HBO₂ influence on ANG-(1-7) actions, possibly via Ca²⁺-activated K⁺ channels, and not via K_ATP channels. However, this hypothesis needs to be further explored in future studies.

Another important question that is raised with HBO₂ is the influence of HBO₂ on arterial blood pressure and oxidative stress. Increase of both could significantly influence the vascular reactivity, as documented in many previous studies [28,29,30,31,32,33]. The data from literature are not univocal: HBO₂ can by various accounts and under different conditions increase [48,49,50], decrease [51] or leave blood pressure unchanged [50,52, 53], but the data cannot be readily compared because of vast differences in hyperbaric protocols (acute or chronic exposure, differences in exposure duration and pressure levels), underlying conditions of the treated groups (diabetic, spontaneously hypertensive, healthy) or experimental models (humans, animals).

We therefore tested whether HBO₂ has any effect on blood pressure under our experimental conditions. In the present study, the mean arterial pressure was similar between rats treated with HBO₂ and control animals (Table 1, facing page), in the range reported previously for healthy Sprague-Dawley rats [7]. Likewise, the indicators of oxidative stress (TBARS and FRAP) were similar between groups. Therefore, according to our results, changes in arachidonic acid metabolism, CYP450 enzyme activity and changes of vascular reactivity in general cannot be simply attributed to changes in blood pressure or oxidative stress, but there are obviously other mechanisms of

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HBO₂ influence that lead to changes of vascular reactivity, vascular sensitivity to EETs and/or EETs synthesis. Figure 9 (facing page) summarizes the observed effects of HBO₂ on vascular responses to ANG II and ANG-(1-7) and the hypothetical pathways that might be responsible for the facilitation of ANG-(1-7) actions by HBO₂, in light of our results.

A better knowledge of the roles of oxygen as a signaling molecule in vascular function is crucial for complete understanding of the microcirculation and the physiological mechanisms which regulate it. As one of the central factors in complex living organisms, oxygen is essential, but can also be damaging. Its actions are convoluted and hardly explainable by only one mechanism (such as, for instance, creation of oxidative stress). The use of HBO₂ in experimental protocols is thus a powerful instrument for physiological analysis of its roles in the vasculature, and the changes it induces a basis for making inferences about regulatory processes in the cardiovascular system. Our results represent one of the steps to a better knowledge of the regulatory properties of oxygen in the circulation. But a very important issue is also how oxygen affects vascular regulation specifically under hyperbaric conditions – because of the significance of HBO₂ in therapy. For a more efficient and a more targeted use in clinical practice, but also for better prediction of possible adverse effects and interactions with drugs (for example, with drugs that influence the renin-angiotensin system or arachidonic acid pathways), a good knowledge of HBO₂ influence on vascular regulation is crucial.

Figure 9. Possible role of HBO₂ in vascular reactivity to ANG II and ANG-(1-7). The observed facilitation of the vasodilator effects of ANG-(1-7) by HBO₂ may partly be a consequence of increase of vascular sensitivity to EETs. An upregulation of CYP4A2 and CYP4A3 remains a possibility, although no firm evidence exists at the moment. Other possible mechanisms (not involving EETs/ arachidonic acid metabolites) cannot be excluded.
Perspectives

These findings suggest an important influence of HBO₂ on vascular reactivity, in particular on reactivity to the vasodilating peptide ANG-(1-7), and furthermore, point to EETs as possible mediators of this influence. A better understanding of how oxygen functions as a signaling molecule in the circulation is not only crucial for research in physiology, but can also have immense implications for clinical practice at a time when therapeutic indications of HBO₂ are broadening and when it is increasingly gaining more importance. Defining the actions of oxygen on vascular function leads to more precise specifications of therapeutic indications, to better understanding of the side effects of such treatment, and is fundamental for future research in this area.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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◆
Psychomotor function during mild narcosis induced by subanesthetic level of nitrous oxide: individual susceptibility beyond gender effect

Miroslav Jakovljević 1,2, Gaj Vidmar 3,4, Igor B. Mekjavic 5

1 International Postgraduate School Jozef Stefan, Ljubljana, Slovenia
2 Department of Physiotherapy, Faculty of Health Sciences, University of Ljubljana, Slovenia
3 University Rehabilitation Institute, Republic of Slovenia
4 Institute for Biostatistics and Medical Informatics, Faculty of Medicine, University of Ljubljana, Slovenia
5 Department of Automation, Biocybernetics and Robotics, Jozef Stefan Institute, Ljubljana, Slovenia

CORRESPONDING AUTHOR: Assist. Prof. Dr. Gaj Vidmar – gaj.vidmar@ir-rs.si

ABSTRACT

Objective: We investigated the effect of narcosis induced by subanesthetic concentrations of nitrous oxide (\(N_2O\)), a behavioral analogue for hyperbaric nitrogen, on psychomotor performance. In particular, we assessed individual susceptibility to narcosis.

Methods: The participants were 12 female and 12 male undergraduate students. Psychomotor assessment was conducted with a computerized Visual Simple Reaction Time (VSRT) test, and Trail Making Tests Part A (TMT-A) and Part B (TMT-B). The tests were conducted on two separate occasions in the following order: VSRT, TMT-A, TMT-B. On the first occasion participants conducted the tests breathing room air (air trial), and during the second test they conducted the tests while breathing a normoxic mixture containing 30% \(N_2O\) (\(N_2O\) trial).

Results: Males had significantly \((p = 0.036)\) shorter VSRT in the air trials. There was no effect of gender on psychomotor performance in the \(N_2O\) trials. Overall, mean performance in the \(N_2O\) trials degraded significantly \((p = 0.004)\) only in VSRT. Performance of individual participants exhibited different and inconsistent direction of change in the \(N2O\) trials.

Conclusion: \(N_2O\)-induced alterations in psychomotor function are primarily dependent on individual susceptibility to narcosis (\(i.e.,\) concentration threshold).

INTRODUCTION

In diving, the most common type of inert gas narcosis is nitrogen narcosis, which is caused by the raised partial pressure of the nitrogen in compressed air [1]. In the broadest sense, the term “narcosis” refers to the reversible depression of function of an organism [2]. The term “inert gas narcosis” refers to the narcotic effects of inert gases. Inert gases are a subgroup of the gaseous and volatile anesthetics, some of which exert a narcotic effect under higher pressure (argon, nitrogen, hydrogen). For practical purposes, neon and helium are considered to be non-narcotic, whereas other gases (nitrous oxide – \(N_2O\), cyclopropane and ethylene) are narcotic at atmospheric pressure [3].

We investigated individual susceptibility to narcosis induced by subanesthetic concentrations of \(N_2O\) through testing psychomotor performance. This is a valid approach for diving research because hyperbaric nitrogen and normobaric \(N_2O\) exert similar effects on cognitive performance and behavior [4].

The signs and symptoms of nitrogen narcosis in diving are first noticed at approximately 30 meters (100 feet) during compressed-air breathing [3]. Compressed-air diving elicits several effects on human performance. Nitrogen narcosis produces significant impairment by decreasing both speed and accuracy of processing in the majority of performance tests [5]. It may also interfere with encoding and/or retrieval of verbal information [6]. Loss of memory during deep air dives has long been well documented [3,7,8]. Narcosis-induced overconfidence and impaired performance represent an important, and probably underestimated, threat to diver safety [9].

Human behavioral studies have concluded that \(N_2O\) in the concentration range from 20% to 30% depresses psychomotor function [10], cognitive performance [11], learning and memory [12]. It is also apparent from these
studies that there is a substantial degree of intersubject variability regarding the magnitude of the narcosis-induced effects on psychomotor performance. This is most likely due to differences in the N₂O concentration threshold for inducing detectable narcotic effects among subjects, as well as differences in the dose-dependent effects of narcosis on psychomotor function [13].

The majority of the studies mentioned above included only male subjects, and those that included both genders did not focus on gender differences. Although it is well established that there is no difference between adult males and females in general intelligence level [14], some distinctions have been reported regarding different aspects of verbal and performance intelligence [15]. Men usually outperform women in mathematical problem-solving [16-18], visual-spatial ability [17,19-23], map reading [20,24] and targeted motor skills [25,26]. Women generally excel in verbal fluency [14,27,28], memory for object location [29,30], fine motor skills [31] and perceptual speed tasks [21,27]. These differences may be attributed to sensory nerve action potential [32-35], volume of white and gray matter and cerebrospinal fluid [36,37], global and regional cerebral glucose metabolism and blood flow [38-41], and activation pattern of the central nervous system [39,41-43].

To investigate individual susceptibility to N₂O-induced mild narcosis, we selected psychomotor tests that are simply and quickly administered, widely accessible and have good metric characteristics. Because of the gender differences in information processing described above and because of the cerebral vasodilatory effects of N₂O [44], we also investigated gender differences in susceptibility (in terms of psychomotor performance) to N₂O-induced mild narcosis. As already emphasized, the main premise of our study is that the findings obtained using N₂O can be generalized to nitrogen narcosis.

**METHODS**

The study protocol was approved by the National Committee for Medical Ethics of the Ministry of Health (Republic of Slovenia). Written informed consent was obtained from each participant before participating in the study. All participants attended a screening interview, during which their medical status was assessed to determine whether there were any contraindications to their participation in the study. None of the participants had any previous experience with N₂O. No female participant was pregnant. Twelve female and 12 male undergraduate physiotherapy students participated in the study. The mean (SD) age of the participants was 21.7 (1.7) years, 21.6 (2.2) years for females and 21.8 (1.2) years for males. For the psychomotor assessment, two timed psychomotor tests were administered, which differed in complexity. The first one, the computerized Visual Simple Reaction Time (VSRT) test, is a sustained attention task that measures attention and response speed to an easily discriminated but temporally uncertain visual signal.

The task is to press a key on the mouse as quickly as possible when the stimulus is presented on the display. The stimulus was a circle; it was triggered by the experimenter; the random latency range between stimuli was two to 10 seconds. After one familiarization trial (five stimuli), five stimuli were presented within one session, and the average was taken as the test result. The temporal resolution of reaction time recording was 1 millisecond. Reliability of the measurement procedure was assessed (using intraclass correlation coefficient – ICC, average measure version, two-way random model for absolute agreement [45]) and was found to be very high (ICC = 0.998 (95% confidence interval 0.996-0.999), and ICC = 0.987 (0.975-0.993) under air and N₂O trials, respectively; see below for explanation).

Psychomotor speed and executive control were assessed with the Trail Making Test Part A (TMT-A) and Part B (TMT-B) [46]. The task in the TMT-A test is to connect 25 circled numbers by lines in sequence; in TMT-B, each circle contains either a letter or a number, and the task is to draw lines alternating from a number to a letter in increasing order (e.g., 1-A-2-B . . . ). The participants performed a short practice trial (TMT-A with eight numbers and TMT-B with four numbers and four letters) followed by the test proper. The accepted cutoff value for TMT is 40 seconds for task A and 91 seconds for task B [47,48].

Each individual experiment lasted approximately 30 minutes. It was conducted at the same time of the day for each subject. The subjects were instructed not to eat food or drink coffee, tea or alcohol drinks four hours prior to the experiment. Before the start of the experiment, each participant’s height and weight were measured in order to calculate the body mass index (BMI). The three psychomotor tests were performed under two experimental conditions: breathing room air (air trial) and breathing a normoxic mixture containing 30% N₂O (N₂O trial), whereby the same sequence was followed for all participants. N₂O is a non-volatile, gaseous, inhaled anesthetic; the dose of 30% was selected because previous studies showed that subanesthetic concentrations (i.e., FN₂O from 0.2 to 0.3) produce marked
TABLE 1: Descriptive statistics and results of statistical tests for Visual Simple Reaction Time (VSRT) and Trail Making Test (TMT)

<table>
<thead>
<tr>
<th>Test</th>
<th>Trial</th>
<th>Subjects</th>
<th>Regression model (p-values)</th>
<th>N₂O effect in pooled sample**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Pooled sample</td>
</tr>
<tr>
<td>VSRT (ms)</td>
<td>air</td>
<td>244</td>
<td>214</td>
<td>229</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(36)</td>
<td>(17)</td>
<td>(31)</td>
</tr>
<tr>
<td>N₂O-0</td>
<td>air</td>
<td>272</td>
<td>223</td>
<td>247</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(44)</td>
<td>(38)</td>
<td>(47)</td>
</tr>
<tr>
<td>TMT-A (s)</td>
<td>air</td>
<td>17.41</td>
<td>15.74</td>
<td>16.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.34)</td>
<td>(3.80)</td>
<td>(4.62)</td>
</tr>
<tr>
<td>N₂O-0</td>
<td>air</td>
<td>18.35</td>
<td>17.14</td>
<td>17.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6.02)</td>
<td>(3.55)</td>
<td>(4.87)</td>
</tr>
<tr>
<td>TMT-B (s)</td>
<td>air</td>
<td>34.72</td>
<td>39.66</td>
<td>37.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10.61)</td>
<td>(14.46)</td>
<td>(12.65)</td>
</tr>
<tr>
<td>N₂O-0</td>
<td>air</td>
<td>37.40</td>
<td>47.51</td>
<td>42.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(22.48)</td>
<td>(23.67)</td>
<td>(23.16)</td>
</tr>
</tbody>
</table>

Data are reported as mean (SD); *p-values in the N₂O rows refer to the change score (air – N₂O); **p-value from paired t-tests; see the Methods section for details.

[49,50] and consistent effects on performance [13]. The participants breathed through a low-resistance T-shaped Hans Rudolph (Hans Rudolph Inc., Kansas City, USA) respiratory valve. They inspired the breathing mixtures via respiratory tubing subsequent to it being humidified by passing the gas through a water bath at room temperature (21-25° C). During the air trial, the participant inspired air for 10 minutes and then executed the tests. Assessment in the N₂O trial commenced after 10 minutes of breathing the N₂O mixture, to ensure a stable N₂O blood saturation of approximately 95% in the brain [51]. In each trial, the VSRT was followed by TMT-A and then TMT-B. Before each test, the procedure was explained to the subject, and a familiarization test performed.

Statistical analysis
First, an a priori comparison of BMI between genders (using independent samples t-test) was performed. Because it revealed a statistically significant difference, the analyses of potential gender effect on psychomotor performance had to account for the potential confounding effect of BMI. For this purpose, baseline (i.e., air trial) psychomotor tests results and their change due to mild narcosis (i.e., change scores computed as the difference between N₂O and air trials, with positive values reflecting a worsening, and negative values an improvement in function under mild narcosis) were analyzed using linear regression as outcome variables with gender and BMI as predictors. Regression diagnostics (probability plots of residuals, standardized residuals vs. standardized predicted values scatterplots, variance inflation factors) were derived and none indicated any substantial departure from the regression model’s assumptions.

Because no significant gender effect on change score was found in any of the regression models, simple comparisons between means of the air and N₂O trials were subsequently performed using paired t-tests on the pooled sample. Since psychomotor tests can be considered as having very high reliability, and thus any test score change as exceeding the minimum detectable change (also known as minimal real difference [52]), participants with zero or negative change score were considered as not having reached the concentration threshold. These binary data were compared between genders using Fisher’s exact test.

Statistical analyses were performed using IBM SPSS Statistics 19 software (SPSS Inc., an IBM Company, 2010). Statistical significance was set at p≤0.05.

RESULTS
BMI differed statistically significantly between genders: on average, females had lower BMI (mean [SD] 22.0 (2.6) kgm⁻²) than males (24.9 [3.4] kgm⁻², p = 0.023).

The results of the psychomotor tests are summarized in Table 1 (above). During the air trials, mean VSRT
was statistically significantly shorter in males than in females ($p = 0.036$). A similar trend was observed in TMT-A, but the gender effect was not statistically significant. Conversely, the observed mean execution time for the more demanding TMT-B was shorter in females, albeit not significantly. There was no statistically significant effect of either gender or BMI on change of performance in the N\textsubscript{2}O trials. Higher BMI was statistically significantly associated with longer TMT-B time during air trials (the raw and standardized regression coefficient, not reported in Table 1, was 2.196 and 0.558, respectively). Overall, N\textsubscript{2}O statistically significantly worsened performance in VSRT ($p = 0.004$), but not in TMT-A ($p = 0.156$) or TMT-B ($p = 0.202$), though the observed mean execution times were prolonged in both TMT parts as well.

The gender difference in the air trial VSRT is depicted in Figure 1 (above). The vertical lines show that the mean VSRT was shorter in males than in females. Additionally, the letters on the horizontal axis clearly indicate that males had higher BMI on average. However, it is also apparent that confounding was not an issue in this comparison, because neither the groups nor the pooled samples exhibited a correlation between BMI and VSRT. This can also be illustrated, albeit not properly statistically tested, by computing the three correlations, none of which was statistically significant ($r = 0.155$, $p = 0.630$ for females; $r = 0.371$, $p = 0.235$ for males; $r = 0.250$, $p = 0.239$ for the pooled sample).

Eight participants (three women and five men) performed VSRT equally or faster during the N\textsubscript{2}O trials.
Six participants (four women and two men) performed equally or better under N₂O in TMT-A, and 11 participants (seven women and four men) in TMT-B. None of the differences between genders in the proportion of (non-) responders was statistically significant (p=0.667, 0.640 and 0.414 for VSRT, TMT-A and TMT-B, respectively). Only four participants performed worse (and could therefore be considered as having reached the concentration threshold) in all three tests in the N₂O trial, and only one performed equally or better on all three tests in the N₂O trial (and could therefore be considered as not having reached the concentration threshold in any of them). During the N₂O trials, none of the participants reached the cutoff time for TMT-A and only two exceeded the cutoff time for TMT-B.

DISCUSSION

The observed gender difference in the air-trial VSRT is in agreement with the finding that males have faster reaction times than females in almost every age group [53,54]. Almost all of the gender differences appear to be accounted for by the lag between the presentation of the stimulus and the beginning of muscle contraction [55]. However, there is some disparity in the results of studies investigating the concentration threshold of N₂O at which such changes are detected. The initial conclusion [56] that the threshold concentration of N₂O for an effect on psychomotor performance (as assessed by choice reaction times) probably lies between 8% and 12% is not supported by more recent studies [57,58], which do not report any significant differences in simple reaction time between N₂O (25% of N₂O and 75% O₂) and control (air) sessions. Our findings of prolonged visual reaction times are similar to those [59] who observed a prolongation of auditory reaction time under sub-anesthetic concentrations of various inhalation anesthetics (including N₂O).

TMT scores are affected by age, education [60-62] and general intelligence [60]. The influence of these factors was minimized in the present study, because the gender groups were age-balanced and the participants were studying in the same university department, at the same level, and had been admitted to the department by meeting the same strict high-school grade criterion for admission (which can be taken as a rough proxy for intelligence). In some studies, gender correlated neither with raw TMT scores [62] nor with derived indices [63]. Our results confirmed the observation [60] that females tend to take a longer time to complete Part A than males.

We observed a clear overall decline in performance in the N₂O trial only regarding VSRT. Previously, significant decrease in Digit-symbol Substitution Test scores has been observed in subjects who inspired 30% N₂O as compared to placebo (air) at five and 15 minutes of the inhalation period [64]. Similarly, inhalation of a normoxic mixture containing as little as 15% N₂O produced significant impairments in cognitive tasks (as measured by the Digit-symbol Substitution Test and the Sentence Verification test) [65]. In contrast, 25% N₂O was used in a study establishing that performance regarding accuracy of digit vigilance between N₂O and control sessions did not differ [58].

The dose-response profiles of various tests used to date reveal substantial differences [13]: no measure showed evidence of a change at the lowest concentrations (5% N₂O), several measures (digit-symbol substitution, choice reaction time – latency and total, tapping, and continuous attention) showed significant impairment at 10% N₂O, and all tests except critical flicker fusion showed substantial effects at the highest dose (40% N₂O). These results indicate that comparisons of profiles of drug-induced changes must take into account the variable effects of dose before interpretations in terms of specific drug effects can be made [13].

There were substantial differences among the participants in our study regarding their responses to N₂O in terms of psychomotor performance. Only about one-fifth of the participants could be classified as responders on all three tests, and only one as a non-responder on all three tests. Given such inter-individual differences, it is not surprising that the results of the three tests could not provide a good indication of a gender effect regarding the proportion of “responders” and “non-responders.” As further explained in the Appendix, it may therefore be very difficult, or at least unproductive, to try to separate gender differences from effects of body stature.

The main effects of inhaling subanesthetic concentrations of N₂O are observed in the central nervous system. The global increase in cerebral blood flow induced by N₂O is distributed unevenly, with the main increases observed in the frontal, temporal, parietal cortex, basal ganglia, insula and thalamic regions [44]. The flow pattern suggests that inhalation of N₂O augments flow through regions associated anatomically with the limbic system, most likely due to selective activation of these areas [44]. In contrast, N₂O deactivates the posterior cingulate, hippocampus, parahippocampal gyrus, and visual association cortices in both hemispheres; the former two regions are known to mediate learning and memory [66]. This may, in part, explain why subjects who reached concentration threshold were not able to execute psychomotor tests equally or better.
A recent animal study provided evidence that N₂O impairs information processing by altering at least the stage of motor adjustment [67]. Since N₂O spared the sensory processes implemented during the stimulus preprocessing stage, the authors concluded that at some concentrations, N₂O displays opposite effects on reaction time and movement time. These results further preclude any universal and dose-independent conclusions regarding psychomotor functioning under nitrogen narcosis, including any straightforward gender differences.

To summarize, we believe that the most likely reason for the lack of agreement between the results of different studies involving N₂O-induced narcosis is the disregard for individual concentration thresholds of the participants. In other words, it seems that some experiments (or groups) may have involved mainly participants who did not reach the concentration threshold, while the opposite goes for the others. The solution to this problem appears to be twofold. The first option may be to carry out all such experiments in a dose-response manner; a second option may be to use a single concentration of N₂O but incorporate a subject inclusion criterion based on preliminary psychomotor tests to select susceptible participants.

APPENDIX – Some statistical considerations
It should be emphasized that conducting either an analysis of variance (mixed-model ANOVA with gender as between-subject and air vs. N₂O trial as within-subject factor, thus ignoring the confounding effect of BMI) or an analysis of covariance (ANCOVA; in an attempt to “adjust” for BMI) on our data would not be valid.

The reason for the latter deserves special emphasis, because in addition to the assumption of homogeneity of regression slopes, ANCOVA also requires that the groups do not differ on the covariate [68]. This is a well-known and widespread issue in quasi-experimental research (i.e., comparison of pre-existing groups, observational studies, non-randomized studies), known as Lord’s paradox [69,70], for which no simple solution exists.

In our analysis we used regression modeling of change scores, since it is arguably the most appropriate approach in such studies [71,72].

Conflict of interest statement
The authors have no conflict of interest to declare.

REFERENCES

Hyperbaric side effects in a traumatic brain injury randomized clinical trial

E. George Wolf¹, Jennifer Prye¹, Robert Michaelson¹, Gerry Brower¹, Leonardo Profenna¹, Otto Boneta²

¹ USAF School of Aerospace Medicine, Hyperbaric Medicine Department, Lackland AFB, Texas
² Evan Army Community Hospital, Ft. Carson, Colorado

CORRESPONDING AUTHOR: Dr. George Wolf – earl.wolf.ctr@us.af.mil

ABSTRACT

Objective: To catalog the side effects of 2.4 atmospheres absolute (atm abs) hyperbaric oxygen (HBO₂) vs. sham on post-concussion symptoms in military service members with combat-related, mild traumatic brain injury (TBI).

Methods: Fifty subjects diagnosed with TBI were randomized to either a sham (1.3 atm abs breathing air) or treatment (2.4 atm abs breathing 100% oxygen) hyperbaric profile. Forty-eight subjects completed 30 exposures. Medical events during hyperbaric exposures were separately annotated by medical staff and chamber operators. After the blind was broken, events were segregated into the exposure groups.

Results: These side effects were observed as rate (sham/treatment): ear block (ear barotrauma) 5.51% (1.09%/5.91%), sinus squeeze 0.14% (0.0%/0.27%), and confinement anxiety 0.27% (0.27%/0.27%). Other conditions that occurred included: headache 0.61% (0.68%/0.54%); nausea 0.2% (0.14%/0.27%); numbness 0.07% (0%/0.13%); heartburn 0.07% (0.14%/0%); musculoskeletal chest pain 0.07% (0%/0.13%); latex allergy 0.07% (0.14%/0%); and hypertension 0.07% (0.14%/0%).

Conclusion: This study demonstrated no major adverse events, such as pulmonary barotraumas, pulmonary edema or seizure. Given the infrequent, mild side effect profile, the authors feel the study demonstrated that hyperbaric oxygen therapy (HBO₂T) was safe at a relatively high treatment pressure in TBI subjects, and these data can be used to evaluate the risk/benefit calculation when deciding to utilize HBO₂T for treatment of various diseases in the TBI population.

INTRODUCTION

The use of hyperbaric oxygen (HBO₂) in neurologic diseases has long been a hotbed of research and has yielded mixed results. An increase in the frequency of United States military traumatic brain injury (TBI) patients from the wars in Afghanistan and Iraq resulted in the Congressionally Directed Medical Research Programs’ Psychological Health and Traumatic Brain Injury (CDMRP PH/TBI) Research Program. It was established in 2007 in response to U.S. Troop Readiness, Veterans’ Care, Katrina Recovery, and Iraq Accountability Appropriations Act, Public Law 110-28. Anecdotal reports purporting the benefits of hyperbaric oxygen for treating traumatic brain injury precipitated the development of the United States Air Force (USAF) HBO-TBI study in 2007. Much of the study design was based on the Agency for Healthcare Research and Quality’s (AHRQ) Evidence Report/Technology Assessment, Number 85, “Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke” [1]. The report recognized the early case reports by Dr. Gaylan Rockswold using hyperbaric oxygen for acute severe traumatic brain injury. AHRQ also stated, “The most important gap in the evidence is a lack of a good quality time-series study or controlled trial of the effects of HBOT on cognition, memory, and functional status in patients with deficits due to mild and moderate chronic TBI.”

AHRQ made recommendations for future research for hyperbaric oxygen and its use for TBI, suggesting strategies to overcome barriers. One barrier was a lack of agreement on the dosage of HBO₂ and the duration of treatment. Unlike oral or intravenous medications that are measured in milligrams, individual dosages of hyperbaric oxygen are measured in partial pressures of oxygen multiplied by time. The partial pressure is calculated by multiplying the amount of oxygen breathed
(up to 100%) times the pressure, usually described in atmospheres absolute (atm abs), with one atmosphere being what we experience at sea level and each additional atmosphere pressure equivalent to 33 feet of sea water (fsw). The dose chosen is then repeated daily until a total dose is achieved as expressed by the numbers of sessions or treatments. Nearly all of the pressures used in the anecdotal reports for treating TBI involved using 100% oxygen at 1.5 atm abs, with duration of one hour per session for a total of 40 sessions per series. AHRQ recommended future studies to look at various doses and treatment duration.

A second barrier was the lack of independent, reliable data on the frequency and severity of adverse events. The AHRQ’s text regarding this barrier follows:

"Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, because HBOT may be harmful, it must be held to the highest standard of proof. A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered.

This reasoning is consistent with the views of most clinicians and with the theoretical underpinnings of rational decision-making (i.e., utility theory). Consider a treatment that has been proven to be harmless and without cost. If there is a 1 percent chance that the treatment works, a rational decision maker would try it – there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it.

The objective of the USAF HBO-TBI study was to track the known potential treatment complications between two hyperbaric exposure groups, one sham and the other a treatment exposure. As many general trauma patients who also have a TBI history are treated with hyperbaric oxygen using higher pressure profiles, risk-benefit considerations are of importance.

METHODS

The study “Treatment of Moderate to Mild Cognitive Dysfunction Caused by Traumatic Brain Injury with Hyperbaric Oxygen Therapy (HBOT)” was submitted through the then Wilford Hall Medical Center Institutional Review Board (IRB). IRB approval was granted in August 2007 and was consistent with the Declaration of Helsinki, CFR Part 50 “Protection of Human Subjects,” and Air Force Instruction 40-402 “Protection of Human Subjects in Biomedical and Behavioral Research.”

Fifty subjects diagnosed with traumatic brain injury and having deficits in cognitive function were identified by neurologists. All patients included in the study suffered a TBI up to six years prior to the start of treatment. There were 48 males and two females. The range of subject ages was from 20 to 51 years of age with a mean of 28.32 years and a standard deviation (SD) of 7.7 years. The subjects were randomly entered into one of two groups, a sham group and a treatment group. Each group had a total of 25 subjects comprising 24 males and one female. The age range was 21 to 46 years in the sham group with a mean of 28.4 years and an SD of 7.4 years. The age range was 20 to 51 years old in the treatment group with a mean of 28.3 years and an SD of 8.1 years. There was one withdrawal from each group.

Hyperbaric exposure profiles

The original protocol submitted to the CDMRP in 2007 was comprehensive and had four exposure (dosage) groups (sham, 1.7 atm abs, 2.4 atm abs and 3.0 atm abs). At the initial review, the research panel recommended that a pilot study be done first; the panel felt the original proposal was “too aggressive” and the researchers had few publications, thus not worthy of the grant. The resultant pilot study reported here continued the AHRQ recommendations to address dose response data and collect information regarding adverse events. The revised study bracketed the anecdotal pressure of 1.5 atm abs with two exposure groups: the treatment group using 100% oxygen (O2) at 2.4 atm abs for 90 minutes (a standard wound treatment pressure and duration) and a sham or control group breathing air (21% O2) for 90 minutes at 1.3 atm abs (about the pressure at 11 fsw). The pressure of 2.4 atm abs was chosen due to its routine clinical use but also to evaluate the safety and side effect aspects at this pressure in the TBI population.

Exposures were done in a multipurpose chamber with the breathing medium delivered using an oxygen treatment hood (Amron International Inc., Vista, Calif.) once the exposure pressure was reached. The chamber was dedicated to the research study with no interference by clinical activities. Exposures were done on weekdays only. Subjects completed five exposures followed by one day given to complete other aspects of the study. The cycle was repeated for a total of 30 exposures.

The 2.4-atm abs treatment exposures had a seven-minute descent to 45 fsw equivalent with 90 minutes of
TABLE 1 – Side effect rates as percentage of events per exposures

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>Events</th>
<th># of subjects</th>
<th>Overall rate</th>
<th># of subjects</th>
<th>Sham rate</th>
<th># of subjects</th>
<th>Treatment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear barotrauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.91</td>
</tr>
<tr>
<td>Sinus squeeze</td>
<td>2</td>
<td>1</td>
<td>0.14</td>
<td>0</td>
<td>1</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Confinement anxiety</td>
<td>4</td>
<td>2</td>
<td>0.24</td>
<td>1</td>
<td>0.27</td>
<td>0.27</td>
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The sham pressure of 1.3 atm abs was used consistent with several prior studies. Van Ophoven [2] used a treatment chamber pressure of 2.4 atm abs with 100% O2 with a sham of 1.3 atm abs breathing normal air, each for 90 minutes. Nighoghossian [3] compared 1.5 atm abs (100% O2 for 40 minutes) to 40 minutes of air at 1.2 atm abs. Rusyniak [4] treated stroke patients at 2.5 atm abs breathing 100% O2 with a control of 1.14 atm abs breathing 100% O2. Clarke [5] evaluated blinding between 2.0 atm abs and 1.3 atm abs with a drift to 1.1 atm abs, demonstrating subject validation of the technique.

The 1.3-atm abs sham exposure consisted of a seven-minute descent to 11 fsw equivalent with the 90 minutes of air broken into three 30-minute periods interspersed by breathing air for a 10-minute period by removing the hood from the subject’s head. This was done to make the two profiles as similar as possible. Upon reaching 1.3 atm abs, the chamber was allowed to slowly drift over a 10-minute period to 6 fsw (1.1 atm abs) as part of routine chamber venting. The pressure remained at this level until the completion of the third breathing period, at which time there was an ascent to surface over 10 minutes.

Side effects and complications
Side effects defined by the Undersea and Hyperbaric Medical Society (UHMS) were tracked throughout the study (see Table 1, above). Medical monitors interviewed each subject for interval medical history from the previous exposure, checked tympanic membranes and auscultated the heart and lungs. Any medical issue was addressed by the medical monitor before the exposure as well as after the exposure, as needed. The medical monitor annotated findings on a subject daily log of operations. In addition, any medical or physical complaint experienced by subjects during the hyperbaric exposure was annotated in the “dive record” by the chamber operator.

After the blind was broken, side effects and complications were segregated into the respective exposure group and compared between the daily medical monitor log and the dive record entries. From all subjects, there
were 1,480 pressurization events including nine make-up exposures required when a subject was removed from the chamber. The number of pressurizations in the sham group was 736 and in the treatment group 744. These numbers were used as the denominator for determining the rate of individual side effects observed in each group.

**Blinding**

The study was written as a single blind study. However, a decision was made to operate the study as a double blind. Each hyperbaric exposure was run by a research crew consisting of the crew chief, chamber operator, inside attendant and the medical monitor. The crew chief is responsible for the safety and mechanical aspects of the chamber. The chamber operator controls the pressurization, venting and depressurization of the chamber. The inside observer attends to the subjects, dons and doffs the hoods as required, and is in communication with the chamber operator at all times. The medical monitor authorizes chamber pressurization and determines any medical interventions needed throughout the hyperbaric exposure.

Obviously, the chamber operators and, most likely, the inside attendants were aware of the exposure profile, but the medical monitors were not. Nondisclosure agreements were signed by each of the research crew prior to starting compression. It specified that no information regarding the exposure pressure would be discussed with anyone including members of the research crew, the research coordinator, subjects or any inquiries from outside the research area.

The inside observers were instructed to perform a Valsalva maneuver every 10–30 seconds during chamber pressurization. The inside observers also breathed oxygen from their mask three times during every exposure to prophylaxis against decompression sickness regardless of exposure profile. The chamber operator would use percentage of depth achieved, if asked by the medical monitor for issues such as ear blocks. Venting of the chamber by the operator was also done in both exposure groups to create similar temperature and noise levels. In addition, all clocks and pressure gauges were removed from inside the chamber, and no watches or electronics were allowed inside the chamber.

Randomization to the exposure groups was done using a computer-generated number assignment (randomizer. org®). The consent agreement included a discussion of sham and experimental exposures, and the subjects were informed they may be assigned to either group. During consent, subjects were told the breathing mixture within the hood could be either oxygen or air. Subjects were assigned specific places with corresponding gas/hood assemblies in the chamber. As part of the precompression checklist, subjects were identified by their subject number, their assigned position and the “breathing gas mixture” confirmed by the inside observer orally where the subjects could hear. However, all 1.3-atm abs exposures used air and all 2.4-atm abs exposures used 100% O₂.

At the conclusion of the data collection, but prior to breaking the blind, a questionnaire was sent to the subjects asking:

*Do you feel that you were in*

1. the treatment group,
2. the placebo group, or
3. have no idea?

Analysis of data was performed at the completion of all exposures and after the blind was broken.

**RESULTS**

In the study as a whole, ear block (ear barotrauma), sinus block and confinement anxiety (Table 1) were the only side effects observed. As all medical issues were tracked, other conditions and rates that occurred included headache (0.61%), nausea (0.2%), numbness (0.07%), heartburn (0.07%), musculoskeletal chest pain (0.07%), latex allergy (0.07%) and hypertension (0.07%). The rates are expressed as the number of events per the number of exposures as a total or in the individual groups. In addition, Table 1 also includes the raw number of subjects who experienced events, as one individual may have had more than one event in a category.

Ear blocks were defined as any time a subject was unable to equalize middle ear pressure during descent and required the pressurization to be stopped. Ear blocks were the most common side effect and paralleled what is seen clinically, with a total of 52 events. Unresolved ear block required removal from the chamber seven times, all from the treatment group. The overall rate of ear blocks was 3.51%, which compares with 2% [6] in the clinical population. The sham group had a 1.09% rate and the treatment group a 5.91% rate. Of the 52 events, 33 occurred at 11 fsw or shallower (63%), which was the maximum depth of the sham exposure. Using the TEED 0-5 scale, there were eight events that were diagnosed with a TEED 2. All others were either 0 or 1. Sinus squeeze events were observed only in the treatment group. Confinement anxiety occurred equally between the groups, with two events each. Progressive myopia (defined as worsening by two or more Snellen lines), cataracts, pulmonary barotraumas or edema, or seizure were not reported.
Other adverse effects reported included nine headaches that occurred while inside the chamber; three cases of nausea; one case each of numbness, heartburn, latex allergy and chest pain; and one subject whose blood pressure gradually increased over the exposure series.

Only 16 of the 50 subjects (32%) responded to the blinding questionnaire regarding their perception as to which group they were in. One responded affirmatively to being in the treatment group, four thought they were in the sham group, and 11 did not know. Of those who guessed their group, two guessed correctly and three guessed incorrectly.

**DISCUSSION**

**Side effects and complications**

*Barotrauma:* In analyzing subjects who had ear block events, there were only 14 individuals (27% of the subjects) who were responsible for the 52 events. Ten were assigned to the treatment (Rx) group, and four were in the sham group. In allowing two events to occur from a “training” perspective, there were only five individuals (10%) who had more than two events, four in the treatment group and one in the sham group. Of these four treatment group subjects, two had allergic rhinitis, one had an upper respiratory infection (URI) that also kept him from exposures for approximately one week, and one had a nasal septal deviation. Interventions for ear and sinus blocks in both groups included educating all subjects in various equalization techniques, reducing the pressure (bouncing) of the chamber to allow better equalization, decongestant sprays or medications, reduced pressurization rate and Otovent use.

Otovent was used in three of the four multiple block subjects after it appeared they had difficulty equalizing pressure (7-8 blocks early in the series). None of them required removal from the chamber after the Otovent was initiated. The URI subject did not require an Otovent. The sham subject responded to chamber bounce and decongestant spray. As no severe barotrauma (TEED 3 or greater) was experienced in the study, it increases the argument for typical hyperbaric oxygen therapy as being safe. One of the allergic rhinitis subjects was responsible for the two sinus blocks that occurred two days apart. These were reverse blocks during ascent that resolved spontaneously without further problems.

*Anxiety:* Anxiety occurred twice in one subject in each group. Both responded to taking off the hood until they felt better and then resuming the exposure to completion. The treatment subject opted to breath via aviator’s mask instead of the hood after the second episode and continued without anxiety for the remainder of his exposures. The sham subject experienced anxiety during his third week in the treatment series. He had been taking clonazepam for anxiety as needed prior to consenting as a subject. He started taking it before hyperbaric exposures on days he felt anxious and tolerated the exposures well thereafter.

*Visual effects:* Progressive myopia did not occur in any of the subjects. Progressive myopia of hyperbaric oxygen exposure is attributed to an alteration in the lens shape with unknown reason [7]. In a retrospective study of 88 patients, most of whom underwent 2.0-atm abs treatments, Dedi [8] found there was a slight trend toward greater loss of acuity than gain in acuity over treatment time. In 20 2.4-atm abs treatments in 52 patients with an average age of 62.9 years, Smerz [9] demonstrated visual changes, predominantly myopia, were common in this particular study population. Finally, 14 patients (average age 54.1 years) treated at 2.4 atm abs (29.6 average sessions) in a report by Churchill [10] showed myopia in 78%.

In this study, there were 93 eyes with visual acuity data (Table 2, above). The number was decreased from

**TABLE 2 – Visual acuity changes post series and at 6-week follow-up**

<table>
<thead>
<tr>
<th>Snellen¹</th>
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<th>Post series L eye</th>
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<th>Post 6 wk L eye</th>
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¹ Positive Snellen lines (1-3) demonstrate improvement in vision whereas negative (-1) indicates worsening by one Snellen line. Zero indicates no change.
1080 due to the two withdrawals, one subject who had one blind eye and the first subject who did not receive a baseline acuity. There were 12 eyes (five sham/seven Rx) with a one-Snellen-line decrease at the end of the series and nine eyes (three sham/six Rx) at the six-week follow-up point. However, there were 34 (36%) eyes that improved by greater than one Snellen line post series and 47 (50%) at the six-week follow-up. The respective changes at these timelines for the groups were 20 sham/14 Rx post series and 25 sham/22 Rx at the six-week follow-up. More interesting was the two-Snellen-line improvement in nine eyes (seven sham/two Rx) post series and 15 (seven sham/eight Rx) at the six-week follow-up point. One sham eye had a three Snellen line improvement at the 6-week follow-up point. The age range in these subjects was 22-46 years (two older than 40) in the sham group and 20-51 years (two older than 40) in the treatment group. All baseline acuities were 20/40 [3] or better, with the majority [10] starting off 20/20.

Kinney [11] showed no decrements in visual acuity or in the size of the field of view in four subjects who lived in a chamber pressurized at either 50 feet or 60 feet. However, in looking at Kinney’s raw data, three subjects remained at baseline, but one subject at the 50-foot level improved vision in his eyes by two to three levels. Just as there is no good explanation as to why hyperbaric oxygen may result in myopia, improvement in these hyperbaric exposures cannot be explained. Considering current research (references above) and the observed changes in this study, it may be both an oxygen effect as well as pressure effect. More research in this area could be beneficial, particularly in military occupations in which better visual acuity beyond 20/20 is desirable, such as infantry, aviation and special operations.

Seizure: There were no seizure events in the study despite the prediction voiced at the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury “Consensus Conference for Hyperbaric Oxygen Therapy in Traumatic Brain Injury” in Alexandria, Va., 5-6 December 2008 (Harch P. Personal communication; 2008). The concern was that HBO₂: T 2.4 is harmful to the brain, and the brain “shuts off” oxygen at that level to protect itself to avoid the induced seizures seen at this oxygen dose. In acute severe TBI, Rockswold [12] treated 22 patients at 1.5 atm abs where critical brain tissue oxygen levels were achieved without biochemical evidence of oxygen toxicity and no seizure. Lin’s study of 22 acute moderate to severe TBI patients treated at 2 atm abs had two subjects who had a seizure [13]. It should be noted, however, that both subjects resumed the hyperbaric therapy without further episodes but were eliminated from the statistical analysis. It is prudent to believe that in acute severe TBI, the brain is in active recovery and more sensitive to oxygen loads. Rockswold’s study above may pave the way for future research to see if the critical level of brain oxygen tissue partial pressure (200 mmHg) can be achieved in >50% [14] of acute severe TBI patients using 2.0 atm abs or higher with continued biochemical evidence of no oxygen toxicity.

Seizures have been seen in the routine treatment of neurological decompression sickness (DCS) and carbon monoxide poisoning, both acute neurological events, as well as daily hyperbaric oxygen treatments for all UHMS indications in patients who may have had previous brain insults. The rate of seizures overall clinically ranges from 0.01% to 0.03% in day-to-day operations but as high 1.8% when treating carbon monoxide poisoning [15]. Acute severe TBI may be a different presentation than seen in this study’s chronic mild TBI population. Realistically, chronic TBI patients have had some recovery from a healing perspective. Although this study did not have any seizure events, the true seizure rate for this subset likely lies between 0.01% and 1.8% referenced above but can only be determined after meta-analysis of this and future published studies.

Headache: Thirty subjects had a history of headaches prior to the study, a common symptom in TBI patients. Some of these subjects had a low-grade headache 24 hours a day. Consequently, the nine events reported were in subjects whose pain level increased during the exposure if they were already experiencing headache upon starting compression or the development of a new headache while in the chamber. Most of these headaches responded to either ibuprofen or acetaminophen or resolved spontaneously. There was one subject who did not have a headache history who developed recurrent headaches on multiple dives. He withdrew from the study for personal reasons. This subject had retained shrapnel in his brain near the pineal gland. A computed tomography (CT) scan impression that was reviewed prior to consent demonstrated this as well as post open reduction and internal fixation of the left infraorbital comminuted fracture without evidence of hardware complication. His ability to equalize ear pressure without difficulty was confirmed by his base physician prior to consent. Upon closer review of the CT report, a lobulated mucosal thickening was reported within the right maxillary sinus and right sphenoid sinus. The acute migraine headache-like symptoms were consistent, particularly with those seen with sphenoid sinusitis. A possible explanation was a
sinus squeeze in the sphenoid sinus, perhaps as a ball valve phenomenon seen rarely in aircrew and divers. As the symptom did not present as a traditional sinus squeeze, it was relegated to the actual complaint of a headache. The subject was in the sham exposure group.

Nausea/heartburn: The nausea that was registered was attributed by two of the subjects to food, and the third developed acute gastroenteritis the evening of the event. The heartburn, also attributed to food by the subject, was resolved with antacids. Nausea is a well-recognized pre-monitoring sign of central nervous system oxygen toxicity. However, all three events occurred 42 minutes or less into the exposures, essentially after only one breathing period. Given the resultant histories, it is very unlikely oxygen toxicity is a concern.

Latex allergy: One subject developed neck irritation but did not have a known latex allergy. It quickly resolved after a non-latex hood ring seal was used.

Numbness: One subject developed numbness in his right arm and hand during ascent on his first compression. The symptoms spontaneously resolved by the time the chamber reached surface. No recurrence of the symptoms occurred. DCS in the subjects was likely not a concern, as in the treatment profile the subjects had adequate denitrogenation, and the sham group was at a depth that would not put the subject at risk for DCS. Air embolism was a possibility but unlikely due to the slow ascent, allowing air exchange in the lungs and no upper respiratory symptoms. Hyperventilation was also a possibility due to the new experience. The subject was in the treatment group.

Chest pain (musculoskeletal): One subject developed musculoskeletal discomfort secondary to neck ring pressure to the left 4th-5th rib intercostal areas while the subject fell asleep during the breathing periods. Upon exam, there was point tenderness on palpation. The discomfort resolved over two days.

Hypertension: One subject arrived with a baseline blood pressure of 139/96. The pressure gradually increased through the first four weeks, with the highest blood pressure being 162/106. This resulted in an internal medicine consult. The subject was started on blood pressure medication and was still elevated at 147/94 at the six-week follow-up. The subject was in the sham exposure group.

Blinding
The sham profile choice was determined by evaluating the published works cited above. A hybrid of the van Ophoven and Clarke profiles was created. It was felt that the Clarke profile had the advantages of minimizing oxygen partial pressure within the sham group and thus minimizing any resultant “treatment” effect as well as validating the blinding. This study had a treatment pressure of 2.4 atm abs, as in the van Ophoven study. The disadvantage was the drift from 1.3 atm abs to 1.1 atm abs, as the study could have left the pressure just at 1.3 atm abs and accepted the higher oxygen partial pressure and the subsequent treatment effect.

Choosing this profile required a more active driving of the chamber by the operator to minimize any detection of pressure changes by the subjects. The chamber operators underwent additional training and “dry runs” before consenting subjects to achieve the sham intent, i.e., the same noise, temperature and pressure effects experienced by the subjects in both exposure groups. Although the post-exposure survey did not obtain the desired number of responses, those who did respond predominantly had no idea which exposure group they were in (69%), and those who guessed were only 40% correct. It is felt that the blind was successful for the study.

CONCLUSION
This single-blinded, randomized, controlled trial was conducted to help determine the potential of hyperbaric oxygen as treatment for traumatic brain injury. A secondary goal was to follow the AHRQ recommendations to produce independent, reliable data on the frequency and severity of adverse events by tracking not only known side effects but also monitoring subjects for any medical conditions that occurred throughout the hyperbaric experience. This was done in both exposure groups. The treatment pressure level used a standard clinical profile (2.4 atm abs) compared to the anecdotal treatment pressure of 1.5 atm abs.

This study demonstrated sham pressure of 1.3 atm abs was used consistent with several prior studies. Van Ophoven [2] used a treatment chamber pressure of 2.4 atm abs with 100% O₂ with a sham of 1.3 atm abs breathing normal air, each for 90 minutes. Nighoghossian [3] compared 1.5 atm abs (100% O₂ for 40 minutes) to 40 minutes of air at 1.2 atm abs Rusyniak [4] treated stroke patients at 2.5 atm abs breathing 100% O₂ with a control of 1.4 atm abs breathing 100% O₂. Clarke [5] evaluated blinding between 2.0 atm abs and 1.3 atm abs with a drift to 1.1 atm abs, demonstrating subject validation of the technique, such as pulmonary barotraumas, pulmonary edema or seizure. It did have subjects who manifested known mild and reversible side effects such as ear barotrauma (ear block), sinus barotraumas (sinus
squeezes) and confinement anxiety, but these side effects were infrequent and caused no discernible lasting injury.

Other incidental medical conditions also occurred: headache, numbness, heartburn, latex allergy, chest pain (musculoskeletal) and hypertension over time. Given the infrequent, mild side effect profile, the authors feel that the study demonstrated that HBO₂T was safe at a relatively high treatment pressure in traumatic brain injury subjects and that, subsequently, these data can be used to alter the risk/benefit calculation when deciding whether to utilize HBO₂T in the treatment of various diseases in the TBI population. Per the AHRQ, the standard of proof of HBO₂T efficacy should be lowered.

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Disclaimer: The opinions expressed in this document are solely those of the authors and do not represent an endorsement by or the views of the United States Air Force, the Department of Defense or the United States Government.

REFERENCES


Effect of hyperbaric oxygen therapy on patients with herpes zoster

Zhengrong Peng, Sue Wang, Xu Huang, Pingtian Xiao

Department of HBO, Xiangya Hospital of Central South University, Changsha City, Hunan Province, China

CORRESPONDING AUTHOR: Dr. Zhengrong Peng – pengzr138@yahoo.com.cn

ABSTRACT

Background: The purpose of this study was to observe the effect of hyperbaric oxygen (HBO₂) therapy on patients with herpes zoster.

Methods: A total of 68 cases with herpes zoster were randomly divided into HBO₂ and control groups. The patients in the control group were treated with drugs, while the patients in the HBO₂ group were treated with both drugs and HBO₂. Parameters of therapeutic efficacy including period of blister resolution, scar formation time and percentage of patients developing post-herpetic neuralgia (PHN) were determined for the patients in both groups. Numeric Pain Rating Scale (NPRS) and Hamilton Depression Rating Scale (HAMD) were also scored for the patients before and after treatment.

Results: The therapeutic efficacy in the control group was 81.25%, which was significantly lower than that (97.22%) in the HBO₂ group (p<0.05). The percentage of patients developing PHN, scar formation time and NPRS score in the HBO₂ groups were significantly lower than those in the control group (p<0.05). HAMD score in the HBO₂ group was significantly lower than that in the control group (p<0.05).

Conclusion: HBO₂ can significantly enhance therapeutic efficacy, relieve pain, accelerate herpes blister healing and lesion resolution, reduce the percentage of patients developing PHN and improve depression in patients with herpes zoster.

INTRODUCTION

Herpes zoster is an infectious disease of ganglia and nerve stems caused by varicella zoster virus [1]. Herpes zoster is characterized by skin flushing, distribution of clustering blisters along a dermatomal nerve distribution, skin burning, extension of pain outside of the skin lesions and persistent neuralgia in some patients after the associated rash has disappeared [2]. Post-herpetic neuralgia (PHN) refers to the persistent pain (one to six months) after the herpetic lesions are healed [3]. Manifesting primarily as persistent irritation, intermittent boring pain, allodynia and itching, PHN is difficult to treat and represents the most common complication of herpes zoster [4]. Typically the trigeminal or intercostal nerves are involved.

Overall, 15% of patients with herpes zoster will develop PHN, with that incidence increasing to 75% in patients over 70 years old [5]. Because of its complex pathogenesis and poor response to treatment, PHN has received extensive attention in the medical literature [6]. Skin burning and excruciating nerve pain in patients with herpes zoster often result in insomnia, irritability, anxiety and depression [7]. Herpes zoster is one of the more stubborn diseases of the middle-aged and elderly populations. Currently, there is no effective clinical treatment for this disease [8].

Hyperbaric oxygen (HBO₂) therapy treatment has been widely applied in clinics. HBO₂ therapy is a treatment by which patients are placed in a sealed, high-pressure environment while breathing high concentrations of oxygen [9]. However, the therapeutic efficacy of HBO₂ treatment on herpes zoster has not been studied. The purpose of this study was to investigate the effect of HBO₂ treatment on the duration and severity of herpes zoster signs and symptoms.

Methods

Subjects

A total of 68 cases with herpes zoster were enrolled from January 2008 to December 2010. Prior to enrollment, the disease course of these patients was less than two weeks. The diagnosis was based on the criteria of acute herpes zoster described in the literature [10,11]. Patients who were excluded from this study included
women who were pregnant, breast-feeding or attempting to conceive; patients with severe heart, liver, lung and kidney dysfunction or systemic failure; those with autoimmune disease (e.g., systemic lupus erythematosus/SLE) or long-term use of corticosteroids or immunosuppressive agents; patients with malignant tumors; patients with contraindications on HBO₂ treatment; and patients with primary diseases that affect pain and depression.

These 68 cases were randomized using a computer-generated randomization scheme into the control group (n=32) and the HBO₂ treatment group (n=36). The patients were classified into three different grades of herpetic disease manifestation severity: mild, medium and severe [12,13]. Mild-grade patients had one to several patches (≤5 patches) of rash with a medium degree of pain, but without systemic symptoms. Medium-grade patients had more rash (>5 patches), obvious inflammation and pain, but still no systemic symptoms. The rash in severe-grade patients was associated with bleeding, ulcers, dissemination and obvious complications (e.g., paresthesias, nerve palsies, ocular involvement or other appropriate examples) [14]. The severe-grade patients had poor general condition. There was no significant difference between the age, gender, disease course and disease grade in the HBO₂ group and those in the control group (p>0.05) (Table 1, above).

### HBO₂ treatment

The patients in the control group were treated with conventional drugs, while the patients in the HBO₂ group were treated with both conventional drugs and HBO₂. Pharmacotherapy included antiviral (acyclovir, 0.5g, intravenous drip, twice a day), nerve nutritive (mecobalamin, 0.5mg, intramuscular injection, once a day), pain relief (tramadol hydrochloride, 50mg, orally, once a day) and antidepressive drugs (nortriptyline, 10mg, orally, three times a day). An air-pressurized chamber (Model: YCQ34230/0.3/0.7 (-0.1) -50 VIII W; Origin: Yantai, Shandong Province, China) was used for HBO₂ treatment. For each treatment, the chamber was pressurized over a period of 15 minutes to 0.22MPa. Subjects then breathed either 100% oxygen by mask or chamber air according to the following schedule: mask oxygen 30 minutes; chamber air five minutes; mask oxygen 20 minutes; chamber air five minutes; mask oxygen 30 minutes The chamber was subsequently decompressed to ambient pressure over a period of 15 minutes. The total duration of each treatment was 120 minutes. Each subject received two HBO₂ treatments daily, five days per week, for a total of 30 HBO₂ sessions.

### Parameters detected for the patients before and after treatments

NPRS 15 (Numeric Pain Rating Scale: 0–10) and HAMD 16 (Hamilton Depression Rating Scale: 17 item; total score: 28.45±7.16) were scored the day prior to the first treatment and the day after completing the 30th HBO₂ treatment. Patients with a total HAMD score of less than 7 were considered to be reporting no depressive symptoms. Patients with a total HAMD score of 7-17 were considered to have mild depression. Patients with a total HAMD score of 17-24 were considered to have moderate depression. Patients with a total HAMD score of greater than 24 were considered to be suffering from severe depression.

The period of blister resolution (i.e., the time between onset of the disease to the disappearance of the herpes blisters) and scar formation time (i.e., the time between onset of the disease and the formation of scars) were recorded for the patients in both groups. All patients were followed for three to six months after completion of HBO₂ treatment and the number of patients developing PHN recorded. The percentage of subjects with PHN was calculated by the following formula:

\[
\text{PHN percentage} = \frac{\text{number of cases with PHN}}{\text{total case number in each group}} \times 100.
\]
Evaluation of therapeutic efficacy
Therapeutic efficacy was evaluated on the day after completing the 30th HBO₂ treatment. The evaluation was conducted according to the criteria described previously [12,13]. The criteria for “healed” were complete subsidence of pain and rash with temporary pigmentation. The criteria for “improved” were significant pain relief and rash subsidence. The criteria for “ineffective” included no significant pain relief and no rash subsidence. Therapeutic efficacy was calculated by the following formula:

\[
\text{therapeutic efficacy} = \frac{\text{number of cases with healing} + \text{number of cases with improvement}}{\text{total case number in each group}} \times 100.
\]

Statistical analysis
All the parameters were expressed as mean ± standard deviation (X ± S). Statistical analysis was conducted using SPSS11.0 statistical software package and Excel 7.0. Chi square analysis was used for comparison of therapeutic efficacy and PHN percentage between the two groups. Paired student t-test was used for comparison of the period of blister resolution, scar formation time, NPRS score and HAMD score between the two groups. Analysis of variance was used for comparison among multiple groups. p<0.05 was considered as statistically significant.

RESULTS
Comparison of therapeutic efficacy between the two groups
The calculated therapeutic efficacy in the HBO₂ group (97.22%) was significantly higher than that in the control group (81.55%) (p<0.05) (Table 2, above).

Comparison of PHN, herpes stopping and scar formation time between the two groups
The percentage of subjects developing PHN in the HBO₂ group was 11.11%, which was significantly lower than that in the control group (31.25%) (p<0.05). There was no significant difference between the period of blister resolution in the HBO₂ group and that in the control group (p>0.05). The scar formation time in the HBO₂ group was significantly shorter than that in the control group (p<0.05) (Table 3, above).

Comparison of NPRS score between the two groups
Before treatment, there was no significant difference of NPRS score between the two groups (p>0.05). NPRS score was decreased after treatment in both groups (p<0.01). In addition, after treatment, NPRS score in the HBO₂ group was significantly lower than that in the control group (p<0.05) (Table 4).

Comparison of HAMD score between the two groups
Before treatment, there was no significant difference of HAMD score between the two groups (p>0.05). HAMD score was decreased after treatment in both groups (p<0.01). However, after completion of HBO₂ treatment, HAMD score in the HBO₂ group was significantly lower than in the control group (p<0.05) (Table 5).

<p>| TABLE 2 – Comparison of therapeutic efficacy |</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Case #</th>
<th>Healed</th>
<th>Improved</th>
<th>Ineffective</th>
<th>Efficacy rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>control group</td>
<td>32</td>
<td>17</td>
<td>9</td>
<td>6</td>
<td>81.25%</td>
</tr>
<tr>
<td>HBO₂ group</td>
<td>36</td>
<td>22</td>
<td>13</td>
<td>1</td>
<td>97.22%</td>
</tr>
</tbody>
</table>

<p>| TABLE 3 – Comparison of PHN percentage, period of blister resolution and scar formation time |</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Case #</th>
<th>PHN case # and %</th>
<th>Period of blister resolution (days)</th>
<th>Scar formation time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control group</td>
<td>32</td>
<td>10 (31.25%)</td>
<td>3.25 ± 1.39</td>
<td>13.94 ± 4.26</td>
</tr>
<tr>
<td>HBO₂ group</td>
<td>36</td>
<td>4 (11.11%)</td>
<td>2.81 ± 1.45</td>
<td>11.08 ± 3.97</td>
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</tbody>
</table>

<p>| TABLE 4 – Comparison of NPRS scores |</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Case #</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>control group</td>
<td>32</td>
<td>8.13 ± 1.68</td>
<td>3.53 ± 4.10</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>HBO₂ group</td>
<td>36</td>
<td>7.97 ± 1.80</td>
<td>1.83 ± 2.72</td>
<td>p = 0.000</td>
</tr>
</tbody>
</table>

<p>| TABLE 5 – Comparison of HAMD scores |</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Case #</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>control group</td>
<td>32</td>
<td>22.06 ± 13.55</td>
<td>10.94 ± 9.73</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>HBO₂ group</td>
<td>36</td>
<td>19.92 ± 12.77</td>
<td>16.53 ± 12.04</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Zhengrong Peng, Sue Wang, Xu Huang, Pingtian Xiao
Comparison of adverse reactions and side effects between the two groups
Because of excessive anxiety (i.e., claustrophobia prevented completion of HBO₂ treatment), assessment could not be completed in one patient in the HBO₂ group. Thus, this patient was excluded from analysis. One patient in the control group had allergic reactions (skin rash) and was also excluded. All the other patients finished examinations successfully. The percentage of cases that did not finish the study was not significantly different between the two groups (p>0.05). Adverse side effects secondary to HBO₂ treatment (e.g., barotrauma, oxygen toxicity, decompression sickness, pulmonary atelectasis, metabolic disorders and acid-base imbalance) did not occur.

DISCUSSION
Herpes zoster is a disease characterized by the presence of pain and herpetic skin lesions in the areas innervated by nerves infected with herpes virus. Under conditions where the human immune function is suppressed, herpes zoster virus spreads to the skin via sensory nerve fibers, which results in inflammation and necrosis of the involved ganglion and nerve pain [17,18]. Consequently, clusters of blisters are formed on the corresponding skin, and inflammation occurs [19]. Clinical and laboratory studies have confirmed that HBO₂ can improve aerobic metabolism in nerve tissues, inhibit nerve tissue inflammatory edema, alleviate pain in the nerves and accelerate skin wound healing [20,21,22].

In this study, we found that the therapeutic efficacy in the HBO₂ group was significantly higher than in the control group (Table 2), indicating that the combination of HBO₂ and conventional drug treatment is more effective than drug treatment alone. We also found that the NPRS score was significantly decreased after treatment in both groups, indicating that both drug treatment and combination of drug and HBO₂ can alleviate pain.

More importantly, after completion of HBO₂ treatment, the NPRS score in the HBO₂ group is significantly lower than that in control group (Table 3), indicating that HBO₂ enhances the alleviation of inflammation, growth of granulation tissue and healing of skin scars [24]. However, the period of blister resolution was not significantly different between the two groups, suggesting that HBO₂ does not play a role in resolution of active herpes infection.

We found in this study that PHN percentage in the HBO₂ group was significantly lower than that in control group, indicating that combination of HBO₂ and drug treatment is more effective in reducing PHN occurrence than drug treatment alone. It also suggests that HBO₂ can inhibit inflammation in nerve tissue, promote healing of nerve injury and reduce the nerve pain occurrence [23].

Skin burning and unbearable nerve pain caused by herpes zoster result in insomnia, irritability, anxiety, long-term psychological burden and depression [25]. We investigated the depression state of patients by determining the HAMD score in both groups. Our results showed that pre-treatment HAMD scores in patients with herpes zoster were significantly increased compared to the score in normal population, demonstrating that PHN induces depression. After completion of 30 HBO₂ treatments, HAMD scores were significantly reduced in both groups. More importantly, HAMD score in the HBO₂ group was significantly lower than that in the control group, indicating that HBO₂ plays an additional role in reversing the associated depression. Our results are consistent with previous reports showing that HBO₂ treatment has an antidepressantlike effect in forced-swimming tests in rats [26].

In summary, herpes zoster virus can invade nerves and cause long-term nerve pain and skin herpetic. In this study, relative to management with medications alone, the addition of a course of HBO₂ treatment was associated with improvements in calculated therapeutic efficacy, a reduction in scar formation time, pain scores, severity of associated depression and a decrease in the percentage of subjects developing post-herpetic neuralgia.

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Conflict of interest statement
The authors have no conflict of interest to declare.
REFERENCES

Top-cited articles on hyperbaric oxygen therapy published from 2000 to 2010

Ching-Hsing Lee M.D. 1,2, Lan Lee M.D. 3, Kun-Ju Yang M.D. 1,4, Teng-Fu Lin M.D. 1

1 Hyperbaric Oxygen Therapy Center, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan
2 Department of Emergency Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan
3 Department of Ophthalmology, Saint Paul’s Hospital, Taoyuan, Taiwan
4 Department of Emergency Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan

CORRESPONDING AUTHOR: Dr. Ching-Hsing Lee – lancellee@gmail.com

ABSTRACT

Objective: Hyperbaric oxygen therapy (HBO₂T) is a specialty with wide clinical applications and study fields. An evaluation of the major research direction of HBO₂T studies would be helpful for researchers in this field. In this study, we identified the most frequently cited HBO₂T articles to analyze the study focus of HBO₂T research in the past 10 years.

Methods: “Hyperbaric oxygen” was used as the keyword to search articles in PubMed between January 2000 and November 2010. The cited times of an article were tracked in Google Scholar. The top 100 most-cited articles were identified and their publication year, author nationalities, journal, study field and style were recorded and analyzed.

Results: In total, 2,362 HBO₂T-related articles were retrieved. The number of HBO₂T articles published per year has been increasing during the past 10 years. More than half of the top-cited articles (52/100) were from studies in the United States. Studies focusing on stroke (20), radiation injury (11), carbon monoxide (10), and wounds (9) accounted for 50% of the top-cited articles.

Conclusion: HBO₂T has been a field of increasing scientific publications in the past 10 years. The focus of research fields were stroke, radiation injury, carbon monoxide and wounds. The United States maintains an important influence on HBO₂T studies.

INTRODUCTION

A citation represents a cited article that is related to an idea, method or result [1]. The number of times an article was cited can be adopted as representative of the number of articles that focused on the same study field in the literature since its publication. The density patterns of bibliographical citations may also derive a profile of relative attention of an article in the medical literature. This concept provided both an objective and qualitative method to evaluate the influence of an article on other studies and the number of relevant studies in a particular field.

Hyperbaric oxygen therapy (HBO₂T) is the therapeutic administration of 100% oxygen to patients in an airtight chamber at pressures >1.4 atmospheres absolute or 1.4 times greater than sea-level pressure [2]. The clinical indications approved by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society (UHMS) are broad [3]. These indications can be classified into a variety of medical specialties, including environmental medicine, toxicology, infectious disease, traumatology, vascular disease, hematology, orthopedics, radiation therapy, reconstruction surgery, and thermal burns.

HBO₂T research fields are even broader than the UHMS-approved clinical applications. In this age of rapidly expanding medical literature, it is difficult for physicians to review all of the recent studies across so many disciplines, not to mention objectively assessing the impact and trend of the studies. The most influential studies and the focus of study fields can be determined objectively and qualitatively by analyzing the most
highly cited articles. In this study, we identified the most frequently cited HBO₂-T articles in the past 10 years, reviewed the characteristics of these top-cited HBO₂-T articles, and analyzed the study focus of HBO₂-T field. The list of the top cited HBO₂-T articles is an important reference for those in undersea and hyperbaric medicine subspecialty training and continuing medical education.

**METHODS**

**Study design**
This was a literature review study; thus, it qualified for a waiver from our institutional review board because no human subjects were involved.

**Study setting and population**
All articles were retrieved from the PubMed database. The number of times an article was cited was tracked in Google Scholar.

**Study protocol**
“Hyperbaric oxygen” was used as the key term to search HBO₂-T-related articles in PubMed. The search date was November 17, 2010. The publication dates were limited to January 1, 2000–November 2010. The total number of articles recorded in the PubMed database in the same period time was also recorded for comparison. The number of times an article was cited was tracked between November 17 and November 20, 2010 in Google Scholar. The total number of HBO₂-T-related articles published from 2000 to 2010 and the number of times the article was cited were recorded. The number of articles published in each year was calculated. These articles were ranked according to the number of times they were cited. The primary interventions or primary outcomes of articles that were not related to HBO₂-T were defined as articles not focus on HBO₂-T. Two physicians independently reviewed the abstracts of the most-cited articles and excluded articles that did not focus on HBO₂-T until the top 100 most-cited articles were identified. Any discrepancies in article exclusion were resolved by consensus. Article title, first author name, country of origin, journal, publication year, style (original or review), and number of times cited were recorded for the top 100 most-cited articles. The study fields of the top 100 most-cited articles were classified independently by two physicians. Any discrepancies were resolved by consensus.

**Measurements**
The primary outcome measures for the HBO₂-T-related articles analysis were trend of the numbers of articles and the distribution of the number of times articles were cited. The primary outcome measures for the top-cited HBO₂-T article analysis were the frequency of country, journal, publication year, style and study field.

**Data analysis**
Linear regression was used to evaluate the trend in the numbers of HBO₂-T-related articles, and the ratios of HBO₂-T-related articles to total PubMed articles from 2000 to 2010. The slope (β) of the linear regression was adopted as representative of trends in the article number increase. The 95% confidence intervals (CIs) of β were calculated. A p-value of <0.05 was considered statistically significant. The distributions of the cited times of the HBO₂-T-related and top-cited HBO₂-T articles, the publication year, countries of origin, journal, article style and study fields of the top-cited articles were analyzed by descriptive statistics. Data were analyzed with SAS version 9.2 (SAS Institute, Cary, N.C.).

**RESULTS**

**The HBO₂-T-related articles**
In total, 2,362 HBO₂-T-related articles were retrieved from PubMed. The numbers of articles published in each year is in Figure 1 (facings page). A linear regression analysis of the numbers of articles published in each year revealed a positive trend (β = 7.673, p-value < 0.001, 95% CI = 5.363 to 9.983). During the same study period, the PubMed database recorded 527,672 new publications in 2000 and the number increased to 827,071 in 2010. The ratios of HBO₂-T to total PubMed articles disclosed the relative increasing rate of HBO₂-T and scientific publications. A linear regression analysis of the ratios revealed the relative trend (β = -5.71 x 10⁻⁶, p-value = 0.001, 95% CI = -8.45 x 10⁻⁶ to -2.98 x 10⁻⁶). Thus, the increase in the number of HBO₂-T-related articles was not faster than the total PubMed recorded articles. The total number of times that all HBO₂-T-related articles were cited was 27,304. The average number and mode of citations for the HBO₂-T-related articles were 11.6 and 0. The 75th, 50th and 25th percentiles for the number of citations were 13, 4 and 1, respectively. The skewness and kurtosis were 6.5 and 76.4. The number of articles in each range of cited times were plotted in Figure 2 (facings page). (Note: The vertical axis was log₁₀ transformed.) The most-cited HBO₂-T-related article was cited 396 times.
The top-cited HBO₂T articles
The top 100 most-cited articles are listed in Table 1 (Pages 1092-96). These articles originated from 19 countries (Table 2, Page 1097). The 100 articles were published in 72 journals. Brain Research published seven of the articles and ranked first. Cochrane Database Systemic Review published four articles and ranked second. Undersea and Hyperbaric Medicine, World Journal of Surgery and Journal of Cerebral Blood Flow and Metabolism published three articles and ranked third. All 100 top-cited articles were published before 2007. Sixty-seven articles were original research, and the remaining 33 were reviews. The top-cited 100 articles were classified into 27 study fields (Table 3, Page 1097). The article with the most citations was published in the New England Journal of Medicine in 2002 and was titled “Hyperbaric oxygen for acute carbon monoxide poisoning” by Weaver et al., which was cited 323 times. The average, median and mode of times an article was cited were 70.6, 62 and 45 (range, 323-41). The skewness and kurtosis were 4.1 and 26.3.

Continued on Page 1096
### TABLE 1– The top 100 most-cited articles on hyperbaric oxygen therapy (HBO₂)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Title</th>
<th>First Author</th>
<th>Country</th>
<th>Journal</th>
<th>Year</th>
<th>Style</th>
<th>Field</th>
<th>Times cited</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Hyperbaric oxygen for acute carbon monoxide poisoning.</td>
<td>Weaver LK</td>
<td>USA</td>
<td>N Engl J Med</td>
<td>2000</td>
<td>Original</td>
<td>CO</td>
<td>323</td>
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<td>2</td>
<td>Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen.</td>
<td>Weaver LK</td>
<td>USA</td>
<td>Am J Respir Crit Care Med</td>
<td>2007</td>
<td>Original</td>
<td>CO</td>
<td>146</td>
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<td>3</td>
<td>Hyperbaric oxygen reduces infarct volume in rats by increasing oxygen supply to the ischemic periphery.</td>
<td>Sunami K</td>
<td>Japan</td>
<td>Crit Care Med</td>
<td>2000</td>
<td>Original</td>
<td>Stroke</td>
<td>133</td>
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<tr>
<td>4</td>
<td>Hyperbaric oxygen therapy for chronic wounds.</td>
<td>Kranke P</td>
<td>Germany</td>
<td>Cochrane Database Syst Rev</td>
<td>2004</td>
<td>Review</td>
<td>Wound</td>
<td>131</td>
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<td>6</td>
<td>Effects of hyperbaric oxygenation therapy on cerebral metabolism and intracranial pressure in severely brain injured patients.</td>
<td>Rockswold SB</td>
<td>USA</td>
<td>J Neurosurg</td>
<td>2001</td>
<td>Original</td>
<td>Brain injury</td>
<td>125</td>
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<td>7</td>
<td>Effect of hyperoxia on vascular endothelial growth factor levels in a wound model.</td>
<td>Sheikh AY</td>
<td>USA</td>
<td>Arch Surg</td>
<td>2000</td>
<td>Original</td>
<td>Wound</td>
<td>124</td>
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<td>8</td>
<td>Inhibition of apoptosis by hyperbaric oxygen in a rat focal cerebral ischemic model.</td>
<td>Yin D</td>
<td>USA</td>
<td>J Cereb Blood Flow Metab</td>
<td>2003</td>
<td>Original</td>
<td>Stroke</td>
<td>112</td>
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<tr>
<td>9</td>
<td>Hyperbaric oxygenation prevented brain injury induced by hypoxia-ischemia in a neonatal rat model.</td>
<td>Calvert JW</td>
<td>USA</td>
<td>Brain Res</td>
<td>2002</td>
<td>Original</td>
<td>Stroke</td>
<td>106</td>
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<tr>
<td>10</td>
<td>Hyperbaric oxygen decreases infarct size and behavioral deficit after transient focal cerebral ischemia in rats.</td>
<td>Veltkamp R</td>
<td>USA</td>
<td>Brain Res</td>
<td>2000</td>
<td>Original</td>
<td>Stroke</td>
<td>106</td>
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<tr>
<td>11</td>
<td>Hyperbaric oxygen: its uses, mechanisms of action and outcomes.</td>
<td>Gill AL</td>
<td>UK</td>
<td>QJM</td>
<td>2004</td>
<td>Review</td>
<td>Introd.</td>
<td>100</td>
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<td>14</td>
<td>Hyperbaric oxygen for delayed radiation injuries.</td>
<td>Feldmeier J</td>
<td>USA</td>
<td>Undersea Hyperb Med</td>
<td>2004</td>
<td>Review</td>
<td>Rad’n injury</td>
<td>97</td>
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<tr>
<td>15</td>
<td>The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial.</td>
<td>Abidia A</td>
<td>UK</td>
<td>Eur J Vasc Endovasc Surg</td>
<td>2003</td>
<td>Original</td>
<td>DM foot</td>
<td>97</td>
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<td>18</td>
<td>Hyperbaric oxygenation accelerates the healing rate of nonschismic chronic diabetic foot ulcers: a prospective randomized study.</td>
<td>Kessler L</td>
<td>France</td>
<td>Diabetes Care</td>
<td>2003</td>
<td>Original</td>
<td>DM foot</td>
<td>95</td>
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<td>19</td>
<td>Preconditioning with hyperbaric oxygen and hyperoxia induces tolerance against spinal cord ischemia in rabbits.</td>
<td>Dong H</td>
<td>China</td>
<td>Anesthesiology</td>
<td>2002</td>
<td>Original</td>
<td>Stroke</td>
<td>92</td>
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<tr>
<td>20</td>
<td>Hyperbaric oxygen therapy as a treatment for stage-I avascular necrosis of the femoral head.</td>
<td>Reis ND</td>
<td>Israel</td>
<td>J Bone Joint Surg Br</td>
<td>2003</td>
<td>Original</td>
<td>Avasc. necrosis</td>
<td>89</td>
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<td>21</td>
<td>The evaluation of subatmospheric pressure and hyperbaric oxygen in ischemic full-thickness wound healing.</td>
<td>Fabian TS</td>
<td>USA</td>
<td>Am Surg</td>
<td>2000</td>
<td>Original</td>
<td>Wound</td>
<td>86</td>
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<td>22</td>
<td>Oxygen in wound healing--more than a nutrient.</td>
<td>Tandara AA</td>
<td>USA</td>
<td>World J Surg</td>
<td>2004</td>
<td>Review</td>
<td>Wound</td>
<td>84</td>
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### TABLE 1– The top 100 most-cited articles on hyperbaric oxygen therapy (HBO₂) – continued

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<th>Country</th>
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<th>Style</th>
<th>Field</th>
<th>Times cited</th>
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<tr>
<td>23</td>
<td>The clinical toxicology of carbon monoxide.</td>
<td>Gorman D</td>
<td>NZealand</td>
<td>Toxicology</td>
<td>2003</td>
<td>Review</td>
<td>CO</td>
<td>83</td>
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<td>26</td>
<td>Hyperbaric oxygen reduces neuronal death and improves neurological outcome after canine cardiac arrest.</td>
<td>Rosenthal RE</td>
<td>USA</td>
<td>Stroke</td>
<td>2003</td>
<td>Original</td>
<td>Stroke</td>
<td>79</td>
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<tr>
<td>28</td>
<td>Effect of hyperbaric oxygen treatment on nitric oxide and oxygen free radicals in rat brain.</td>
<td>Elayan IM</td>
<td>USA</td>
<td>J Neurophysiol</td>
<td>2000</td>
<td>Original</td>
<td>Oxygen toxicity</td>
<td>78</td>
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<td>29</td>
<td>Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the DRN96 study group.</td>
<td>Annane D</td>
<td>France</td>
<td>J Clin Oncol</td>
<td>2004</td>
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<td>Rad’n injury</td>
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<td>30</td>
<td>Down regulation of COX-2 is involved in hyperbaric oxygen treatment in a rat transient focal cerebral ischemia model.</td>
<td>Yin W</td>
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<td>Brain Res</td>
<td>2002</td>
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<td>31</td>
<td>Accuracy of a peristaltic finger-type infusion pump during hyperbaric oxygen therapy.</td>
<td>Dohgomori H</td>
<td>Japan</td>
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<td>33</td>
<td>Neurologic manifestations of cerebral air embolism as a complication of central venous catheterization.</td>
<td>Heckmann JG</td>
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<td>Crit Care Med</td>
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<td>35</td>
<td>The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients.</td>
<td>Fife CE</td>
<td>USA</td>
<td>Wound Repair Regen</td>
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<td>37</td>
<td>Oxidative stress and antioxidant status in patients undergoing prolonged exposure to hyperbaric oxygen.</td>
<td>Benedetti S</td>
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<td>2004</td>
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<td>38</td>
<td>Dual effect of HBO on cerebral infarction in MCAO rats.</td>
<td>Badr AE</td>
<td>USA</td>
<td>Am J Physiol Regul Integr Comp Physiol</td>
<td>2001</td>
<td>Original</td>
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<td>39</td>
<td>Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot.</td>
<td>Wunderlich RP</td>
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<td>Diabetes Care</td>
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<td>41</td>
<td>Hyperbaric oxygen preconditioning induces neuroprotection against ischemia in transient not permanent middle cerebral artery occlusion rat model.</td>
<td>Xiong L</td>
<td>China</td>
<td>Chin Med J</td>
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<td>Hyperbaric oxygen reduces blood-brain barrier damage and edema after transient focal cerebral ischemia.</td>
<td>Veltkamp R</td>
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<td>Stem cell mobilization by hyperbaric oxygen.</td>
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<td>Regulation of the brain’s vascular responses to oxygen.</td>
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<td>Circ Res</td>
<td>2002</td>
<td>Original</td>
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### TABLE 1– The top 100 most-cited articles on hyperbaric oxygen therapy (HBO₂) – continued

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<tr>
<th>Rank</th>
<th>Title</th>
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<td>47</td>
<td>Cardiovascular manifestations of moderate to severe carbon monoxide poisoning.</td>
<td>Satran D</td>
<td>USA</td>
<td>J Am Coll Cardiol</td>
<td>2005</td>
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<td>48</td>
<td>Effect of hyperbaric oxygen on apoptosis in neonatal hypoxia-ischemia rat model.</td>
<td>Calvert JW</td>
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<td>J Appl Physiol</td>
<td>2003</td>
<td>Original</td>
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<td>50</td>
<td>Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning.</td>
<td>Henry CR</td>
<td>USA</td>
<td>JAMA</td>
<td>2006</td>
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<td>The effect of hyperbaric oxygen treatment on oxidative stress in experimental acute necrotizing pancreatitis.</td>
<td>Yasar M</td>
<td>Turkey</td>
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<td>2003</td>
<td>Original</td>
<td>Pancreatitis</td>
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<td>Effect of hyperbaric oxygen on striatal metabolites: a microdialysis study in awake freely moving rats after MCA occlusion.</td>
<td>Badr AE</td>
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<td>59</td>
<td>Nitric oxide and cerebral blood flow responses to hyperbaric oxygen.</td>
<td>Demchenko IT</td>
<td>Russia</td>
<td>J Appl Physiol</td>
<td>2000</td>
<td>Original</td>
<td>Nitric oxide</td>
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<td>60</td>
<td>Neuroprotective effects of hyperbaric oxygen treatment in experimental focal cerebral ischemia are associated with reduced brain leukocyte myeloperoxidase activity.</td>
<td>Miljkovic-Lolic M</td>
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<td>Brain Res</td>
<td>2003</td>
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<td>61</td>
<td>Hyperbaric oxygen: does it promote growth or recurrence of malignancy?</td>
<td>Feldmeier J</td>
<td>USA</td>
<td>Undersea Hyperb Med</td>
<td>2003</td>
<td>Review</td>
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<td>62</td>
<td>Hyperbaric oxygen—an effective tool to treat radiation morbidity in prostate cancer.</td>
<td>Mayer R</td>
<td>Austria</td>
<td>Radiother Oncol</td>
<td>2001</td>
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<td>64</td>
<td>Outcome analysis in patients with primary necrotizing fasciitis of the male genitalia.</td>
<td>Dahm P</td>
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<td>Urology</td>
<td>2000</td>
<td>Original</td>
<td>Necrot. fasciitis</td>
<td>56</td>
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<td>67</td>
<td>Hyperbaric oxygen therapy and mandibular osteoradionecrosis: a retrospective study and analysis of treatment outcomes.</td>
<td>David LA</td>
<td>Canada</td>
<td>J Can Dent Assoc</td>
<td>2001</td>
<td>Original</td>
<td>Rad’n injury</td>
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### TABLE 1– The top 100 most-cited articles on hyperbaric oxygen therapy (HBO₂T) – continued

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<th>Rank</th>
<th>Title</th>
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<td>69</td>
<td>Hyperbaric oxygen preconditioning induces tolerance against spinal cord ischemia by upregulation of antioxidant enzymes in rabbits.</td>
<td>Nie H</td>
<td>China</td>
<td>J Cereb Blood Flow Metab</td>
<td>2006</td>
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<td>Hyperbaric oxygen therapy for calcific uremic arteriolopathy: a case series.</td>
<td>Basile C</td>
<td>Italy</td>
<td>J Nephro</td>
<td>2002</td>
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<td>Genotoxicity of hyperbaric oxygen.</td>
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<td>73</td>
<td>Effects of hyperbaric oxygen therapy on cerebral oxygenation and mitochondrial function following moderate lateral fluid-percussion injury in rats.</td>
<td>Daugherty WP</td>
<td>USA</td>
<td>J Neurosurg</td>
<td>2004</td>
<td>Original</td>
<td>Brain injury</td>
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<td>75</td>
<td>Osteoblastic activity and neoangiogenesis in distracted bone of irradiated rabbit mandible with or without hyperbaric oxygen treatment.</td>
<td>Muhonen A</td>
<td>Finland</td>
<td>Int J Oral Maxillofac Surg</td>
<td>2004</td>
<td>Original</td>
<td>Rad’n injury</td>
<td>48</td>
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<td>76</td>
<td>Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen.</td>
<td>Corman JM</td>
<td>USA</td>
<td>J Urol</td>
<td>2003</td>
<td>Original</td>
<td>Rad’n injury</td>
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<td>79</td>
<td>Induction of heme oxygenase-1 and adaptive protection against the induction of DNA damage after hyperbaric oxygen treatment.</td>
<td>Speit G</td>
<td>Germany</td>
<td>Carcinogenesis</td>
<td>2000</td>
<td>Original</td>
<td>Genotoxicity</td>
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<td>82</td>
<td>A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation.</td>
<td>Hess CL</td>
<td>USA</td>
<td>Ann Plast Surg</td>
<td>2003</td>
<td>Review</td>
<td>Wound</td>
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<td>83</td>
<td>Preconditioned hyperbaric oxygenation protects the liver against ischemia-reperfusion injury in rats.</td>
<td>Yu SY</td>
<td>Taiwan</td>
<td>J Surg Res</td>
<td>2005</td>
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<td>Isch./reper. injury</td>
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<td>84</td>
<td>Hyperbaric oxygen therapy of cerebral ischemia.</td>
<td>Helms AK</td>
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<td>Cerebrovasc Dis</td>
<td>2005</td>
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<td>85</td>
<td>Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy.</td>
<td>Golden ZL</td>
<td>USA</td>
<td>Int J Neurosci</td>
<td>2002</td>
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<td>86</td>
<td>Hyperbaric oxygen pretreatment induces catalase and reduces infarct size in ischemic rat myocardium.</td>
<td>Kim CH</td>
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<td>Pflugers Arch</td>
<td>2001</td>
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<td>Myoc. infar.</td>
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<td>87</td>
<td>Evaluation of mutagenic effects of hyperbaric oxygen (HBO₂) in vitro. II. Induction of oxidative DNA damage and mutations in the mouse lymphoma assay.</td>
<td>Rothfuss A</td>
<td>Germany</td>
<td>Mutat Res</td>
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<td>88</td>
<td>Hyperbaric oxygen reduces the progression and accelerates the regression of atherosclerosis in rabbits.</td>
<td>Kudchodkar BJ</td>
<td>USA</td>
<td>Arterioscler Thromb Vasc Biol</td>
<td>2000</td>
<td>Original</td>
<td>Atherosclerosis</td>
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**TABLE 1– The top 100 most-cited articles on hyperbaric oxygen therapy (HBO₂T) – continued**

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<tr>
<th>Rank</th>
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<td>90</td>
<td>Hyperbaric oxygen reduces cerebral blood flow by inactivating nitric oxide.</td>
<td>Demchenko IT</td>
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<td>Hyperbaric oxygen induces rapid protection against focal cerebral ischemia.</td>
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<td>Brain Res</td>
<td>2005</td>
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<td>92</td>
<td>Multiple effects of hyperbaric oxygen on the expression of HIF-1 alpha and apoptotic genes in a global ischemia-hypotension rat model.</td>
<td>Li Y</td>
<td>USA</td>
<td>Exp Neurol</td>
<td>2005</td>
<td>Original</td>
<td>Stroke</td>
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<td>94</td>
<td>Nitric oxide production is enhanced in rat brain before oxygen-induced convulsions.</td>
<td>Demchenko IT</td>
<td>USA</td>
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<td>2001</td>
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<td>95</td>
<td>Endothelial progenitor cell release into circulation is triggered by hyperoxia-induced increases in bone marrow nitric oxide.</td>
<td>Goldstein LJ</td>
<td>USA</td>
<td>Stem Cells</td>
<td>2006</td>
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<td>96</td>
<td>Hyperbaric oxygen therapy for late radiation tissue injury.</td>
<td>Bennett MH</td>
<td>Australia</td>
<td>Cochrane Dbase Syst Rev</td>
<td>2005</td>
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<td>97</td>
<td>Influence of an orally effective SOD on hyperbaric oxygen-related cell damage.</td>
<td>Muth CM</td>
<td>Germany</td>
<td>Free Radic Res</td>
<td>2004</td>
<td>Original</td>
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<td>99</td>
<td>Correlation between hyperbaric oxygen exposure pressures and oxidative parameters in rat lung, brain, and erythrocytes.</td>
<td>Oter S</td>
<td>Turkey</td>
<td>Clin Biochem</td>
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<td>100</td>
<td>Continuous measurements of cerebral tissue oxygen pressure during hyperbaric oxygenation–HBO effects on brain edema and necrosis after severe brain trauma in rabbits.</td>
<td>Niklas A</td>
<td>Germany</td>
<td>J Neurol Sci</td>
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</table>

CO = Carbon monoxide; DM = Diabetes mellitus; Dbase = Database; Rad’n = Radiation

**Continued from Page 1091**

**DISCUSSION**

The distribution of the number of times an HBO₂T-related article was cited was extremely skewed with a long tail, indicating that some articles were frequently cited, and most articles were seldom cited. This phenomenon is referred to as Bradford’s Law and also occurs in a citation analysis of articles included in Journal Citation Reports (JCR) [4]. The citations for HBO₂T-related articles reflected the overall citing pattern in the scientific literature. The top 100 most-cited articles were 4.2% (100/2,362) of the total HBO₂T-related articles but accounted for 25.9% (7,060/27,304) of the total number of times an article was cited. This discrepancy indicated that the influence of the top 100 most-cited HBO₂T articles and the intensity of research in those study fields were much higher than those of other articles and fields. Thus, one could identify the most influential studies in HBO₂T and the focus of HBO₂T study objectively by analyzing the top cited articles. In the past decade, the four major HBO₂T research fields were stroke, radiation injury, carbon monoxide and wounds. These four fields accounted for 50% of the top cited articles and 55.4% of citations of the top-cited articles.

The countries of origin of the articles were not evenly distributed. More than half of the top-cited articles (52/100) were from U.S.-based research. The ratio in other disciplines were higher than the HBO₂T field: emergency medicine journals (85% U.S.) [5], otolaryngology-head and neck surgery journals (84% U.S.) [6], general surgical journals (78% U.S.) [7], anesthetic journals (69% U.S.) [8], critical care medicine (69% U.S.) [9] and rehabilitation journals (69% U.S.) [10]. The study population of other disciplines was taken from a JCR category, but our articles were retrieved from the PubMed database using keywords. The main reason for the
difference is that JCR has no independent HBO₂T journal category. This difference does not obscure the result that the United States maintains an important influence on medical research throughout multiple disciplines that include HBO₂T. The percentage of the top-cited HBO₂T studies originating from outside the United States was higher than that of other disciplines, indicating that countries all over the world contribute substantially to the HBO₂T field.

The top cited HBO₂T articles were published in 72 journals from diverse disciplines. The publications in other categories were limited to five to 11 journals (15-55% of the source journals) [5-10] This difference may have resulted from the different study population selection process in our study compared to that of others. It may also point out the wide application of HBO₂T and indicate that HBO₂T studies were accepted by journals of different disciplines.

We chose Google Scholar as our tracking database. It is a free search engine, and full-text research material is available through Google Scholar on the Web. These features are important to researchers not affiliated with a large medical center or university. Two other
databases, such as Web of Science [11] and Scopus [12], provide information on the number of times articles have been cited. The differences between these databases for tracking the number of citation times were analyzed in previous studies [13,14]. The advantage of Google Scholar is free access, and it retrieves a greater number of citations from all electronic resources. The disadvantage of Google Scholar is the use of automated robot Web crawlers to track citations without a publicly known algorithm, which is updated less often, and the citation accuracy is slightly lower. The completeness of citations retrieved from different databases depends on the field and publication year of the article [15]. Therefore, the ranking of the top-cited HBO2T articles may have varied if we had chosen a different database.

There were three limitations of this study. First, no articles published between 2008 and 2010 reached the threshold of a top-cited study. Thus, the importance of articles may have been underestimated, and the focus of the HBO2T study was not evident within this period.

Second, we adopted the number of times an article was cited as representative of its importance. Our study investigated the number of times an article was cited instead of the “real” importance or impact of the articles. The number of times cited and importance are equivalent only when the impact of articles is well recognized. Highly cited articles might be influential and important. Nevertheless, seldom-cited articles might be potentially influential but their importance is not yet understood. Thus, the importance of rarely cited articles may have been underestimated.

Third, the contribution of articles published and cited in December 2010 were not calculated, but it will not influence the main results of our study. The increasing trend in the numbers of HBO2T-related articles will be more evident if the number of articles published in December 2010 was added. The cited times of an article may increase within a limited range in one month, but it is unlikely that it has a dramatic change that leads to a significant reordering of the ranking of top-cited articles.

In conclusion, HBO2T research has been a growing field over the past 10 years. The United States maintains an important influence on HBO2T studies. Stroke, radiation injury, carbon monoxide and wounds comprised the main focus of the HBO2T study fields.

**Conflict of interest statement**

The authors have no conflict of interest to declare.

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**REFERENCES**


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Ching-Hsing Lee, Lan Lee, Kun-Ju Yang, Teng-Fu Lin
Recommendations for rescue of a submerged unresponsive compressed-gas diver

S.J. Mitchell 1,2, M.H. Bennett 1,3, N. Bird 1,4, D.J. Doolittle 1,5, G.W. Hobbs 1,6,7, E. Kay 1,8, R.E. Moon 1,6, T.S. Neuman 1,9, R.D. Vann 1,4, R. Walker 1,6,7, H.A. Wyatt 1,10

1 The Undersea and Hyperbaric Medical Society Diving Committee
2 Department of Anesthesiology, University of Auckland, New Zealand
3 Department of Anesthesia, University of New South Wales, Sydney, Australia
4 Divers Alert Network, Durham, North Carolina, USA
5 Navy Experimental Diving Unit, Panama City, Florida, USA
6 Center for Hyperbaric Medicine and Environmental Physiology, Duke University Medical Center, Durham, North Carolina, USA
7 Rubicon Foundation Incorporated, Durham, North Carolina, USA
8 HealthForce Partners and University of Washington, Seattle Washington, USA
9 University of California San Diego, San Diego, USA
10 Department of Hyperbaric Medicine and Wound Care, West Jefferson Medical Center, Marrero, Louisiana, USA

CORRESPONDING AUTHOR: Dr. Simon Mitchell – sj.mitchell@auckland.ac.nz

The Diving Committee of the Undersea and Hyperbaric Medical Society has reviewed available evidence in relation to the medical aspects of rescuing a submerged unresponsive compressed-gas diver. The rescue process has been subdivided into three phases, and relevant questions have been addressed as follows.

Phase 1, preparation for ascent: If the regulator is out of the mouth, should it be replaced? If the diver is in the tonic or clonic phase of a seizure, should the ascent be delayed until the clonic phase has subsided? Are there any special considerations for rescuing rebreather divers?

Phase 2, retrieval to the surface: What is a “safe” ascent rate? If the rescuer has a decompression obligation, should they take the victim to the surface? If the regulator is in the mouth and the victim is breathing, does this change the ascent procedures? If the regulator is in the mouth, the victim is breathing, and the victim has a decompression obligation, does this change the ascent procedures? Is it necessary to hold the victim’s head in a particular position? Is it necessary to press on the victim’s chest to ensure exhalation? Are there any special considerations for rescuing rebreather divers?

Phase 3, procedure at the surface: Is it possible to make an assessment of breathing in the water? Can effective rescue breaths be delivered in the water? What is the likelihood of persistent circulation after respiratory arrest? Does the recent advocacy for “compression-only resuscitation” suggest that rescue breaths should not be administered to a non-breathing diver? What rules should guide the relative priority of in-water rescue breaths over accessing surface support where definitive CPR can be started?

A “best practice” decision tree for submerged diver rescue has been proposed.
INTRODUCTION

The Diving Committee of the Undersea and Hyperbaric Medical Society (UHMS) acts as a bridge between the members of the Society and divers. The Committee is occasionally asked to address a specific question of practical significance to divers, but which requires scientific or medical interpretation, and to make recommendations to the diving community.

This paper is a Diving Committee initiative to address the medical aspects of rescue and resuscitation of an unresponsive diver. This initiative was prompted by requests from diver training agencies who wish to revise training material and by specific questions from the scientific diving community. There is ongoing debate over the optimal approach to rescue of an unresponsive diver from depth. There is a paucity of related research, and this means that any recommendations on rescue technique will defer largely to “expert opinion.”

Nevertheless, the UHMS Diving Committee is an appropriate resource to consider relevant questions and promulgate recommendations. Indeed, with the exception of the South Pacific Underwater Medicine Society Policy on Initial Management of Diving Injuries and Illnesses [1] (which is now 14 years old and addressed in-water resuscitation) and the UHM Diving Committee initiative on Immediate Medical Care of an Unresponsive Diver [2], there is a conspicuous absence of recommendations from expert groups in relation to this matter.

SCOPE OF THE REVIEW

This review addresses the course of action on finding an unresponsive diver underwater in circumstances either where the disabling event was witnessed or where the period of unresponsiveness is uncertain and resuscitation must therefore be considered possible. Thus, it does not apply to “body recovery,” where resuscitation will not be attempted. The focus is on diver rescue.

Methods of resuscitation per se are not discussed except where they have implications for the conduct of the in-water phase of the rescue; neither is post-resuscitation care discussed. This review considers only compressed-gas bounce dives (dives in which the duration from leaving to returning to surface is on the order of minutes or hours) and dives conducted using a half-face mask and separate mouthpiece. The principal focus is on recreational diving using open circuit “scuba” equipment supplying air, or occupational diving using similar equipment configurations.

Some of the controversies considered are also relevant to recreational “technical diving,” in which gases other than air and equipment such as rebreathers are customarily used, and in which decompression dives are commonly performed. Advanced occupational scenarios such as diving with helmets and surface-supplied gas, saturation diving, and bell diving are not discussed.

For the purpose of this review a “rescuer” is a diver who has received specific training in diver rescue. This is appropriate given that this review is largely a response to questions about the content of such training. There is no attempt to define appropriate practice for divers who have not received training in rescue techniques.

Finally, the purpose of this paper is to address certain medical aspects of diver rescue; and particularly those that cause controversy. It does not address mechanical details of practical rescue techniques (methods of buoyancy control during ascent, for example) unless there is particular relevance to a medical consideration. The prescription of practical techniques is left to the respective diver training agencies. As a basis for discussion, this paper will refer to the methods recommended in the Professional Association of Diving Instructors (PADI) Rescue Diver Manual [2].

METHODS

The key steps in the rescue of an unresponsive diver were defined, and a set of important questions in relation to those steps were generated. Two members of the diving committee (SJM, MHB) reviewed the relevant literature and drafted responses to these questions. These were distributed to participating committee members for discussion. All participating members were invited to submit comments, and where necessary, these were discussed prior to modification of the recommendations. It can be assumed that recommendations made in this paper that are not referenced to external sources of evidence represent the consensus opinion of the listed authors from the UHMS Diving Committee. The overall content is endorsed by the committee. It should be noted that no participating members were employees of a diving training organization, nor were there any other potential conflicts of interest. The finalized recommendations were submitted for consideration by the UHMS Publications Committee, and for peer review and publication in Undersea and Hyperbaric Medicine.
KEY STEPS IN DIVER RESCUE  
AND RELATED QUESTIONS

It is universally agreed that on finding an unresponsive diver underwater the overarching priority should be to retrieve the diver to the surface and initiate resuscitative measures as quickly as practicable while avoiding harm to the rescuer. This process can be broken down into three phases:

- preparation for ascent;
- retrieval to the surface; and
- procedures at the surface.

Preparation for ascent

When an unresponsive diver is found at depth the rescuer will take steps to position the victim appropriately and initiate an ascent while controlling buoyancy and maintaining his/her own safety. The PADI Rescue Diver Manual [2] states that if the regulator is in the mouth it be held there throughout the ascent. The committee identified the following relevant questions:

1. If the regulator is out of the mouth, should it be replaced?
2. If the diver is in the tonic or clonic phase of a seizure, should the ascent be delayed until the clonic phase has subsided?
3. Are there any special considerations for rescuing rebreather divers?

Retrieval to the surface

During the ascent the PADI Rescue Diver Manual [2] recommends the rescuer maintain a “safe” ascent rate and holds the victim’s head in a neutral position. The committee identified the following relevant questions:

1. What is a “safe” ascent rate?
2. If the rescuer has a decompression obligation, should he/she take the victim to the surface?
3. If the regulator is in the mouth and the victim is breathing, does this change the ascent procedure?
4. If the regulator is in the mouth, the victim is breathing and the victim has a decompression obligation, does this change the ascent procedure?
5. Is it necessary to hold the victim’s head in a particular position?
6. Is it necessary to press on the victim’s chest to ensure exhalation?
7. Are there any special considerations for rescuing rebreather divers?

Procedure at the surface

Once at the surface the PADI Rescue Diver Manual [2] instructs as follows: The diver be positioned face-up, and positive buoyancy be established for both victim and rescuer. A call for help should be made and the victim’s airway opened followed by rescue breathing if there is no spontaneous respiration.

After two breaths with no victim response, the manual prescribes evaluation of distance from surface support. If surface support is less than five minutes away, intermittent rescue breaths should be continued while towing the victim until surface support is reached and the diver is removed from the water (at which time a cardiopulmonary resuscitation [CPR] protocol should be initiated).

If surface support is more than five minutes away the rescuer should remain where he/she is and provide rescue breaths for one minute and check for response. If there is no response the rescuer should assume that cardiac arrest has occurred and tow the victim to surface support as quickly as possible without rescue breaths, remove the victim from the water, and initiate a CPR protocol. The committee identified the following relevant questions:

1. Is it possible to make an assessment of breathing in the water?
2. Can effective rescue breaths be delivered in the water?
3. What is the likelihood of persistent circulation after respiratory arrest?
4. Does the recent advocacy for “compression-only resuscitation” suggest that in-water rescue breaths should not be administered to a non-breathing diver?
5. What (if any) rules should guide the relative priority of in-water rescue breaths over accessing surface support where definitive CPR can be started?

COMMITTEE DETERMINATIONS ON CONTROVERSIES

Before addressing the specific controversies, the committee felt that several general comments in relation to diver rescue were appropriate. First, any diver who becomes unresponsive underwater is in a perilous situation. All divers must understand that even a textbook rescue will frequently not achieve a good outcome. Interpretations of accidents and any commentary on the outcome of attempted rescues should therefore be made with great caution.

Second, there are many contextual issues that could influence the correct course of action in any particular situation. Although best evidence, logic and experience
have been applied in answering the questions posed in the previous section, it is not claimed that these answers will invariably be correct in all situations.

PREPARATION FOR ASCENT
If the regulator is out of the mouth, should it be replaced?
There is no relevant evidence to guide discussion on this question. It was the committee’s consensus that no attempt should be made to replace a dislodged regulator even in a witnessed loss of consciousness, except in an overhead environment, where there is no option for a direct ascent and where the victim’s only hope is resumption of spontaneous ventilation underwater (a virtually unsalvageable scenario). In such a case the regulator should be purged before replacement.

Manipulating the airway risks the entry of water, and any advantage is uncertain. In particular there was doubt that a regulator held in place would protect the airway any more than a mouth held closed. There was general agreement that if the regulator remained in the mouth at the time the diver was discovered, an attempt should be made to keep it there, especially if the victim still appears to be breathing.

If the diver is in the tonic or clonic phase of a seizure, should initiation of the ascent be delayed until the clonic phase has subsided?
There is a long-standing belief that if a diver suffers a generalized convulsion underwater he/she should be held at a fixed depth until the clonic phase of the convulsion has subsided. Although there are minor variations, this is generally reflected in relevant recommendations in the U.S. Navy Diving Manual [3]. This advice is based on the notion that the glottis will spasm shut during a convulsion and that the diver would therefore trap expanding gas in the lungs during ascent, leading to pulmonary barotrauma.

There are several reasons to critically review this concern. First, as many emergency physicians know, patients suffering prolonged generalized convulsions actually do ventilate the lungs, and can also be ventilated with a bag and mask. It thus appears that glottal obstruction in this condition is partial rather than total.

Second, a study by Leaming et al. [4] using video-laryngoscopy in pigs during generalized seizures appeared to suggest that airway obstruction was primarily inspiratory, and that glottal patency at the onset of expiration was relatively normal.

Finally, the end of the clonic phase may be marked by resumption of deep breathing, and during immersion with an unprotected airway this would almost certainly result in drowning.

Taken together, one interpretation of these observations is that the clonic phase of a convulsion (prior to resumption of coordinated breathing) is actually an appropriate time to bring the victim to the surface. However, this matter deserves cautious interpretation. The observations of glottal patency by Leaming were of such interest that two committee members (RW, REM) obtained the original video-loops made during the experiments. Careful study of these videos suggests closure of the glottis throughout the seizure periods recorded, with no clear opening on expiration. It is not possible to interpret the degree to which expiration is obstructed from this observation but it does raise concerns about wholesale abandonment of the current recommendation.

It follows from the above that the committee’s determination is as follows: If a compressed-gas diver is discovered in the clonic phase of a seizure at depth and the regulator is not in the mouth the diver should be retrieved to the surface without delay. If the regulator is in the mouth, then every attempt should be made to hold it in place while sealing the lips around the mouthpiece; surfacing should be delayed until the seizure has resolved.

This recognizes the committee’s perception that without the regulator in place, drowning on resumption of breathing probably represents the greatest threat to life, and with the regulator held in place, pulmonary barotrauma during an ascent with a closed glottis becomes the greater concern.

Are there any special considerations for rescuing rebreather divers?
If the mouthpiece is out of the mouth, the committee could see no reason to depart from the generic rescue recommendations contained elsewhere in this paper. No attempt should be made to replace the mouthpiece, and ascent should be initiated immediately. If the mouthpiece and mask are in place then it is possible the diver is breathing. For this scenario, specialist groups providing rebreather instruction may consider adapting the following principles to an algorithm specific to the devices they teach.

First, attempt to retain the mouthpiece in place and seal the lips around it as well as is practicable. Assume...
that the diver is breathing, and expend no time trying to verify this.

Second, if the rebreather has a pO₂ monitor and the rescuer is familiar with the victim’s unit, check the loop pO₂. Hyperoxia (pO₂ > 1.6 atm abs) should be ignored and ascent initiated unless the diver is actively convulsing, in which case the rescuer should wait until the seizure has finished before ascending. Hypoxia (pO₂ < 0.2 atm abs) should be corrected by manually adding oxygen into the loop. Gross hyperoxia should be avoided, but time should not be wasted in an attempt to titrate the pO₂ to a particular level beyond establishment of normoxia or even mild hyperoxia (since the pO₂ will fall during ascent).

If there is no pO₂ monitoring (either because it is not a feature of the rebreather or due to loss of electronics) a flush of diluent to “fill” the loop will, under most circumstances, ameliorate both loop hypoxia and hyperoxia to some extent. It will also help establish positive buoyancy (that will not subsequently change if the loop is filled) to begin the ascent.

These recommendations for checking pO₂ and taking corrective action are broadly confluent with those prescribed by the U.S. Navy [3]. If the rescuer is unfamiliar with the rebreather, the rebreather oxygen or diluent supplies are exhausted, or there are any other logistical barriers to performing a simple “check and correct,” as described here, within 10 to 20 seconds, then no more time should be expended on attempts to manipulate the loop gas composition, and an ascent should be initiated.

RETRIEVAL TO THE SURFACE

What is a safe ascent rate?

This question was raised because a “safe ascent rate” is referred to (but not defined) in the PADI Rescue Diver Manual [2]. The committee felt there was no generic answer to this question. Indeed, for the victim, the safest ascent rate is likely to be “as fast as possible” in many cases and will almost invariably be faster than a safe rate for the rescuer. Moreover, prescribing an actual rate invites a potentially unhelpful fixation on trying to adhere to it. In reality, a rescuer would be doing well just to maintain a reasonably controlled ascent. The “safe ascent rate” is a context-sensitive matter for the rescuer to determine.

If the rescuer has a decompression obligation, should he/she take the victim to the surface?

For the purposes of this discussion, the committee considered that the practice of inserting a “safety stop” during ascent from a “no-decompression dive” does not represent a “decompression obligation.” With that acknowledged, it is a general principle of emergency response that first responders should not put themselves at unreasonable risk in order to effect a rescue. Although omitting decompression stops will not invariably result in DCS, the presence of a significant decompression obligation and a consequent risk of DCS with a direct ascent could certainly be construed as unreasonable risk.

History tells us that rescuers may be prepared to expose themselves to such risk [5,6] but also that they may injure themselves doing so [6]. The difficulty in defining “unreasonable risk” and the myriad factors that can influence it in any practical diving situation make it impossible for the committee to say anything other than it is acceptable for rescuers to avoid exposing themselves to risk.

Risk acceptance in these situations is a personal matter for the rescuer. In the event that a rescuer elects not to bring a victim to the surface, there is little choice other than to make the victim positively buoyant and let that person go. This strategy has been used successfully in at least one technical diving accident occurring at extreme depth; the victim survived because the surface support crew was vigilant, saw him arrive at the surface and were able to retrieve and resuscitate him [7].

If the regulator is in the mouth and the victim is breathing, does this change the ascent procedure?

There was no relevant evidence to guide discussion on this question, but it was the committee’s consensus that the primary goal should still be to get the diver to the surface as quickly as possible—accompanied and managed by the rescuer. If the regulator is in place and the diver is breathing, this increases the importance of retaining the regulator in the mouth and sealing the lips around the mouthpiece as well as practicable.

If the regulator is in the mouth, the victim is breathing and the victim has a decompression obligation, does this change the ascent procedure?

It is reiterated that for the purposes of this discussion the committee considered that the practice of inserting a “safety stop” during ascent from a “no-stop dive” does not represent a “decompression obligation.”
As a general rule it was considered that it would be very difficult to protect and manage the airway in an unresponsive diver for long enough to complete any meaningful decompression stops. Any attempt to do so might result in drowning, which, depending on the amount of omitted decompression, would likely represent a greater threat to life than decompression sickness (DCS) arising from a direct ascent.

It is acknowledged that there is anecdote describing successful airway management underwater. In one event that followed an oxygen convulsion at a 12-meter decompression stop, a rescuer held an open-circuit scuba regulator in place while bringing the victim to the surface over six minutes [5]. It is notable that the rescuer in this event was a highly experienced technical diver.

It is evident that under some circumstances the airway could be protected adequately to allow a period of decompression under ideal conditions, and this would be even more likely if the victim were using a full face mask or a properly designed and deployed mouthpiece-retaining device. Any decision to attempt this would depend entirely upon context, and it is reiterated that the path of least risk in the majority of circumstances will be to bring the victim directly to the surface.

Is it necessary to hold the victim’s head in a particular position?
The object of head positioning for ascent is to facilitate the escape of expanding gas from the victim’s lungs in order to avoid pulmonary barotrauma. Thus, any position that tends to close the airway, such as extreme flexion of the neck, should be avoided. The committee consensus is that the neck should be held in a neutral to slightly extended position, if possible. Based on cases in which the authors have been involved and where unresponsive divers have been recovered from moderate depths, it appears that expanding gas passes passively out of the airway and pulmonary barotrauma is rare. As a sidebar to this discussion, this expansion and outward flow of gas during ascent may help prevent aspiration of water into the lungs.

Is it necessary to press on the victim’s chest to ensure exhalation?
Compression of the chest during ascent to promote exhalation and thereby minimize the risk of pulmonary barotrauma has featured in previous diver rescue recommendations. There is no evidence that it is more effective in preventing barotrauma than merely ensuring the airway is patent: Its principal disadvantage is that it potentially “task loads” the rescuer who may simultaneously be trying to control buoyancy, maintain appropriate head position, and possibly ensure retention of a regulator.

The committee does not recommend this technique.

Are there any special considerations for rebreather divers?
In an ascent with mouthpiece retained, the rescuer should avoid dislodging the mask or firmly blocking the nose in any way. The mask will prevent water entering the nose, but expanding gas in the rebreather loop will still be able to escape by that route. Depending on the rebreather configuration, this may be important for avoiding lung barotrauma.

The rescuer should not attempt to manipulate the gas composition of the loop while trying to control the ascent.

PROCEDURE AT THE SURFACE
Is it possible to make an assessment of breathing in the water?
It is acknowledged that there may be difficulty with assessing breathing under some circumstances, but the most likely error would be failure to detect breathing when it is present rather than to perceive breathing when it is absent. Since it seems unlikely that harm would accrue from attempting to administer rescue breaths to someone who is already breathing, the rescuer should not hesitate to deliver rescue breaths as recommended below if there is any suspicion that the victim is not breathing.

Can effective rescue breaths be delivered in the water?
This question was directly addressed by a study in which trained lifeguards demonstrated delivery of effective rescue breaths (average tidal volumes by individual lifeguards from 629-750 ml) while unsupported in deep water [8]. In this same experiment, the delivery of seven to nine breaths over a 50-meter victim (manikin) tow increased the duration of the tow from 70 seconds to 84 seconds (on average).

It thus seems clear that effective rescue breaths can be delivered in deep water. Divers would be more cluttered with equipment than the lifeguards in this experiment, but on the positive side, they are also supported by buoyancy devices and wearing fins. The experience of several members of the committee exposed to rescue diver training is consistent with the results of the experiment. The committee thus has little hesitation in endorsing in-water rescue breaths as a plausible technique,
but the likelihood of successful delivery is dependent on prior training (and preferably regular practice) in the technique.

**What is the likelihood of persistent circulation after respiratory arrest?**

It is well recognized that there may be a variable interval between respiratory and cardiac arrest, and that this is context-sensitive [9]. The question is therefore impossible to answer in a definitive way. There is some evidence from individual cases that the interval can be of practical significance. For example, the previously cited resuscitation of three non-breathing divers without defibrillation or intervention with cardiac drugs [5-7] implies persisting circulation following an apneic period measured in minutes.

Similar inference can be drawn from a small but unique observational study by Szupilman and Soares [9] in which drowning victims who received in-water expired air resuscitation were less likely to require full CPR or any other additional resuscitation measures than victims who were retrieved from the water prior to any intervention.

The committee therefore endorses the view that in a dive accident leading to respiratory arrest there is likely to be a variable window of opportunity within which commencement of expired air resuscitation may prevent progression to full cardiac arrest.

**Does the recent advocacy for “compression-only resuscitation” suggest that in-water rescue breaths should not be administered to a non-breathing diver?**

Discussion of “compression only resuscitation” (in which first responders administer only chest compressions and do not attempt rescue breathing) has occurred over many years. Recent publications suggesting its superiority over “conventional” CPR in certain circumstances have created significant interest in the diving community.

Three studies in which subjects suffering out of hospital cardiac arrest were randomized to compression-only resuscitation or conventional CPR by an emergency dispatcher who instructed untrained first responders (by phone) in undertaking one technique or the other were entered into a meta-analysis [10]. This showed a small but significant increase in survival (absolute increase 2.4%, number needed to treat = 41) if compression-only resuscitation was used. These studies excluded cases in which there was intervention by bystanders trained in CPR, and consequently, the meta-analysis has been criticized as simply demonstrating that it is “not possible to teach untrained laypersons chest compressions in combination with ventilation via the telephone in an emergency” [11]. A meta-analysis of non-randomized observational cohort studies showed no advantage for either technique. [10] However, one large cohort study published subsequently did suggest a survival advantage for compression-only resuscitation [12] but this was in the context of both a concerted regional publicity campaign favoring the latter, and a consequent massive swing away from the use of conventional CPR. The interpretation of apparent benefit deserves cautious analysis.

There are plausible advantages for compression-only resuscitation, including:

- eliminating hesitancy by rescuers who are uncomfortable using mouth-to-mouth techniques;
- avoiding deterioration of forward flow during pauses to deliver rescue breaths;
- avoiding the flow inertia that prevails after such pauses;
- avoiding the reduction in venous return that may occur with positive-pressure ventilation; and others. [12].

However, all of these, and indeed the results of the outcome studies in out-of-hospital cardiac arrest (where collapse and cessation of breathing is frequently due to the cardiac arrest itself), are of uncertain relevance to the diving situation, where respiratory arrest is more likely to be due to asphyxia, and where there may be a significant interval before cardiac arrest, as discussed above.

Therefore, in divers, rescue breaths may prevent progression to cardiac arrest. Not surprisingly, commentators representing expert groups have argued that in drowning victims the correction of hypoxia is the first priority [13], and failure to provide ventilation to the victim may jeopardize outcome [14].

On this basis, the committee believes that the current advocacy for compression-only resuscitation in community cardiac arrest may not be relevant to diver rescue situations. The committee therefore recommends rescue breathing as prescribed in Figure 1 (Page 1106). It remains true that the underlying cause of the respiratory arrest is a crucially important factor in determining the likelihood of successful resuscitation.
FIGURE 1 – Rescue breathing protocol

Summary of important recommendations and decision-making in rescue of an unresponsive diver from depth. This chart should be considered along with the relevant comments made in the relevant sections of this paper.

S.J. Mitchell, M.H. Bennett, N. Bird et al.
In the rescue of a non-breathing diver how should the rescuer prioritize delivery of in-water rescue breaths versus accessing surface support where definitive CPR can be started?

The unresponsive non-breathing diver is either in a state of respiratory arrest or cardiorespiratory arrest, and the committee believes there is no reliable means of separating these states in water. Rescue breaths alone are unlikely to benefit a victim in full cardiorespiratory arrest, and effective chest compressions cannot be administered in the water. Therefore, any delay in removing the immersed victim to a stable platform allowing full CPR in order to deliver in-water rescue breaths is, in effect, a gamble on the possibility that they are in respiratory but not cardiac arrest.

As discussed above, the committee believes this gamble is worth taking at least in part because, in the absence of early paramedic-level advanced life support, a successful resuscitation from cardiac arrest is extremely unlikely, regardless of management. Nevertheless, there is a need for guidance on when to shift the priority from attempting rescue breaths to removing the victim from the water. The committee considered two key questions in this regard.

The first is whether there is any situation, other than concern about personal safety or an inability to deliver rescue breaths efficiently, in which a trained rescuer would not attempt in-water rescue breaths at all in favor of removing the victim from the water as quickly as possible.

One plausible circumstance might be when rescuer and victim surface immediately adjacent to suitable surface support such that there would be no delay at all initiating assisted retrieval. A relevant observation from actual incidents that have involved members of the committee is that removal of a fully equipped unresponsive scuba diver from the water is difficult and can take minutes.

Moreover, committee members have participated in rescues where resumption of breathing has occurred immediately on delivery of the first rescue breath. This supports the recommendation for delivery of initial rescue breaths as quickly as possible. However, the “breathe or remove from water decision” is very context-sensitive, so the committee is reluctant to recommend directive “rules” around these situations.

Its view on the matter is best summed up by the statement: “Even when surfacing immediately adjacent to surface support, a trained rescuer should consider positioning the victim on the back, establishing positive buoyancy, opening the airway, and delivering two rescue breaths before initiating attempts to remove the victim from the water. However, these steps can be set aside if circumstances suggest that removal of the victim from the water can be expedited in less than one minute.”

Second, what should be done if surface support is not immediately available on surfacing? The committee believes that the advice in the PADI Rescue Diver Manual [2] is logical and consistent with the recommendations of the European Resuscitation Council [13]. Thus, on surfacing, initial rescue breaths are given as above. Then, if surface support is less than approximately five minutes away, intermittent rescue breaths should be continued while towing the victim (or waiting) until surface support is reached/arrives and the diver is removed from the water. CPR can then be initiated if it is determined that there is a concomitant cardiac arrest. If at any time during the tow the rescuer feels that delivery of rescue breaths is becoming too difficult or causing excessive delay, he or she should reduce the frequency of rescue breaths or omit them entirely.

If surface support is more than five minutes away the rescuer should remain where he/she is and provide rescue breaths for approximately one minute and then check for response. If there is no response, the rescuer should assume that cardiac arrest has occurred and tow the victim to surface support as quickly as possible without rescue breaths, remove the victim from the water, and initiate a CPR protocol supplemented, if possible, by high fractions of inspired oxygen.

SUMMARY OF RECOMMENDATIONS

We have generated a diver rescue algorithm which summarizes the important recommendations made in this paper (Figure 1). Readers are reminded that in the absence of relevant definitive data, many of these recommendations are based on the consensus opinion of experts.

The committee also re-emphasizes several other key contextualizing comments: First, application of this pathway is contingent on appropriate diver rescue training. Second, it is entirely appropriate for rescuers to avoid causing harm to themselves in applying these rescue strategies. Third, recent changes in protocols for community cardiac arrest are of doubtful relevance to diver rescue interventions. Fourth, it is acknowledged that there may be circumstances in diver emergencies that are not adequately accounted for in these recommendations. It is difficult to provide a universally applicable guideline without the risk of it being hopelessly
These recommendations should not be seen as immutable rules for all situations.

Finally, it is reiterated that rescue and resuscitation of an unresponsive diver from depth is frequently unsuccessful. Notwithstanding this attempt to optimize current advice, unresponsive divers rescued from depth have a poor prognosis.

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REFERENCES


CASE REPORTS
Therapeutic effect of hyperbaric oxygen on inclusion body myositis

Max Pell D.O. 1, Poovendran Satthasivam M.D. 2, Peter L. Stephens M.D. 3,4, George Mychaskiw II D.O. 4

1 Philadelphia College of Osteopathic Medicine, Philadelphia, Pennsylvania USA
2 Drexel University College of Medicine, Philadelphia, Pennsylvania USA
3 Hyperbaric Therapy of the Low Country, LLC, Hilton Head, South Carolina USA
4 University of Central Florida, College of Medicine, Orlando, Florida USA

CORRESPONDING AUTHOR: Dr. George Mychaskiw – gmychaskiw@yahoo.com

ABSTRACT

An inflammatory myopathy, inclusion body myositis (IBM) presents with progressive muscle weakness against a background of elevated creatine kinase and diffuse endomysial damage. Typically occurring in patients greater than 50 years of age, it is commonly misdiagnosed as polymyositis or other rheumatological disease and is often ineffectively treated with steroids [1].

The approach to IBM is frequently a clinical challenge due to its unique and often aberrant response to common treatment modalities. Here we report an apparent improvement in the clinical course of and associated laboratory findings in a patient with co-existing IBM following the use of hyperbaric oxygen therapy as an adjunct for managing ischemic colitis.

CASE REPORT

A 70-year-old female patient with a history significant for inclusion body myositis (IBM) was admitted with complaints of abdominal pain and bloody diarrhea. The pain was sudden in onset and crampy in nature, localized to the left upper quadrant and associated with bloody diarrhea. Her past medical history was significant for IBM, hypertension, L1 compression fracture, hypothyroidism and asthma. Medications were omeprazole, aspirin, atenolol, lisinopril, montelukast, salmeterol/fluticasone inhaler, estropipate, Vitamin D and calcium.

Review of systems revealed the patient was unable to flex her fingers for the past two years, was experiencing increased weakness in the left hand over the past six months and had difficulty in swallowing secondary to the IBM. At the time of presentation, the patient was in her 21st year of IBM, confirmed by laboratory studies.

In the month preceding this admission, her creatine kinase (CK) was measured at 322 u/l (normal 96-140) and aldolase at 13.6 u/l (normal 1.0-7.5). The patient’s creatinine kinase increased steadily after an initial level of 200u/l at the time of diagnosis, 20 years previously.

On this admission, lab results showed hemoglobin of 10 g/dL, hematocrit of 29, platelet count of 177,000, normal BUN, CK 317 u/l and aldolase 11.3 u/l. A computerized tomography scan of the abdomen and pelvis revealed thickening of the colonic wall and pericolonic inflammatory changes at the splenic flexure watershed area. The patient was diagnosed with ischemic colitis and treated conservatively with antibiotics and bowel rest. At the time of discharge six days later, she required PO meperidine for her abdominal pain, which she rated as a 5-6 (on a scale of 1-10) without medication and 3-4 with medication.

Hyperbaric oxygen (HBO2) therapy as an adjunct treatment for the ischemic colitis was instituted on the day following discharge. The patient received 12 sessions of HBO2 therapy with 100% O2 at 2 atmospheres absolute (atm abs) pressure for 1.5 hours daily. Her abdominal pain subsided after three sessions and disappeared completely after the fourth session.

Coincidentally, following HBO2 therapy the patient demonstrated substantial improvement in her clinical symptoms of IBM. She was noted to have improvement in her ability to swallow and decreased anxiety of choking with deglutition. Improvements were noted on physical exam, including an improved ability to flex her fingers, which had not been observed in the preceding six months.

Following HBO2 therapy, the patient’s CK decreased to 92 u/l, and the serum aldolase level also decreased to 6.5 u/l. Subsequently, the patient has continued regular HBO2 sessions and reports consistent improvement in her IBM symptoms.
DISCUSSION
Based on a study population in Minnesota and the 2000 U.S. Census, it has been estimated that there are 7.9 cases per million of IBM in the United States [2,3]. It is a complicated diagnosis due to the non-specific nature of the symptoms, their variable presentation and the obscurity of the disease [1]. Frequently, patients undergo several months or years of misdiagnosis and incorrect therapy before a definitive diagnosis of IBM is made. Thus, treatment-resistant “polymyositis” in patients exceeding the age of 50 is often IBM.

The condition typically affects proximal and distal musculature asymmetrically, and it is often mistaken for a neurological disorder due to loss of distal reflexes, quadriceps and biceps weakness, and dysphagia [1,3]. It is often found concomitantly with lupus, mixed connective tissue disease, scleroderma, thyroid dysfunction, sarcoidosis, diabetes mellitus, vasculitis and peripheral neuropathy. Histology of muscle biopsy demonstrates mononuclear cell invasion of necrotic endomysial fibers, intracellular amyloidosis found with Congo Red stain, eosinophilic intracytoplasmic inclusions (increased with ubiquitin staining), rimmed vacuoles, increased Major Histocompatibility Complex Class 1 expression and apparent loss of cyclooxygenase staining [1,3,4].

The exact etiology of sporadic IBM remains elusive to investigators. There are two proposed etiologies pertaining to its pathogenesis: autoimmune processes and degenerative changes. Indeed, genetic susceptibility studies appear to demonstrate a link between IBM and HLA-DR3 (human immune response, D-related antigen), a known marker of autoimmunity [3,4]. Evidence supporting the autoimmune hypothesis includes identification of clonally expanded T-cells invading myofibers with a 2:1 CD (cluster designation) 8+ to macrophage ratio [1,2]. Humoral adaptive immunity has also been suggested to play a role [3,4]. However, phosphorylated tau protein, beta-amyloid, presenilin and parkin deposits suggest that a degenerative process is at play, which has been theorized to be due to improper disposal of misfolded proteins [3,5,6,7]. The debate remains active, with literature implicating hereditary factors such as mitochondrial DNA or possibly even viral pathogenesis [1,3,5,8,9].

Typical treatment modalities are of limited benefit and include oral steroids and/or IVlg (intravenous immunoglobulin G). Their effectiveness is restricted, although they have demonstrated improvement in dysphagia [3,10,11]. Etanercept, an anti-tumor necrosis factor-alpha agent, and high-dose beta interferon 1-a have both been demonstrated to improve handgrip as a demonstration of increased muscle strength [3,13,14]. The use of lithium has also been explored due to its supposed ability to improve the clearance of misfolded proteins via induction of autophagy [3,12,15].

Hyperbaric oxygen therapy is the administration of 100 percent oxygen under increased pressure conditions. To achieve the increased pressure the patient must be compressed in a hyperbaric chamber. Historically, recompression therapy has been the primary management for decompression sickness (the bends) and arterial gas embolism. Although, hyperbaric therapy has been used since 1662 its clinical importance did not become fully appreciated until Boerma’s seminal paper, “Life without Blood” was published in 1959.

Other well-established uses of HBO2 therapy include treatment of carbon monoxide poisoning, gas gangrene, radiation damage to soft tissue, threatened flaps and grafts and probably its most important and frequent application to facilitate the healing of select problem wounds [16].

Among the investigational uses of HBO2-T is treatment of inflammatory bowel disease (IBD). Given the nature of IBD, it is reasonable to suspect that HBO2-T would be an effective treatment, considering its anti-inflammatory effect. In IBD, activated macrophages elaborate proinflammatory cytokines, including TNF-alpha, IL-6 and IL-8 [17]. Several studies have reported improvement in IBD following HBO2-T, and a recent meta analysis by Rossignol demonstrates that, of the 13 studies and case reports of HBO2-T in Crohn’s disease and six studies and case reports of its use in ulcerative colitis (UC) in the literature, clinical improvement following HBO2-T was seen in 78% of Crohn’s patients and 100% of patients with UC [17].

When proinflammatory cytokines were measured, numerous decreases were seen, including IL-1, IL-6 and TNF-alpha, as well as decreases in markers of immune dysregulation, including neopterin, myeloperoxidase activity nitric oxide, nitric oxide synthase and prostaglandin E2 [17]. Although well-controlled large prospective studies of HBO2-T in IBD remain to be done, this appears to be an emerging indication that will likely be approved in the future.

However, research or case reports demonstrating the efficacy of HBO2-T in autoinflammation and autoimmunity are not readily available. Multiple theorized mechanisms exist pertaining to the anti-inflammatory/immune-modulating nature of HBO2 therapy. Breathing greater than 1 atm abs of oxygen has been shown
to promote the production of reactive oxygen species (ROS) which, together with reactive nitrogen species (RNS), serve as modulators of pathways involving various cytokines, growth factor and hormones [16]. Production of reactive oxygen species coordinates various cytokines, growth factor and hormones [16]. Neutrophil β2 integrin function is impaired following exposure to hyperbaric oxygen while maintaining both neutrophil viability and function, including typical immune responses such as phagocytosis, oxidative burst and degranulation. This reduces inflammation while avoiding immunocompromise [16,18,19]. Additionally, hyperbaric oxygen therapy has been shown to impair pro-inflammatory cytokine elaboration by monocyte-macrophages in animals and human beings possibly leading to reduced levels of circulating pro-inflammatory cytokines [16,20-23]. The exact molecular mechanism is not known, but it has also been postulated that hyperbaric oxygen may have a role in the enhancement of the heme oxygenase-1 and heat shock proteins [16]. It has been demonstrated in animal models that hyperbaric oxygen has an anti-inflammatory effect similar to aspirin treatment in rheumatoid arthritis [24]. Further study is warranted to examine the effect of hyperbaric oxygen on these specific pathophysologies.

**CONCLUSION**

We report a case of long-standing sporadic IBM that demonstrated improvement in symptoms following HBO2 therapy for ischemic colitis. HBO2 appears to have potent anti-inflammatory effects and may be a promising modality for management of rheumatologic and inflammatory conditions, especially IBD and the inflammatory myopathies. Further study is warranted to elucidate its mechanisms of action and specific applications.

**REFERENCES**


Conflict of interest
Dr. Peter L. Stephens is a principal of Hyperbaric Medicine of the Low Country, Hilton Head, S.C.; Dr. George Mychaskiw is the Chief Medical Officer for Oxygen Theraputry, LLC.
Anal canal mucinous adenocarcinoma with invasion of gluteus and perineum treated with surgery and hyperbaric oxygen therapy

C. Jacomini, AEMR Junqueira, ALNR Almeida, R.S. Parra, J.J.R. Rocha, O. Fères

Division of Coloproctology, Department of Surgery and Anatomy. School of Medicine of Ribeirão Preto, University of São Paulo, Barzil

CORRESPONDING AUTHOR: Omar Fères Ph.D. – omar.feres@hspaulo.com.br

ABSTRACT

The case of a 66-year-old female patient with late diagnosis of giant anal canal mucinous adenocarcinoma invading the gluteal and vulvar regions is reported. Because of the patient’s severe clinical status and disease morbidity, surgical resection of the lesion was accomplished, with no adjuvant chemo- or radiotherapy. In the postoperative period, the patient received hyperbaric oxygen therapy, which facilitated and even accelerated local healing. Total closure of the raw flesh area was achieved, with no recurrence signals of cancer being detected after one-year follow-up. We are convinced that, in this difficult case, hyperbaric oxygen therapy played a crucial role in patient recovery and wound healing, allowing for early closure with good progression.

INTRODUCTION

Anal canal mucinous adenocarcinoma is a rare condition representing between 3% and 9% of anal canal carcinomas [1,2,3]. The tardy onset of symptoms makes early diagnosis difficult, which culminates in severe local invasion [4].

Surgery as the only therapeutic measure represents the best chance of cure for this condition, since the real efficacy of radio- and chemotherapy for the treatment of this type of lesion remains unknown [5]. Patient survival varies and depends on tumor staging [6].

Hyperbaric oxygen therapy is a medical treatment that contributes to enhanced healing process. It facilitates closure of surgical wounds and may promote early patient return to work.

CASE REPORT

A female patient aged 66 years complained of expansive and painful lesion on the left gluteus, noticed two years previously. The patient denied rectal tenesmus, weight loss or hematochezia. She had not sought previous medical assistance because of embarrassment at being subjected to rectal examination.

Rectal evaluation detected an ulcerated lesion in the left gluteus region measuring approximately 20 cm, extending as far as the anal canal. A gynecological examination demonstrated that the vulvar region had also been affected (Figures 1 and 2, Page 1116). Palpation showed hardened lateral rectal wall. There were no vegetative lesions in the mucosa.

Abdomen tomography revealed extensive perineal lesion indicative of neoplasia involving the anal region and the left gluteus, with inguinal lymph node enlargement but no secondary hepatic lesions (Figure 3, Page 1116).

Exploratory laparotomy was accomplished, which detected expansive lesion invading the left gluteus and perineal region, with bulging of intra-abdominal peritoneum and enlarged inguinal lymph nodes. Terminal sigmoidostomy and tumor excision from the anal canal were performed via the perineum, as well as left inguinal lymphadenectomy.

Histopathological examination evidenced ulcerated mucinous adenocarcinoma measuring 22.0 x 16.5 cm and infiltrating the skin, subcutaneous region, and musculature, with 17.5 cm length in the longer axis. The lymph nodes were actually mucinous adenocarcinoma metastases. The resected area remained open, and hyperbaric oxygen (HBO₂) therapy was initiated (Figure 4, Page 1116).

The patient was submitted to 10 120-minute sessions in a monoplace chamber on a daily basis, using 2.4 atmospheres absolute. The surgical wound progressed without signs of inflammation; granulation tissue was detected, which allowed for primary closure of the
Figure 1: Giant mucinous adenocarcinoma with invasion of the gluteus

Figure 2: Mucinous adenocarcinoma seen from a lateral perspective, infiltrating the gluteus.

Figure 3: Abdominal tomography evidencing large pelvic-perineal mass as shown by the arrow.

Figure 4: Raw flesh perineal area involving gluteus, anus and vagina after tumorectomy.

Figure 5: Perineum with granulation and reduced raw flesh area after 10 hyperbaric oxygen therapy sessions.

Figure 6: Wound after hyperbaric oxygen therapy and suture.
Lesion after detachment of the adjacent subcutaneous lesion (Figures 5 and 6, facing page).

The patient progressed satisfactorily, with surgical wound healing and closure. Chemotherapy was initiated for treatment of secondary lung lesions. No signs of local tumor recurrence were detected upon oncological follow-up.

**DISCUSSION**

Anal canal cancer is a rare condition corresponding to 3% of all the neoplasias affecting the large bowel [4,7]. The most common histological type in this region is the squamous cell carcinoma, responsible for 80% of the cases, followed by adenocarcinoma, which accounts for 17% of the cases. Other less common histological types are Kaposi’s sarcoma, cloacogenic tumor and melanoma [8,9,10].

Anal canal adenocarcinomas are classified into three groups: rectal type; anal gland or mucinous; and those detected in chronic anorectal fistulas [11]. Mucinous adenocarcinoma consists of anal glands with scarce mucin production, which slowly invade the anorectal wall without an intraluminal component [12]. However, prognosis is not favorable because it is generally diagnosed tardily and at advanced stages, with detection of local or distant metastases [5].

The main symptoms are bleeding upon defecation, pain, palpable mass, itching and weight loss [13]. Diagnosis is based on patient history, symptomatology and rectal examination and confirmed by lesion biopsy.

Computerized tomography, endorectal ultrasound scan and MRI are imaging methods that furnish information about the level of lesion infiltration and locoregional invasion, thus aiding physicians in planning therapeutics [6]. Metastases manifest as inguinal or retrorectal lymph nodes [1]. Colonoscopy is accomplished in order to discard synchronous lesions [14]. Treatment involves surgery and consists of local resections or rectal abdominoperineal amputation, accompanied or not by pre- or postoperative radio- and chemotherapy [6].

Unfortunately, all of these therapeutic strategies to cure cancer in the anorectal region generate an adverse environment for healing – e.g., edema and ischemia. Additionally, the contaminated and hypoxic tissues easily become infected, generating a vicious circle of surgical site infection and refractory wound healing [15,16]. The patient is often elderly, has diabetes as well as other factors as a “compromised host.”

Hyperbaric oxygen therapy is a therapeutic modality consisting in application of 100% pure oxygen at high pressure (higher than atmospheric pressure) [15]. Various studies have proved its efficacy in treating wounds of difficult management. Hyperbaric oxygen improves healing through enhanced fibroblast proliferation and collagen synthesis; increases the immune response via stimulation of the phagocytic ability of leukocytes; and reduces the inflammatory process and tissue edema [16-18], thereby shortening hospitalization periods and accelerating patient recovery.

The tardy diagnosis in the present case culminated in broader surgery. We decided to leave the raw flesh area because of contamination of the perineal region. We are convinced that, in this difficult case, hyperbaric oxygen therapy played a crucial role in patient recovery and wound healing, allowing for early closure with good progression.

A prospective trial on prophylactic HBO2 to speed up wound healing and reduce postoperative infections and complications in this type of surgery is recommended.
HYPERBARIC OXYGEN THERAPY INDICATIONS

PART 4
HBO₂ AND DELAYED RADIATION INJURY

PART 1 – CONTINUED FROM UHM 39-3
HBO₂ AND INFECTIOUS DISEASES: ABSTRACTS
Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update

John J. Feldmeier D.O., FACRO, FUHM

Professor and Chairman, Radiation Oncology, University of Toledo Medical Center, Toledo, Ohio, USA

EMAIL: jfeldmeier@aol.com

ABSTRACT / RATIONALE

Informal surveys at CME meetings have shown that approximately one-third of patients in the United States receive hyperbaric oxygen (HBO₂) for delayed radiation injury. More than 600,000 patients receive radiation for malignancy in our country annually, and about one-half will be long-term survivors. Serious radiation complications occur in 5-10% of survivors. A large population of patients is therefore at risk for radiation injury. HBO₂ has been applied to treat patients with radiation injury since the mid-1970s. Published results are consistently positive, but the level of evidence for individual publications is usually not high level, consisting mostly of case series and case reports. Only a rare randomized controlled trial has been accomplished.

Radiation injury is one of the UHMS “approved” indications, and third-party payors will usually reimburse for this application. This updated review summarizes the publications available reporting results in treating radiation-injured patients. Mechanisms of HBO₂ in radiation injury are discussed briefly. Outcome is reported on a mostly anatomic basis though due to the nature of the injury a positive outcome at one anatomic site is supportive of HBO₂ at other sites. The potential benefit of prophylactic HBO₂ before frank damage is also discussed in high-risk patients. The concerns of HBO₂ enhancing growth of or precipitating recurrence of malignancy is discussed and largely refuted.

INTRODUCTION

Hyperbaric oxygen (HBO₂) has had one of its most studied and most frequent applications in the treatment of delayed radiation injuries. Informal surveys accomplished by the author at continuing education meetings indicate that roughly one-third of patients treated in the United States receive hyperbaric oxygen for radiation injuries. This application of hyperbaric oxygen to the treatment and prevention of delayed radiation injury will be the topic of this paper. The management of delayed radiation injury, especially when bone necrosis is present, requires multidisciplinary management. The nature of delayed radiation injury, the mechanisms whereby hyperbaric oxygen is effective, clinical results, the effects of hyperbaric oxygen on cancer growth and future areas for research will be discussed.

THE NATURE OF RADIATION INJURY

Radiation injuries should be further subclassified as acute, subacute or delayed complications [1]. Acute injuries are due to direct and essentially immediate cellular toxicity caused by free radical-mediated damage to DNA. Many cells suffer a mitotic or reproductive death, i.e., enough damage has been rendered to the DNA that successful subsequent mitosis is prevented. Acute injuries to normal tissues are usually self-limited within a few weeks and are treated symptomatically. However, they can be very debilitating during their duration. Subacute injuries are typically identifiable in only a few organ systems. Subacute injuries have been shown to occur in the lung with a clinical syndrome mimicking bronchi-tis (radiation pneumonitis). They have also been shown to occur in the spinal cord as the result of temporary demyelinization which causes the so-called Lhermitte’s syndrome, where patients experience electriclike shocks down their legs with spinal extension. These, too, are generally self-limited but occasionally evolve to become delayed injuries.

Some subacute injuries may persist for several months. No specific treatment is especially effective, although steroids are commonly employed. Delayed radiation complications are typically seen after a latent period of six months or more and may occasionally develop many years after the radiation exposure. Sometimes, acute
injuries are so severe that they never resolve and evolve to become chronic injuries indistinguishable from other delayed radiation injuries [2]. These are termed “consequential effects” and are not characterized by a symptom-free latent period. Often, delayed injuries are precipitated by an additional tissue insult such as surgery within the radiation field.

A role for hyperbaric oxygen in acute and subacute radiation injuries has not been well-studied or established, although there is some interest in pursuing this application [3].

THE ETIOLOGY OF DELAYED RADIATION INJURY

The exact causes and biochemical processes leading to delayed radiation injury are complex and only partially understood at this time. In virtually all organ systems that demonstrate radiation damage, we observe vascular changes characterized by obliteratorive endarteritis. Because hyperbaric oxygen has been shown to enhance angiogenesis in hypoxic tissues, the hyperbaric oxygen community has postulated that the enhancement of angiogenesis was the primary, if not the sole, therapeutic effect of hyperbaric oxygen in radiated tissues. Some radiation biologists are now convinced that in some organ systems vascular changes play a relatively minor role in the evolution of delayed radiation injury [4].

A more complex model of radiation damage continues to evolve in the radiation oncology community. In the past, radiation oncologists had made a distinction between the causes of acute and delayed injuries. The belief was that they were not directly related. Indeed, it is not uncommon to find a patient with serious acute reactions who will not suffer significant delayed complications or someone with severe delayed complications who had experienced no worse than minor acute reactions to the radiation. Radiation researchers now appreciate that the process of radiation injury begins at the time of radiation treatment and involves the elaboration and release of many bioactive substances including, very prominently, fibrogenetic cytokines [5].

A major mechanism whereby therapeutic radiation inflicts damage on normal tissues has been termed the fibro-atrophic effect [4]. This model emphasizes the consequences of the observed depletion of parenchymal stem cells and de-emphasizes the impact of vascular damage. It also highlights the exuberant fibrosis usually found in severely damaged irradiated tissues [4-8]. In this model vascular damage and stenosis continue to be recognized as a consistent finding in tissues exhibiting radiation damage including frank necrosis; however, endarteritis as a causative factor for delayed radiation injuries is de-emphasized.

A recent review of the delayed fibro-atrophic effects of radiation has been accomplished by Fleckenstein et al. [5]. This paper identifies TGF-beta as the most frequently studied cytokine associated with radiation injury. Additional cytokines associated with radiation injury include IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-alpha and GMCSF.

Many studies of cytokines and radiation injuries have been accomplished in animal models of radiation-induced pneumonitis [9]. At the present time, we are not able to make practical clinical application of these observed associations. No single marker is likely to provide us with a reliable estimate of future radiation damage [10]. Similarly, no practical strategies have as yet been developed to prevent or reduce the production of these cytokines or reduce their impact in a prophylactic fashion. We know that there is a very wide range of tolerance to radiation by individual patients and that some patients are much more sensitive to radiation injury. If reliable predictors of delayed radiation injury were available during or before treatment, adjustments to the radiation dosing scheme could be made for the radiosensitive patient. Some patients might be advised to seek alternative therapies instead of radiation. Moreover, prophylactic interventions such as hyperbaric oxygen or other yet-to-be-developed pharmacologic interventions could possibly be applied during the latent period but before the manifestation of the chronic injury. The hope and expectation would be that, by identifying a group at risk and intervening in this group before manifestation of the injury, delayed radiation injury could be prevented or at least reduced in its severity. Obviously, this postulate will have to be subjected to clinical trials, and the most important consideration is to do nothing that jeopardizes tumor control.

THE EFFECTS OF HYPERBARIC OXYGEN ON IRRADIATED TISSUES

Because a consistent cause and manifestation of radiation injury is vascular obliteration and stromal fibrosis, the known impact of hyperbaric oxygen in stimulating angiogenesis is an obvious and important mechanism whereby hyperbaric oxygen is effective in radiation injury. HBO2 induces neovascularization in hypoxic tissues. Marx [11] has demonstrated the enhanced
vascularity and cellularity in heavily irradiated tissues after hyperbaric oxygen therapy by comparing histologic specimens from patients pre- and post-hyperbaric oxygen. Marx [6] has also demonstrated the serial improvement in transcutaneous oxygen measurements of patients receiving hyperbaric oxygen as an indirect measure of increased vascular density. Marx et al. [12] in an animal model have shown increased vascularity in rabbit mandibles after exposure to hyperbaric oxygen.

Feldmeier and his colleagues [7,8] in a murine model of radiation damage to the small bowel have shown that hyperbaric oxygen given seven weeks after radiation can reduce the degree and mechanical effects of fibrosis by being applied prior to the manifestation of radiation injury. Assays of the murine bowel for collagen content included a mechanical stretch assay of compliance as well as quantitative histologic morphometric assays of fibrosis in the tunica media of the animal bowel utilizing Mason’s trichrome staining.

This author has personally observed significant reduction in the woody fibrosis of soft tissues seen frequently in head and neck cancer patients after radiation with a course of hyperbaric oxygen intended to treat mandibular necrosis. To my knowledge, this effect has not yet been systematically studied.

The hyperbaric study group headed up by Dr. Thom [13,14] at the University of Pennsylvania has published studies demonstrating the mobilization of stem cells mediated through nitric oxide with HBO2. These papers include a group of head and neck cancer patients who had received radiation treatments. A putative effect on increasing stem cells at the site of radiation injury is confirmed to some extent by Marx’s [6] demonstration of increased cellular density in histologic preparations from patients who have received hyperbaric oxygen for mandibular osteoradionecrosis.

The impact of hyperbaric oxygen in terms of its beneficial effects is likely to involve all three of the above mechanisms in irradiated tissues:

1) Hyperbaric oxygen stimulates angiogenesis and secondarily improves tissue oxygenation;
2) Hyperbaric oxygen reduces fibrosis; and
3) Hyperbaric oxygen mobilizes and induces an increase of stem cells within irradiated tissues.

Hyperbaric oxygen has been applied as a therapy for delayed radiation injury for more than 30 years. Hyperbaric oxygen also has a frequent application in the prevention of mandibular osteoradionecrosis when dental extractions are required from heavily irradiated mandibles. The following sections will address the application of hyperbaric oxygen to radiation complications on an anatomic basis beginning with mandibular osteoradionecrosis.

**HYPERBARIC OXYGEN AS TREATMENT FOR MANDIBULAR RADIATION NECROSIS (ORN)**

The most widely applied and most extensively documented indication for hyperbaric oxygen in chronic radiation injury is its application in the treatment and prevention of radiation necrosis of the mandible. Multiple publications describing the use of hyperbaric oxygen in the treatment of mandibular necrosis have appeared in the medical literature since the 1970s.

The likelihood of mandibular necrosis as a result of therapeutic radiation varies widely among several reports. Bedwinek [15] has reported a 0% incidence below doses of 6,000 cGy increasing to 1.8% at doses from 6,000 to 7,000 cGy and to 9% at doses greater than 7,000 cGy. In his comprehensive review of radiation tolerance, Emami [16] estimates a 5% incidence when a small portion of the mandible (less than one-third) is irradiated to 65 Gy or higher and a 5% incidence at 60 Gy or higher when a larger volume of the mandible is irradiated. The recent application of IMRT (intensity-modulated radiation therapy) has been reported to reduce mandibular radiation necrosis compared to older radiation techniques [17]. It has been reported that 85% or more of cases resulting in exposed mandibular bone will resolve spontaneously with conservative management [18]. Unfortunately, the remaining cases generally become chronic and may become progressive, often further complicated by associated soft tissue necrosis.

Much of the early work in this area considered radiation-induced mandibular necrosis to be a subset of mandibular osteomyelitis [11]. Also, hyperbaric oxygen was delivered along with antibiotics frequently as treatment for mandibular necrosis without appropriate surgical management after failure of more conservative therapy. Although many cases would show temporary improvement, almost all cases of moderate to severe ORN would recur if hyperbaric oxygen was administered without appropriate surgical intervention [19].

Robert Marx D.D.S. [19,20] elucidated many basic principles in the etiology and management of mandibular ORN which have led to a rational approach to its management. He has provided several key principles in the understanding of the pathophysiology of mandibular necrosis. He has demonstrated that infection is not the primary etiology of mandibular necrosis by obtaining
deep cultures of affected bone and showing the absence of bacteria. We now understand that osteoradionecrosis is the result of an avascular, aseptic necrosis. Marx [6] has also shown that for hyperbaric oxygen to be consistently successful, it must be combined with surgery in an optimal fashion. Marx has developed a staging system for classifying mandibular necrosis. This staging system is applied to determine the severity of mandibular necrosis. In addition, it permits a plan of therapeutic intervention, which is a logical outgrowth of the stage/severity of necrosis.

Stage I ORN
This stage includes those patients with exposed bone who have none of the serious manifestations found in Stage III as described below. Generally, before hyperbaric oxygen, these patients have had chronically exposed bone or they have rapidly progressive ORN. These patients begin treatment with 30 HBO$_2$ sessions followed by minor bony debridement. If these patients’ response is adequate, an additional 10 daily treatments are given, and the patients are followed to complete clinical resolution.

Stage II ORN
If patients are not progressing appropriately at 30 daily treatments or if a more major debridement is needed, they are advanced to Stage II and receive a more radical surgical debridement in the operating room followed by 10 postoperative treatments. Surgery for Stage II patients must maintain mandibular continuity. If mandibular segmental resection is required, patients are advanced to Stage III.

Stage III ORN
In addition to those failing treatment in Stage I or II, patients who present initially with grave prognostic signs such as pathologic fracture, orocutaneous fistulae or evidence of lytic involvement extending to the inferior mandibular border are treated as Stage III from the outset. When a patient is assessed to be at Stage III, mandibular segmental resection is a planned part of the treatment. In Stage III, patients are entered into a reconstructive protocol after mandibular resection. Marx has established the principle that all necrotic bone must be surgically eradicated here just as in Stages I and II. Stage III patients receive 30 daily hyperbaric treatments prior to mandibular resection followed by 10 post-resection treatments.

Typically after a period of several weeks, the patients complete a reconstruction, which may involve various surgical techniques including free flaps or myocutaneous flaps. In the original reports, the reconstruction made use of freeze-dried cadaveric bone trays from a split rib or iliac crest combined with autologous corticocancellous bone grafting. In his original work at Wilford Hall USAF Medical Center, Marx had reconstruction patients complete a full additional course of hyperbaric treatments in support of the reconstruction. Marx has subsequently found that the vascular improvements accomplished during the initial 40 hyperbaric exposures are maintained over time, and patients can undergo reconstruction without a second full course of HBO$_2$. Patients do receive 10 hyperbaric treatments after the reconstructive surgery to support initial tissue metabolic demands.

Marx [6] has reported his results in 268 patients treated according to the above protocol. In his hands with this technique, successful resolution has been achieved in 100% of patients. Unfortunately the majority of patients (68%) required treatment as Stage III patients necessitating mandibular resection and reconstruction. Dr. Marx requires that patients achieve reasonable cosmetic restoration as well as the success in supporting a denture before he counts them a success. These two issues, cosmesis and restoration of dentition for mastication, are necessary components in improving quality of life in this group of patients.

Feldmeier and Hampson [21] published a review of hyperbaric oxygen in the treatment of radiation injury in 2002. A total of 14 papers reporting the results in the treatment of mandibular necrosis were included. All but one of these was a case series. A single study by Tobey et al. [22] was a positive randomized controlled trial. It was a small study, with only 12 patients enrolled; however, it was double-blinded and reported to be a positive trial by the authors. Details of randomization and outcome determinants were not clearly stated. Patients received either 100% oxygen at 1.2 atmospheres absolute (atm abs) or 2.0 atm abs. The paper states that those treated at 2.0 atm abs “experienced significant improvement” compared to the control group.

Of the reports included in this review paper of 2002, only one report, the publication by Maier et al. [23], failed to report a positive outcome in applying hyperbaric oxygen to the treatment of mandibular ORN. Maier and colleagues added hyperbaric oxygen to their management only after the definitive surgery was done. They failed to heed Marx’s guidance that the optimal management of mandibular ORN requires that the majority of HBO$_2$ be given prior to surgical debridement, resection or reconstruction in order to improve the quality of tissues prior to surgical wounding.
Since the review by Feldmeier and Hampson [21], several papers have been added to the literature. A multi-institutional randomized controlled trial by Annane et al. [24] reported negative results in their study applying hyperbaric oxygen to Marx Stage I ORN. These results have created a stir in the hyperbaric oxygen community and prompted criticism of its methods from several sources. Patients were randomized to receive either 90 minutes of 100% O₂ at 2.4 atm abs or a breathing gas mix equivalent to air at sea level for 30 daily treatments. The study design has received criticism from several circles. The most serious flaw in the study design was its failure to adhere to Marx’s guidance and to integrate hyperbaric oxygen into a multidisciplinary approach to ORN treatment. The study’s apparent intent was to investigate whether the application of hyperbaric oxygen could obviate the need for surgery in early mandibular ORN. It is not surprising that the study had negative results, because more than two decades earlier Marx had shown an absolute necessity of surgically eradicating all necrotic bone. The need to debride all necrotic bone to achieve resolution was also confirmed by Feldmeier et al. in their review of chest wall necrosis, including some cases with ORN of the ribs and sternum [25]. Results are very poor overall in the Annane trial compared to other modern trials for what constitutes a Marx Stage I ORN, with only 19% in the hyperbaric group and 32% in the control group achieving resolution [24].

Additional criticisms of this study by Annane [24] have been made. Moon et al. [26] have shown that nearly two-thirds of the hyperbaric group received fewer than 22 hyperbaric treatments. Laden [27] points out that the patients assigned to the control group had a risk for developing decompression sickness with the gas mix they breathed (9% oxygen and 91% nitrogen) at 2.4 atm abs. This gas mix was designed to provide an inspired oxygen partial pressure equivalent to air at sea level.

In another recent report, Gal and associates [28] have published their results in treating a series of 30 patients with Marx Stage III mandibular ORN with debridement and reconstruction employing microvascular anastomosis. Twenty-one of these patients had previously been treated with hyperbaric oxygen without resolution. The specific number and profile of hyperbaric treatments was not described for any of these patients. At least some patients had some debridement prior to coming to Gal.

Once in Dr. Gal’s hands, all patients had appropriate debridement and reconstruction with free flaps. Those patients who had not seen hyperbaric oxygen previously had a complication rate of 22%, while the group who had received at least some hyperbaric oxygen had a much higher rate of complications – 52%. Of course, this was not a randomized trial, and even the authors suggest that the hyperbaric group may have represented a group with more refractory mandibular ORN. Obviously, those principles previously established by Marx, i.e., an emphasis on presurgical hyperbaric oxygen, debridement of all necrotic bone followed by reconstruction with postoperative hyperbaric oxygen were not followed. The authors of this paper also discuss that Marx Stage III ORN patients represent a heterogeneous group with a broad range of injuries, severity of injuries and a subsequent broad range of outcomes.

Teng and Futran [29] have recently published their opinion that hyperbaric oxygen has no role in treating ORN. Their article presents no new clinical data and is a review article. The authors base their conclusions on the Annane study and the advancement of the fibro-atrophic model of radiation injury as now dominant in the opinion of many experts of radiation pathology. Mendenhall [30], a radiation oncologist from the University of Florida, in an editorial accompanying the Annane paper in the Journal of Clinical Oncology, points out that the Annane paper was underpowered and therefore subject to question. He goes on, however, to state his belief that hyperbaric oxygen is not indicated for mandibular ORN although he remarks that it is hard to understand why the HBO₂ group in the Annane study did worse than the control group.

Hampson et al. [31] have recently reported a series of 411 patients treated for radiation injury involving multiple anatomic sites at the Virginia Mason Hyperbaric Center since 2002. The outcome of many of these patients has been previously reported in earlier publications. Among these patients, 62 patients were treated for mandibular necrosis. Forty-three were available for analysis and, among these, 73% showed resolution, 21% had 50-90% improvement, and the other 5% were unchanged.

Suffice it to say that recent papers addressing the efficacy of hyperbaric oxygen in the treatment of ORN have expressed divergent opinions in regard to the efficacy of HBO₂. Only one of these recent publications was a randomized controlled trial, and it is subject to the criticisms in design discussed above. If we look at the total body of literature reporting the impact of hyperbaric oxygen on mandibular ORN, we find the following: In the publications reviewed in the Feldmeier/Hampson review [21], a total of 371 cases of mandibular ORN are reported with a positive outcome in 310, or
83.6%. Unfortunately, some of the papers report improvement rather than resolution as their outcome determinate. Of course a better determination of outcome would be resolution. In Marx’s [6] reports, resolution is reported in 100%. Marx also indicates that success in Stage III patients requires not only re-establishment of mandibular continuity but also rehabilitation with a denture for cosmesis and mastication. By contrast, if we look at the recent “negative” trials, only 22 patients are included in the Gal report [28] and 31 patients randomized to hyperbaric oxygen in the Annane [24] trial, for a total of 53 patients. In the recent review by Hampson et al. [31], in 43 evaluable patients 73% had complete resolution. Practitioners of hyperbaric oxygen who treat mandibular ORN must do so in a multidisciplinary manner and insure that treatment includes an oral surgeon who can accomplish the needed extirpation of all necrotic bone. For Stage III patients, after resection and resultant discontinuity, patients must have the advantage of skilled reconstructive surgeons and the best modern surgical techniques.

HBO2 FOR PROPHYLAXIS OF OSTEORADIONECROSIS

Extraction of teeth from heavily irradiated jaws is a common precipitating factor for mandibular necrosis. Marx [32] has published the results of a randomized prospective trial wherein patients who had received a radiation dose of at least 6,800 cGy were randomly assigned to pre-extraction HBO2 vs. penicillin prophylaxis. Those patients assigned to the hyperbaric group completed 20 pre-extraction daily HBO2 treatments with 10 additional post-extraction daily hyperbaric treatments. Thirty-seven patients were treated in each group. In the penicillin group, a total of 29.9% of patients developed ORN while only 5.4% of patients in the hyperbaric group developed necrosis. Also, the severity of subsequent ORN was more pronounced in the penicillin group, with nearly three-quarters requiring treatment as Stage III patients; neither patient with ORN from the hyperbaric group required a resection and reconstruction, and both resolved with treatment as Stage I ORN patients with additional hyperbaric oxygen and appropriate debridement.

The important principles advocated by Marx in the treatment as well as prevention of ORN include an emphasis on pre-surgical hyperbaric oxygen to improve tolerance to surgical wounding. Other practitioners have applied these principles established by Marx and his colleagues and have had similar success in the prevention and treatment of mandibular necrosis.

Two additional case series reporting positive outcomes in applying hyperbaric oxygen prior to dental extractions were included in the review by Hampson and Feldmeier [21]. In the publication of Vudiniabola et al. [33] following the Marx protocol in ORN prophylaxis, one of 29 patients experienced ORN, while in a similar case series from David et al. [34] one of 24 patients experienced mandibular ORN after extractions from a radiated mandible following the prophylactic application of hyperbaric oxygen. If the results from Marx’s study are combined with these two cited series, four of 90 patients (4.5%) developed ORN after treatment with hyperbaric oxygen. Recall that in Marx’s control group when radiation doses exceeded 6800 cGy the resultant incidence of ORN was nearly 30% without hyperbaric oxygen.

More recent publications include the report of 40 patients by Chavez and Atkinson [35] in whom hyperbaric oxygen was applied in the manner prescribed by Marx (20 pre-extraction hyperbaric treatments followed by 10 post-extraction). The authors report the uncomplicated healing of tooth sockets was observed in 98.5% of extractions.

Sulaiman et al. [36] from Sloan-Kettering report their results in dental extractions in a series of 187 previously irradiated patients. Only three patients in this group received hyperbaric oxygen, and the authors report that most received radiation doses between 6000 and 7000 cGy. Mandibular ORN developed in only four of the 180 (2.2%). The authors attribute this excellent result to their “atraumatic” technique in extracting the teeth. They question the need for hyperbaric oxygen if their surgical techniques are emulated.

Obviously, though it includes a large number of patients, this report is itself only a case series without controls. Marx’s patients in his prophylactic study all had doses of 6800cGy or greater while in the Sulaiman report 68% received doses lower than 6900 cGy. A total of 21% received doses less than or equal to 5900 cGy.

Michael Wahl [37], a dentist in private practice, published a review article in 2006 in the most prominent radiation oncology journal. No new data was presented in this paper. In this review he concluded: “There is insufficient evidence to support the use of prophylactic HBO treatments . . . before extractions or other oral surgical procedures in radiation patients.”

Some have suggested that mandibular ORN is decreasing in incidence due to modern radiation techniques, including intensity-modulated radiation (IMRT).
[38]. On the other hand, there has been a major shift to primary radiation with chemotherapy sensitization, requiring higher doses of radiation in an attempt to avoid radical surgical resections. In 2003, Reuther and colleagues [39] from the University of Heidelberg reported their experience in a 30-year review of head and neck radiotherapy. They reported an incidence of ORN in this group of 830 patients as 8.2%. In the recent review by Hampson et al. [31], a total of 210 patients were treated prior to dental extractions to prevent frank ORN. One hundred sixty-six patients were available for evaluation, and among this group 92% had no evidence of ORN, and 8% of this group had 50-90% healing of the extraction sockets.

**LARYNGEAL NECROSIS AND OTHER SOFT TISSUE NECROSSES OF THE HEAD AND NECK**

Laryngeal necrosis is an uncommon complication of radiation therapy for head and neck cancer. In well designed and appropriately fractionated radiation treatments, its incidence should be less than 1% [40,41]. However, when persistent edema, fetid breath or visible necrosis persist for more than six months after completion of irradiation, the standard recommendation has been to accomplish a laryngectomy because the likelihood of persistent tumor is very high and because effective therapies to reverse necrosis were not known [42]. Biopsy in order to eliminate the presence of cancer may be necessary. Biopsies, however, must be done with caution and are subject to sampling error. Often, the residual cancer is not readily visible on endoscopy and may be submucosal, thus requiring several random biopsies. Extensive surgical wounding of already injured tissues may further exacerbate tissue damage.

Chandler [43] has established a system to grade the severity of laryngeal necrosis: Most with Grade 1 and 2 levels of necrosis will resolve; patients suffering from Grade 3 or 4 necrosis have a high likelihood of requiring laryngectomy. Five institutions have now published case series in applying hyperbaric oxygen to the treatment of radiation laryngeal necrosis [44-47]. Additionally, a new single case report has also been published [48]. In these five reports most patients were treated for severe laryngeal necrosis (Chandler Grade 3 or 4). The outcome in a total of 43 cases is reported, and only six patients were failures to treatment and required laryngectomy. The other 37 patients maintained their voice box and most ultimately had good voice quality.

In the recent very large case series reported by Hampson et al. [31], there were 27 patients treated and evaluable for soft tissue radiation necrosis of the larynx. Improvement by at least 50% was seen in 82% of these patients. Patients were retrospectively graded by the Chandler system described above, and the majority were Grade 3 or 4.

In addition to laryngeal necrosis, there are several published reports addressing the results of hyperbaric oxygen treatment in other soft tissue injuries of the head and neck. Many of these deal with soft tissue necrosis of the neck and failing flaps within irradiated fields. In the textbook *Hyperbaric Medicine Practice*, edited by Dr. Eric Kindwall, Marx [6] reported extensive experience in treating soft tissue radiation injuries of the head and neck. In a controlled but non-randomized report of 160 patients, he compared wound infection, dehiscence and delayed healing in the hyperbaric group vs. a control group. He found that HBO2 patients experienced 6% wound infection vs. 24% control; 11% dehiscence vs. 48% control; and 11% delayed wound healing vs. 55% control. All differences are statistically significant when the chi-square test is applied.

These results have also been duplicated by other authors. Davis and his colleagues [49] have reported successful treatment in 15 of 16 patients with soft tissue necrosis of the head and neck, including many with extensive necrotic wounds.

In 1997, Neovius and colleagues [50] reported a series of 15 patients treated with hyperbaric oxygen for wound complications after surgery within an irradiated field. They compared this group to a carefully matched historical control group from the same institution. Twelve of the 15 patients in the hyperbaric group healed completely, with improvement in two and only one without benefit. In the control group only seven of 15 patients healed. Two patients in the control group also developed life-threatening hemorrhage, and one of these did indeed exsanguinate. Any practitioner experienced in the management of head and neck cancer patients has experienced at least one patient in his or her career who has died from exsanguination as the result of a soft tissue necrosis of the neck which progressed to erode into the carotid artery or other major vessel.

In another group of patients, Feldmeier and colleagues [51] have reported the successful prophylactic treatment of patients undergoing radical surgical resection for salvage of head and neck cancer following failure of initial cancer treatment, which included full-course irradiation. Serious surgical complications, including occasional fatalities, have been reported to occur in
more than 60% of patients undergoing radical surgery within a previously irradiated field without the benefit of HBO₂ [52,53]. With a short course of HBO₂ initiated immediately after surgery (median number of treatments 12), 87.5% of patients healed their surgical wounds with no serious complications. In this group, no deaths occurred in the immediate postoperative period.

CHEST WALL NECROSIS
Radiation therapy after lumpectomy has become the preferred treatment for most early breast cancers. After this treatment, fat necrosis of the intact breast has been reported but is a fairly uncommon clinical problem. Hyperbaric oxygen has not been reported as a therapeutic strategy in this condition.

Radiation therapy is frequently used as an adjuvant treatment following mastectomy in more advanced cancers for large tumors or when axillary metastases are present. When a patient is irradiated after mastectomy, the radiation dose to the skin is intentionally high, with the goal of preventing tumor failure in the dermal lymphatics. As a result of this standard radiation technique, most women irradiated after mastectomy are subject to brisk acute radiation reactions. Some patients experience large areas of moist desquamation with superficial ulceration. Frank necrosis of the chest wall is fairly uncommon but is very difficult to manage when it does occur. Traditional treatment for chest wall necrosis has required extensive surgical debridement and, frequently, closure with omental or myocutaneous flaps originating outside the radiation field to insure vascular supply that is unimpaired by radiation vascular injury.

Hart and Mainous [54] in 1976 reported the successful application of hyperbaric oxygen as an adjunct to skin grafting in women treated for necrosis of the chest wall after mastectomy. Feldmeier and colleagues [25] in 1995 reported the outcome in applying hyperbaric oxygen as treatment of both soft tissue and bony necrosis of the chest wall. In this report, all cancer-free patients who suffered only soft tissue necrosis were treated successfully. However, only eight of 15 patients treated resolved when ORN of the sternum or ribs was present. The common characteristic in all of these failed cases was the failure to eliminate surgically all necrotic bone. As discussed above, Marx had previously demonstrated the necessity of total extirpation of necrotic bone for the treatment of mandibular necrosis. This general principle should apply to osteoradionecrosis at any site.

Vanderpuye and his colleagues also discuss the need to address necrotic bone in their review of ORN [55].

Writing from the University of Düsseldorf in 1998 Carl and Hartmann [56] reported a single case of a patient who had experienced painful breast edema following lumpectomy and postoperative radiation. After 15 daily hyperbaric treatments of 90 minutes of 100% hyperbaric oxygen at 2.4 atm abs, the patient experienced complete resolution of pain and edema.

In 2001 Carl and his associates [57] reported the outcome of 44 patients who experienced complications following lumpectomy and irradiation for early breast cancers. These patients were found to have pain, edema, fibrosis and telangiectasias as a consequence of their irradiation. Each patient experienced these complications in various combinations and to varying degrees of severity. The severity of symptoms was assessed with a score for each patient based on a modified scale for late effects in normal tissues subjective, objective, management and analytic scores (LENT-SOMA). Each patient was assessed a score from 1 to 4 in the severity of symptoms in the categories of pain, edema, fibrosis/fat necrosis and telangiectasia/erythema. Only patients with at least Grade 3 pain (persistent and intense) or a summed LENT-SOMA score of 8 were studied.

Thirty-two patients agreed to undergo hyperbaric oxygen treatment, while 12 women refused HBO₂ and constituted the control group. Hyperbaric oxygen treatments resulted in a statistically significant reduction in the post-treatment SOMA-LENT scores in women who received treatment compared to those who did not. Fibrosis and telangiectasia were not reduced. Women in the control group continued to demonstrate symptoms at the completion of the trial, with no improvement in pain or edema. Seven women in the hyperbaric group had complete resolution of their symptoms.

RADIATION CYSTITIS
Radiation therapy is commonly applied to tumors of the pelvis, which include rectal cancers, gynecologic malignancies and prostate cancer. Radiation cystitis is not a common complication but can be very difficult to manage when it does occur. In its most serious manifestations, it may even require cystectomy and diversion of the urinary stream. Conservative measures include the instillation of formalin or alum as chemical cautery agents into the bladder lumen. Feldmeier and Hampson [21], in the previously cited review article, discuss 17 papers wherein hyperbaric oxygen has been delivered for this
indication. At the time of this review, the paper by Bevers et al. [58] was the largest series. It was a prospective but non-randomized and non-controlled trial. All of the other reports were case series. Many, if not most, of the patients reported in these series and subsequent series had already failed other conservative measures. Since this review article, there have been additional reports of hyperbaric oxygen for radiation cystitis. Neheman et al. [59] from Israel have published their results in a case series of seven patients. These patients received a mean number of 30 daily hyperbaric oxygen treatments. Patients were treated at 2.0 atm abs for 90 minutes of 100% oxygen exposure. All seven patients had initial resolution of their hematuria. Two recurred and again received hyperbaric oxygen, with an additional 30 and 37 treatments, respectively. Hematuria again resolved. Another patient had resolution of hematuria after 20 hyperbaric oxygen treatments but had progressive tumor (a primitive neuroectodermal tumor) and died.

In a recent publication by Corman et al. [60], the authors report a 2003 series from Virginia Mason Medical Center of 57 patients treated for radiation cystitis with HBO₂. Chong et al. [61] have updated this series in 2005 with an additional three patients. At the time of publication this paper represented the largest series of patients treated for radiation-induced cystitis. In this report, the average number of treatments was 33 at 2.36 atm abs for 90 minutes of 100% oxygen. In the first paper, 80% of those treated had either complete or partial resolution. For those experiencing clot retention, six had complete resolution and 26 partial resolution. Eight had no change, and two worsened.

In the second publication, the authors report the importance of early intervention. In their analysis, they found that the rate of improvement increases from 80% to 96% when HBO₂ begins within six months of onset of hematuria. Improvement in clot retention was seen in 100% of those who began treatment within six months. Another notable advantage of this trial is that outcomes were reported at least 12 months after completion of HBO₂ treatment. The evaluation at this point is indicative of a durable response and does not include that group which may see early response but then experience recurrence in a relatively short time period.

Hemorrhagic cystitis is often a serious and, occasionally, a life-threatening disorder. Cheng and Foo [62] have reported their results in treating nine patients with refractory radiation-induced hemorrhagic cystitis without hyperbaric oxygen. Six of these patients required bilateral percutaneous nephrostomies, while three patients required ileal loop diversions of their urinary stream. In spite of aggressive surgical intervention, 44% of the patients in this series died as the result of their cystitis. In another review by Sun and Chao [63], the authors report a 3.7% mortality rate in their review of 378 patients experiencing hemorrhagic cystitis. All of these patients had been irradiated for cervical cancer.

In summary, 18 of 19 published series applying hyperbaric oxygen to radiation cystitis are positive reports. When we combine those patients included in the review by Feldmeier and Hampson [21] with the additional patients reported since then, of the 257 patients in published series 196 (76.3%) had either partial or complete response. This success rate is especially noteworthy when compared to those publications cited above, which note a poor outcome and significant mortality rate when HBO₂ is not employed.

In the recent large review by Hampson et al. [31], a total of 44 patients treated for radiation cystitis were evaluable. Many of these were reported by this author and his associates previously. The authors report 57% to have had complete resolution and another 32% to have improved by 50-90%.

**Radiation Proctitis and Enteritis**

A controlled animal study has been reported by Feldmeier and associates [64,65] wherein HBO₂ was shown to be highly successful in preventing radiation-induced enteritis. In this study, experimental animals received HBO₂ in a prophylactic setting seven weeks after radiation exposure. When animals were euthanized seven months after the radiation exposure, both gross and histologic morphometry demonstrated a statistically significant reduction in signs of enteritis in the experimental group compared to the radiation-only control group. Both quantitative histologic morphometry and a mechanical stretch test demonstrated reduction in submucosal fibrosis and an increase in mechanical compliance for hyperbaric-treated animals.

In the review by Feldmeier and Hampson [21], nine clinical papers reporting the results of hyperbaric oxygen in the treatment of enteritis or proctitis were identified. These publications present a total of 114 cases. Forty-one (36%) of these patients were treated with complete resolution while another 68 (60%) had improved symptoms; 4% of patients had no benefit from treatment.

Bredfeldt and Hampson [66] from Virginia Mason Medical Center have reported in abstract form their
experience in applying hyperbaric oxygen to the treatment of 19 patients with chronic radiation injury to the GI tract [80]. Injuries included radiation proctitis (some with ulceration), gastroduodenal bleeding and an esophageal ulcer. Patients were treated with 30 hyperbaric treatments at 2.36 atm abs. Complete resolution was achieved in 47%, with improvement in another 37%, and no improvement in the remaining 16%. A case report by Neurath and colleagues [67] documents the successful resolution of severe malabsorption due to established radiation enteritis in a 53-year-old female following 20 hyperbaric treatments at 3.0 atm abs for 90 minutes.

Since this review, additional publications on this topic have been published. Jones et al. [68] have published their experience in treating 10 patients with HBO2 for radiation-induced proctitis. Three of their patients had Grade 3 toxicity (bleeding necessitating transfusion). The seven remaining patients had Grade 2 toxicity, due to rectal pain and/or diarrhea. Six of the seven had rectal bleeding but had not required transfusion. Nine of these 10 patients completed treatment without complications. Rectal bleeding resolved in four patients while improvement was seen in three others. Two failed to respond. Rectal pain resolved in three of five patients affected. In those suffering chronic diarrhea, one of five resolved and three improved. Of the 10 patients in this series only two failed to experience demonstrable improvement. In this study median follow-up was 25 months again showing durability.

In another series from Girnius et al. [69] from Cincinnati, nine patients with hemorrhagic proctitis were treated with hyperbaric oxygen. Five patients had previously required transfusion, and three had been unsuccessfully treated with argon plasma coagulation or electrocautery. The authors report, with median follow-up of 17 months, complete resolution in seven of the nine. The remaining two had improvement but still had some bleeding.

A large published experience in radiation injury to the GI tract is from the Virginia Mason group [70,71]. These results are published in two papers. A total of 65 patients are reported, 37 male and 28 female. All had endoscopic documentation of their injury. The injuries included 54 rectal injuries, with 15 in the more proximal GI tract (four stomach, seven small bowel, six colon and six duodenum). More than 65 injuries are reported because some patients had multiple injuries. These patients had an initial 30 HBO2 treatments at 2.36 atm abs for 90 minutes of 100% O2. In those patients demonstrating a partial response at this point, additional treatments were delivered (six to 30 treatments). Complete response rate overall was 43% (28 patients), and partial response 25% (16 patients). The results were somewhat worse for rectal cancer, with a response rate of 65% compared to 73% for proximal lesions.

When we combine all of those cases from the above citations, we find published experience in 199 cases of proctitis, colitis and enteritis treated by HBO2 (having combined the total Virginia Mason experience). Eighty of these patients (41%) had complete resolution, while 169 (86%) experienced at least partial response. Only 14% failed to respond at all.

In a randomized controlled blinded trial sponsored by the Baromedical Research Foundation, Clarke et al. [72] have reported their results in applying hyperbaric oxygen to patients with refractory chronic radiation-induced proctitis. A total of 150 patients were enrolled in the trial, and 120 were evaluable. Patients were assessed utilizing the SOMA-LENT scoring systems, which have become standard in studies of radiation injuries/complications. Patients in the active arm were treated on 100% O2 at 2.0 atm abs. Sham patients were exposed to very slightly elevated pressures (1.1 atm abs) breathing air. The intent was to give the control patients the sense of pressurization without enhanced oxygenation.

After 30 treatments, reassessment was made by the referring physician, who was blinded and, in select patients who had shown partial response, an additional 10 treatments were accomplished. Control patients were offered the opportunity to cross over to hyperbaric oxygen, and all but three agreed to do so. With an average follow-up of two years (minimum one year), those patients in the active arm showed a statistically increased improvement in their SOMA-LENT scores (5.00 vs. 2.61) with a p-value of 0.0019. Responders in the active arm were 88.9% vs. 62.5% in the control arm (p=0.00009). The absolute risk reduction was 32%, and the number needed to treat was 3. These results are impressive. The study group is to be commended in the rigorous design and conduct of the trial. This report adds an important contribution of Level 1 evidence to the case series and reports discussed above.

The updated experience in treating radiation-induced proctitis and enteritis from the Virginia Mason group reports a resolution rate of 25% – an improvement of 50-90% in 38%; an improvement of less than 50% in 25%; and an unchanged status in 12% [31].
OTHER ABDOMINAL AND PELVIC INJURIES
In 1978 Farmer and associates [73] reported a single case of vaginal necrosis which resolved with hyperbaric oxygen. In 1992, Williams and colleagues [74] reported their results in treating 14 patients with vaginal necrosis. Thirteen of 14 patients had complete resolution, although one patient required a second course of hyperbaric oxygen. In 1996 Feldmeier and co-authors [75] published their results in a review of 44 patients treated with HBO₂ for a variety of pelvic and abdominal injuries. The results in treating large- and small-bowel injuries were included in the discussion in the section above. Thirty-one patients received at least 20 hyperbaric treatments for radiation injuries to the perineum, groin, vagina and pelvic bone. Twenty-six (84%) of these patients had complete resolution of their radiation injury.

In a recent publication by Fink et al. [76], a series of 14 patients treated with HBO₂ for a variety of pelvic injuries is reported. Six of these patients had vaginal injuries (four with ulcers, one with stenosis and one characterized only as vaginitis). Several of these patients had injuries to more than one organ simultaneously. In those treated for vaginal injury either alone or in combination with other injuries, the outcome was complete resolution in one, four with greater than 50% response and one with less than 50% improvement. In the entire group the authors report that 71% had greater than 50% improvement. Most patients received only 30 hyperbaric treatments at 2.4 atm abs.

If we combine the results in these four series including only those with vaginal injury from the Fink paper [76], the combined results show that 45 of 52 (87%) had at least a partial response for miscellaneous radiation injuries to the pelvis – not including cystitis or GI injury, which are discussed above as separate topics.

In a recent review article, Craighead and colleagues [77] from Canadian cancer centers and hyperbaric centers reported their conclusions after conducting a literature search and analysis of two randomized trials and 11 non-randomized trials wherein hyperbaric oxygen was delivered for late radiation injuries after pelvic radiation for gynecologic malignancies. These injuries included radiation-induced cystitis, proctitis and enteritis as well as bone necrosis and quality of life assessments. The authors conclude that HBO₂ is effective for delayed radiation injury especially in the treatment of anal and rectal injuries. The authors further conclude that there is limited but consistent evidence that, when given pre-operatively, HBO₂ has utility in reducing complications in women undergoing surgery within a radiated area to surgically address radiation-induced necrosis.

RADIATION INJURIES OF THE EXTREMITIES
Radiation necrosis of the extremities is a very unusual occurrence. In part, this rarity reflects the relative paucity of primary malignancies of the extremities. However, radiation therapy for bony metastases in the extremities is often delivered. In metastatic disease, radiation doses are only moderate, and patients with metastases may not survive in large numbers long enough for radiation injury to become manifest.

In the review by Feldmeier and Hampson [21] only two publications were discovered which report results of hyperbaric treatment in radiation injuries of the extremities. In 1978 Farmer and associates [73] reported a single patient treated for radiation necrosis of the foot without improvement. Feldmeier et al. [78] in 2000 reported a series of 17 patients treated for extremity radiation necrosis. Eleven of 17 patients had complete resolution of their injury with treatment. In those patients for whom follow-up was available and who were not found to have recurrent malignancy in the wound, 11 of 13 (85%) resolved.

Certainly, the published experience in applying hyperbaric oxygen to radionecrosis of the extremities is limited. However, based on the successful treatment of radiation necrosis of both bone and soft tissues in other anatomic sites, it is reasonable to recommend hyperbaric oxygen for this indication.

Oxygen in the hyperbaric setting has often been referred to as a “drug.” Just as an antibiotic can be recommended for treatment of an infection of one anatomic site based on success at other sites, we can recommend hyperbaric oxygen for radiation injury of the extremities based on success in other tissues.

Hampson and his co-authors [31] report their results in applying hyperbaric oxygen to soft tissue injuries resulting in cutaneous wounds. These wounds were not limited to the lower extremity. A total of 58 patients were evaluable in this group, with resolution in 26%, 50-90% improvement in 50%, less than 50% improvement in 9% and no improvement in 16%. No patients deteriorated after HBO₂.
NEUROLOGIC INJURIES SECONDARY TO RADIATION

In the review article previously cited, Feldmeier and Hampson [21] have identified 14 publications that report hyperbaric oxygen treatment for a variety of neurologic injuries. These include radiation-induced transverse myelitis (spinal cord injury), brain necrosis, optic nerve injury and brachial plexopathy. Since their review article, a small additional number of papers on this topic have been published.

Radiation myelitis

Radiation myelitis is a very serious but, fortunately, very rare consequence of radiation. Marcus and Million [79] reviewed their experience in the incidence of myelitis in 23 years of treatment of head and neck cancers. They reported an incidence of two patients in a total of 1,112 treated (0.2%). In 1976, Hart and Mainous [54] published their results in the treatment of five cases of transverse myelitis. Glassburn and Brady [80] reported nine cases of transverse myelitis in 1977. In the report by Hart, no improvement in motor function was demonstrated, while in Glassburn’s report six of nine patients had improvement, including some improvement in motor function. In 2000 Calabro and Jinkins [81] reported one case of transverse myelitis treated with hyperbaric oxygen who experienced both clinical and MRI imaging evidence of improvement. In a murine study by Feldmeier et al. [82], delay but no permanent prevention of myelitis was seen for HBO2-treated animals administered before objective signs of myelitis seven weeks after a fairly extreme radiation exposure. In another animal model Sminia et al. [83] investigated HBO2 given right after radiation or at intervals of five, 10 or 15 weeks after radiation. Animals had received an initial fractionated dose of 6500 cGy, followed by an additional single dose of 2000 cGy. In this study, animals did not demonstrate radioprotection by the hyperbaric oxygen. The HBO2 regimen consisted of 30 daily treatments at 2.4 atm abs, each consisting of 90 minutes of 100% oxygen exposure.

No other known successful treatments for radiation-induced myelitis exist, and besides the obvious drastic impact of resultant paralysis, there is a high incidence of mortality in these patients, with two-thirds dying within four years as a result of onset of this condition [84]. Although hyperbaric treatment has not been universally successful because of the severe consequences of transverse myelitis and the total lack of other useful treatments, hyperbaric therapy should be considered on a humanitarian basis for the treatment of radiation-induced transverse myelitis.

Brain necrosis

In the 1976 paper by Hart and Mainous [54] a single case of radiation caused brain injury improved with HBO2. Chuba and co-workers [85] have reported a series of 10 children with radiation-induced brain necrosis treated with hyperbaric oxygen. All children in this group improved initially. By the time of their publication, four patients had died due to recurrent/progressive tumor, while five of the six remaining patients had maintained their improvement as a result of hyperbaric treatment.

Leber and colleagues [86] have reported two cases where patients developed brain necrosis after radiosurgery procedures for arteriovenous malformations. In both of these patients, the authors report a reduction in the size of necrosis after hyperbaric oxygen therapy demonstrated by imaging studies, and one had complete resolution, as seen by MRI. Cirafsi and Verderamae [87] have published their experience in the treatment of a single case of brain necrosis secondary to radiation. This patient had no improvement with hyperbaric oxygen. The patient had also failed to respond to steroids and anticoagulants.

In a more recent report, Dear and colleagues [88] report that nine of 20 patients with radiation brain necrosis improved with hyperbaric oxygen. Eleven of the patients in this group had glioblastoma multiforme, and only one patient with this diagnosis showed improvement. Since seven of the 11 patients with glioblastoma had died by the time of the report, it is likely that some, if not a substantial part, of their neurologic deficits were the result of tumor as well as radiation injury.

In the largest series to date Gesell and her colleagues [89] have reported the outcome in 29 patients treated with hyperbaric oxygen for radiation-induced brain injury. Objective neurologic exam improved in 58% of these patients, and the need for steroids reduced in 69%.

A problem in the study of these patients is the difficulties in distinguishing radiation necrosis from tumor. Often they occur simultaneously. Necrosis can cause a mass effect and on anatomic based imaging be indistinguishable from a tumor mass. Metabolic imaging with PET scans and MRI spectroscopy can provide useful information, but PET in particular suffers from poor spatial resolution.
When we combine the reports above, we have information on 65 patients who have received HBO₂ for radiation-induced brain injury with improvement in 44 (68%). Again based on humanitarian considerations in the absence of any other effective treatment except surgery, and in consideration of the dire consequences of radiation necrosis of the brain, hyperbaric oxygen should be considered in these instances.

Optic neuritis
A total of four publications reporting the application of hyperbaric oxygen to the treatment of optic neuritis have been published [90-95]. The three case reports demonstrate strongly positive results with hyperbaric treatment while two small case series give mixed but predominately negative results. Borruat et al. [93] have reported on a single patient with bilateral optic neuritis. After hyperbaric oxygen treatment, this patient had complete resolution of optic neuritis in the eye most recently affected and some, but less than total, resolution in the first eye affected. This experience supports the need to intervene early with HBO₂. In 1991, Fontanesi et al. [92] reported a case of a pediatric patient treated for a CNS tumor. This patient sustained loss of visual acuity, and these changes were refractory to steroids. Hyperbaric oxygen for 20 treatments at 2.0 atm abs each for 90 minutes substantially improved vision in both eyes. Boschetti et al. [94], in another case study, report their results in a 41-year-old who sustained visual damage after radiosurgery to the pituitary for Cushing’s disease; the damage consisted of blindness in the left eye and temporal hemianopia in the right eye refractory to corticosteroid treatment. After hyperbaric oxygen, blindness persisted in the left eye, but the patient had objective improvement in visual fields in the right eye by formal visual field-mapping. Hyperbaric oxygen consisted of 41 treatments at 2.2 atm abs, each session delivering 60 minutes of 100% oxygen. Guy et al. [90], in a series of four patients, report that two who had prompt treatment (within 72 hours of onset) improved, while if treatment was delayed by more than 72 hours, no improvement was detected. In the largest series by Roden et al. [91], no improvement occurred in any of the 13 patients treated in this series.

When the results are combined in all of these publications, seven patients in this entire group of 20 (35%) demonstrated improvement with hyperbaric oxygen.

Based on these results, a definitive case for hyperbaric oxygen cannot be made in the treatment of radiation-induced optic neuritis. However, its application here can be supported based on the same mechanisms active in brain necrosis and radiation-induced myelitis. Furthermore, since there are no other known useful therapies and since the prognoses in progressive optic neuropathy – including blindness – are so dire, treatment based on humanitarian considerations should be considered. However, these results do show clearly that treatment must be initiated promptly, probably within 72 hours of onset, in order to be effective.

Brachial plexus and sacral plexus
In 1999, a single case report by Videtic and Verkatesan [95] reports a positive resolution of neural symptoms in a patient receiving hyperbaric oxygen for a radiation-induced sacral plexopathy. After treatment, this patient again became ambulatory, and all narcotic analgesics were discontinued.

A randomized controlled trial by Pritchard and associates [96] has been conducted in regard to hyperbaric oxygen therapy for brachial plexopathy. Unfortunately, this trial is negative in terms of failing to show a statistically significant improvement in the hyperbaric group compared to the control group. The median time of entry into the study after development of the neuropathy was 11 years, and the injuries were certainly fixed over time. Though no improvement was observed, the hyperbaric group of patients had less further deterioration than did the control group after treatment. Unexpectedly, six patients with lymphedema in the hyperbaric group showed improvement in their arm swelling after hyperbaric oxygen, with no corresponding improvement in the control group.

SUMMARY FOR NEUROLOGIC INJURIES
The supporting evidence for hyperbaric oxygen for radiation-induced neurologic injury is certainly anecdotal. More study is certainly indicated and justified by the above results. Given the severe and permanent consequences of progression of injury, especially in the CNS and in the complete absence of other effective treatment, serious consideration for hyperbaric treatment should be given.

SPECIAL CONSIDERATION
Hyperbaric oxygen as prophylaxis for radiation injury
Most of the literature cited above reports the results of application of HBO₂ to already expressed radiation injury. A growing body of literature supports the use of HBO₂ in the prevention of radiation injury, usually in the setting of surgery within an irradiated field, where the likelihood of complications is very high.
The first published clinical report investigating prophylactic HBO₂ is that by Marx [32], where hyperbaric oxygen has been shown to decrease the incidence of mandibular osteoradionecrosis from 29.9% to 5.4% when a course of 20 daily HBO₂ treatments was delivered prior to dental extractions from heavily irradiated mandibles. In this protocol, an additional 10 treatments are delivered after extractions to support tissue metabolic demands after surgical wounding. Marx [6] has also reported the benefit of hyperbaric oxygen in the enhancement of osseointegration of dental implants in irradiated bone. Most oral surgeons are reluctant to attempt dental implants in irradiated jaws due to the very high rate of failure and the risk of precipitating osteoradionecrosis. Both Marx [6] and Granstrom [97] have reported the benefit in supporting dental implants in radiated tissues, with significant improvement in osseous integration of the dental implant in patients receiving hyperbaric oxygen. Using the same protocol as for osteoradionecrosis prophylaxis (20 preoperative and 10 postoperative HBO₂ treatments), Marx [6] has achieved an 81% osseointegration success rate, with prevention of osteoradionecrosis in 100% of the patients so treated. A total of 19% failed to osseointegrate as compared to 6% in non-irradiated patients undergoing dental implants. Ueda and colleagues [98] have reported a success rate of 92.3% (in a total of 21 implants) using a similar regimen of HBO₂ in conjunction with dental implants [98].

As already cited above, Feldmeier et al. [51] have reported the utility of hyperbaric oxygen in preventing serious wound complications in patients with recurrent head and neck cancer who had salvage procedures, including radical resection within irradiated fields. In that report, 87.5% of patients had prompt wound healing without complication, whereas previous publications report up to a 60% incidence of serious complications in this setting without prophylactic HBO₂. Pomeroy and his associates [99] have reported their results in applying preoperative hyperbaric oxygen as an adjunct to surgery for soft tissue injuries of the pelvis. All five patients in this report had an uneventful postoperative course, although two of five required a second surgical procedure to resolve the radiation injury. In an animal model, Feldmeier and associates have shown the effectiveness of hyperbaric oxygen in the prevention of radiation injury to the small bowel [64,65].

A promising area for clinical application will be the further definition of prophylactic hyperbaric oxygen in the prevention of radiation injury. The development of reliable biochemical predictors of radiation injury would permit the identification of the population at risk for development of radiation injury. At the present time, a reasonable approach is to provide adjunctive HBO₂ when surgery is planned to occur in a heavily irradiated bed. The medical literature is consistent in demonstrating a high rate of serious complications and even death when radical surgical procedures are required in irradiated tissues without prophylactic HBO₂ [50-51]. Third-party insurance carriers must be convinced that such prophylactic intervention is not only valuable for humanistic reasons but also for financial reasons. It is hoped that the literature cited above will provide the individual practitioner with the needed documentation to make a case for the prophylactic application of HBO₂. Hyperbaric oxygen in a preventative setting is likely to be more cost-effective than a prolonged course of rehabilitation and reconstructive surgeries in a corrective fashion.

In summary, the use of hyperbaric oxygen prior to surgery in an irradiated field may prevent or decrease the incidence of catastrophic events such as wound breakdown with bony or hardware exposure, vascular rupture, infection, fistula formation and/or flap loss and prevent further surgical intervention in an already compromised patient.

**Concerns related to potential carcinogenesis or cancer growth enhancement**

A frequently expressed concern by those considering hyperbaric oxygen for a patient with radiation injury is the fear that hyperbaric oxygen will somehow accelerate malignant growth or cause a dormant malignancy to be reactivated. In Marx’s [6] very large group of patients treated with HBO₂ for radiation injury of the mandible, there was no increased likelihood of tumor recurrence or second tumor development. In 1994, Feldmeier and his colleagues [100] reviewed the available literature related to this issue. An overwhelming majority of both clinical reports and animal studies reviewed in this paper showed no enhancement of cancer growth. A small number of reports actually showed a decrease in growth or rates of metastases. Feldmeier [101] updated this material for the Consensus Conference held in 2001 jointly sponsored by the European Society of Therapeutic Radiology and Oncology (ESTRO) and the European Committee for Hyperbaric Medicine (ECHM). In this update, Feldmeier emphasized the differences known in tumor and wound healing angiogenesis, with similar but distinct processes operative in each case. He also showed that there are significant differences
in the growth and inhibition factors, which modulate angiogenesis, in both circumstances. He summarized the literature demonstrating that tumors that are hypoxic are less responsive to treatment, less subject to death by apoptosis and more prone to aggressive growth and lethal metastases. Most experienced practitioners of hyperbaric oxygen no longer fear that hyperbaric oxygen will promote malignant growth.

Since the reviews by Feldmeier et al., additional publications have investigated the impact of hyperbaric oxygen on malignancy. Chong and co-workers [102] in 2004 reported their experience in an animal model of transplanted prostate cancer. In this study there was no increase in proliferative index and no increase in tumor vascularity in animals exposed to hyperbaric oxygen vs. control animals. Six additional studies have also been conducted on this subject [103-108]. Specific topics studied have included chemically induced mammary tumors in mice, xenografts of human head and neck tumors transplanted in experimental animals and murine colorectal cancer cells implanted to cause liver metastases. All of these papers are negative in terms of observing enhanced tumor growth as the result of hyperbaric oxygen. One paper by Granowitz et al. [106] actually shows inhibited growth in a transplanted human mammary tumor.

Lin and collaborators [109] published a retrospective review of 22 patients who underwent salvage surgery for recurrent head and neck cancer after failing primary radiation. Eleven of these patients experienced necrosis and received HBO₂. The other 11 healed without complication and did not receive HBO₂. In the HBO₂ group, nine patients experienced a local failure while in the non-HBO₂ group only four patients sustained recurrence. The authors indicate that all patients were demonstrated to be tumor-free before starting HBO₂ including negative biopsies. The authors suggest that recurrent cancers have a different biology than primary cancers, and while they agree that HBO₂ has not been shown to enhance recurrence of primary tumors, they believe that their results suggest that HBO₂ does likely enhance the re-recurrence rate of salvaged tumors. The numbers are very small, and the groups were not truly matched in that the control group did not experience necrosis. The results could have been just as validly interpreted that necrosis, not HBO₂, enhances re-recurrence.

**UTILIZATION REVIEW**

Utilization review should be accomplished after 60 treatments when HBO₂ is applied to the treatment of radiation injury. Characteristically, most treatment courses for radiation injury will be in the range of 30 to 60 treatments when the course of treatment is carried out with daily treatments at 2.0 to 2.5 atm abs for 90 to 120 minutes of 100% oxygen.

**COST IMPACT**

Soft tissue and bony radiation necrosis are fortunately uncommon sequelae of therapeutic irradiation. Approximately 600,000 patients receive therapeutic radiation annually in the United States. The likelihood of serious complications is somewhere between 1-5% of the total, or potentially between 6,000 to 30,000 patients annually. Frequently, these complications require surgery within an irradiated field where the likelihood of significant postoperative complications is on the order of 50%. By either avoiding surgery or supporting surgical healing, HBO₂ therapy can significantly reduce the dollar and human costs of radiation complications. Marx accomplished a dollar cost estimate of the treatment of mandibular osteoradionecrosis [33]. In 1992 U.S. dollars, the cost of management is reduced from about $140,000 when HBO₂ is not utilized to about $42,000 when HBO₂ and surgery are combined in optimal fashion. Similar cost advantages are anticipated in the treatment of radiation injuries of other tissues.
REFERENCES


Literature review supplement: Abstracts for hyperbaric indications for papers appearing in UHM 39-3 – Infectious diseases

Intracranial abscess

Robert C. Barnes M.D., ABIM-IM, ID ABPM-UHM

Hyperbaric Center Sacred Heart Medical Center, Springfield, Oregon USA

EMAIL: Dr. Robert C. Barnes – rbarnes@peacehealth.org

ABSTRACT / UHM 2012; vol. 39, no. 3, 727-730

Hyperbaric oxygen therapy may provide benefit in the treatment of intracranial abscesses likely to respond sub-optimally to conventional treatment of drainage and antimicrobial therapy. Although a role for hyperbaric oxygen therapy in treatment of intracranial abscess is plausible based on physiological principles and animal studies, no randomized controlled human trials have defined the efficacy of adjunctive hyperbaric oxygen therapy for this indication. A limited number of case series may suggest improvement in mortality from historical controls. Anticipated failure of conventional treatment such as in multiple abscess, abscess(es) in deep or neurologically dominant location, abscesses (particularly Mucorales infections) in immunocompromised hosts, and inadequacy of drainage are situations in which adjunctive hyperbaric oxygen therapy might provide additional benefit.

Clostridial myonecrosis (gas gangrene)

Dirk J. Bakker M.D., Ph.D.

Academic Medical Center, University of Amsterdam, The Netherlands

EMAIL: Dr. Dirk J. Bakker – d.jbakker01@freeler.nl

ABSTRACT / UHM 2012; vol. 39, no. 3, 731-737

Gas gangrene is an acute, rapidly progressive, non-pyogenic, gas-forming and necrotizing infection of muscles, skin and subcutaneous tissues. This infection is caused by anaerobic spore-forming bacteria of the genus Clostridium, primarily Clostridium welchii or perfringens (in more than 95% of cases).

Contamination with spores in an area of lowered oxygen tissue tension takes place post-traumatic, postoperatively or, initially, without a known port of entry. When under (relatively) anaerobic circumstances the spores flourish into the vegetative form of the bacteria, and toxin production starts. Among many produced toxins the Alpha (α)-toxin and the Theta (θ)-toxin are the most important. They cause tissue destruction, hemolysis, suppression of the acute inflammatory response, hypotension and shock, followed by death. Death occurs sometimes within a few hours after the onset of infection.

Gas-forming as featherlike air figures between muscle fibers is a very characteristic picture on an X-ray. The initial diagnosis is made on the clinical picture and a Gram-stained smear showing Gram-positive rods without leukocytes.

Treatment is a three pronged approach of hyperbaric oxygen, antibiotics and surgery (in that order). The rapid progression of the disease, sometimes 15cm per hour, depends on the continuous production of α-toxin. It has been shown that under hyperbaric circumstances, when the tissue pO2 is above 250 mmHg, the toxin production stops completely. This is the most rapid way to stop the progression of gas gangrene.

Hyperbaric oxygen treatment stops toxin production, quickly clarifies the demarcation between dead and viable tissue and lowers the mortality considerably. This has been a constant finding between 1959 and 2012 in many treatment centers.
Necrotizing soft tissue infections

Irving ‘Jake’ Jacoby M.D., FACP, FACEP

Clinical Professor of Medicine & Surgery Department of Emergency Medicine, UC San Diego School of Medicine, La Jolla California USA

EMAIL: Dr. Jake Jcoby – ijacoby@ucsd.edu

ABSTRACT / UHM 2012; vol. 39, no. 3, 739-752

Hyperbaric oxygen therapy is a recognized accepted adjunct to surgical debridements, antibiotic therapy and maximal goal-directed critical care therapy for infections of soft tissues that result in necrosis. A number of clinical scenarios, specific lesions and syndromes have been described over the years, based on the affected tissues and location of infection, the etiologic organism or combination of organisms involved in the infection, and particular host immunologic and vascular risk factors. In all of these clinical situations, there appears to be the common denominator of the development of hypoxia resulting in necrosis.

Osteomyelitis (Refractory) with literature review supplement

Brett Hart M.D.

Navy Medicine Operational Training Center, Pensacola, Florida USA

EMAIL: Dr. Brett Hart – Brett.Hart@med.navy.mil

ABSTRACT / UHM 2012; vol. 39, no. 3, 753-775

Refractory osteomyelitis is characterized either by a chronic bone infection that persists or recurs after appropriate interventions have been performed or by an acute bone infection that does not respond to accepted management techniques. To date, no randomized clinical trials examining the effects of hyperbaric oxygen (HBO₂) therapy on refractory osteomyelitis exist. However, based on this comprehensive review of the scientific literature, the addition of HBO₂ therapy to routine surgical and antibiotic treatment of previously refractory osteomyelitis appears to be both safe and associated with improved infection resolution rates. In most cases, the best clinical results were obtained when HBO₂ treatment is administered in conjunction with culture-directed antibiotics and initiated soon after thorough surgical debridement. In cases where extensive surgical debridement or removal of fixation hardware was relatively contraindicated (e.g., cranial, spinal, sternal or pediatric osteomyelitis), a trial of limited debridement, culture-directed antibiotics and HBO₂ therapy prior to more radical surgical interventions still provided a reasonable chance for osteomyelitis cure. Summarizing effective treatment practices, HBO₂ therapy should ordinarily be delivered on a daily basis for 90-120 minutes using 2.0-3.0 atmospheres absolute. Where prompt clinical improvement is seen, the existing regimen of antibiotics and HBO₂ therapy should be continued for approximately four to six weeks. Typically, 20-40 HBO₂ sessions are required to achieve sustained therapeutic benefit. In contrast, if prompt clinical response is not noted or osteomyelitis recurs after this initial treatment period, then continuation of the current antibiotic and HBO₂ treatment regimen is unlikely to be effective. Instead, clinical management strategies should be re-assessed and additional surgical debridement and/or modification of antibiotic therapy considered.
Book Review

In *Death Is Not An Option*

Dr. Weiss does a great job of documenting the animosity of mainstream medicine toward any therapy that is not understood.

Again, in Russia, a prize fighter is treated with HBO₂ every day he fights. This is to prevent post-traumatic encephalopathy, a disease we see by the thousands in our athletes and soldiers, and just ignore. We have shown time and again that HBO₂-T helps and prevents post-traumatic encephalopathy. But, without FDA approval, which requires double blind studies, this treatment is being withheld.

In America, these 100 clinics have been treating autism, cerebral palsy, stroke, concussion, post-traumatic encephalopathy, post-traumatic stress disorder and some rare developmental disorders with very encouraging results. The same problem exists: These studies are anecdotal. The FDA wants double-blind studies, which are very difficult and expensive. They will not accept the many thousands of studies that have been done around the world.

But, there is light ahead. Currently, four double-blind studies are under way for TBI and PTSD at Camp LeJeune, Fort Carson, Brooks and Camp Pendleton, with preliminary reports very promising. We expect their completion in the next six to 12 months. This should open the door to treat the millions of soldiers and athletes with acute concussion, post-traumatic encephalopathy and PTSD. The life-saving, quality of life and financial impacts on society are obvious.

Dr. Weiss does a great job of documenting the animosity of mainstream medicine toward any therapy that is not understood. Even a well-respected surgeon and scientist is looked upon with jaundiced eyes by his colleagues because of his “out of the box” ideas. Then, after he shows that he was right, he is shunned by the same people, obviously because of their embarrassment.

He accurately describes the problems within the health insurance industry, FDA and drug companies, revealing their waste, inequities, and unconscionable distribution of health care funds while life saving procedures go unreimbursed.

Written in an engaging format, Weiss engages the reader throughout the chronicle of his son’s progress.

-- Pete L. Stephens M.D.
UHMS-ACCREDITED
CLINICAL HYPERBARIC MEDICINE FACILITIES

UHM PAPERS BY ISSUE

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THANKS TO 2012 REVIEWERS
The UHMS clinical hyperbaric medicine facility accreditation program recognizes clinical hyperbaric facilities that demonstrate their commitment to patient care and facility safety.

* indicates facilities that serve with distinction
† Medical Center Joint Commission-Accredited

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  - (251) 460-5461
- † Wound Care & Hyperbaric Medicine Department
- † Princeton Baptist Health System
  - Birmingham, Alabama
  - (205) 783-3727

#### ARIZONA
- * Wound Healing & Hyperbaric Oxygen Center
- † Chandler Regional Hospital
  - Chandler, Arizona
  - (480) 732-7705

#### CALIFORNIA
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- † UCLA Medical Center
  - Los Angeles, California
  - (310) 794-9014
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- † Redlands Community Hospital
  - Redlands, California
  - (909) 555-6247
- * Hyperbaric Medicine Flight
- † David Grant USAF Medical Center
  - Travis AFB, California
  - (707) 423-3987

#### COLORADO
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- † Poudre Valley Hospital
  - Fort Collins, Colorado
  - (970) 495-8770

### THE HYPERBARIC MEDICINE SERVICE
- † Memorial Hospital
  - Colorado Springs, Colorado
  - (719) 365-5920

#### CONNECTICUT
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- † Hartford Hospital
  - Hartford, Connecticut
  - (860) 545-4325
- * Wound & Hyperbaric Care
- † MidState Medical Center
  - Meriden, Connecticut
  - (203) 694-8763
- † Wound Care & Hyperbaric Medicine Center
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  - (203) 735-7421

#### FLORIDA
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  - (214) 395-5866
- † Center for Wound Care & Hyperbaric Medicine
- † Boca Raton Community Hospital
  - Boca Raton, Florida
  - (561) 955-5334
FLORIDA — continued

Center for Wound Care & Hyperbaric Medicine
† Lakeland Regional Medical Center
Lakeland, Florida
(863) 284-1700

Center for Wound Care & Hyperbaric Medicine
† Sacred Heart Hospital
Pensacola, Florida
(850) 416-2935

Wound Healing Institute
† University Community Hospital-Brandon
Brandon, Florida
(813) 615-7100

* Wound Healing Institute
† University Community Hospital-Carrollwood
Tampa, Florida
(813) 390-2344

GEORGIA

Cobb Hyperbaric Medicine
Marietta, Georgia
(770) 422-0517

Columbus Regional Wound Center
† Columbus Regional Medical Center
Columbus, Georgia
(706) 660-6500

* HyOx Medical Treatment Center
Marietta, Georgia
(678) 303-3200

Hyperbaric Medicine Services
† Dwight D. Eisenhower Army Medical Center
Fort Gordon, Georgia
(706) 787-3113

HyperbarX at Dekalb
Lithonia, Georgia
(770) 593-9450

HyperbarX at North Atlanta
Atlanta, Georgia
(678) 843-5394

HyperbarX at North Forsyth
Cumming, Georgia
(770) 771-6400

HAWAII

Hyperbaric Treatment Center
† John A. Burns School of Medicine
Honolulu, Hawaii
(808) 587-3425

IDAHO

Elks Wound Center
Idaho Elks Rehabilitation Hospital
Boise, Idaho
(208) 489-5800

Elks Wound Center
Idaho Elks Rehabilitation Hospital
Meridian, Idaho
(208) 489-5800

ILLINOIS

* Carle Foundation Hospital Hyperbaric Center
† Carle Foundation Hospital
Urbana, Illinois
(217) 326-4322

* Methodist Center for Wound & Hyperbaric Medicine
† Methodist Medical Center of Illinois
Peoria, Illinois
(309) 672-4582

IOWA

Genesis Wound & Hyperbaric Institute
† Genesis Health System
Davenport, Iowa
(563) 421-1585

* Great River Wound & Hyperbaric Clinic
† Great River Medical Center
West Burlington, Iowa
(319) 768-4124

Trinity Center / Wound Care & Hyperbaric Medicine
† Trinity Hospital
Davenport, Iowa
(563) 742-5122

LOUISIANA

The Hyperbaric & Wound Center
† Ochsner Medical Center-Kenner
Kenner, Louisiana
(504) 464-8686
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<td>Department of Hyperbaric Medicine</td>
<td>Meridian, Mississippi</td>
<td>(601) 703-4200</td>
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<td>Rochester, Minnesota</td>
<td>(507) 266-4602</td>
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<td>† Saint Joseph Health Center</td>
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<td>(816) 995-2115</td>
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<td>The Wound Care Center</td>
<td>North Kansas City, Missouri</td>
<td>(816) 691-5055</td>
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<td>† North Kansas City Hospital</td>
<td>North Kansas City, Missouri</td>
<td>(816) 691-5055</td>
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NEW JERSEY

Central Jersey Wound & Hyperbaric Treatment Center
† CentraState Healthcare System
Freehold, New Jersey
(866) 659-6863

* Hyperbaric Medicine Unit
† Morristown Memorial Hospital
Morristown, New Jersey
(973) 971-6015

The Hyperbaric Medicine Program
† Englewood Hospital & Medical Center
Englewood, New Jersey
(201) 894-3898

Hyperbaric Program
† Overlook Hospital
Summit, New Jersey
(908) 522-5900

Wound Healing Center
† Warren Hospital
Phillipsburg, New Jersey
(908) 213-6653

NEW MEXICO

Christus St. Vincent Regional Wound & Hyperbaric Ctr
† Christus St. Vincent
Santa Fe, New Mexico
(505) 946-3180

NEW YORK

* Center for Wound Care & Hyperbaric Medicine
† St. Joseph’s Hospital Health Center
Fayetteville, New York
(315) 329-7770

Hyperbaric Medicine & Wound Care
† Plainview Hospital
Plainview, New York
(516) 796-1313

* Hyperbaric Medicine and Wound Care Center
† Upstate University Hospital
Syracuse, New York
(315) 464-4910

Hyperbaric and Wound Healing Center
† St. Joseph Hospital
Bethpage, New York
(516) 520-2788

Institute for Wound Care & Hyperbaric Medicine
† Hudson Valley Hospital Center
Cornell Manor, New York
(914) 734-3050

Westchester Hyperbaric Center
† Westchester Medical Center
Valhalla, New York
(914) 493-1500

Wound Care Center
† Vassar Brothers Medical Center
Poughkeepsie, New York
(845) 431-2400

Wound & Hyperbaric Institute at Good Samaritan
† Good Samaritan Hospital
Suffern, New York
(845) 368-5590

The Wound Healing Center at Kingston Hospital
† The Kingston Hospital
Kingston, New York
(845) 334-4325

Wound Healing Center & Hyperbaric Medicine Program
† Winthrop-University Hospital
Mineola, New York
(516) 663-8498

NORTH CAROLINA

* Center for Hyperbaric Medicine & Environmental Physiology
† Duke University Medical Center
Durham, North Carolina
(919) 684-6726

Comprehensive Wound Care
Kinston, North Carolina
(252) 527-9928

Park Ridge Wound Center & Hyperbaric Medicine
† Park Ridge Health
Hendersonville, North Carolina
(855) 774-5433
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| OKLAHOMA      | * Midwest Wound Care  
† Midwest Regional Medical Center  
Midwest City, Oklahoma  
(405) 610-8056 |
| OHIO          | * Wound Care & Hyperbaric Medicine Center  
† Kettering Medical Center  
Wright-Patterson AFB, Ohio  
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Membership in the Undersea and Hyperbaric Medical Society (UHMS) is not a prerequisite for publication in the journal. Manuscripts are accepted for publication on the condition that they are contributed solely to this journal. Authors submitting a manuscript do so with the understanding that if it is accepted for publication, copyright for the article is assigned exclusively to the UHMS. On request, permission will be given to quote from papers or to use tables and illustrations in other publications, provided credit is given to the original source.

Acceptance of a manuscript is based on originality and quality of the work as well as the clarity of presentation. Two or more members of the Editorial Board or guest referees will evaluate all manuscripts for significance, soundness and conformance to journal format.

Authors should recommend three qualified individuals to act as independent referees for their papers; the Editor-in-Chief welcomes these suggestions but is not obliged to follow such recommendations.

After papers have been accepted, authors are asked to submit the final version of the paper electronically.

Fees

Authors of accepted papers will be assessed a flat publication fee of $250 U.S. dollars. Additional fees will be incurred for color reproduction.

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Proofs are sent to authors to be checked carefully. Necessary changes must be clearly indicated on the galley, with corrections typed in a color text or highlighting. Proofs must be sent back within the time specified by the managing editor. Authors can find reprint instructions on the final two pages of the journal or at http://www.uhms.org/?page=Journal under “Reprint Order Form.”

TREATMENT OF SUBJECTS

The UHMS endorses the principles of the Declaration of Helsinki on the treatment of human subjects and the guiding principles in the care and use of animals approved by the Council of the American Physiological Society. For more on these topics see the sections entitled “Scope of the Journal” and “Recommendations from the Declaration of Helsinki” in the following pages.

TYPES OF ARTICLES IN THIS PUBLICATION

To meet its responsibilities to its readers and to the public at large, the Undersea and Hyperbaric Medicine Journal strives to provide unbiased scientific information and fair analyses through its publication of the following types of papers.
1. **Research Reports:** Results of experimental, theoretical and clinical investigations on topics important to the understanding of undersea, submarine and hyperbaric medicine. Short reports that make a substantial scientific contribution as well as extensive studies will be considered.

2. **Clinical communications and clinical case reports:** Observations of an exceptionally revealing nature.

3. **Review articles:** May cover scientific and practical subjects and may express personal opinions of the author.

4. **Current issues:** Well-reasoned essays on topics of interest to the journal’s readers; may draw on new or published experimental data and may be controversial in nature.

5. **Technical communications:** Descriptions of new methods or equipment; must include data to support contentions.

6. **Proceedings of symposiums or workshops:** Usually a group of short communications that have the flavor of reviews.

7. **Letters to the editor:** Discussion of scientific papers that have appeared in the journal or scientific issues of interest to the journal’s readers; should include an informative title and be as short as possible. References may be used if necessary, but tables and figures are discouraged.

**PREPARATION OF MANUSCRIPTS**
The overriding principles are that the composition is correct and unambiguous, clear and concise. When writing, the active voice is usually preferable to the passive voice.

Parallel construction of groups of like items and/or concepts aids in comprehension. Figures should be uncomplicated and legible. Abbreviations and acronyms should not be overused, be clearly defined at first appearance in the abstract as well as in the text and avoided in the title.

Specific items of information should appear only once in the manuscript. There should not be verbatim repetition of Copyright©2012 Undersea and Hyperbaric Medical Society, Inc. in the text of material that appears in a table or figure, duplication of data in graphs and tables; neither should there be repetition in Discussion of information that appears in Results.

Authors are encouraged to use papers that have appeared in recent issues of Undersea & Hyperbaric Medicine as models for their manuscript preparation. All accepted manuscripts are subject to final editing by the editors to improve readability and conserve space.

**MANUSCRIPT REQUIREMENTS:**
1. Manuscripts must be submitted electronically, formatted on an 8½-by-11-inch letter-size document with 1-inch margins with double-spacing between lines (this facilitates reading by reviewers).
2. References and legends for illustrations must be adjacent to the graphics. Graphics can be embedded in the text or placed at the end of the paper with their placement clearly marked at the spot in the text where they are to appear.
3. A cover sheet must accompany the manuscript. It should give the title of the paper, the names and affiliations of the authors, a short title (referred to as the running head) and the name, address, telephone and fax numbers – as well as the e-mail address – of the corresponding author.

**Please note:** Both reviewers and authors for UHM are blinded to one another’s identities; authors’ names should appear only on the cover sheet.

4. An accompanying letter must include a statement that all authors have read and approved the manuscript, that the material in the paper has not been published elsewhere (except as an abstract), and that the paper is not currently being considered for publication by another journal.

5. Conflict of interest forms must be submitted. All submissions should be accompanied by clear disclosures from all authors, noting any affiliations, funding sources or financial holdings that could raise questions about possible sources of bias.

In the event of no conflict in the viewpoint of the authors a statement to that effect should accompany the manuscript.

Before manuscript acceptance, UHM will ask authors to sign an authorship/conflict-of-interest form. Specific information will be provided at the onset of the review process.

6. **Author responsibility:** If a submission is the work of a group within one center or at multiple centers, that group should select one individual who accepts direct responsibility for the manuscript’s content as well as the agreed sequence of contributing authors. This person will serve as corresponding author or guarantor, and this designation must be clearly stated on the title page of the manuscript, with the following contact information: mailing address, email address, telephone number and fax number.

8. **Title page:** Should include the following.
   a. title of no more than 85 characters, including spaces;
   b. authors’ names;
   c. laboratory or institution of origin, with city and state or country;
   d. a running head, not to exceed 50 characters, including spaces;
   e. a complete address for mailing proofs; plus
   f. telephone and fax numbers and email address.
   Titles should be informative; the implication that a manuscript is one of a series of related papers is discouraged (e.g., *Decompression sickness studies I*).

9. **Abstracts:** An informative abstract of 200 words or fewer, suitable for abstracting agencies without rewording, should state the purpose of the research, what was done, what was found, and what was concluded. Titles should contain indexable words.

10. **Text:** Except in unusual situations, the manuscript should be divided into Introduction, Methods, Results and Discussion. Long stretches of text should be broken by suitable subheadings, but subheadings should not be overused.
   Unusual symbols should be avoided.

11. **References:** Authors are responsible for supplying complete references and verifying them against the original documents. References must be numbered consecutively in the order in which they first appear in the text, and identified in the text by Arabic numerals in parentheses or brackets.
   References cited only in tables or legends should be numbered in accordance with a sequence corresponding to the first mention of the table or figure in the text.

12. **Authors:** List names and initials of all authors when six or fewer; when seven or more, list only the first three authors and add *et al.* Citations in the reference list are to be in the form used by the U.S. National Library of Medicine and *Index Medicus*.


Manuscripts that have been accepted should be cited in the reference list as regular references, with ‘in press’ in place of journal pages. Citations such as unpublished observations, personal communication, manuscript in preparation or to be published are not to appear in the reference list, although reference to such a communication, if it exists in written form, may be cited in the text in parentheses. References to government reports should not be cited unless such reports are easily available to all readers.

13. **Equations:** Equations should appear in the text in an appropriate type style (*italics, bold* type, etc.). Authors should carefully distinguish between capital and lower-case letters, Roman and Greek characters and letters and numerals.
   Number equations sequentially, in parentheses on the left edge of the text. All constituent terms should be defined when they initially appear. Authors are responsible for correct formatting of each term in the equation and, because of potential conversion problems, they must be sent using the Times New Roman font in a TIFF file. Equations should be considered camera-ready when they are submitted.

14. **Tables:** Tables should be limited to material needed to make the point of the paper and should be nearly self-explanatory. They should be numbered consecutively in Arabic numerals and bear a short title.
   Explanatory matter, excluding definitions of abbreviations, should appear in table footnotes. Statistical measures of variation (SD, SE, etc.) should be stated.
   Tables should be in one- or two-column widths and no more than eight rows by eight columns of data, with one row for the column headings. Headings should use only horizontal text – no vertical text. Preferred font is Times New Roman.

15. **Acknowledgments:** Acknowledgments of persons who aided in the work and of funding agencies, along with any other special considerations about the manuscript, should appear at the end of the text, before the references.
16. **Footnotes:** Footnotes to material in the text are discouraged. Footnotes to tables are acceptable and should be identified in sequence by lowercase letters of the alphabet in italic superscript.

17. **Units of measure:** The Système Internationale d’Unités (SI units) format will be used to express measurements of pressure, depth, length, weight, time, temperature, energy, power, force and concentration [Standard Practice for Use of the International System of Units (SI) Document E380-89a, American Society for Testing and Materials, Philadelphia, Pa. 1989].

If the subject matter makes it appropriate to use non-SI units such as fsw, msw, atm or bar, a parenthetical conversion to pascals, kilopascals or megapascals should accompany the first mention of a pressure value in the abstract and in the text.

Units of fsw and msw should not be used to express partial pressure or when the nature of the subject matter requires precise evaluation of pressure. The proper method for the expression of other units or appreciations may be found in *Br Med J* 1978; 1:1334–1336 and *Aviat Space Environ Med* 1984; 55: 93–100.

Authors must include after all units a small parenthetical (a) or a small parenthetical (g) to indicate whether units are in absolute or gauge terms.

18. **GRAPHICS**

**General:** All graphics, which includes anything other than text, should be numbered in Arabic numerals, in sequence as they appear in the text and must conform to one-column (3.125") width or two-column width (6’’). Each is to be accompanied by a suitable legend not exceeding 40 words.

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Diagrams, charts and other line drawings should be sharp and clear.

Freehand or typewritten lettering on figures is not acceptable. Lettering must be proportional to the size of the illustration to ensure that it is legible after reduction. Size to fit the journal page should be considered.

An internal scale marker (a bar of defined length) should be drawn directly on all micrographs, and the length specified in the legend.

Good line drawings of equipment are usually more effective than photographs.

Upon acceptance of the manuscript, authors must be prepared to submit graphics in TIFF format, 300 dpi or better. Grayscale is preferable to color, both for simplicity and because the author will be assessed a substantial charge for color printing.

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**Depiction of animals:** *Animals must be depicted only by line drawing or other form of animation.*

It is the journal’s policy not to publish photographs that might be perceived as raising animal welfare concerns.

**Depiction of patients:** *Undersea and Hyperbaric Medicine* publishes only photos of subjects who have provided express, written permission to the author to do so. The terms of the subject/patient consent determine whether a de-identified photo (i.e., with a black box obscuring the identity of the subject) would need to be used. *UHM* will insert an editorial comment in articles in which such photos are included specifically documenting that consent was obtained.

**AUXILIARY PUBLICATIONS**

Detailed tables, appendices, mathematical derivatives, extra figures and other supplementary matter may be deemed too voluminous to be included in the journal article. Such material may be submitted for deposition with the American Society for Information Sciences (ASIS), National Auxiliary Publication Service, at no charge. The information is deposited by the editorial office with the consent of the author, and a footnote will appear in the published article to the effect that photoprint or microfiche copies are available at a moderate cost.

*Revised September 2012*
SCOPE OF THE JOURNAL

Undersea & Hyperbaric Medicine accepts manuscripts for publication related to the areas of diving research and physiology, hyperbaric medicine and oxygen therapy, submarine medicine, naval medicine and clinical research related to the above topics. Scientific papers must deal with significant and new research in an area related to biological, physical and clinical phenomena related to the above environments.

The following types of papers are published: Original Research (theoretical and experimental); Clinical Communications (which may include case reports if they include control observations of a revealing nature); Current Issues; Technical and Preliminary Notes; Letters to the Editor; and Book Reviews.

Reports of major contributions or symposiums will be considered and may be published as supplements to regular issues. Authors are referred to “Instructions for Authors” for more details on the categories of papers.

Undersea & Hyperbaric Medicine is abstracted and/or indexed in Chemical Abstract Service, Excerpta Medica, Oceanic Abstracts, Bioscience Information Service of Biological Abstracts, Current Contents, Index Medicus and Current Awareness in Biological Sciences. Undersea & Hyperbaric Medicine is available on 16-, 35- and 105-mm microfiche from University Microfilms International, 300 North Zeib Road, Ann Arbor, MI 48106.

On file in the administrative offices of the Society are two documents pertaining to Institutional Review Board regulations CFR50 and 21cfr56. The UHMS, as publisher of the UHM journal, acknowledges that all human research requires informed consent and IRB approval in accordance with the laws of the country in which the work was performed. This includes abstracts as well since they are published in UHM.

The Society endorses the principles embodied in the Declaration of Helsinki (see below) and expects that all investigations involving man reported in its journal will have been conducted in conformity with these principles.

The Society expects that the Guiding Principles in the Care and Use of Animals (see below) will have been observed in all animal experimentation reported in its journal.

Recommendations from the

DECLARATION OF HELSINKI

BASIC PRINCIPLES

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research to which the personality of the subject is liable to be altered by drugs or experimental procedures.

CLINICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if, in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient’s freely given consent after the patient has been given a full explanation.

In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.
NON-THERAPEUTIC CLINICAL RESEARCH

1. In the purely scientific application of clinical research carried out on human beings, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.

2. The nature, the purpose and risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue research if in his or their judgment, it may, if continued, be harmful to the individual.

GUIDING PRINCIPLES IN THE CARE AND USE OF ANIMALS

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort; they must be kindly treated, properly fed and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthetics is necessary during the study, acceptable technique to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from the anesthesia, the animal must be killed in a humane manner at the conclusion of the observation.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of Veterinary Medicine.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

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<td>e. Total Free or Nominal Rate Distribution (Sum of 15d (1), (2), (3) and (4))</td>
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<td>110</td>
</tr>
<tr>
<td>f. Total Distribution (Sum of 15c and 15e)</td>
<td>1867</td>
<td>1867</td>
</tr>
<tr>
<td>g. Copies not Distributed (See instructions to Publishers #4 (page 3))</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>h. Total (Sum of 15f and g)</td>
<td>1900</td>
<td>1900</td>
</tr>
<tr>
<td>i. Percent Paid (15c divided by 15f times 100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Total circulation includes electronic copies. Report circulation on PS Form 3526-X worksheet.

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- [ ] If the publication is a general publication, publication of this statement is required. Will be printed in the sixth issue of this publication.
- [ ] Publication not required.

### Signature and Title of Editor, Publisher, Business Manager, or Owner

Renee Duncan, Managing Editor, UHN

Date: 9-27-2012

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PS Form 3526, August 2012 (Page 2 of 3)
# PRESSURE CONVERSION TABLE

The units of pressure preferred for manuscripts submitted to *Undersea & Hyperbaric Medicine* are the pascal (Pa = Newton / m²), kilopascal (kPa), or megapascal (MPa), defined by the International System of Units (SI). If the nature of the subject matter makes it appropriate to use non-SI units, such as fsw, msw, atm or bar, a parenthetical conversion to pascals, kilopascals, or megapascals should accompany the first mention of a pressure value in the abstract and in the text.

Atmospheres absolute is a modified unit of pressure due to the appendage “absolute”; the use of “atm abs” is an acceptable abbreviation; “ATA” is also recognized.

<table>
<thead>
<tr>
<th>1 atm</th>
<th>1 atm = 1.013250 bar</th>
<th>1 atm = 33.08 fsw</th>
<th>1 atm = 10.13 msw</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 atm</td>
<td>101.3250 kPa</td>
<td>1 bar = 32.646 fsw</td>
<td>1 bar = 10.00 msw</td>
</tr>
<tr>
<td>1 atm</td>
<td>14.6959 psi</td>
<td>1 fsw = 3.063 kPa</td>
<td>1 msw = 10.00 kPa</td>
</tr>
<tr>
<td>1 atm</td>
<td>760.00 torr</td>
<td>1 fsw = 22.98 torr</td>
<td>1 msw = 1.450 psi</td>
</tr>
<tr>
<td>1 bar</td>
<td>100.000 kPa</td>
<td>1 psi = 2.251 fsw</td>
<td>1 msw = 75.01 torr</td>
</tr>
<tr>
<td>1 bar</td>
<td>100,000 Pa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 bar</td>
<td>14,503.77 psi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 bar</td>
<td>750.064 torr</td>
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<td></td>
</tr>
<tr>
<td>1 MPa</td>
<td>10,000 bar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 psi</td>
<td>6,894.76 Pa</td>
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</tr>
<tr>
<td>1 psi</td>
<td>51.7151 torr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 torr</td>
<td>133.322 Pa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*a Primary definition for fsw; assumes a density for seawater of 1.02480 at 4°C (the value often used for depth gauge calibration).

*b These primary definitions for fsw and msw are arbitrary since the pressure below a column of seawater depends on the density of the water, which varies from point to point in the ocean. These two definitions are consistent with each other if a density correction is applied. Units of fsw and msw should not be used to express partial pressures and should not be used when the nature of the subject matter requires precise evaluation of pressure; in these cases investigators should carefully ascertain how their pressure-measuring devices are calibrated in terms of a reliable standard, and pressures should be reported in pascals, kilopascals, or megapascals.

*c Primary definition for msw; assumes a density for seawater of 1.01972 at 4°C.

*d Signifies a primary definition (1) from which the other equalines were derived.
