UNDERSEA AND HYPERBARIC MEDICAL SOCIETY

Undersea and Hyperbaric Medicine JOURNAL

VOLUME 49 ✦ NUMBER 3 ✦ THIRD QUARTER 2022

UNDERSEA AND HYPERBARIC MEDICINE

The Journal of the Undersea & Hyperbaric Medical Society Inc.

VOLUME 49, NUMBER 3 ✦ THIRD QUARTER 2022

Undersea and Hyperbaric Medicine (ISSN 1066-2936) is published quarterly by the Undersea & Hyperbaric Medical Society, 631 U.S. Highway 1, Suite 307, North Palm Beach, FL 33408 USA.

Print subscription price/annual
U.S.-based associates $86; non-U.S. associates $168; U.S. members $120; internat'l members $185; non-members/institutions $400; active military $108 – for a quarterly volume of approx. 100-180 pages, including postage. PDF versions free to subscribers.

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The UHM JOURNAL is a member periodical of the Undersea and Hyperbaric Medical Society printed for subscribers and posted on its website at *www.uhms.org* for all UHMS members.

THE UHM JOURNAL provides a forum for ideas and information to the undersea and hyperbaric medical community and welcomes ideas, commentary and support from its readers.

Unless noted, all authors have declared that no conflicts of interest exist with their respective submissions. UHMS does not sell or trade its mailing lists.

UNDERSEA & HYPERBARIC MEDICINE

International Multicenter Registry for Hyperbaric Oxygen Therapy: Results through June 2021

Nicole P. Harlan, MD [1]; Judy A. Ptak, RN [2]; Judy R. Rees, MPH, PhD [3]; Devin R. Cowan, MS [3]; Abigail M. Fellows, MA [3]; Rachel A. Moses, MD [1]; Judith A. Kertis, RN [1]; Pamela M. Hannigan, RN [1]; Saeed A. Juggan, BS [4]; Janet Peacock, PhD [3,5]; Michael Bennett, MD [6]; Jay C. Buckey, MD [3] for the Multicenter Registry for Hyperbaric Oxygen Therapy Consortium [7]

[1] Dartmouth-Hitchcock Medical Center, Lebanon, NH, US; [2] Independent Consultant, Plainfield, NH, US; [3] Geisel School of Medicine at Dartmouth, Lebanon, NH, US; [4] Dartmouth College, Hanover, NH, US; [5] King's College, London, UK; [6] Prince of Wales, Hospital, Randwick, NSW, Australia

[7] Consortium members listed at end of manuscript

CORRESPONDING AUTHOR: Nicole P. Harlan – *nicole.p.harlan@hitchcock.org*

ABSTRACT

Harlan NP, Ptak JA, Rees JR, et al. International Multicenter Registry for Hyperbaric Oxygen Therapy: Results through June 2021. Undersea Hyperb Med. 2022 Third Quarter; 49(3): 275-287.

Introduction: The International Multicenter Registry for Hyperbaric Oxygen Therapy (International Report Registered Identifier DERR1-10.2196/18857) was established in 2011 to capture outcomes and complications data for both Undersea and Hyperbaric Medical Society (UHMS) approved and selected unapproved hyperbaric oxygen (HBO_2) therapy indications.

Methods: A Research Electronic Data Capture (REDCap) template was designed and distributed to all participating centers for prospective data collection. Centers contributed de-identified demographic, treatment, complications, and outcome data. This report provides summary data on sites and enrollment, as well as pre- and post-treatment data on quality of life (EQ-5D-5L questionnaire), head and neck radiation outcomes, non-healing wounds (Strauss score), and idiopathic sudden sensorineural hearing loss. Data were analyzed mainly using the Wilcoxon signed-rank test.

Results: Twenty-two centers contributed data for 2,880 patients. The most common UHMS-approved indication was delayed radiation injury, followed by enhancement of wound healing, and carbon monoxide poisoning. One hundred and twenty-five patients were treated for non-UHMS approved indications. Quality of life, head and neck radiation symptoms, Strauss wound scores, and hearing were significantly improved after HBO_2. Complication rates were low and comparable to previous reports. The registry also offered the ability to analyze factors that affect outcomes, such as smoking and severity of hearing loss.

Discussion: The registry accrues prospective data on defined outcomes from multiple centers and allows for analysis of factors affecting outcomes. This registry does not have a control group, which is a limitation. Nevertheless, the registry provides a unique, comprehensive dataset on HBO_2 outcomes from multiple centers internationally. ∎

KEYWORDS: hyperbaric medicine; hyperbaric oxygen therapy; pulmonary function

INTRODUCTION

Currently hyperbaric oxygen (HBO_2) therapy is approved by the Undersea and Hyperbaric Medical Society (UHMS) to treat 14 different conditions. Data supporting the use of HBO_2 in these conditions can range from level A evidence, supported by multiple randomized controlled trials and meta-analysis data, to level C, supported by limited data or expert opinion. Use of HBO_2 for carbon monoxide poisoning, enhancement of healing in problem

wounds, and idiopathic sudden sensorineural hearing loss (ISSNHL) are supported by level A evidence, while all other indications are supported by levels B and C evidence. Multiple reasons exist for the limited supporting evidence for HBO_2. Certain indications, such as intracranial abscess or air embolism, may be seen infrequently by individual centers, making these indications difficult to study.

Additionally, common indications such as delayed radiation injury and enhancement of healing in selected problem wounds require a large commitment in time and effort by both patient and facility that make sham-controlled trials problematic. Enrolling and treating enough patients to study a particular indication at any one center presents a challenge to executing large studies. In 2001, ethicists Chan and Brody argued for the importance of patient registries in hyperbarics as a means of evaluating off-label uses of hyperbarics and defining populations in whom a clinical trial might be warranted [1].

The International Multicenter Registry for Hyperbaric Oxygen Therapy (MRHOT) was started in 2011 at the Geisel School of Medicine at Dartmouth (Lebanon, New Hampshire, U.S.) to strengthen our understanding of HBO_2's impact and to generate a large and prospective cohort detailing the outcomes of treatment. A consortium agreement in 2016 joined Dartmouth-Hitchcock Medical Center with Elliot Hospital (Manchester, New Hampshire, U.S.) as the first centers in the registry consortium. The Wesley Center for Hyperbaric Medicine (Auchenflower, Queensland, Australia) joined in 2017. In 2019 several additional centers joined the registry consortium and started entering data (Figure 1). The registry uses a uniform Research Electronic Data Capture (REDCap) template at all centers for entry of de-identified data on patients, their indications for HBO_2, and specific outcome measurements for each indication. Details of the registry design have been reported elsewhere [2]. In this review, we report the enrollment of the centers in the registry, the number of patients enrolled by indication, and selected outcomes related to quality of life, radiation injury, problem wounds, and ISSNHL. We also report on the complications experienced by patients during or after HBO_2.

METHODS

The organization and data collected within the registry have been described previously [2]. Briefly, centers join the registry by signing a consortium agreement which includes language about data sharing, publications from the data, intellectual property, liability, insurance, and confidentiality. All centers obtain Institutional Review Board (IRB) and ethics approval. Patient consent is obtained or the IRB at the enrolling site waives patient consent. Data are entered into REDCap for each patient. Centers state that they will enter data for at least 95% of the patients seen and sign a certification that they have entered all patient data once per quarter.

We then analyze the data for outliers and inappropriate data types reported in order to ensure data accuracy. Not all data collection instruments have been in the registry since its inception. The EQ-5D-5L quality of life questionnaire, for example, was added to the registry template in October 2018. Most of the questionnaires are available in Spanish as well as English. The steering committee for the registry can add or modify data collection instruments based on feedback from centers.

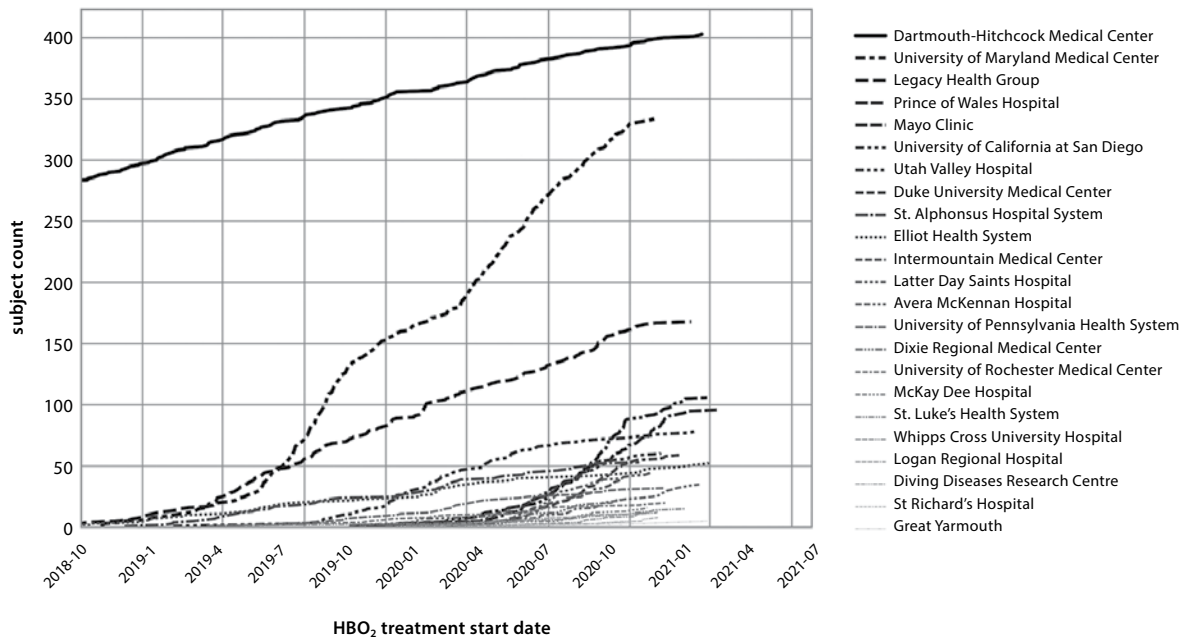
Statistical methods

The primary statistical test used thus far has been the Wilcoxon signed rank test, which is used to compare questionnaire scores, pure-tone averages, and other readings before and after HBO_2 treatment.

RESULTS

The first patient was enrolled September 6, 2011. From then to June 1, 2021, there have been 2,880 patient entries, 1,773 patients who started treatment, 1,708 patients who completed treatment, and a total of 30,577 treatments recorded. Not all enrolled sites have started entering data, as noted in Table 1. A total of 196 patients had reasons recorded for not being treated. Of these, 25 percent

Figure 1. Patient recruitment by site since 2019



At present, the three largest contributors to the registry are Dartmouth-Hitchcock Medical Center, the University of Maryland, and Legacy Health Group.

of patients were not treated because they did not meet UHMS criteria, 9.7% of patients had a contraindication to treatment, 8.7% of patients did not have a Wagner Grade 3 ulcer, and 56.6% were not treated for a reason not listed. These "other" reasons included onset of hearing loss greater than four weeks before referral, active cancer or workup for cancer, and wound healing without HBO_2.

Delayed radiation injury was the most common indication for treatment, followed by enhancement of healing in selected problem wounds and carbon monoxide poisoning (Table 2). Overall, the most commonly used treatment pressure was 2.4 ATA (Figure 2). The numbers of patients with complete data for each indication varies because of differences in implementation of various questionnaires at each center, particularly as centers started data collection and learned to work with the registry. Patient numbers also vary due to data incompleteness attributable to patients ending treatment early and patients still undergoing treatment at the time of data submission. The "Consent" variable was added later in data collection, but once it was added, only one patient did not consent to their information being used in the registry, while 2,069 consented.

Quality of life outcomes

For the 464 patients who completed both the pre- and post-HBO_2 EQ-5D visual analog scale, patient quality of life improved significantly after hyperbaric treatment ($p<0.001$, Figure 3), from a mean of 69.2 (95% confidence interval 67.3-70.9) to a mean of 75.6 (95% CI 74.0-77.2), with 0 being the worst quality of life imaginable, and 100 being the best. The visual analog scale showed improvement for 59% of the 464 patients; 22% of the cases showed a decline on this measure (Figure 3). Visual analog scales improved in every different indication treated (Table 3).

Table 1. Participating sites and locations entering data in the Multicenter Registry

Avera McKennan Hospital, Sioux Falls, SD (AVERA) – Started 11/22/19
Dartmouth-Hitchcock Medical Center, Lebanon, NH (DHMC) – Started 05/28/11
DDRC Healthcare, Hyperbaric Medical Centre, Plymouth, UK (DDRC) – Started 3/01/2021
The Diver Clinic, Poole, UK – Pending Start
Dixie Regional Medical Center, St. George, UT (DRMC)* – Started 12/31/19
Duke University Medical Center, Durham, NC (DUKE), – Started 12/21/19
East of England – LHM Hyperbaric Unit, James Paget University Hospital, Great Yarmouth (EOE) – Started 3/01/2021
Elliot Health System, Manchester, NH (EHS) – Started 05/09/18
Hyperbaric Medicine Unit, St Richard's Hospital, Chichester, UK (CHI) – Started 3/01/2021
Intermountain Medical Center, Salt Lake City, UT (IMC)* – Started 04/04/20
Latter Day Saints Hospital, Salt Lake City, UT (LDSH)* – Started 11/07/19
Legacy Health Group, Portland, OR (LHG) – Started 03/03/18
Logan Regional Hospital, Logan, UT (LMRC)* – Started 01/21/20
Mayo Clinic, Rochester, MN (MAYO), – Started 11/09/19
McKay Dee Hospital, Ogden, UT (MKD)*, Started 02/05/20
Midlands Diving Chamber, Rugby, UK – Pending Start
North England Medical and Hyperbaric Services, Hull, UK – Pending Start
Northwest Recompression Unit, Birkenhead, UK – Pending Start
Prince of Wales Hospital, Randwick, NSW, Australia (PWH) – Started 12/26/2019
St. Alphonsus Hospital System, Boise, ID (SAHS)) – Started 12/05/2018
St. Luke's Health System, Boise, ID (SLHS) – Started 03/19/20
The Hyperbaric Unit, Whipps Cross University Hospital, London, UK (LHM) – Started 3/01/2021
University of California at San Diego, San Diego, CA (UCSD) – Started 02/16/19
University of Maryland Medical Center, Baltimore, MD (UMMC) – Started 10/30/18
University of Pennsylvania Health System, Philadelphia, PA (UPENN) – Started 04/07/19
University of Rochester Medical Center, Rochester, NY (URMC) – Started 04/10/19
Utah Valley Hospital, Provo, UT (UVH)* – Started 01/01/20
Wesley Hyperbaric, Auchenflower, AU – Pending Start

*Indicates part of Intermountain Health Care System. Dates indicate when the center started data entry.

Figure 2. Most commonly used treatment pressures

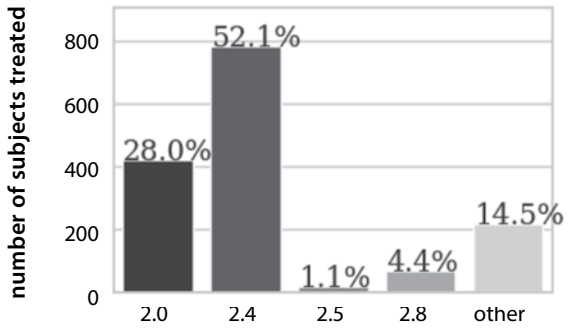
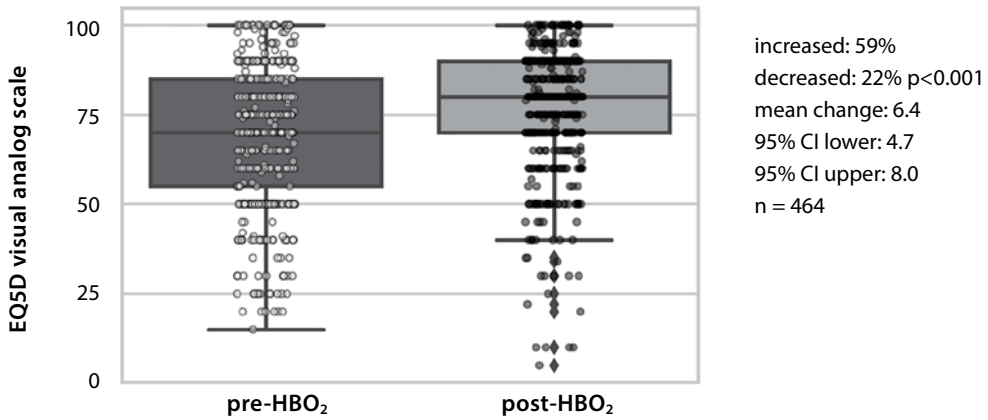


Table 2. Number of patients treated under each indication

indication	number	%
delayed radiation injury (not compromised grafts/flaps)	684	32.1
enhancement of healing in selected problem wounds (not compromised grafts/flaps)	322	15.1
carbon monoxide	306	14.4
compromised grafts and flaps	187	8.8
necrotizing soft tissue infections	173	8.1
other non-UHMS indication	109	5.1
osteomyelitis, refractory	97	4.6
idiopathic sudden sensorineural hearing loss	68	3.2
research protocol	45	2.1
central retinal artery occlusion	31	1.5
acute ischemia (not crush injury or compartment syndrome)	29	1.4
decompression sickness	26	1.2
crush injury, compartment syndrome	22	1
air or gas embolism (not to extremities)	19	0.9
gas gangrene	6	0.3
intracranial abscess	4	0.2
acute thermal burn injury	2	0.1
severe anemia	1	0

Figure 3. Post-HBO_2 quality of life



There was significant improvement in the EQ-5D visual analog slider measure of quality of life after HBO_2. On the EQ-5D visual analog scale, 100 represents the best quality of life imaginable and 0 the worst.

Table 3. EQ-5D visual analog scales improved across all indications treated
(where 0 represents the worst quality of life and 100 represents the best)

indication	EQ-5D visual analog scale change from before to after HBO_2 (N)
acute ischemia (not crush injury or compartment syndrome)	6.2 (5)
carbon monoxide	12.4 (14)
central retinal artery occlusion	50.0 (1)
compromised grafts and flaps	6.3 (47)
crush injury	12.5 (4)
decompression sickness	16.3 (11)
delayed radiation injury (not compromised grafts/flaps)	5.5 (239)
enhancement of healing in selected problem wounds (not compromised grafts/flaps)	0.2 (57)
idiopathic sudden sensorineural hearing loss	4.8 (25)
intracranial abscess	10.0 (1)
necrotizing soft tissue infections	11.3 (6)
osteomyelitis	14.1 (27)
other non-UHMS indication	12.6 (22)
research protocol	13.3 (3)

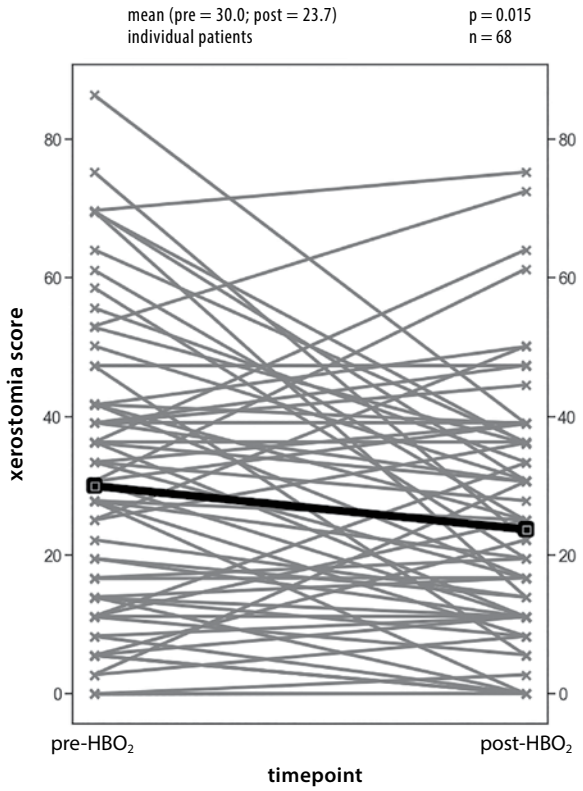
Delayed radiation injury

Delayed radiation injury (DRI) was the most common indication, with 822 patients referred. Of those referred, 709 had HBO_2 indicated with an intention to treat the person at the given center (i.e., not to be referred elsewhere). A total of 506 patients completed treatment for DRI, and the other 203 had incomplete data likely due to several factors, including patients being lost to follow-up, measures not completed at final visit, and treatment still under way at the time of data download.

The most commonly treated sites of radiation injury included the bladder (N=224), jaw/mandible (N=163), and rectum (N=71). Individuals with head and neck cancer completed a questionnaire that included questions from the EORTC QLQ H&N 35 and GRIX xerostomia questionnaires. Figure 4 shows the results from the GRIX questionnaire. Overall patients are reporting a significant improvement in xerostomia scores.

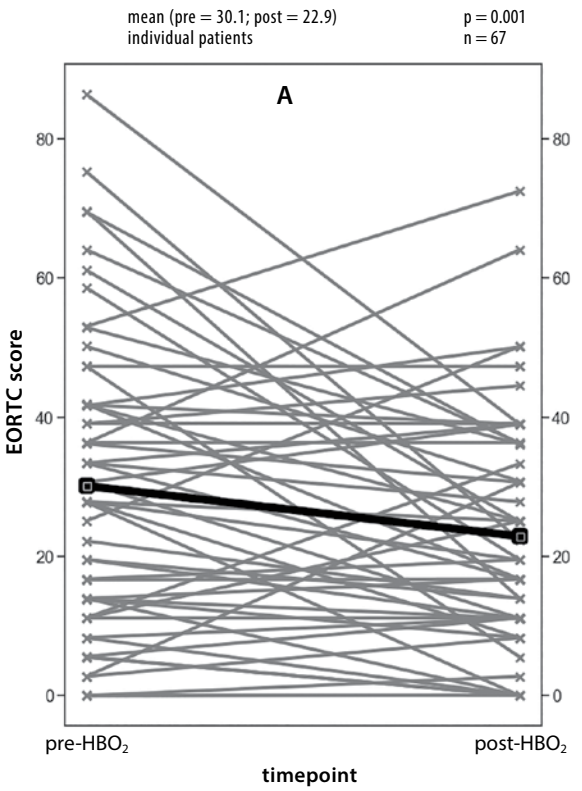
Overall, patients report improvement on the head and neck questionnaire (Figure 5). Average scores on the questionnaire dropped from 30.0 pre-HBO_2 (95% CI 25.0-35.3) to 23.7 post-HBO_2 (95% CI 19.5-28.4) (n=82, p<0.001). This change in score over the treatment period differed according to smoking status on subgroup analysis. The patients who were not smokers or had not been smoking for a year or more showed significant improvement (n=67, p<0.001)) on the head and neck questionnaire, while those who reported smoking the past year did not (n=11, p=0.14).

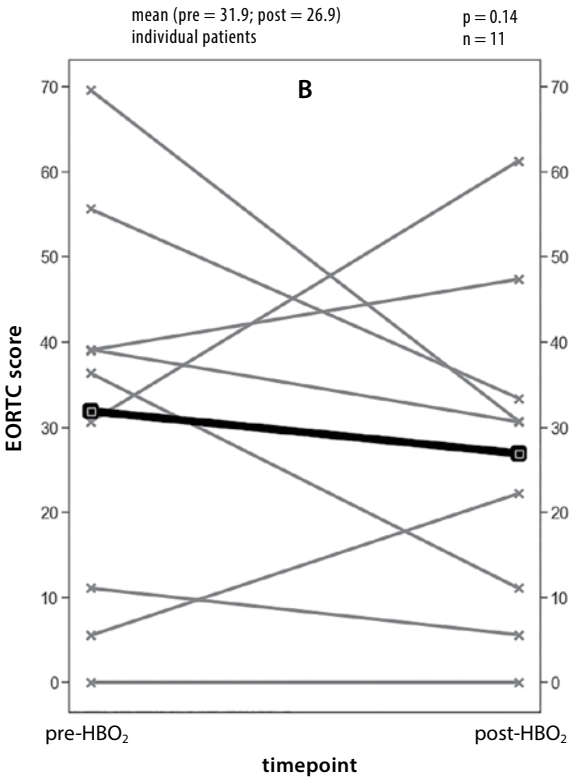
Figure 4. Xerostomia symptoms



Patients with head and neck cancer treated with HBO_2 showed significant improvement in xerostomia overall. Scores of 0 represent no symptoms, while higher scores represent more xerostomia symptoms.

Figure 5: Smokers vs. non-smokers





Figures 5A-B – right column ▶
Patients who are former smokers or non-smokers had a significant improvement in their symptoms: 5A top, p<0.001, n = 67, 49% of cases improved compared to 39% whose EORTC score worsened.

Patients who were current smokers or who quit in the last year did not have significant improvement in their symptoms as reported by the head and neck questionnaire (5B bottom, p = 0.14, n = 11). Lower EORTC scores represent fewer patient-reported symptoms.

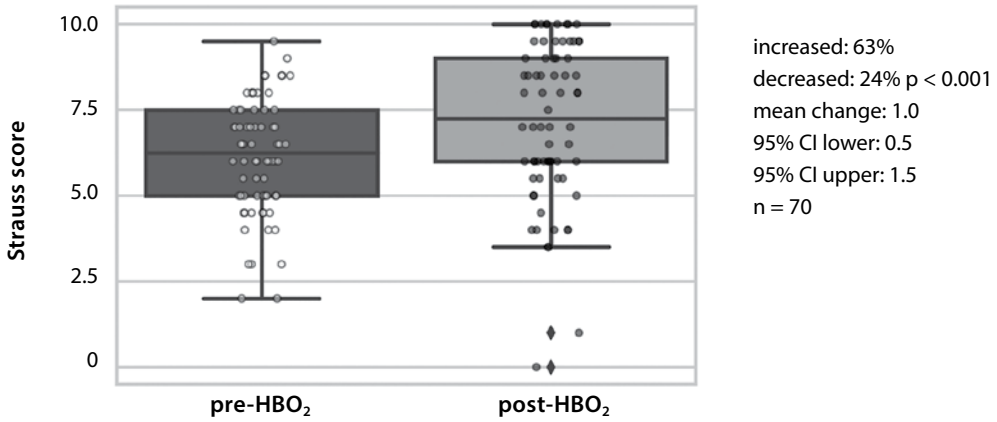
Enhanced healing in selected problem wounds

A total of 517 patients were evaluated for treatment for enhancement of healing in selected problem wounds. For 326 of these patients HBO_2 was indicated and the patient was going to be treated at the center doing the evaluation. Of those, 231 had completed HBO_2 at the time of this report. Of these patients 120 had diabetic foot wounds, 100 were listed as "other (cannot be compromised graft or flap)," and seven were diabetic wounds in locations other than the foot. The "other" wounds included two wounds from pyoderma gangrenosum, two wounds related to critical limb ischemia, two wounds related to CREST syndrome, four wounds related to surgery, including knee replacement, amputation, and penile implant. Because the Strauss measure was only recently added to the REDCap template, only 71 patients had pre- and post-HBO_2 Strauss scores recorded. Of those, 63% showed improvement on the Strauss Score and 24% worsened. In diabetic foot wounds, the Strauss score improved significantly from a median of 6.25 (range 2-9.5) pre-treatment to 7.25 (range 0-10) post-treatment ($p<0.001$, Wilcoxon signed-rank test).

Idiopathic sudden sensorineural hearing loss

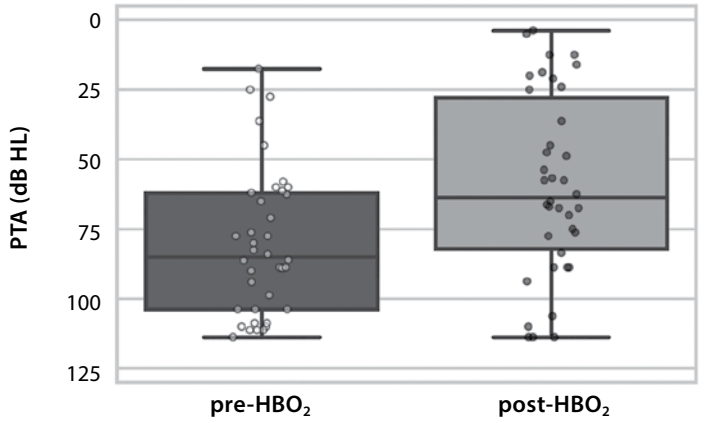
One hundred eighteen patients were referred for idiopathic sudden sensorineural hearing loss (IS-SNHL). Of these, 84 received a formal evaluation/consultation and 83 had HBO_2 indicated. Of those, 11 declined treatment and four were treated at a different center, leaving 68 patients who were treated. For the 38 patients with hearing test data before and after HBO_2, the four-frequency pure-tone average (500, 1,000, 2,000, 4,000 Hz averaged from the audiogram) improved significantly from 80.2 dB (95% CI 71.8-88.5) to 59.4 dB (95% CI 49.0-69.8) after HBO_2 ($p<0.001$, Wilcoxon signed-rank test, Figure 7). Seventy-six percent of the patients had improved PTA values following HBO2 while 16% had worsening in PTA. Nineteen patients had word recognition scores (WRS) before and after HBO_2. WRS improved significantly after HBO_2, with the mean percent correct increasing from 26.5% to 53.5%, a change of 26.9%, (95% CI 13.9% - 44.1% Figure 8). WRS improved for 53% of the 19 patients and none of the patients had a worse WRS after treatment. For the patients treated from 0-14 days after their hearing loss, there was a significant improvement in pure-tone average ($p<0.001$, N=23, 87% of subjects improved), while patients treated after 14 days had less significant improvement ($p=0.019$ N=15, 60% of patients improved, Figure 9).

Figure 6. Enhanced healing in select problem wounds



The Strauss score improved significantly after HBO_2, from a mean of 6.1 (95% CI 5.8-6.5) to 7.2 (95% CI 6.6-7.7). Strauss scores of 0-3 represent "futile" wounds, 4-7 represent "problem" wounds, and scores of 8-10 represent "healthy" wounds.

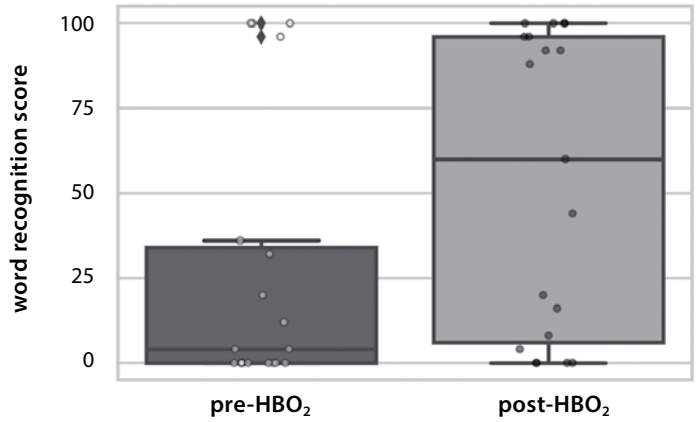
Figure 7. Pure-tone hearing averages



increased: 16%
decreased: 76% p<0.001
mean change: -20.8
95% CI lower: -28.6
95% CI upper: -14.6
n = 38

Pure-tone average (PTA) improved significantly after HBO_2 (mean PTA 80.2 dB HL pre-treatment, 59.4 dB HL post-treatment). Pure-tone hearing average of <25 dB represents normal hearing, while >95 dB represents profound hearing loss.

Figure 8. Word recognition scores

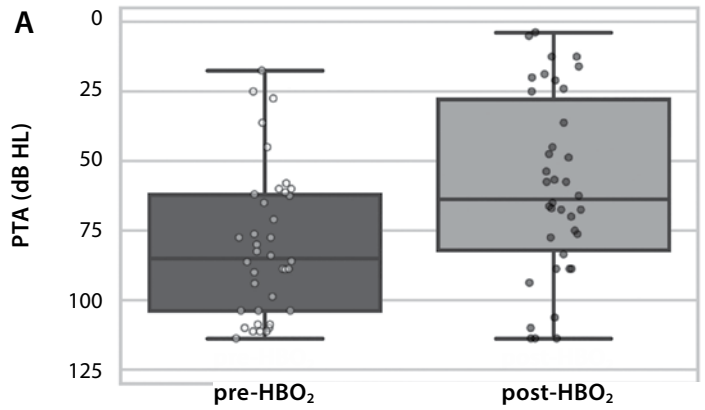


increased: 53%
decreased: 0% p = 0.005
mean change: 26.9
95% CI lower: 13.9
95% CI upper: 44.1
n = 19

Complications

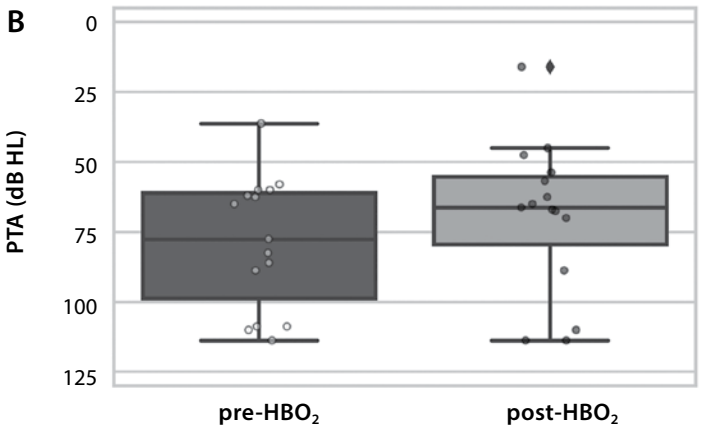
Complications are reported from the 1,773 patients who have started treatment. When difficulties arise with equalization of middle ear pressure, patients are sometimes referred to the ear, nose and throat (ENT) service for evaluation for myringotomy or pressure-equalization tubes (ear tubes). One hundred fifty-four (8.7%) patients were evaluated by ENT for middle ear barotrauma (MEBT), and 91 (5.1% of all patients) had an intervention in order to proceed with hyperbaric treatments. Thirty-three patients (1.9%) had unilateral ear tubes, and 49 (2.8%) had bilateral ear tubes placed. Nine (0.51%) had unilateral myringotomies. Of the patients with otic barotrauma, 42.9% were in monoplace chambers for more than 90% of their treatments, and 57.1% of patients were treated in a multiplace chamber more than 90% of the time. Fifty-five (3.1%) experienced sinus barotrauma, and four (0.23%) experienced dental barotrauma.

Figure 9. Pure-tone average scores



increased: 16%
decreased: 76% p<0.001
n = 38

PTA improved in 87% of patients who received HBO_2 within 14 days of hearing loss (mean PTA 81.2 dB HL pre-treatment, 52.8 dB HL post-treatment).



increased: 27%
decreased: 60% p = 0.019
mean change: -9.1
95% CI lower: -15.6
95% CI upper: -3.9
n = 15

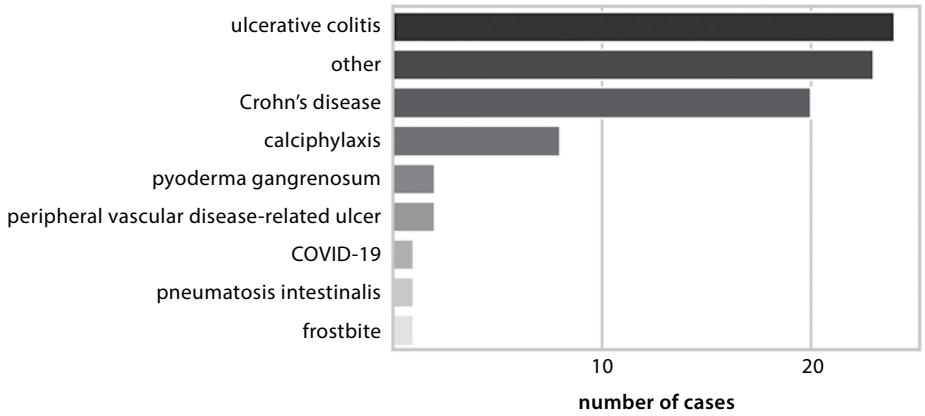
PTA improved in 60% of patients who received HBO_2 after 14 days of hearing loss (mean PTA 78.7 dB HL pre-treatment, 69.6 dB HL post-treatment).

Two (0.11%) patients developed pulmonary edema while in the chamber. One was an emergency treatment at 2.8 ATA for carbon monoxide poisoning, and the other was a non-emergency treatment at 2.0 ATA.

Seven (0.39%) patients experienced seizures, and 20 (1.1%) others had other signs of possible CNS toxicity. Three seizures occurred at treatment pressures of 2.8 ATA, and four at 2.4 ATA. The overall seizure rate was 2.3 per 10,000 treatments, with a rate of 1.1 per 100 treatments at 2.8 ATA and 1.4 per 10,000 treatments for pressures at 2.5 ATA and below. Two seizures occurred during treatment for carbon monoxide poisoning and were emergency treatments. The other seizures occurred during treatments for osteomyelitis, delayed radiation injury, compromised graft/flap, and a non-UHMS indication. There were no seizures reported at 2.0 ATA.

One hundred sixty-seven (9.4%) of patients had some confinement anxiety. Out of these patients, in 55 (3.1%) the anxiety was severe enough to stop their treatment course; 29 (1.6%) patients stopped a single treatment but were able to continue their treatment course; and 83 (4.7%) had anxiety that could be managed without interrupting treatments. Fifty-three (3.0%) patients experienced sweating excessive enough to soak the linens in the chamber. Two hundred fifteen (12.1%) patients reported visual changes during their treatment course. No pneumothoraces developed during treatment.

Figure 10. Non-UHMS indications for HBO_2 by number of cases



Inflammatory bowel disease (ulcerative colitis and Crohn's disease) makes up the greatest number of non-UHMS referrals reported in the registry.

DISCUSSION

The registry now includes data from 22 centers, having grown substantially over the last two years. These descriptive data are important in establishing a baseline understanding of hyperbaric programs caseloads, patient characteristics, indications for treatment, outcomes, and complications of HBO_2. HBO_2 is resource-intensive both for centers and for patient,s as it involves daily two-hour treatments for up to two months, depending on the indication. For many patients, this treatment regimen can affect their employment and may involve lost wages and substantial travel costs. Despite these barriers to HBO_2, the significant net improvements in reported quality of life with this treatment are important findings that justify future observational and intervention studies to compare the impacts of HBO_2 with other forms of treatment. The international multicenter registry provides a critical infrastructure to support this kind of research.

The most commonly treated indications were delayed radiation injury and enhancement of healing in selected problem wounds. The most commonly documented non-UHMS approved indications were inflammatory bowel disease and calciphylaxis (Figure 10). The registry provides an important mechanism to study treatment outcomes for these uncommon, emerging non-UHMS approved indications because it allows the pooling of data from small numbers of patients at multiple centers, with the potential to provide adequate statistical power for meaningful analyses.

As more patient entries accumulate in the registry it becomes possible to analyze factors affecting outcomes. An example of this is shown in the analysis of the head and neck questionnaire among patients with head and neck radiation (Figure 5). When the subgroup of patients who had smoked in the last year was analyzed, these patients did not show a significant improvement in their scores on the questionnaire, while the "non-smoker" and those who had quit over one year ago, did have significant improvement. The number of smokers is limited, however, and this result may change as more patients are entered into the registry. Nevertheless, this shows the kind of analyses that can be done with the registry.

In patients with diabetic foot wounds, the Strauss score may be used to measure whether wounds fall into the "futile" (0-3), "problem" (4-7), or "healthy" (8-10) range [3]. Average wound scores improved significantly from a median of 6.25 to 7.25, indicating that for some patients their wounds progressed from being indolent "problem" wounds to a healthy, healing wound. This supports existing evidence for the use of HBO_2 in diabetic foot wounds

[4-6], but highlights the need to study predictors of better outcomes, as well as the potential benefit of earlier referral and the role of HBO_2 as part of multidisciplinary diabetic foot care. As entries in the registry expand it will be possible to analyze the factors associated with the variability in response.

The four-frequency pure-tone average and word recognition scores in patients treated for ISSNHL improved significantly on average. Consistent with what has been seen in other studies, patients treated two or more weeks out from initial hearing loss had less significant improvement in pure-tone average compared to patients who received HBO_2 within two weeks of losing their hearing [7]. As data accrue, it will be possible to quantify more precisely the clinical benefits of treatment according to the delay since symptom onset.

Previous studies have reported risk of seizure during treatment at 4.5 per 1,000 patients at a single center, or approximately 2.3 in 10,000 treatments [8]. Here, we report seven seizures in 1,773 patients across these centers and a rate of 2.3 seizures in 10,000 treatments. Notably, no seizures were reported at pressures lower than 2.4 ATA (although many more patients were treated at 2.4 ATA compared to 2.0 ATA). As noted in other studies, otic barotrauma was common, with 8.9% of patients being referred to ENT for evaluation and 5.1% having either an ear tube or myringotomy. This is somewhat higher than a 2016 study, in which 2.4% of patients required intervention for HBO_2-related otic trauma [9].

As the registry grows, it will be possible to study the effects of factors such as age, smoking history, diabetes, and specific disease characteristics on HBO_2 outcomes, and to identify patients most and least likely to benefit from treatment. For example, the results of the head and neck questionnaire in our radiation injury patients shows differences in outcomes by smoking status, which could potentially change practice patterns. The registry also offers the ability to examine practice variability and complications at different sites, prospectively identifying areas for quality improvement.

One major limitation of this registry is that patients are not randomized to HBO_2, and there are no data on untreated controls. We can report the trends of HBO_2 use around the world, demonstrate improvement among patients who do receive treatment and identify predictors of response to treatment. This infrastructure can be used as a starting point for randomized controlled trials and observational studies at participating centers. The expense of HBO_2 and small caseloads at each center contribute to the difficulty of doing such studies, and the ability to perform multicenter studies may increase patient enrollment and enhance our ability to study the less common indications for HBO_2.

As with any new registry, a major challenge is monitoring and ensuring data completeness. We are currently assessing completeness for key variables, and participating centers will be required to remediate where necessary to continue participating in the registry consortium. We have limited the number of data points required to minimize the time requirement to participate in the registry, because the data collection for the registry must take place within the framework of routine clinical operations.

Funding details

The Department of Medicine at the Dartmouth-Hitchcock Medical Center provided funding support through the DOM Scholarship Enhancement in Academic Medicine (SEAM) Award Program.

Acknowledgments

The authors at the individual registry sites are: Brian Pruss, CHT, Avera McKennan Hospital, Sioux Falls, SD; Judy Kertis, RN, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Mark Bettley-Smith, MBBS, MRCGP, DRCOG, The Diver Clinic, Poole, UK; Gary Smerdon, PhD, DDRC Healthcare, Hyperbaric Medical Centre, Plymouth, UK; Dixie Regional Medical Center, St. George, UT; Richard Moon, MD, Duke University Medical Center, Durham, NC; Pieter Bothma, MD, LHM Hyperbaric Unit, James Paget University Hospital, Great Yarmouth, UK; Renee Woodring, RN, Elliot Health System, Manchester, NH; Hyperbaric Medicine Unit, St Richard's Hospital, Chichester, UK; Lindell Weaver, MD, Intermountain Medical Center, Salt Lake City, UT; Latter Day Saints Hospital, Salt Lake City, UT; Enoch Huang, MD, Legacy Medical Group, Portland, OR; Logan Regional Hospital, Logan, UT; Gary Toups, MD, Mayo Clinic, Rochester, MN; McKay Dee Hospital, Ogden, UT; Midlands Diving Chamber, Rugby, UK; Bruce Mathew, MD and Gerard Laden, North England Medical and Hyperbaric Services, Hull, UK; Northwest Recompression Unit, Birkenhead, UK; St. Alphonsus Hospital System, Boise, ID; St. Luke's Health System, Boise, ID; The Hyperbaric Unit, Whipps Cross University Hospital, London, UK (LHM); Ian Grover, MD and Hideaki L. Tanaka, MD, University of California at San Diego, San Diego, CA; Kinjal Sethuraman, MD, University of Maryland Medical Center, Baltimore, MD; Zachary Gaskill, MD University of Pennsylvania Health System, Philadelphia, PA; Tammy Roman, EdD, MSN, RN, NEA-BC and Jennifer Wright, RN, BSN, CHRN, University of Rochester Medical Center, Rochester, NY; Marc Robins, DO, Utah Valley Hospital, Provo, UT (UVH); Graeme Kay, MBBS, Wesley Hyperbaric, Auchenflower, AU; Bolaji Coker and Alessandra Bisquera manage the United Kingdom Central Registry at King's College London.

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UNDERSEA & HYPERBARIC MEDICINE

Decompression sickness with incidental pulmonary cyst

Mariesa N. Norton, PA-C [1]; Lindell K. Weaver, MD [1,2]

[1] Division of Hyperbaric Medicine, Intermountain Medical Center, Murray, Utah and Intermountain LDS Hospital, Salt Lake City, Utah, U.S.

[2] Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, U.S.

CORRESPONDENCE: Lindell Weaver – *lindell.weaver@imail.org*

ABSTRACT

Norton MN, Weaver LK. Decompression sickness with incidental pulmonary cyst. Undersea Hyperb Med. 2022 Third Quarter; 49(3):289-293.

Decompression sickness (DCS) is a known complication of scuba diving. DCS occurs when bubbles are formed as pressure is reduced during and after ascent from a dive, following inert gas uptake during the dive. The bubbles cause inflammation and hypoxia. The definitive treatment for decompression sickness is hyperbaric oxygen therapy. We present a case of a healthy 16-year-old male who presented with decompression sickness and an incidental pulmonary cyst discovered by chest CT, likely congenital. The patient was successfully treated with U.S. Navy Treatment Table 6 (TT6) for his decompression sickness, but he continued to have chest pain, requiring hospitalization and consultation with pediatric pulmonology and cardiothoracic surgery from the cyst. Three years later he complained of chest pain with changes in altitude. Chest CT showed persistence of this cyst, and additional cysts. Case conference with pulmonologists and chest radiologist could not offer a definite etiology without lung biopsy, felt to not be indicated. We believe that the changes in pressure/volumes during the dives and TT6 exacerbated his pulmonary cyst.

KEYWORDS: case report; decompression sickness; lung; pulmonary cyst

INTRODUCTION

There are more than 9 million recreational scuba divers in the United States, and the Divers Alert Network records more than 1,000 diving-related injuries annually. Some of the more complicated diving injuries include hypothermia, trauma and submersion injuries [1]. We present a case of decompression sickness with an incidental pulmonary cyst seen on the chest CT in a 16-year-old healthy male presenting after his fourth freshwater dive.

CASE REPORT

A healthy 16-year-old Caucasian male with a past medical history of premature birth at 27 weeks gestation was undergoing scuba instruction over a two-week interval. He uses albuterol periodically for what he referred to as his "asthma," a condition for which we did not have either records or objective evidence. His dives were located at a fresh warm-water source at 5,600 feet of elevation. After his initial dive, he experienced left anterior pleuritic chest pain immediately after surfacing from a 30-foot dive; the pain lasted two hours.

Two weeks later he dove again. On dive #1 he descended to 19 feet of freshwater (ffw) for 20 minutes, followed by a surface interval of approximately 20 to 30 minutes. Then, he made a second dive to 58 ffw, with a total bottom time of 22 minutes, though at depth he recalls being at 58 ffw for only five minutes' duration. He made a three-minute safety stop at 15 ffw and without rapid ascent.

Immediately upon surfacing he experienced sharp left-sided inspiratory chest pain, without cough or hemoptysis. Using cross corrections for

altitude, after the second dive he would have been on an 80-foot dive for 35 minutes (with 13 minutes of residual nitrogen), which exceeds a PADI sports limit of 30 minutes but is within the U.S. Navy limit of 40 minutes. He denied making a rapid or uncontrolled ascent.

Moments after surfacing he again experienced left anterior chest pain and shortness of breath, without hemoptysis. Over the next one to two hours he developed achy lower extremity joints, which progressed to include his upper extremity joints, patchy paresthesias, left shoulder pain, headache and fatigue.

That evening he was taken to a local emergency department, where brain computed tomography and chest CT scans were obtained. His brain CT was normal, but his chest CT showed a gas-filled thick-walled pulmonary cyst in the left lower lobe superior segment, measuring 3.4 cm x 2.2 cm, which appeared to be chronic (Figure 1).

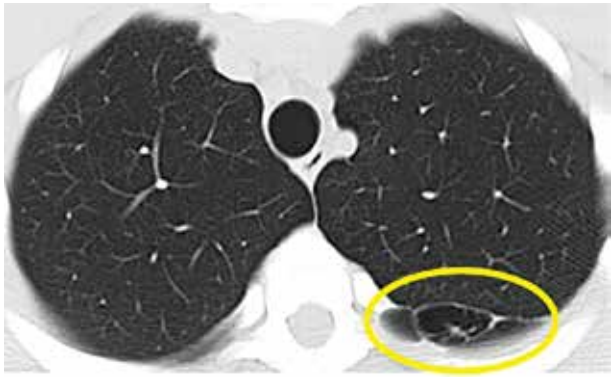

Figure 1. Chest CT image with yellow circle depicting left posterior lung cyst that is not fluid-filled.

He was transferred to the local children's hospital and was ultimately referred for evaluation for hyperbaric oxygen (HBO_2) therapy at our facility. He was successfully treated for his decompression sickness with HBO_2 therapy using U.S. Navy Treatment Table 6 (TT6) in a monoplace hyperbaric chamber [2,3] commencing approximately 30 hours after his last dive. At 2.8 atmospheres absolute (ATA) he became asymptomatic except for continued chest pain. At the end of the TT6, he had resolution of all his other symptoms except continued chest pain, which had not changed.

He was evaluated again the following day. He complained of extreme fatigue, headache, sleepiness and non-remitting left chest pain. This pain, located in the left anterior and left lateral chest, was pleuritic and without palpable tenderness. He denied any shortness of breath but reported that he had an occasional non-productive cough. His neurological exam was normal. He had scattered rhonchi in the left lung base. The patient's gait, balance problems and joint pains had resolved. Due to his continued chest pain, likely from irritation of his pulmonary cyst, he was not treated again with HBO_2 therapy. This decision was reviewed with other hyperbaric medicine clinicians. All expressed concern that HBO_2 might incrementally worsen the lung cyst, along with potential risk for arterial gas embolism.

Another chest radiograph showed no acute changes. A few days following his appointment with pediatric pulmonology his left-sided chest pain worsened. A repeat chest CT showed interval increase in the amount of fluid, with 90% opacity by fluid (Figure 2).

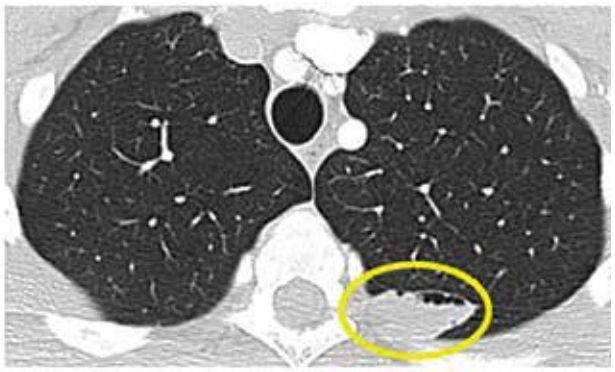

Figure 2. Chest CT image with yellow circle depicting left posterior lung cyst that is fluid-filled. CT done 15 days after image in Figure 1.

Due to his continued symptoms he was admitted to the children's hospital for additional evaluation and treatment. Because the cyst was now fluid-filled, there was concern for bleeding in the cyst. Cardiothoracic surgery was consulted about surgical removal of the cyst. The cardiothoracic team did not feel that there would be benefit from

draining or excising the cyst but recommended follow-up with outpatient pulmonology and repeat CT scanning in six to 12 weeks. He was prescribed meloxicam initially, which was later switched to ketorolac for three days as well as acetaminophen with codeine. His pain was minimally helped with the ketorolac, and he was ultimately discharged from the hospital with naproxen.

Two weeks later a repeat chest CT showed that the cyst was slightly less apparent, and the fluid that was previously within had resolved (Figure 3).

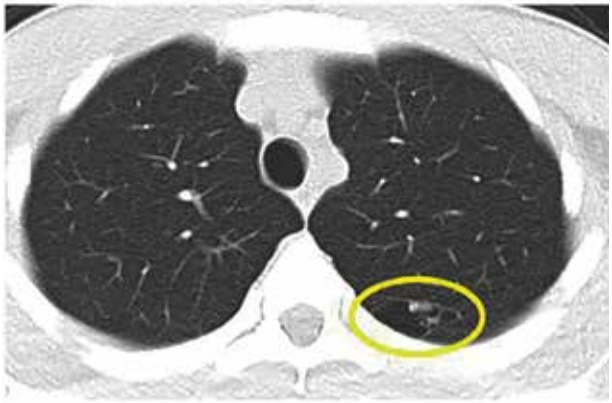

Figure 3. Chest CT image with yellow circle depicting left posterior lung cyst that is not fluid-filled. CT done 28 days after image in Figure 1 and 17 days after image in Figure 2.

This chest CT (Figure 3) demonstrated a new nodule present within the septum of the cyst. This likely represented an area of fibrosis or scarring. Over the next few weeks the patient continued to experience chest pain, exaggerated with changes in altitude. Due to the continuation of his symptoms, cardiothoracic surgery was consulted again to discuss surgical removal of the cyst. Due to uncertainty that excision would provide symptomatic relief, they recommended that additional time be taken before proceeding with excision. Also, the patient was encouraged to use his Flovent inhaler to decrease the risk for his asthma to worsen during that time. He was also instructed not to resume scuba diving or vigorous contact sports.

Three years later he was evaluated by adult pulmonology because he continued to complain of chest pain with changes in altitude. Repeat chest CT demonstrated the left posterior cyst (Figure 4). Also, this CT demonstrated additional small thin-walled air-filled pulmonary cysts (Figure 5). In retrospect these could be seen on the prior CT scans, but they were much less discernible.

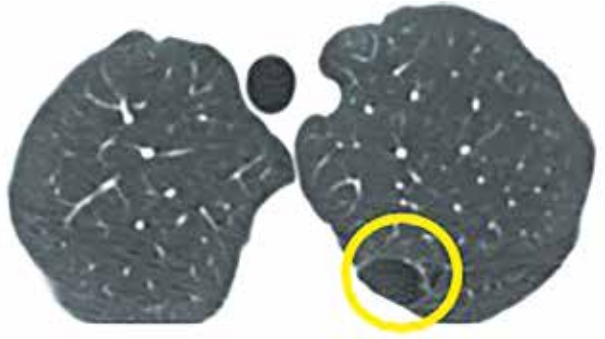

Figure 4. Chest CT image with yellow circle depicting left posterior lung cyst that is not fluid-filled. CT done three years later.

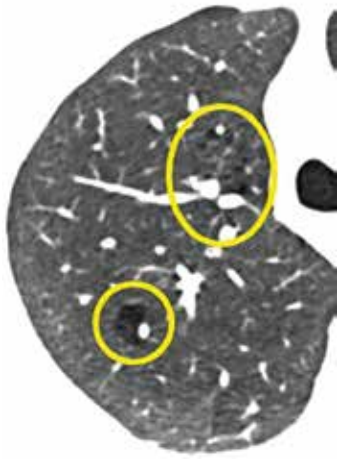

Figure 5. Chest CT image 3 years later with yellow circles depicting multiple cysts in the right lung.

This patient was presented to several practicing and academic pulmonologists and two pulmonary-focused radiologists. A pathological etiology for these cysts was not offered. Lung biopsy was discussed, but in the absence of more serious and progressive symptoms, plus risk for causing iatrogenic harm, this procedure was declined. The patient will be followed for symptoms and likely future imaging.

DISCUSSION

Based upon initial presentation, the patient had decompression sickness that was treated successfully with HBO_2 using a TT6. His continued chest pain was most likely associated with the incidental pulmonary cyst seen on his chest CT. The characterization of the cyst on the initial chest CT describes the appearance of the cyst as chronic. The thick-walled nature of the cyst and lack of fluid do not support a barotrauma-related cause for the cyst. Also, there was no evidence of barotrauma lung injury due to treatment with HBO_2.

The etiology of this pulmonary cyst is unclear, although it may be related to premature birth and subsequent need for assisted mechanical ventilation after birth. Possible etiologies include congenital pulmonary airway malformation, pulmonary sequestration syndrome, or bronchogenic cyst [4]. The differential diagnosis of cystic lung disease is long (Table 1) [5,6]. However, a case conference with expert pulmonary and radiologic clinicians did not offer a precise etiology.

Boyle's law states that at a fixed temperature, the volume of a gas is inversely proportional to the pressure exerted on the gas. We can conclude that the gases present in his cyst during diving with changes in ambient pressure would be under the same influences as described in Boyle's law. We postulate that the tensile forces on the cyst during his dives most likely contributed to the development of chronic inflammation, causing the persistent chest pain that varies with changes in atmospheric pressure.

The first chest CT scan was obtained after diving and before HBO_2. That CT showed a gas-filled thick-walled cyst. The next chest CT was taken three weeks after HBO_2, demonstrating a fluid-filled cyst. The next CT was done 2.5 weeks later, showing the cyst to be gas-filled. The final CT, taken three years later, shows multiple gas-filled cysts, including the original one. The first observed cyst was thick-walled supporting that it was chronic. Also, the dives done two weeks before the "event dives" were associated with similar left-sided chest pain, suggesting barotrauma to the cyst at that time. Yet, the first chest CT did not show a fluid-filled cyst, but the next one (three weeks later) did. One TT6 and time had elapsed since. Three of the four chest CTs show a gas-filled cyst. It is difficult to accept that the diving did not cause hemorrhage or fluid to accumulate in the cyst, yet a single TT6 with a very slow change in pressure did, but three weeks after the TT6. We have no good explanation for why the second CT showed fluid, whereas the others did not. This case demonstrates that four scuba dives and one TT6 did not result in gas embolism. Yet his pain with pressure changes certainly is concerning for serious pulmonary barotrauma risk.

Of note, the patient complains of pain with changes in altitude while driving over mountain passes, which is common near his residence. Since the cysts are air- or gas-filled, they must ventilate, although ventilation to them could be slow. However, the pressure changes by a few thousand feet of altitude do not seem significant. For example, going from 4,500 feet (0.85 ATA) to 6,500 feet (0.79 ATA) is a change of only 0.06 ATA

Table 1

pulmonary langerhans cell histiocytosis
lymphocytic interstitial pneumonia
lymphangioleiomyomatosis
Birt-Hogg-Dubé syndrome
amyloidosis
light chain deposition disease
tracheobronchial papillomatosis
infections
atypical mycobacterial
tuberculosis
Staphylococcus aureus
cocci
paragonimiasis
malignancy
adenocarcinoma in situ
sarcomas
lymphoma
GI* and GU** adenocarcinomas
pleuropulmonary blastoma

* gastrointestinal ** genitourinary

(2 fsw). However, the lung is fragile, and any volume change to a loculated, slowly ventilated cyst could cause pain. Alternatively, perhaps since the patient is aware of changes in altitude, he is just more sensitive to sensations in and about his chest.

In addition to recommendations about avoidance of scuba diving, it is reasonable to have a focused discussion about potential life-threatening risk if the patient were to need HBO_2, especially since he is developing more cysts. Also, should he be advised to not fly in commercial aircraft? Cases of bronchogenic cyst have been lethal with excursion to commercial flight altitudes (<8,000 feet) [7]. However, he does not have a bronchogenic cyst, and since the cysts are gas-filled, he should not develop pulmonary barotrauma with commercial air travel. Also, he experienced considerably more pressure change than a commercial flight with his dives and while treated with hyperbaric oxygen, supporting that air travel should be safe. Nevertheless, over a three-year interval his cysts have increased in number and prominence, so he may be at risk for pulmonary barotrauma with commercial air travel.

CONCLUSION

We present a case of decompression sickness of a 16-year-old male under scuba instruction found to have an incidental pulmonary cyst by chest CT. The patient was successfully treated for his decompression sickness with HBO_2 and was followed for three years.

This case represents DCS complicated by congenital lung cysts. Hyperbaric oxygen resolved the DCS, but he had continued problems from the cysts, mostly with periodic chest pain that seems caused by changes in altitude. Three years later the bilateral lung cysts are more apparent and without clear etiology. He will continue to be followed by pulmonary and he is recommended to not dive.

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UNDERSEA & HYPERBARIC MEDICINE

Hyperbaric oxygen for COVID-19 patients with severe hypoxia prior to vaccine availability

Deepa Jansen, MD [1]; Daniel R. Dickstein, MD [1]; Kasandra Erazo, MD [1]; Ellen Stacom [5]; David C. Lee, MD [3,4]; Sandra K. Wainwright, MD [2]

[1] Department of Internal Medicine, Yale New Haven Health - Greenwich Hospital
[2] Department of Pulmonary and Critical Care Medicine, Yale New Haven Health - Greenwich Hospital
[3] Department of Emergency Medicine, NYU Grossman School of Medicine
[4] Department of Population Health, NYU Grossman School of Medicine
[5] Department of Hyperbaric Oxygen and Wound Care, Yale New Haven Health - Greenwich Hospital

CORRESPONDENCE: Sandra K. Wainwright – *Sandra.Wainwright@greenwichhospital.org*

ABSTRACT

Jansen D, Dickstein DR, Erazo K, Stacom E, et al. Hyperbaric oxygen for COVID-19 patients with severe hypoxia prior to vaccine availability. Undersea Hyperb Med. 2022 Third Quarter; 49(3):295-305.

Introduction: Few treatments have demonstrated mortality benefits among hospitalized hypoxic COVID-19 patients. We evaluated the use of hyperbaric oxygen (HBO_2) therapy as a therapeutic intervention among hospitalized patients with a high oxygen requirement prior to vaccine approval.

Methods: We extracted data on patients with COVID-19 hypoxia who required oxygen supplementation ranging from a 6L nasal cannula up to a high-flow nasal cannula at 100% FiO_2 at 60L/minute with a 100% non-rebreather mask at 15 L/minute and were eligible for off-label HBO_2 therapy from October 2020 to February 2021. We followed the Monitored Emergency use of Unregistered and Investigational Interventions or (MEURI) in conjunction with the consistent re-evaluation of the protocol using the Plan-Do-Study-Act (PDSA) tool [1]. We compared patient characteristics and used Fisher's exact test and a survival analysis to assess the primary endpoint of inpatient death.

Results: HBO_2 therapy was offered to 36 patients, of which 24 received treatment and 12 did not receive treatment. Patients who did not receive treatment were significantly older ($p < 0.01$) and had worse baseline hypoxia ($p = 0.06$). Three of the 24 (13%) patients who received treatment died compared to six of 12 (50%) patients who did not receive treatment (RR ratio: 0.25, $p = 0.04$, 95% CI: 0.08 to 0.83). In the survival analysis, there was a statistically significant reduction in inpatient mortality in the treatment group (HR: 0.19, $p = 0.02$, 95% CI: 0.05-0.74). However, after adjusting for age and baseline hypoxia, there was no difference in inpatient mortality (hazard ratio: 0.48, $p = 0.42$, 95% CI: 0.08-2.86).

Conclusions: The survival benefit of HBO_2 therapy observed in our unadjusted analysis suggests that there may be therapeutic benefits of HBO_2 in treating COVID-19 hypoxia as an adjunct to standard care.

KEYWORDS: ARDS; COVID-19; HBO_2; hypoxemia; mortality

INTRODUCTION

The novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has overwhelmed health systems across the United States and the world, causing more than one million deaths in the United States and more than six million worldwide [2]. Symptomatic COVID-19 disease varies in severity, ranging from asymptomatic, mild pneumonia and mild hypoxia to critical illness involving respiratory failure and multiorgan dysfunction [3]. The rates of severe and critical illness are higher in hospitalized patients with COVID-19, with higher mortality in mechanically ventilated patients [3-6]. The clinical syndrome of COVID-19 is atypical for a viral respiratory infection, with severe degrees of hypoxemia and a disproportionate lack of respiratory distress [7,8].

Treatment of hypoxic patients with COVID-19 has been evolving throughout the course of this pandemic, with ongoing investigations into antiviral and anti-inflammatory therapies. Dexamethasone, a glucocorticoid, has been shown to decrease mortality rates in hospitalized patients with hypoxia due to COVID-19 based on data from prospective randomized trials [9-10]. In subsequent months, tocilizumab [12] and remdesivir [13] have also been found to have mortality benefit, particularly in conjunction with glucocorticoid therapy.

Several case series have shown that hyperbaric oxygen (HBO_2) therapy may be a possible therapeutic intervention for COVID-19 respiratory failure [14–16]. HBO_2 therapy has been used extensively to treat conditions with impaired gas exchange in the setting of severe infections or thromboses. Through its ability to improve tissue oxygenation and its anti-inflammatory effects [17–19] HBO_2 therapy could be a useful intervention to treat hypoxemic respiratory failure caused by COVID-19. As critically ill as these patients are – though the hypoxemia had systemic effects – the organ that was the source hypoxemic failure was mostly limited to the pulmonary system. This made patient selection for hyperbaric exposure unique. In the setting of a pandemic with limited resources, what devices are relatively available and can deliver oxygen safely and effectively at a higher partial pressure and less pulmonary mechanical harm than a ventilator?

Although vaccine development and administration were in progress at the time of the study, the search for an efficacious treatment for COVID-19 respiratory failure continues. Despite vaccination efforts, patients may continue to acquire COVID-19, leading to multiorgan sequelae from infection [20,21]. Therefore, we sought to investigate HBO_2 as a therapeutic intervention for hospitalized patients with COVID-19 with, in essence, single organ failure.

METHODS

Study cohort

This was a retrospective analysis of hospitalized COVID-19 patients who were eligible to receive HBO_2 therapy between October 16, 2020, and February 1, 2021, as an investigational treatment for moderate to severe hypoxia. Patients were deemed eligible for HBO_2 therapy if they were age 18 years or older, had a laboratory-confirmed SARS-CoV-2 infection, and had moderate to severe hypoxemia, which was defined as having a baseline supplemental oxygen requirement of 6 liters/minute or higher. Patients were excluded if they were pregnant, had radiographic evidence of a pneumothorax or other chest barotrauma (e.g., pneumomediastinum, pneumopericardium, significant subcutaneous emphysema, or pulmonary blebs), required invasive or non-invasive mechanical ventilation (e.g., BiPAP, CPAP), were too critically ill to be safely transported to the hyperbaric chambers, or did not have the capacity to provide informed consent. Patients were categorized into treatment and non-treatment groups based on whether they received HBO_2 therapy during the hospitalization to address COVID-19 respiratory failure. All patients who were deemed eligible for HBO_2 were considered for treatment, but some were unable to be treated due to limited availability of HBO_2 staffing and resources, patient refusal, or inability to follow instructions. Oxygen supplementation and other

COVID-19 therapies such as steroids, antivirals and anti-inflammatory agents were applied per the standard-of-care guidelines at our institution during the study period. This study was deemed exempt by the Institutional Review Board at our institution.

Patient characteristics

We reviewed the electronic health records (EHR) of hospitalized COVID-19 patients who were candidates for HBO_2 and extracted patient demographics, pre-existing comorbidities (e.g., hypertension, hyperlipidemia, and diabetes), baseline vital signs and lab results, sequential organ failure assessment (SOFA) scores [22,23], use of other COVID-19 treatments (e.g., dexamethasone, remdesivir, convalescent plasma, tocilizumab), treatment toxicities (seizures, pneumothoraces, arrhythmias, pulmonary edema, hypoglycemia, ear/sinus barotrauma, and anxiety), and baseline oxygen requirements. Patients ranged in age from 29 to 87 years old. This data represents our best effort to collect real-world evidence (RWE) during a global health crisis.

Outcomes

The primary outcome was all-cause in-hospital mortality, which was defined as death while hospitalized due to COVID-19. Secondary outcome was progression to invasive mechanical ventilation (IMV), defined as intubation for respiratory failure due to COVID-19.

Statistical analysis

We compared the median age and BMI in addition to the range for these values using Wilcoxon rank-sum tests and average SOFA scores using t-tests. We analyzed the sex, ethnicity, medical comorbidities, baseline supplemental oxygen requirements, and proportion receiving other COVID-19 treatments using Fisher's exact tests. Given the small sample size of the study cohort, we used a p-value of 0.10 to flag baseline characteristics that differed between the HBO_2 treatment and non-treatment groups.

For our primary outcome, we analyzed the relative risk ratio of inpatient mortality between the two groups using a two-sided Fisher's exact test. We performed a survival analysis using competing risk regression spanning the dates from hospital admission to discharge or inpatient mortality with a competing outcome of hospital discharge. Survival curves were depicted as cumulative incidence. We also analyzed inpatient mortality by stratifying the outcome across key predictors that differed between the two groups, and adjusted the survival analysis accordingly.

For the secondary outcome, we analyzed progression to intubation between the two groups using Fisher's exact test. A p-value of 0.05 was used to identify statistically significant results for all outcomes. All statistical analyses were performed in Stata 16.2.

RESULTS

Patient characteristics

Thiry-six COVID-19-positive patients were evaluated to determine whether they were eligible for and would consent to treatment with off-label HBO_2. Among these 36 patients, 12 (33%) were evaluated on hospital days 0 or 1, 12 (33%) were evaluated on hospital days 2 or 3, and 12 (33%) were evaluated on hospital days 4 through 9. Of the 36 patients, 24 (67%) were appropriate for treatment, and 12 (33%) of the eligible patients were unable to be treated. The reasons for non-treatment were HBO_2 resource limitations (83%) and patient refusal of treatment (17%).

In comparing the demographic characteristics, medical comorbidities, baseline oxygen requirements, and SOFA scores at the time of evaluation for HBO_2, we found that there was a statistically significant trend toward older patients in the non-treatment group ($p < 0.01$) as well as a trend toward worse baseline oxygen requirements among patients in the non-treatment group ($p = 0.06$).

Other patient characteristics including baseline SOFA scores did not statistically differ between the two groups ($p > 0.10$). Patient and treatment characteristics are outlined in Table 1.

Table 1: Characteristics of study population (all ages)

patient characteristics (n = 24)	received treatment (n = 12)	no treatm't	p-value
age			
median	56	72	< 0.01
range	29 to 79	37 to 87	
sex			
male	79%	83%	1.00
ethnicity			
Hispanic	50%	42%	1.00
BMI			
median	28	27	0.28
range	20 to 50	17 to 40	
medical history			
hypertension	38%	50%	0.50
hyperlipidemia	29%	42%	0.48
diabetes	29%	17%	0.69
baseline supplemental oxygen			
nasal cannula	25%	8%	0.06
non-rebreather mask	50%	25%	
high-flow oxygen	25%	67%	
SOFA score			
average	2.6	2.8	0.44
other COVID-19 treatments			
dexamethasone	100%	100%	n/a
remdesivir	96%	92%	1.00
convalescent plasma	33%	17%	0.44
tocilizumab	25%	58%	0.07
ASA	92%	92%	n/a
therapeutic or intermediate dose anticoagulation	50%	67%	0.48

Treatment characteristics and tolerability

All patients in both the treatment and non-treatment groups received dexamethasone as a standard-of-care COVID-19 treatment. There was no statistically significant difference between the two groups with respect to other concurrent COVID-19 treatment (low-dose aspirin, remdesivir, convalescent plasma, therapeutic or intermediate doses of anticoagulation). There was a higher proportion of patients in the non-treatment group who also received tocilizumab (p = 0.07).

Of the 24 COVID-19 patients who were treated with HBO_2, 15 (63%) completed all five planned treatment sessions and nine (38%) prematurely discontinued treatment. The reasons for discontinuation included disease progression (4), improvement in hypoxia leading to hospital discharge (3), staffing limitations (1), and anxiety (1). Six patients experienced minor adverse events in the form of ear barotrauma (1) and anxiety (6). No patients experienced seizures, pneumothoraces, arrhythmias, pulmonary edema, or hypoglycemia.

Outcomes

Of the 24 patients who were treated with at least one session of HBO_2, three (13%) patients died during their inpatient hospitalization. In comparison, six (50%) of the 12 patients in the non-treatment group died during their inpatient hospitalization. There was one additional patient who required invasive mechanical ventilation and had a prolonged hospitalization longer than 100 days. Without adjusting for differences in characteristics such as age and baseline oxygen requirements, we found a statistically significant difference in mortality between the treatment and non-treatment groups with a relative risk ratio of 0.25 (p = 0.04, 95% CI: 0.08 to 0.83). However, there were substantial baseline differences between the two groups. Therefore, we stratified these results by patient age and by baseline supplemental oxygen requirements.

We noted no deaths among the youngest age group (29 to 39 years) and patients on 6 L/minute supplemental oxygen via nasal cannula. In addition, we noted that there were three patients in the non-treatment group who were in the oldest age category (80 to 87 years). In all other age and baseline supplemental oxygen requirements strata, there were fewer deaths in the treatment group (three of 24) compared to the non-treatment group (six of 12). Inpatient mortality stratified by patient characteristics is outlined in Table 2.

When not adjusting for other factors, patients treated with HBO_2 had a statistically significant reduction in inpatient mortality (subdistribution hazard ratio [HR] of 0.19 (95% Confidence interval [CI]: 0.05-0.74, p = 0.02; Figure 1). However, after controlling for patient age and baseline supplemental oxygen requirements as continuous variables, there was no statistically significant difference in inpatient mortality those treated with and without HBO_2 (subdistribution HR: 0.48, 95% CI: 0.08-2.86, p = 0.42; Figure 2).

We also observed that there were fewer cases of progression to IMV in the treatment group. Of the 24 patients who received HBO_2, three patients (13%) required IMV, compared to seven out of the 12 patients (58%) in the non-treatment group.

Table 2: Inpatient mortality stratified by patient characteristics

patient characteristics	received treatment (n = 24)	no treatment (n = 12)
age strata		
29 to 39 years old	0 of 5 (0%)	1 of 1 (100%)
40 to 59 years old	0 of 10 (0%)	1 of 2 (50%)
60 to 79 years old	3 of 9 (33%)	3 of 6 (50%)
80 to 87 years old	N/A	1 of 3 (33%)
baseline supplemental oxygen		
nasal cannula (6 liters)	0 of 6 (0%)	0 of 1 (0%)
non-rebreather mask (15 liters)	2 of 12 (17%)	1 of 3 (33%)
high-flow oxygen (30 to 60 liters)	1 of 6 (17%)	5 of 8 (63%)

FIGURE 1

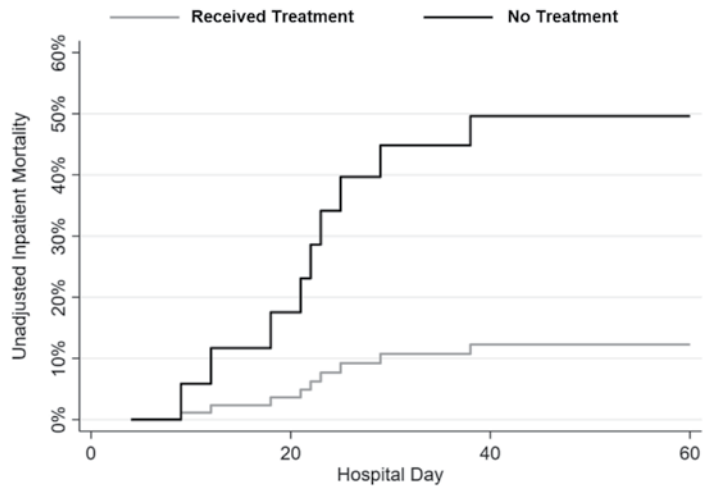

FIGURE 2

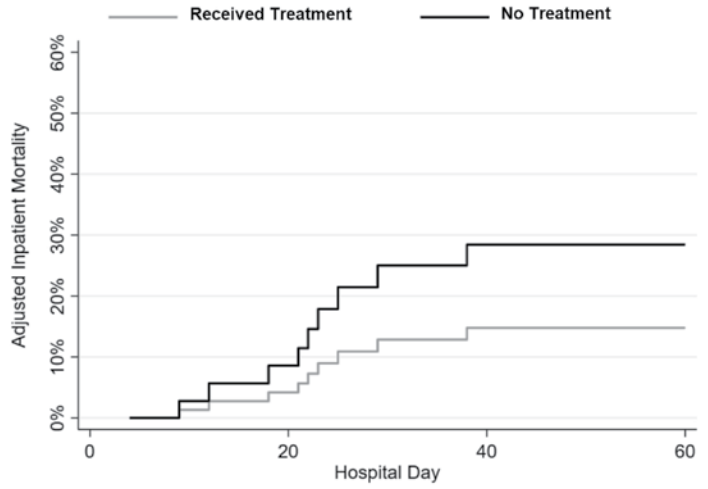

FIGURE 1 (at left)
Unadjusted cumulative incidence curves for inpatient mortality among severe COVID-19 patients treated versus not treated with hyperbaric oxygen therapy

FIGURE 2 (bottom left)
Adjusted cumulative incidence curves for inpatient mortality among severe COVID-19 patients treated versus not treated with hyperbaric oxygen therapy

All patients who progressed to IMV had higher baseline supplemental oxygen requirements. Notably, 100% (three of three) of the younger patients in the age range 29 to 59 years in the non-treatment group progressed to IMV, while none (0 of 15) of the treatment group in the same age range were intubated. Fisher's exact test comparison of intubation rate between the two groups did show statistical significance with p = 0.007. We also observed that in our cohort including both treatment and non-treatment groups, mortality in intubated patients was significantly

higher than mortality in non-intubated patients who required escalation beyond nasal cannula oxygen supplementation ($p < 0.001$). Intubation rate stratified by patient characteristics is listed in Table 3.

Table 3: Rate of intubation stratified by patient characteristics

patient characteristics	received treatment (n = 24)	no treatment (n = 12)
age strata		
29 to 39 years old	0 of 5 (0%)	1 of 1 (100%)
40 to 59 years old	0 of 10 (0%)	2 of 2 (100%)
60 to 79 years old	3 of 9 (33%)	3 of 6 (50%)
80 to 87 years old	N/A	1 of 3 (33%)
baseline supplemental oxygen		
nasal cannula (6 liters)	0 of 6 (0%)	0 of 1 (0%)
non-rebreather mask (15 liters)	2 of 12 (17%)	1 of 3 (33%)
high-flow oxygen (30 to 60 liters)	1 of 6 (17%)	5 of 8 (63%)

DISCUSSION

To our knowledge, this is the first study to compare mortality outcomes in patients with COVID-19 respiratory failure treated with HBO_2 among an unvaccinated cohort of patients, all of whom received dexamethasone, which at the time of the study had been the only clearly effective treatment for COVID-19 [11]. Previous reports have shown preliminary efficacy of HBO_2 in COVID-19, but many of these studies were performed earlier, when steroids were not standard-of-care and early intubation was preferred. Our results showed that among hospitalized patients with COVID-19 respiratory failure the addition of HBO_2 to standard-of-care therapy was associated with a decrease in rate of intubation and mortality.

The impact of HBO_2 on improved outcomes in COVID-19 patients may be attributed to the beneficial effects on the respiratory system as well as on the inflammatory cascade. The SARS-CoV-2 virus induces a dysregulated immune response in the host, involving a massive release of cytokines and chemokines, and pulmonary inflammatory cell infiltration, resulting in acute lung injury and acute respiratory distress syndrome (ARDS) [4,24]. Ventilation-perfusion (V/Q) mismatch due to blood perfusing lung tissue with impaired or no ventilation is thought to be a major mechanism of hypoxemia in COVID-19 respiratory failure [25]. Coagulopathic mechanisms leading to microemboli and hemoglobin poisoning affecting its oxygen-carrying capacity may also play a role [26-28]. HBO_2 is thought to reduce inflammatory cytokines and tissue inflammation, as seen in the treatment of radiation injuries, soft tissue wounds, infections [17-19], and therefore, it may also reduce inflammatory cytokines and tissue inflammation seen in COVID-19. The ability to increase the amount of dissolved oxygen in plasma at hyperbaric pressures would allow for enhanced hemoglobin-independent tissue oxygen delivery in COVID-19 hypoxemia [29]. In patients requiring high rates of supplemental oxygen or fraction of inspired oxygen (FiO_2), HBO_2 received at the earliest possible juncture could improve tachypnea, reduce work of breathing, and ward off the inflammatory cascade progressing into multiple organ dysfunction syndrome [30].

At the time of the study few effective therapeutic interventions were available in the inpatient setting. Hyperbaric oxygenation addressed the fundamental issues of hypoxemia and subsequent hypoxia. "Off-label" therapy by the World Health Organization's definition is 'A repurposed, unregistered, experimental, unproven, untested or a trial investigational Drug' [36]. In this study, the established application of HBO_2 in the treatment of symptomatic acute blood loss anemia was repurposed to address the needs of the COVID-19 patients. Our data showed a lower mortality in the HBO_2 treatment group, across all age strata. Our data also showed a lower intubation rate in the treatment group. After adjusting for differences in age and baseline oxygen requirements in the survival analysis between the two groups, the difference in mortality was not statistically significant.

The treatment group included younger patients with likely fewer comorbidities at the time of treatment. The baseline oxygen requirements were also lower in the treatment group. The extent of COVID-19 disease at the time of hospitalization was likely more advanced in the non-treatment group, relegating this group to higher mortality regardless of HBO_2 [4].

We noted a higher rate of tocilizumab administration in the non-treatment group. This may have been correlated with worsening clinical course of COVID-19 hypoxia in this group which required escalation of care with an anti-inflammatory agent that was not part of the standard-of-care treatment regimen.

Practice patterns at our institution with respect to invasive mechanical ventilation (IMV) for COVID-19 hypoxia were fairly consistent during the duration of the study, and early intubation was avoided. Our analysis showed a statistically significant correlation ($p = 0.03$) between treatment with HBO_2 and lower rates of progression to IMV. As seen in other studies conducted during the earlier months of the pandemic [4,5], we did note significantly higher mortality in intubated patients, irrespective of treatment with HBO_2.

It is worth noting that a number of patients with higher oxygen supplementation requirements were unable to be offered HBO_2 treatment due to being too unstable for transport to the HBO_2 suite and due to not having any additional means to "step up" their oxygen delivery after each hyperbaric oxygen therapy These patients were not included in our analysis; however, this highlights the need for early identification and evaluation of patients eligible for HBO_2 in addition to receiving standard-of-care therapies such as steroids and antivirals.

Our study also showed that HBO_2 is a safe intervention, similar to other reports that have been published in this realm [14-16,31]. We did observe that upon exiting the chamber, some of our patients developed hypoxemia below pre-hyperbaric "baseline." After multiple observations, we concluded that V/Q mismatching is the likely cause. We postulate that oxygen under pressure facilitated alveolar recruitment and higher alveolar oxygen tensions, leading to increased perfusion to these lung units. Upon exiting the chamber, patients experienced sea-level atmospheric pressure delivery of oxygen. They would become more hypoxemic for about 30 to 60 minutes and required close monitoring as well as occasionally a "step up" to temporary non-invasive positive-pressure ventilation for transportation back to their units. This suggests V/Q mismatching of perfusion to alveoli with now-lower oxygen tension – with a time allotment needed for physiologic redistribution of blood flow to the remaining ventilated lung units. A consistent and poignant observation was that for the time our patients were at pressure, they experienced relief from severe COVID-19 symptoms for the first time in days or weeks. In the hyperbaric chamber the patients found it easier to sleep, expectorate, drink water and reported greater lung excursion with inspiration. Our cohort had a small number of minor adverse events from HBO_2, with a single instance of ear barotrauma, confirming the safety profile that has been established over the years for HBO_2 in general, as well as in the case series which specifically evaluated HBO_2 therapy in COVID-19 respiratory failure [14-16,32].

Limitations

Our study had several limitations inherent to a retrospective analysis with a small study cohort. Due to the size and non-randomized nature of the cohort, there were differences in the baseline characteristics of the compared groups, which limited the statistical significance of our results. With a larger cohort we could potentially control for the effects of other treatments (e.g., remdesivir, tocilizumab), age, and comorbidities, all of which are potential effect modifiers. In addition, this study occurred prior to the deployment of COVID-19 vaccines; therefore, mortality may decrease in general as older and high-risk patients are vaccinated [20, 21,33]. We acknowledge that several non-random-

ized studies for COVID-19 treatments (convalescent plasma, antiviral and immune-modulating agents) initially showed great potential for therapeutic benefit but failed to reveal definitive results in randomized trials [13,34,35]. HBO_2 therapy may meet with the same fate, but given the effect size observed in our study, further investigation is warranted.

CONCLUSIONS

This study revealed data suggestive of reduced inpatient mortality and a reduction in progression to IMV in COVID-19 patients treated with hyperbaric oxygen therapy. It also demonstrated that pulmonary barotrauma and possibly pulmonary oxygen toxicity did not occur with hyperbaric oxygen exposure despite the degrees of lung injury seen in COVID-19 patients. This data represents real-world evidence collected with existing resources and the many limitations of health care restraints during this pandemic time. It represents a juxtaposition of conducting a trial in the context of a public health challenge. It also reflects how research may need to move as quickly as the virus.

As other drugs were being repurposed for use in SARS-CoV-2 and the FDA was providing "expanded access," it became clear that access to a readily available and potentially but as yet not broadly studied therapeutic drug poses some ethical dilemmas. Dr. Zuckerman et al. elegantly discuss the ethics of "compassionate therapies" in times of catastrophic pandemics [1]. They suggest a protocol designed by the WHO – the Monitored Emergency use of Unregistered and Investigational Interventions or (MEURI) – in conjunction with consistent re-evaluation of the protocol using the Plan-Do-Study-Act (PDSA) tool [1]. Our data reflect the philosophy of using a known safe drug to offer a potential therapeutic benefit to patients with severe COVD-19 infections. The PDSA tool was based upon prior case reports in China [37] and the United States [14,16,38]. This provided the planning and feedback for our study, and we re-evaluated our practices during the five month time frame. Conducting any type of research in the midst of a pandemic with the limitations of staffing and human resilience for the purpose of delivering a compassionate use drug to patient sufferers is difficult. It is not ethical to apply the rigors of a randomized controlled trial in this instance.

This study highlights the ethical dilemmas we face in hyperbaric medicine: "difficulties in organizing clinical trials center on the issues of creating conditions for a control population, blinding, randomization, and patient consent" [39]. We followed the recommendation to incorporate informed consent for patients and physicians caring for these patients for the off-label use of HBO_2 therapy in COVID-19. This study exemplified the dynamic MEURI – Monitored Emergency Use of Unregistered and Investigational Interventions – using the Plan-Do-Study-Act PDSA tool for implementing therapeutics during a public health emergency. The PDSA tool was exemplified by our building upon previous collaborators' experiences – specifically Drs. Gorenstein [14] and Denham [40], as well as the collaborative effort of the authors of the UHMS Position Statement for COVID-19 patients [40].

What we have shown in this case series is that there is room for ethical use of hyperbaric oxygen therapy even in off-label applications during unprecedented times like the SARS-CoV2 pandemic. We should not capitulate to the usual "our study should serve as impetus for larger, randomized multicentered trial." There is a growing body of evidence comparing RCTs and real-world experience [41,42]. The pandemic provided a propitious opportunity for us to study the application of HBO_2 in the real-world setting. We demonstrated HBO_2 as a safe and potentially efficacious treatment to address COVID-19 hypoxic respiratory failure, COVID-19 sequelae, and/or potentially other acute respiratory inflammatory syndromes with similar pathophysiology. Questions that arose during our study that would be helpful to pursue would include standardizing HBO_2 therapy dosage,

what phenotypic characteristics of COVID-19 sufferers would benefit more from HBO_2 and as such define eligibility criteria. Was length of stay significantly impacted with the addition of HBO_2? In short, future trials do not have to rely solely on the placebo-controlled randomization typical of larger drug trials. Using the pragmatic design suggested by the MEURI-PDSA tool improves access to compassionate therapeutics and addresses the ethics of these therapies in times of global health emergencies.

DECLARATIONS

Ethics approval and consent to participate:

This study was reviewed by the Institutional Review Board at our institution in accordance with the Declaration of Helsinki and was deemed exempt from ethics approval.

Availability of data and materials:

The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

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UNDERSEA & HYPERBARIC MEDICINE

Comparison of four low-level carbon monoxide alarms suitable for home use or when traveling

Neil B. Hampson, MD; James R. Holm, MD

Section of Hyperbaric Medicine, Virginia Mason Medical Center, Seattle, Washington U.S..

CORRESPONDENCE: Neil Hampson – *neil.hampson@gmail.com*

ABSTRACT

Hampson NB, Holm JR. Comparison of four low-level carbon monoxide alarms suitable for home use or when traveling. Undersea Hyperb Med. 2022 Third Quarter; 49(3):307-313.

Introduction/Background: Interest in carbon monoxide (CO) alarms that are more sensitive than is required for standard residential CO alarms is growing, as reflected by increased marketing of "low-level" alarms capable of measuring CO levels as low as 10 PPM. At the same time, publicity surrounding CO poisoning events among travelers in lodging facilities has stimulated interest in travel CO alarms. We sought to evaluate four low-level alarms that could be used in the home and especially when traveling.

Materials/Methods: Two each of four brands of low-level alarms (CO Experts, Forensics, Kidde, and Sensorcon) were acquired by retail purchase and tested. The eight alarms were simultaneously exposed in an environment with a slowly increasing level of CO from indoor burning of charcoal briquets. CO levels displayed on the alarms were recorded once per minute. Activation of preset alerts on the alarms were noted. Finally, alarms were compared for ease of use and features available.

Results: All brands of alarms measured CO similarly over the range from 10-120 PPM. All alarms performed as claimed by their manufacturers, both regarding range of CO reported and preset alert activation. Each alerted at CO levels below that required by the Underwriters Laboratories 2034 Standard.

Summary/Conclusions: Since all low-level CO alarms tested measured CO similarly, consumers seeking a low-level CO alarm for use while traveling should base their decision on features desired and price. There are definite differences between the alarms tested, in terms of features, expected durability, ease of operation and price. ∎

KEYWORDS: alarm; carbon monoxide; toxicity; travel

INTRODUCTION

In response to reports of hotel and motel carbon monoxide (CO) poisoning published in the medical literature and publicized by the lay media [1-4], interest has grown in travel CO alarms. As a result, some portable CO detectors are being marketed specifically for the traveling public to carry and use for protection while staying in lodging facilities. Other CO alarms are being marketed as more sensitive than is required by the current Underwriter's Laboratories standard for residential CO alarms [5]. The logic for such a "low level" alarm is that an individual should presumably want to be alerted to an impending significant CO exposure as early as possible, or that CO exposure at low level on a chronic basis may be hazardous to health.

Some devices are appropriate both for travel (portable size, battery operation) and low-level CO detection. Presuming that the traveler seeking a CO alarm would want to be alerted to low levels of CO, we compared four of several commercially available CO alarms marketed as low-level

Table 1. Photographs, physical characteristics, and cost of the four CO alarms tested

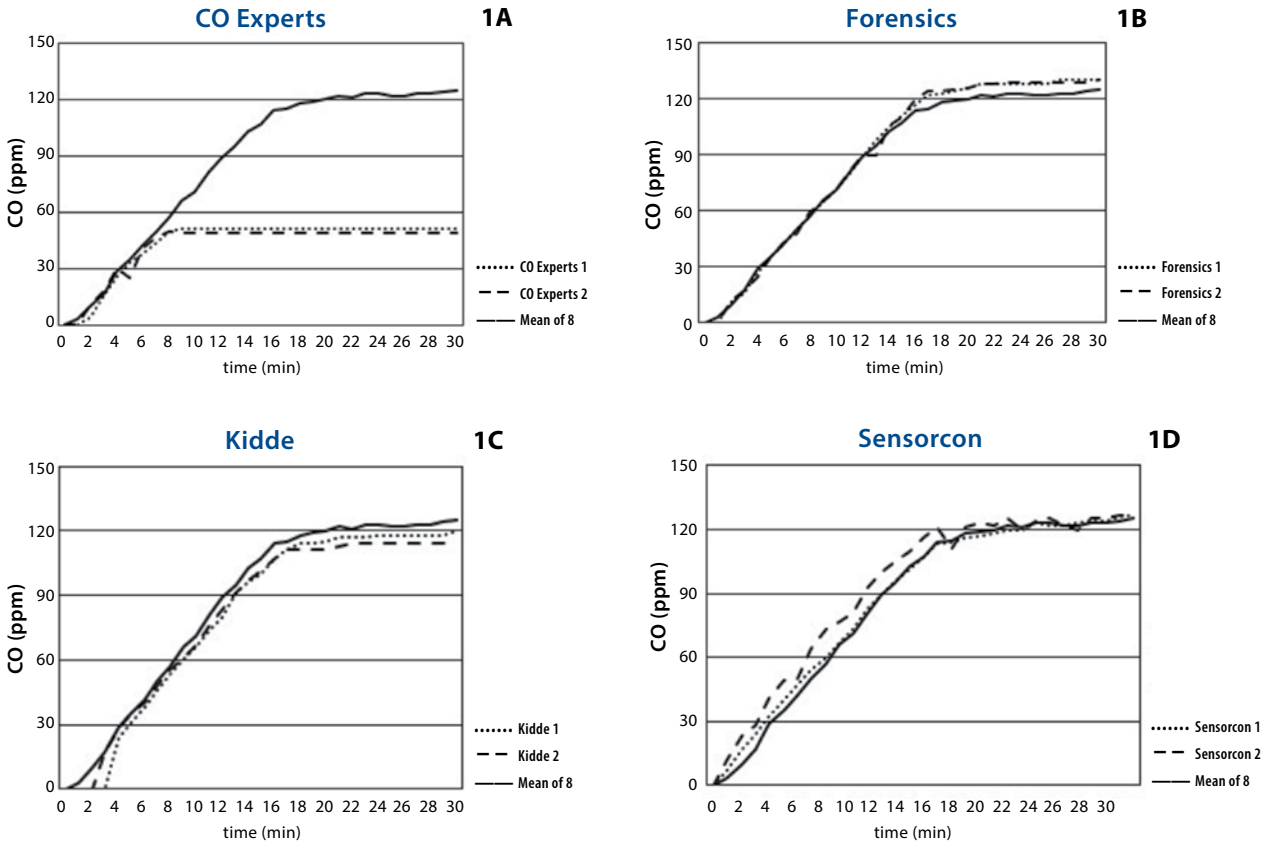
	Manufacturer	Model	Power	Size	Retail Cost *
	CO EXPERTS	"Ultra" Low Level Carbon Monoxide Health Monitor	2 AAA batteries	2.0 x 1.5 x 3.0" 4 ounces	$209
	FORENSICS	Travel & Personal CO Detector Model TRAVEL001	2 CR2 batteries	2.5 x 1.75 x 0.65" 2 ounces	$100
	KIDDE	KN-COU-B Ultrasensitive Carbon Monoxide Monitor	3 AA batteries	4.5 x 1.5 x2.8" 5.3 ounces	$63
	SENSORCON	The Inspector Industrial Pro	1 CR123A battery	3.2 x 2.2 x 0.9" 4 ounces	$159

* Amazon.com 09/2020

with the goal of determining whether there are characteristics that would make one be selected over another as a travel alarm. The study was not intended to be an exhaustive review of all devices on the market, but rather to contrast features of four in the hope that they would guide the reader when selecting one for personal use.

METHODS

A pair of each of four commercially available CO alarms was acquired through online retail purchase (Amazon.com) (Table 1). No devices, funding or input of any type were provided by the manufacturers. Those selected are small enough for travel, use batteries for power, have a reasonable price point, have digital displays of ambient CO



Figures 1A-D
Ambient CO levels measured by each pair the four brands of low-level alarm tested, compared to the mean level measured simultaneously by all eight alarms.

and are claimed to report CO levels at least as low as 10 parts per million (ppm).

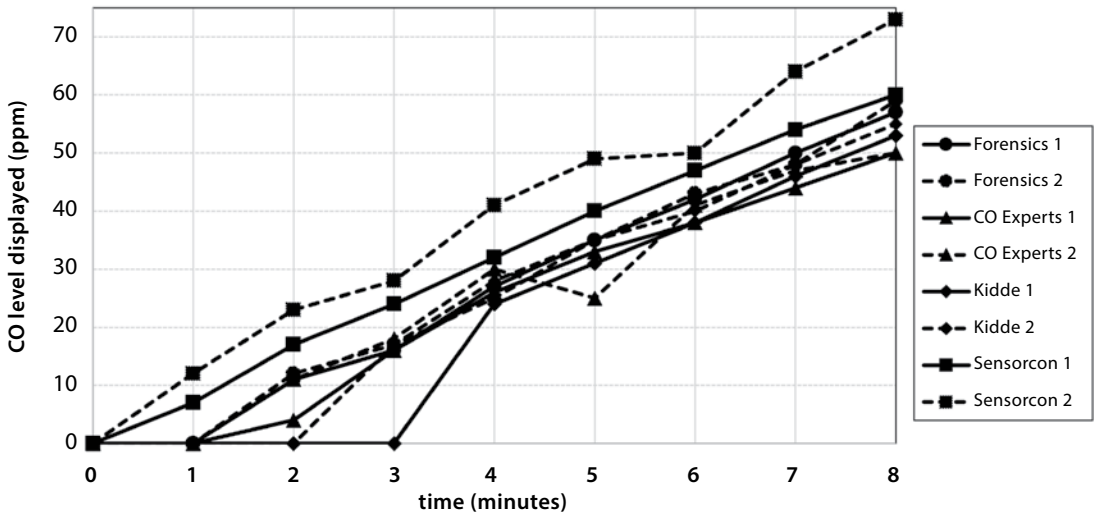
The devices were operated per their accompanying instructions. CO testing was performed in a one-car detached garage as previously described [6]. The devices were placed on a shelf in the garage at a height halfway from the floor to the ceiling. Digital readouts, auditory and visual alerts were easily assessed through a glass window. Measurements of CO concentration as displayed on each device were recorded once per minute for 30 minutes while burning 2.3 pounds of charcoal in the garage as a CO source. The ignited charcoal was not placed in the garage until the surfaces of briquettes were ash gray in color, with little visible smoke production, indicating a smoldering burn. It was our goal to achieve an exposure that was below that which would trigger an alert from a residential CO alarm manufactured to the UL 2034 standard.

RESULTS

Figures 1A-D display the CO levels measured by the devices and recorded from their digital readouts. Each graph shows the results from two alarms of the same brand and compares them with the mean from all eight devices tested. As would be expected from a source producing a relatively constant amount of CO, the level in the garage rose in a linear fashion until reaching equilibrium with leaks in the building construction and diffusion through walls.

Figure 2

CO levels (ppm) displayed on each of the eight alarms tested over the range from 0 to approximately 50 ppm.



From a practical and clinical standpoint, all devices measured CO similarly over the range tested. The detectors manufactured by CO Experts displayed peak CO concentration of 50 pp, (Figure 1A), consistent with their claim of displaying that as a maximum level. Figure 2 displays the individual CO measurements of the eight alarms over the range of 0 to approximately 50 ppm. Alerts (visual, auditory and vibratory) occurred as claimed by their manufacturers within the CO range tested (Table 2).

DISCUSSION

Home residential CO alarm performance is regulated by UL 2034 [5]. This standard was designed to prevent acute CO exposures that would result in a carboxyhemoglobin level greater than 10%. Residential alarms must alert if CO is present at a level of 70 ± 5 ppm for 60 to 240 minutes, 150 ± 5 ppm for 10 to 50 minutes, or 400 ± 10 ppm for four to15 minutes. All four of the devices tested alert at CO levels far below this standard.

As can be seen in Table 2, levels triggering alerts on these devices are variously 5, 9, 25, 35, 50 and 200 ppm CO. Many of these levels appear to have been adapted from standards of various U.S. federal agencies or organizations. The Environmental Protection Agency (EPA) has established the U.S. National Ambient Air Quality Standard for CO at 9 ppm for eight hours and 35 ppm for one hour [7]. They have not established a CO standard for indoor air [7].

The National Institute for Occupational Safety and Health (NIOSH) [8] has established a recommended workplace exposure limit for CO of 35 ppm as an eight-hour time weighted average and 200 ppm as a ceiling [8]. The NIOSH limit is based on the risk for cardiovascular effects. The current Occupational Safety and Health Administration (OSHA) permissible exposure limit in the workplace is 50 ppm as an eight-hour time-weighted average [9].

The literature and manuals accompanying the devices frequently explain the levels chosen for their devices. Literature accompanying the device manufactured by CO Experts notes that the device does not replace a UL 2034 device if one is required in the residence, but instead it is intended to be a "CO Health Monitor," designed to "provide the vital protection you and your entire family needs from

Table 2. Threshold CO levels and alerts issued by each of the four alarms.

Manufacturer	CO Range Display	Threshold (ppm CO)	Alert
CO Experts	>4 – 50 ppm	5-24 ppm x 24 h	Red LED flashes 1/m plus one set of 4 beeps/m
		25-34 ppm x 8 h	Red LED flashes 1/m plus one set of 4 beeps/m
		35-50 ppm x 1 h	Red LED flashes 2/m plus one set of 4 beeps 2 times/m
		>50 ppm x 4 m	Red LED flashes 3/m plus one set of 4 beeps 3 times/m
Forensics	9 - 999 ppm	9 ppm	Red LED flashes
		25 ppm X 1 m	Red LED flashes plus buzzer
		50 ppm immediate	Red LED flashes plus buzzer
Kidde	10 - 999 ppm	"Low" level	Green LED flashes 4 times, then off x 10 s
		"Mid" level	Green LED flashes 4 times, red LED flashes 2 times, chirps 2 times/10 s
		"CO Alarm" level	Red LED flashes 4 times, chirps 4 times/5 s
Sensorcon	0 - 1,999 ppm	35 ppm (default, adjustable 5-100 PPM)	4 red LEDs flash every 3 s, audible alarm, vibration
		200 ppm (default, adjustable)	4 red LEDs flash every 2 s, audible alarm, vibration

Chronic Low Level CO Poisoning." It is marketed not as an alarm for prevention of acute, severe CO poisoning, but instead as a "health monitor" which is said to be appropriate for "pregnant women, infants, young children, the elderly and people with chronic medical illness." Its lowest alert occurs when 5 ppm CO is detected for 24 hours. This is a level that would probably be exceeded in many homes from time to time. According to the EPA, average levels in homes without gas stoves vary from 0.5 to 5 ppm [7]. Levels near properly adjusted gas stoves are often 5 to 15 ppm; those near poorly adjusted stoves may be 30 ppm or higher [7].

The device manufactured by Forensics is marketed as a "Travel and Personal CO Detector." It has progressive alerts at 9, 25, and 50 ppm CO. It should be noted that the 9 ppm alert is visual only and an audible alert does not occur until 25 ppm. Instructions instruct the user to ''ensure the detector in line of sight for visual alarm in case buzzer alarm cannot be heard."

The Kidde monitor has three alert levels, designated as "Low," "Mid," and "CO Alarm" alerts. The accompanying literature contains a table that subdivides each of these into numerous time (minutes) x concentration (CO ppm) products at which various alerts occur (Figure 3). As can be seen in Figure 3, the device has no alert at CO concentrations lower than 20 ppm. After 20 to 115 minutes at 20 ppm, the device issues the "Low" level alert, which is visual only. When 20 ppm has been present for longer than 115 minutes, the device emits a "Mid" alert, which adds an auditory cue. The lowest level of CO that causes a "CO Alarm" alert is 40 ppm, when present for more than 475 minutes. It is unlikely even a sophisticated consumer has the knowledge necessary to navigate these time-concentration products to discern the relative risks associated with each. The three alert levels are represented by various combinations of red and green LED flashes and chirps (Table 2). As the signaling system is complex, a reference card explaining the various combinations of signals is provided by the manufacturer for mounting on the wall adjacent to the device.

Sensorcon's Inspector Industrial Pro is actually marketed as a personal CO monitor for use in the industrial workplace. However, its size, battery operation and CO sensing range make it appropriate for use as a travel alarm, as well. It has

Figure 3. Approximate low-level, mid-level or alarm times

ppm of CO concentration	display	times in minutes		
		low-level	mid-level	CO alarm
<10	display '0'	no alert	n/a	n/a
10		no alert	n/a	n/a
20		20-115	>115	n/a
30		0-55	>55	n/a
40		0-40	40-475	>475
50	display CO concentration in parts per million (ppm)	0-30	30-175	>135
60		0-25	25-115	>100
70		0-20	20-60	60-240
80		0-15	16-65	>65
90		0-12	12-45	>45
100		0-10	10-30	>26
150		0-7.5	7.5-21	10-50
250		0-5	5-12	>8
400		0-4	3-8	4-15

default alarms set at 35 and 200 ppm, probably because of its intended workplace application and NIOSH regulations described above. The low-level alarm can, however, be adjusted anywhere from 5 to 100 ppm CO and the high-level alarm from 5 ppm higher than the low setting to 200 ppm. It displays CO concentrations from 0 tp 1,999 ppm alerts with a combination of visual, auditory and vibratory stimuli. It is easy to use and understand.

CONCLUSIONS

So, is one of the devices tested best for use as a low-level CO alarm and for travel? The answer is dependent upon the consumer's desire. All four of them worked exactly as claimed. In our opinion the device manufactured by CO Experts is limited by its range of CO display (maximum 50 ppm) and potential for frequent alarms, especially in a natural gas-heated environment. The device made by Forensics does not issue an audible alert until the CO concentration is 25 ppm, and some may desire a lower threshold. We found the Kidde alarm to be overly complex with regard to interpretation of the threshold levels programmed and alert signaling system. We had no criticisms of the Sensorcon alarm. The ability for the consumer to adjust the alarms to the level desired seems to be an advantageous feature, the device displays CO concentrations from 0 to 1,999 ppm, and its industrial construction suggests that it will hold up under travel conditions. Its system of auditory, visual, and vibratory alerts was excellent. While this device was designed for industrial use it would be an ideal low-level travel CO alarm.

It must be recognized that this study was limited by the fact that the marketplace for low level CO alarms is a large and fluid one. Other low-level alarms are undoubtedly available which might be suitable for travel use that were not examined. Some may be different models manufactured by the same companies. This study was not meant to be exhaustive, testing every alarm available for sale. Hopefully this discussion of features and operating characteristics will provide guidance in evaluation of those available for purchase.

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UNDERSEA & HYPERBARIC MEDICINE

Effects of hyperbaric oxygen therapy on exercise-induced muscle damage

Nicole Presti, MS [1]; Enoch Huang, MD [2]; J. Luke Pryor, PhD [1]; David Hostler, PhD [1]

[1] University at Buffalo, Department of Exercise and Nutrition Science, Center for Research and Education in Special Environments, Buffalo, New York U.S.

[2] Legacy Emanuel Hyperbaric Medicine , Portland, Oregon U.S.

CORRESPONDENCE: David Hostler – *dhostler@buffalo.edu*

ABSTRACT

Presti N, Huang E, Pryor JL, Hostler D. Effects of hyperbaric oxygen therapy on exercise-induced muscle damage. Undersea Hyperb Med. 2022 Third Quarter; 49(3):315-327.

Purpose: To perform a literature review on hyperbaric oxygen (HBO_2) therapy as a treatment for exercise-induced muscle damage (EIMD).

Methods: PubMed, Web of Science and Google Scholar were searched for articles related to HBO_2 therapy as a treatment for exercise-induced muscle damage. Inclusion criteria included HBO_2 therapy as the primary intervention to treat EIMD. Articles used in this review ranged from 1995-2021.

Conclusion: Current literature on the effectiveness of HBO_2 therapy to treat EIMD is mixed. Early and frequent treatments seem to be important factors when it comes to the success of HBO_2 therapy. Additional research is needed to determine if HBO_2 therapy has potential to treat more severe forms of EIMD and the role HBO_2 therapy has on inflammation and satellite cell function after EIMD.

KEYWORDS: athletes; delayed onset muscle soreness; inflammation

INTRODUCTION

Athletes and sports science practitioners continue to search for better methods to speed recovery and enhance performance [1]. Inadequate recovery leads to fatigue, decreased performance, and an increased probability of becoming injured [2]. Prolonged periods of inadequate recovery can lead to non-functional overreaching and overtraining syndrome if left unaddressed [3]. For professional athletes, rapid return to play after injury is important given the financial impact of players who cannot compete [4]. In 2015 Major League Baseball spent $610,339,397 in collective salary for injured athletes and $84,495,962 on their replacements [4]. Rapid recovery would also benefit military personnel who need to deploy [5].

Exercise-induced muscle damage (EIMD) is defined as skeletal muscle discomfort after unaccustomed exercise, peaking 24 to 48 hours after insult [6]. Damaged tissue after such exercise can cause the release of inflammatory cytokines, increased vascular permeability, migration of neutrophils, and edema [6]. After EIMD, edema causes hypoxia and tissue necrosis in the muscle by increasing the diffusion distance for oxygen while simultaneously reducing perfusion by increasing extracellular pressure [6]. EIMD is self-limiting and, if left untreated, subsides on its own in five to seven days [6]. Given the financial, competitive, and training implications of EIMD, athletes and practitioners often treat EIMD with one or several concomitant interventions to speed this timeline (anti-inflammatory drugs, antioxidants, massage, ultrasound, supplements, stretching, cryotherapy and compression) [7-10]. Unfortunately, most interventions claiming benefit show questionable or no scientific evidence of effectiveness, yielding an unmet need [7-10].

Hyperbaric oxygen (HBO_2) therapy is a treatment that administers 100% oxygen under pressure greater than one atmosphere absolute (ATA) [1]. HBO_2 therapy is a potential treatment for major injuries, including compartment syndrome and crush injuries [11]. HBO_2 therapy hyperoxygenates blood and tissues, which enhances white blood cell function and reduces the odds of infection and ischemia [7]. Additionally, HBO_2 therapy constricts blood vessels, which reduces edema, inflammation and secondary necrosis [7]. Therefore, HBO_2 therapy has the potential to be an effective treatment plan for EIMD, but there is limited research examining this treatment option [7].

HBO_2 therapy can help reduce inflammation and edema by increasing oxygen delivery without increasing vascular dilation [6]. During the early stages of muscle damage, repair satellite cells are activated, which initiates muscle regeneration [6,9]. As a result, the muscle is able to transition from the inflammatory phase to the proliferative phase faster, which will accelerate muscle recovery [6]. It is believed that HBO_2 therapy can enhance satellite cell proliferation and differentiation [6,9,10].

Previous studies in humans have not shown HBO_2 therapy to be an effective treatment for minor EIMD, but animal studies have shown benefits [12]. This may be due to the degree of muscle damage induced in animal models as opposed to humans. While human studies typically involve minor muscle damage induced by eccentric muscle contractions, animal models usually involve a higher degree of muscle damage because muscle damage is often induced by administering muscle toxins or a crush injury. This would suggest that HBO_2 therapy would be a more effective treatment for muscle rhabdomyolysis and is one reason why it is indicated for crush injuries [11].

HBO_2 therapy is a relatively safe treatment, and the majority of adverse side effects are mild and reversible [6]. The main concerns with HBO_2 therapy are barotrauma and oxygen toxicity. Barotrauma is the inability to equalize pressure between gas-filled spaces in the body. The most common place to experience barotrauma is in the middle ear, and in the more severe cases it can lead to a rupture in the tympanic membrane. Oxygen toxicity is another serious side effect that can affect the pulmonary and central nervous system. Oxygen toxicity of the central nervous system can cause visual changes, ringing in the ears, nausea, twitching, anxiety, confusion, dizziness, and seizures. Pulmonary oxygen toxicity is less common with typical treatment schedules, but it can lead to edema, hemorrhage, cell destruction, fibrosis and hyperplasia. Given the potential benefit for HBO_2 therapy to accelerate recovery from muscle damage and the safety profile of HBO_2 therapy, we performed a literature review of human and animal studies of HBO_2 therapy as a treatment for EIMD.

METHODS

We searched PubMed, Web of Science and Google Scholar. Keywords included *delayed onset muscle soreness, hyperbaric oxygen therapy, recovery*, and *exercise*. Articles used in this review were from 1995 to 2021. Inclusion criteria included HBO_2 therapy being the primary intervention to treat EIMD. Research articles had to be written in English. All other research articles were excluded.

HBO_2 therapy in untrained subjects

Woo et al. investigated the effects of HBO_2 therapy in subjects exercising in normobaric/normoxic, hypobaric/hypoxic, and hyperbaric/hyperoxia environments [13]. The participants in this study included 18 fit and healthy males. They were divided into three groups of six: an NN group that exercised in normobaric/normoxic conditions and did not receive HBO_2 therapy; an HNN group that received HBO_2 therapy after exercising in normobaric/normoxic conditions; and an HHH group that received HBO_2 therapy after exercising in hypobaric/hypoxic conditions. All group participants ran on a treadmill for 60 minutes at 70% to 85% of their maximum heart rate in their assigned condition. The HBO_2 therapy protocol included one treatment of 100% oxygen at 2.5 ATA for 60 minutes after the exercise protocol. Oxygen was delivered for three 20-minute periods with five-minute breaks in

between. Inflammation was assessed by measuring plasma fibrinogen, serum interleukin (IL-6), and tumor necrosis factor-alpha. Oxidative/antioxidant balance was investigated by measuring the derivatives of reactive oxygen metabolites and biological antioxidant potential. Creatine kinase and lactate dehydrogenase were used to measure muscle damage. Blood samples were taken before exercise, after exercise and after HBO_2 therapy. Results of the study showed the HNN group had significantly lower plasma fibrinogen levels after HBO_2 therapy when compared to the pre-exercise level. In addition, there was lower serum IL-6 and lactate dehydrogenase after HBO_2 therapy in the HNN and HHH groups when compared to their after-exercise levels. Lastly, there was a decrease in creatine kinase after HBO_2 therapy in the HHH group when compared to their after-exercise levels. The results of this study show that HBO_2 therapy can lower some markers of inflammation and muscle damage after EIMD, but the recovery of muscular function was not assessed.

Webster et al. investigated the use of HBO_2 therapy to accelerate recovery from EIMD [14]. This study included 12 healthy males. Muscle damage was induced by performing five sets of calf raises to failure using 80% of their one-repetition maximum (RM) with a two-minute rest between sets. Participants were split into two groups. One group received HBO_2 therapy and the second group received a placebo. Subjects in the HBO_2 therapy group were compressed to 2.5 ATA and breathed 100% oxygen for 60 minutes. Subjects in the placebo group were compressed to 1.3 ATA and inhaled air for 60 minutes. HBO_2 therapy or the placebo was given three to four hours after the exercise protocol was completed and 24 and 48 hours after the first treatment. Peak torque, peak isometric torque, and muscle endurance were measured twice at baseline and on days 1, 2, 3 and 5 post exercise. Pain and unpleasantness were measured using the Descriptor Differential Scale once at baseline and after the isokinetic testing on days 1, 2, 3 and 5. Maximum circumference of the right calf, inorganic phosphate levels, and transverse relaxation time (T2 relaxation time) was measured at baseline and on days 1, 3 and 5. There was a decrease in isometric peak torque from baseline to days 1 and 2 in the placebo group but not the HBO_2 therapy group. The HBO_2 therapy group also scored significantly lower pain and soreness on day 5 when compared to the placebo group. HBO_2 therapy did not improve isometric peak torque but it may have prevented it from declining. Lower pain scores were found in the HBO_2 therapy group on day 5. However, pain scores are subjective, which leaves room for bias.

Aunampai et al. reported changes in creatine kinase levels, pain, inflammation, and peak torque after EIMD [15]. Thirty healthy males were assigned to HBO_2 therapy or control. To induce muscle damage subjects performed 10x10 maximal vertical jumps with a one-minute rest between sets. HBO_2 therapy was provided immediately after, 24 hours, and 48 hours after, the exercise protocol. Subjects in the HBO_2 therapy group received 100% oxygen at 1.7 ATA for 60 minutes. Subjects in the control group rested in a supine position while being exposed to room air. Pain, thigh circumference, and knee extension peak torque were collected at baseline, one, 24, 48 and 72 hours post exercise. Creatine kinase levels were measured at baseline and one, 24, and 48 hours post exercise. Lower creatine kinase levels were reported 48 hours after the exercise protocol in the HBO_2 therapy group when compared to the control group. In both groups thigh circumference was greater 24 hours after the exercise protocol when compared to baseline. Percent change in peak torque was reduced up to 72 hours after exercise but there was no difference between groups. Pain scores were significantly higher 72 hours after the exercise protocol in the control group when compared to baseline. It is important to note that subjects were not blinded to their treatment plan, which could explain why the control group had higher pain scores 72 hours after exercise.

Babul et al. investigated the effects of intermittent exposure of HBO_2 therapy on EIMD (16). Sixteen females were assigned to HBO_2 therapy or control.

The exercise protocol consisted of 300 maximal eccentric contractions on their non-dominant leg on an isokinetic dynamometer completed as 30 sets of 10 repetitions with a 15-second rest between each set. The HBO_2 therapy group received 100% oxygen for 60 minutes at 2 ATA. The control group was compressed to 1.2 ATA and instructed to wear a gas mask, where they received normoxic air (21% oxygen). After reaching 1.2 ATA the chamber was reduced to barometric pressure for the remainder of the 60 minutes for subjects to experience a tympanic membrane sensation that is associated with an increase in pressure to better blind the subjects from their group assignment. Four sessions in total were administered over the four days following the muscle damage protocol. Perceived muscle soreness, eccentric strength, and quadricep circumference were measured at baseline and after each of the four treatment sessions. Creatine kinase and malondialdehyde were measured at baseline, four hours post exercise, and 30 minutes after each treatment session. Muscle signal intensity was investigated via a magnetic resonance imaging (MRI) at baseline, 24 and 72 hours post exercise. There were no differences identified between the control and hyperbaric groups. This study was the only study completed exclusively in females. However, with a small sample size we cannot draw any conclusions as to how HBO_2 therapy affects delayed onset muscle soreness (DOMS) in females

Mekjavic et al. investigated the effects HBO_2 therapy had on recovery of muscle strength, perceived soreness, and edema after muscle damage [17]. Twenty-four healthy male subjects were assigned to either HBO_2 therapy or placebo. Subjects were tested for maximal isometric strength at baseline, 10 minutes after the maximal workout, and then daily for six consecutive days. The maximal isometric strength protocol consisted of performing three trials of preacher bench curls with a five-minute rest period in between each trial. After the maximal isometric strength test, participants performed a maximal eccentric workout consisting of a modified preacher curl bench with the elbow fully flexed to about 150 degrees. Participants performed six sets of 12 maximal effort repetitions with a five-minute rest between sets.

Subjects in the HBO_2 therapy group received 100% oxygen at 2.5 ATA for 60 minutes. The placebo group received a breathing gas that contained 8% oxygen at 2.5 ATA for 60 minutes. There were seven treatment sessions starting immediately post exercise and then daily for six days. Perceived muscle soreness was measured before the isometric strength test, immediately after each treatment, on days 1 through 7, and at any time on days 8 through 10. Arm circumference was measured before each maximal voluntary contraction (MVC) test. Transcutaneous oxygen content ($TcPO_2$) was measured once during one of the HBO_2 treatments during days 2 through 5. Results of the study showed a significant difference in $TcPO_2$ levels between the HBO_2 therapy group (1420 ± 144 mmHg) and the placebo group (91 ± 23 mmHg) ($p<0.001$) [21]. Even though $TcPO_2$ measurements confirmed elevated tissue oxygen tension in the HBO_2 therapy group, there were no signs of accelerated healing.

Germain et al. investigated the effects HBO_2 therapy had on EIMD in six untrained college-aged males and 10 untrained college-aged females [7]. The exercise protocol consisted of unilateral leg extensions set at 120% of their peak force during an isokinetic dynamometer test at 60 degrees per second, then leg flexion over the same range of motion for four seconds. The exercise was repeated until the subject could no longer lower the weight for the required four seconds. At that point, the weight was lowered by 7 kg until they reached 7 kg and could no longer lower the weight. The hyperbaric protocol consisted of the subject breathing 95% oxygen at 2.5 ATA for 100 minutes, with two five-minute air breaks given at the 30- and 65-minute mark. Subjects were assigned to HBO_2 therapy or control. The HBO_2 therapy group received five separate treatments. The treatments were given an hour after exercise, six hours later, the following day; and subjects received two treatments that

were separated by six hours two days after the exercise protocol. Leg circumference and soreness were assessed at baseline and on days 0 to 4, 7 and 14. Plasma creatine kinase was measured from blood at baseline and on days 0, 1, 4, 7 and 14. Isokinetic peak torque and average power were measured at baseline and on days 2, 4 and 14. There were no differences between groups.

Delayed HBO_2 therapy

Staples et al. was the largest study completed in humans investigating HBO_2 therapy on DOMS [18]. DOMS was induced in the non-dominant quadriceps muscle in 66 untrained males. Pain perception was taken before exercise, after exercise, and after each HBO_2 therapy session. The mean maximal torque was measured before and after exercise. Pain perception was measured on a 0-10 visual analog scale. Mean maximal torque test was performed on an isokinetic dynamometer. The protocol consisted of three submaximal and one maximal contraction, rest, and then participants performed four maximal contractions. The maximal torque was the mean of the last three maximal contractions. After the pre-exercise testing, participants performed 30 sets of 10 maximal eccentric contractions on the dynamometer. Each set lasted 45 seconds with a 15-second recovery period. Each subject's eccentric quadricep muscle torque was measured 48 and 96 hours after exercise.

Phase I consisted of 40 untrained males [18]. Four subjects were removed from the study for having an abnormal response to eccentric exercise. The purpose of Phase I was to determine the efficacy of providing HBO_2 therapy immediately after exercise as opposed to delaying treatment. Subjects were divided into a control group, an HBO_2 therapy group, a delayed HBO_2 therapy group, and a sham group. HBO_2 therapy treatments consisted of receiving 100% oxygen at 2.0 ATA for one hour. The sham treatment consisted of receiving 21% oxygen at 1.2 ATA for one hour. For Phase I the HBO_2 group received HBO_2 therapy 0, 24, and 48 hours after exercise and then were given sham treatments at 72 and 96 hours after exercise. The delayed HBO_2 therapy group received sham treatments 0 and 24 hours after exercise and then received HBO_2 therapy 48, 72 and 96 hours after exercise. The sham group received sham treatments 0, 24, 48, 72 and 96 hours after exercise. The control group received no treatment. There was an improvement in eccentric torque from hour 0-96 in the HBO_2 therapy group when compared to the three other groups ($p=0.021$).

Phase II determined the efficacy of the sham treatment and investigated the effects of HBO_2 therapy three and five days after the exercise protocol [18]. Phase II studied 30 untrained men assigned to one of three groups. Group 1 (three-day HBO_2 therapy group) received HBO_2 therapy immediately, 24 and 48 hours after the exercise and sham treatments 72 and 96 hours after exercise. Group 2 (five-day HBO_2 therapy group) received HBO_2 therapy immediately, 24, 48, 72 and 96 hours after exercise. Group 3 received sham treatments immediately, 24, 48, 72 and 96 hours after exercise. There was greater improvement in eccentric torque when comparing the five-day HBO_2 therapy group to the three-day HBO_2 treatment group and the sham group ($p=0.005$). There was also an improvement in mean torque in the five-day HBO_2 group when compared to the sham group ($p=0.02$). There were no additional significant findings between groups.

Harrison et al. examined the use of HBO_2 therapy to treat exercise-induced muscle injuries in 18 untrained college-aged males [19]. Subjects were assigned to a control group, an immediate HBO_2 therapy group, or a delayed HBO_2 therapy group. Muscle injury was induced in the non-dominant arm, with six sets of 10 eccentric preacher curls performed at 120% of the concentric maximum. The load was raised after each eccentric set, and each repetition lasted 10 seconds. The HBO_2 therapy protocol consisted of subjects receiving 100% oxygen for three 30-minute periods with a five-minute air break between each period at 2.5 ATA. During the sham treatment subjects received

ambient air (20.93% oxygen) for 100 minutes. To prevent subjects from knowing what group they were assigned to, the pressure in the chamber was brought to 140 mmHg above barometric pressure so subjects would experience tympanic membrane sensation. After reaching the target pressure the chamber was brought back to barometric pressure for the treatment session.

The immediate HBO_2 therapy group received HBO_2 therapy two hours after the exercise protocol and for the following four days. The delayed HBO_2 therapy group received a sham treatment after the exercise protocol and HBO_2 therapy on days 1 through 4. The control group received no treatment. Serum creatine kinase was measured before the exercise protocol and on days 1, 2, 7 and 15. Forearm flexor isometric strength and rating of perceived soreness was measured on days 1-4, 7 and 15. MRI, measuring T2 relaxation time, was measured at baseline, and on days 2, 7 and 15. There was no significant difference between groups for any measure. While there is evidence that the exercise protocol did result in a significant muscle injury, there is no evidence that HBO_2 therapy had an effect on the recovery. The results of this study suggest that HBO_2 therapy does not aid in the recovery of soft tissue athletic injuries, but more research is needed to confirm.

HBO_2 therapy in athletes

Branco et al. investigated the effects of HBO_2 therapy on post-training recovery after two typical training sessions in 11 experienced male Brazilian jiu-jitsu athletes [1]. This study used a randomized crossover design where subjects were their own controls. The training sessions consisted of a warm-up, technical training, and six combat simulations. The HBO_2 therapy protocol consisted of breathing 100% oxygen for 89 minutes at 2.39 ATA after the training sessions. The control phase was passive recovery for two hours. Cortisol and total testosterone were used to measure hormonal action in the plasma. Cell damage was assessed by measuring lactate dehydrogenase, creatine, creatine kinase, aspartate aminotransferase, and alanine aminotransferase from serum. Lactate and rate of perceived exertion was assessed during pretraining and after each of the six combat simulations. Rate of perceived recovery was assessed pretraining two and 24 hours after treatment. Blood was collected before treatment, immediately after treatment, and at two and 24 hours after treatment. Higher perceived recovery was reported in the HBO_2 therapy group at two ($p=0.012$) and 24 hours ($p=0.018$) post training session when compared to the control group, but this may be due to a placebo effect. Blood lactate levels were higher after the jiu-jitsu fight in both groups. There were no condition or interaction effects on hormones or cellular damage markers.

Chen et al. investigated the efficacy of HBO_2 therapy as a treatment option for muscular injury recovery in 41 adult baseball players who sustained prolonged exercise-induced muscular soreness or who were diagnosed with a grade 1 muscle strain of the extremities [20]. The athletes maintained their training schedules during the duration of the study. The athletes were assigned to HBO_2 therapy or placebo. Athletes assigned to HBO_2 therapy received normal air for 15 minutes while the chamber pressurized to 2.5 ATA. After reaching 2.5 ATA, the athletes received 100% oxygen for three 25-minute sessions, with a five-minute air break between each session. During the last session the last 15 minutes were used to depressurize the chamber to 1 ATA. Athletes in the placebo group were pressurized to 1.3 ATA and received 100% oxygen only during the time of depressurization. The athletes received HBO_2 therapy or the placebo twice per week for five weeks. Blood samples were taken before the first session, after the fifth session, after the 10th session, and two weeks following the 10th session to measure creatine phosphokinase, myoglobin, lactate, blood urea nitrate, and glutamic oxaloacetic transaminase.

Pain intensity and interference were measured before the first session and after the 10th session. Pain intensity was measured via four questions be-

fore the first session and at the end of the 10th session. Subjects had to rate their pain level now, and their highest, lowest, and average pain levels over the last week. Pain interference was measured with seven questions before the first session and after the 10th session. Researchers asked how pain interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. At the end of the fifth and 10th sessions, the HBO_2 therapy group experienced a reduction in glutamic oxaloacetic transaminase ($p=0.004$) and myoglobin ($p<0.001$). There was lower creatine phosphokinase ($p<0.001$) and pain ($p=0.005$) in the HBO_2 therapy group after the end of the 10th session. The HBO_2 therapy group saw improvement in all four items in the pain and intensity questions after the 10th session, but the control group did not. When comparing the HBO_2 therapy group to the control group for pain interference, the HBO_2 therapy group saw a greater improvement in general activity, mood, walking ability, normal work continued, sleep, and enjoyment in life after the 10th session. The control group saw improvements only in mood, normal work continued, and sleep. HBO_2 therapy reduced creatine phosphokinase, glutamic oxaloacetic transaminase, myoglobin, and pain interference, which can indicate recovery from a muscular injury.

HBO_2 therapy in animal models

Best et al. investigated HBO_2 therapy as a treatment option for a muscle stretch injury to the tibialis anterior muscle tendon in 18 rabbits [21]. Twenty-four hours after the stretch injury the rabbits in the HBO_2 therapy group were placed in a hyperbaric chamber where oxygen levels were greater than 95% at 2.5 ATA for 60 minutes. The control group was returned to their cages. Ankle isometric torque measurement and a tissue analysis were performed seven days after the injury. The rabbits in the HBO_2 therapy group showed less discomfort three days after the injury when compared to the control group. Seven days after the injury, the control group had higher average isometric torque deficit than the HBO_2 therapy group ($p=0.001$). Lastly, hypercellularity and muscle fiber damage was found in the control group. There was less cellularity as well as fiber damage found in the HBO_2 therapy group.

Haapaniemi et al. investigated whether HBO_2 therapy could reduce ischemia-induced muscle damage in 48 male rats [22]. The rats were assigned to one of four groups. Groups 1 and 2 had a tourniquet applied to their left thigh for three hours. Group 1 received HBO_2 therapy treatment and group 2 did not. Groups 3 and 4 had a tourniquet applied to their left thigh for four hours. Group 3 received HBO_2 therapy treatment and group 4 did not. The HBO_2 therapy groups received 100% oxygen at 2.2 ATA for 45 minutes and treatments were given 0, 4, 8, 16, 24, 32 and 40 hours after the tourniquet was released. A muscle biopsy was taken from the anterior tibialis muscle 48 hours after the tourniquet was released. Technetium-pyrophosphate, adenosine triphosphate, phosphocreatine, and lactate were measured 48 hours after the tourniquet was released. There was a decrease in technetium-pyrophosphate uptake in the HBO_2 therapy groups when compared to the control groups ($p<0.05$), which indicates less skeletal muscle injury. There were higher levels of adenosine triphosphate and phosphocreatine ($p<0.001$) and lower levels of lactate ($p<0.001$) in the HBO_2 therapy groups when compared to the control groups. Lastly, the HBO_2 therapy group had less skeletal muscle injury.

Yamamoto et al. investigated the optimal timing of HBO_2 therapy after a muscle injury in 220 male rats [23]. Muscle injury was induced by dropping a 640-gram aluminum cylinder from 250 mm on the belly of the right medial calf. After the injury, the rats were assigned to one of 10 groups. Group 1 received HBO_2 treatment immediately after the muscle injury. Group 2 received HBO_2 therapy one day, group 3 three days, and group 4 five days after the muscle injury. Groups 5-8 received a total of three HBO_2 treatments. Group 5 received HBO_2 therapy treatments 0 to two days; group 6 one to three days; group 7 three to five days; and group 8 five to seven days after the muscle injury. Group 9 received a total of five HBO_2 treatments

on days 0 to 4 and group 10 received no treatment. The HBO_2 therapy protocol consisted of receiving 100% oxygen at 2.5 ATA for two hours.

Macrophage accumulation of CD68- and CD206-positive cells and changes in Pax7+MyoD- and Pax7+MyoD+ satellite cells were investigated one, three, five and seven days after the muscle injury. The cross-sectional areas of five rats in each group and regenerating myofibers were measured five days after the muscle injury. Muscle tensile isometric strength, twitch force, and tetanic force were measured seven days after the muscle injury. The tetanic force in groups 5 through 7 was recovered to baseline when compared to group 8 ($p<0.001$). The twitch force in groups 5 and 9 was recovered when compared to group 10 ($p<0.001$). The mean of the cross-sectional area of the regenerating muscle fibers in groups 5 through 7 and 9 was larger than the mean of group 10 ($p<0.001$). The regenerating muscle fibers in groups 5 through 7 and 9 increased when compared to group 10 ($p<0.001$). CD68-positive cells in groups 1, 2, 6 and 9 increased three days after the injury ($p<0.001$). CD206-positive cells in groups 1, 2, 5, 6, 7 and 9 increased three to five days after the injury ($p<0.002$). The number of Pax7-MyoD+ cells in groups 2, 5, 6 and 9 increased three to five days after the injury ($p<0.001$). Pax7-MyoD+ cells in groups 7 and 9 were increased at day 5 when compared to group 3 ($p<0.001$).

The results of this study show that the most effective treatment for recovery is three HBO_2 therapy treatments within three days after a muscle injury. While studies completed on animals show that HBO_2 therapy maybe benefit recovery in muscle injuries, results in animal research will not always have the same results in humans.

DISCUSSION

The literature examining the utility of HBO_2 therapy to treat exercise-induced muscle damage is small, and interpretation is difficult. It is important to take into consideration the volume of muscle damage the subjects sustained during each study when assessing the potential benefit of HBO_2 to treat muscle damage. While most studies used blood markers to document that muscle damage occurred, it is often not clear if the damage was mild, moderate or severe. There was also a variety of methods and muscle groups used to induce muscle damage. Babul et al. recruited 16 untrained females whose muscle damage protocol consisted of 300 maximal voluntary eccentric contractions on an isokinetic dynamometer [16]. The muscle damage was induced to the subjects quadricep muscle on their non-dominant leg. This is a very different paradigm when compared to Chen et al., who did not induce muscle damage at all but studied baseball players who had pre-existing exercise-induced muscle soreness or pain with grade I muscle strain of the extremities [20]. Additionally, the population recruited as subjects is a factor since subjects who are resistance-trained are more resistant to muscle damage and would have a faster recovery when compared to untrained subjects [7].

When investigating perceived pain and recovery the results are inconclusive. While Chen et al., Webster et al., Aunampai et al. and Bronco et al. reported improvements after HBO_2 therapy, Germain et al., Babul et al., Harrison et al., Makjavic et al. and Staples et al. did not [1,7,14-17,19,20]. The mixed results could be due to the way perceived pain and recovery were measured. Most studies used 10-point scales, but other studies used 100-mm scales, descriptor scales, and questionnaires. Perceived pain perceptions were also taken at different times. Some studies measured pain after the exercise protocol was completed, while others measured after the HBO_2 therapy session. Subjectiveness of pain perception may also be a factor. Pain and recovery perception are subjective, and different subjects have different pain thresholds and tolerance levels [16]. In all of the studies cited in this report, pain and recovery perceptions were asked multiple times but not a consistent number of times. Frequency in sampling can give biased results because the subjects are aware

of their previous response, which could affect their subsequent responses [16].

The placebo effect is an additional factor to consider when evaluating pain perception. While most of the subjects were blinded to their treatment plan, some were not. Aunampai et al. had their subjects in the control group rest in a supine position, while the subjects in the HBO_2 therapy group entered the hyperbaric chamber [15]. The lack of blinding could partially explain why the control group reported higher pain scores when compared to baseline when the HBO_2 therapy group did not. Similar to Aunampai et al., Branco et al. did not blind their subjects [1]. The Branco et al. study was a crossover design where their subjects were their own controls. When subjects were in the HBO_2 therapy group they entered the hyperbaric chamber for treatment. When subjects were in the control group they received passive recovery for two hours. Branco et al. reported higher ratings of perceived recovery in the HBO_2 therapy group when compared to the control group at two and 24 hours after injury. Future studies in this area should take care to blind subjects to treatment and assess the quality of blinding among the subjects.

Blood tests are a common way to measure muscle damage. Markers in the blood that are indicative of muscle cell damage include creatine phosphokinase, myoglobin, glutamic oxaloacetic transaminase, urea nitrogen, lactate dehydrogenase, creatine kinase, aspartate aminotransferase, and alanine aminotransferase [20]. Changes in these enzymes are a reflection of muscle activity and are frequently used to monitor muscle injury, cell damage, and muscle breakdown. Woo et al. and Aunampai et al. found a difference in creatine kinase levels after HBO_2 therapy when Germain et al., Branco et al., Babul et al. and Harrison et al. did not [1,7,13,15,16,19]. Woo et al. and Haapanemi et al. found lower levels of lactate dehydrogenase levels in the HBO_2 therapy group compared to the control; however, the Haapanemi et al. study was done in rats, which may not directly translate to humans (13,22). Branco et al. and Chen et al. also investigated changes in lactate dehydrogenase levels; however, they did not find any significant difference between the HBO_2 therapy group and the control groups [1,20]. This may be due to the fact that Branco et al. and Chen et al. were the only two studies that used athletes [1,20]. Even though HBO_2 therapy may be useful to treat muscle injuries in athletes, it may be more beneficial in untrained individuals.

Woo et al. was the only study that investigated inflammation with biomarkers IL-6, tumor necrosis factor-alpha, and fibrinogen [13]. Aunampai et al., Germain et al. and Babul et al. estimated inflammation by measuring the circumference of the injured limb, while Webster et al. and Harrison et al. measured the cross-sectional area of the injured muscle using an MRI [7,14-16,19]. Woo et al. found lower levels of IL-6 and fibrinogen after HBO_2 therapy [13]. There were no differences found between groups when measuring circumference or when investigating cross-sectional areas [7,14-16,19]. While MRI is highly reliable, measures of circumference are influenced by the skill and repeatability of the individual making the measurements and may not be the best measure of the effectiveness of HBO_2 therapy in this population.

Reports of isometric peak torque changes after HBO_2 therapy are mixed. Webster et al. and Best et al. reported improvement in isometric peak torque after the HBO_2 therapy while Mekjavic et al. and Harrison et al. did not [14,17,19,21]. This may be due to the way Mekjavic et al. and Harrison et al. induced muscle damage [17,19]: Both research teams induced muscle damage with a preacher curl, while Webster et al. induced muscle damage in the calf [14,17,19]. Muscles of the anterior arm and triceps surae muscles have different mass and may have different fiber type composition. There may be some threshold volume or severity of muscle damage where HBO_2 therapy is more effective. It is not clear which form of EIMD is most likely to respond to HBO_2 therapy. The marker performance and blood markers discussed above are

largely indirect measures of muscle damage and recovery.

We propose that the mixed findings of HBO_2 therapy on EIMD is that studies have not quantified satellite cell activation and proliferation after varying levels of EIMD. It is unknown how much satellite cell activation and proliferation is needed after varying levels of EIMD. It is likely that minor EIMD needs little satellite cell activation; thus, HBO_2 therapy would not be indicated.

CONCLUSIONS

Current literature regarding HBO_2 therapy for treatment of EIMD is mixed, and more research needs to be done. HBO_2 therapy has the potential to be successful when treating more severe forms of muscle damage caused by crush injuries but may be less effective for minor injury [12]. Although the mechanisms of crush injury and EIMD differ, the evidence supporting HBO_2 therapy for crush injury may support treatment of severe EIMD. Strauss et al. reported in their review that more than 600 clinical cases reported in more than 20 publications agree with the usefulness of HBO_2 therapy in treating crush injuries [24]. About 80% of the overall outcomes were positive. One important factor when it came to the success in using HBO_2 therapy in treating crush injuries was early and frequent treatments [12]. Animal work shows early and often (60 to 120 minutes/day) for at least three days is optimal [21-23]. When investigating HBO_2 therapy in traumatic ischemias, Schramek reported a 100% salvage rate with six HBO_2 treatments per day [25]. Lorder reported 80% complete or partial recoveries with three treatments per day [26], and Slack reported 59% of patients recovered well with one HBO_2 therapy session per day [27].

While the literature does not support HBO_2 therapy to treat EIMD, there is not a sufficient number of high-quality negative studies to rule it out. HBO_2 therapy is useful in moderating inflammation and satellite cell function in animal models. Most studies using human subjects are not measuring variables for which HBO_2 therapy may have a direct effect because that would require a muscle biopsy, which may not be commonly available in all labs. This, along with better blinding and placebo-controlled studies, are needed to measure the variables where HBO_2 therapy would be effective. Notably absent are studies examining minor and moderate injury using a single paradigm, a direct comparison of trained and untrained individuals, and the number treatments required for full recovery. We propose that the gold standard for efficacy is recovery of function compared to an adequately blinded control group.

AUTHOR	N	SUBJECTS	SHAM GROUP	MUSCLE DAMAGE PROTOCOL	HBO_2 THERAPY PROTOCOL	HBO_2 THERAPY TIMING	PRIMARY CONCLUSION
Woo et al. (13)	18	untrained males	no	running	100% O_2 at 2.5 ATA for 60 mins with two 5-min air breaks	After exercise	HBO_2 therapy lowered some markers of inflammation
Webster et al. (14)	12	untrained males	yes	calf raises	100% O_2 at 2.5 ATA for 60 mins	HBO_2 therapy 3-4 hours after exercise, 24, and 48 hours after first treatment	lowered pain and soreness scores
Aunampai et al. (15)	30	untrained males	no	vertical jumps	100% O_2 at 1.7 ATA for 60 mins	Immediately after, 24 and 48 hours after exercise	HBO_2 therapy lowered creatine kinase levels
Babul et al. (16)	16	untrained females	yes	eccentric contractions	100% O_2 at 2.0 ATA for 60 mins	Immediately after exercise and the following 3 days	HBO_2 therapy showed no improvement
Mekjavic et al. (17)	24	untrained males	yes	preacher curls	100% O_2 at 2.5 ATA for 60 min	Immediately after exercise and the following 6 days	HBO_2 therapy improved $TcPO_2$ levels
Germain et al. (7)	16	untrained males and females	no	leg extensions	95% O_2 at 2.5 ATA for 100 mins with two 5-min air breaks	1 hour, 6 hours, next day, and 2 treatments 2 days after exercise	HBO_2 therapy showed no improvement
Staples et al. (18)	36	untrained males	yes	eccentric contractions	100% O_2 at 2 ATA for 60 mins	Group 1: 0, 24, 48 hours after exercise Group 2: 48 ,72, 96 hours after exercise	HBO_2 therapy improved eccentric torque
Staples et al. (18)	30	untrained males	yes	eccentric contractions	100% O_2 at 2 ATA for 60 mins	Group 1: 0, 24, 48 hours after exercise Group 2: 0, 24, 48, 72, 96 hours after exercise	Five days of HBO_2 therapy improved eccentric torque on a mean torque

AUTHOR	N	SUBJECTS	SHAM GROUP	MUSCLE DAMAGE PROTOCOL	HBO_2 THERAPY PROTOCOL	HBO_2 THERAPY TIMING	PRIMARY CONCLUSION
Harrison et al. (19) males	18	untrained	yes	preacher curls	100% O_2 at 2.5 ATA for 100 mins with two 5-min air breaks	Group 1: 2 hours after exercise and on the following 4 days Group 2: Days 1-4 after exercise	HBO_2 therapy showed no improvement
Branco et al. (1)	11	Brazilian jiu-jitsu athletes	no	Brazilian jiu-jitsu practice	100% O_2 at 2.39 ATA for 89 mins	After exercise	HBO_2 therapy improved perceived recovery rates
Chen et al. (20)	41	baseball players	yes	baseball	100% O_2 at 2.5 ATA for 85 mins with two 5-min air breaks	Twice per week for 5 weeks	HBO_2 therapy reduced glutamic oxaloacetate transaminase, myoglobin, creatine phosphokinase, and pain levels
Best et al. (21)	18	rabbits	no	stretch injury	>95% O_2 at 2.5 ATA for 60 mins	24 hours after stretch injury	HBO_2 therapy improved isometric torque and discomfort. HBO_2 therapy reduced cellularity and fiber damage.
Haapaniemi et al. (22)	48	rats	no	tourniquet	100% O_2 at 2.2 ATA for 45 mins	0,4,8,16,24,32,& 40 hours after the tourniquet was released	HBO_2 therapy reduced skeletal muscle injury and mortality
Yamamoto et al. (23)	220	rats	no	modified mass drop method	100% O_2 at 2.5 ATA for 120 mins	Group 1: 0 days after injury Group 2: 1 day after injury Group 3: 3 days after injury Group 4: 5 days after injury Group 5: 0-2 days after injury Group 6: 1-3 days after injury Group 7: 3-5 days after injury Group 8: 5-7 days after injury Group 9: 0-4 days after injury	The most effective treatment for recovery is three HBO_2 therapy treatments within three days of muscle injury.

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UNDERSEA & HYPERBARIC MEDICINE

A novel source of carbon monoxide for suicide attempt

Nicholas James Brady, BA [1]; Priya Sunilkumar Patel, BS [1]; Siamak Moayedi, MD [2,3]; Douglas Sward, MD [2,3]

[1] University of Maryland School of Medicine, Baltimore, Maryland, U.S.
[2] Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, Maryland, U.S.
[3] Department of Hyperbaric Medicine, R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland, U.S.

CORRESPONDENCE: Siamak Moayedi – *Mak.Moayedi@som.umaryland.edu*

ABSTRACT

Brady NJ, Patel PS, Moayedi S, Sward D. A novel source of carbon monoxide for suicide attempt. Undersea Hyperb Med. 2022 Third Quarter; 49(3) 329-331.

Carbon monoxide (CO) inhalation is a common method of suicide. The combination of formic acid with sulfuric acid creates carbon monoxide. This novel method is described in readily accessible internet-based resources. We present the case of a 35-year-old woman who developed CO toxicity by using this method. It is important for hyperbaric medicine physicians to be aware of this source of CO toxicity.

KEYWORDS: carbon monoxide; formic acid; hyperbaric medicine; suicide; sulfuric acid

BACKGROUND

The inhalation of carbon monoxide (CO) is a common method of suicide. Most cases of intentional CO poisoning are vehicle-related [1]. In rare cases, people have attempted or completed suicide by combining formic acid with sulfuric acid to create CO. The first case of this method of suicide documented in an English-language journal occurred in Indiana in 2005 [2]. Since that initial report, there have been seven additional case reports on the subject [2-9]. Because this method of suicide is rising in frequency, it is important that hyperbaric medicine physicians are aware of it.

CASE PRESENTATION

A 35-year-old transgender woman with a past psychiatric history of depression and multiple suicide attempts was found by her wife in a parked car with the windows rolled up. Around 6:00 a.m. the patient had attempted to commit suicide inside the car by combining formic acid with Liquid Fire drain cleaner. About 8:30 a.m., her wife found her, opened the car door, and called 911. When emergency medical services arrived, the patient was alert but dizzy and complained of a headache. She was transported to a local emergency department where her carboxyhemoglobin level was measured at 28.9%. Beyond her dizziness and frontal headache, the patient denied any chest pain, shortness of breath or loss of consciousness. She was treated with oxygen through a non-rebreather mask and was later transferred to a tertiary care hospital for hyperbaric oxygen (HBO_2) therapy.

The patient was treated at 2.8 atmospheres absolute (ATA) for 73 minutes, followed by a second treatment the next day at 2.0 ATA for 120 minutes. She was asymptomatic at the end of the first treatment, with resolution of her frontal headache and dizziness. After medical clearance she was admitted to the psychiatric unit for major depressive disorder and suicide attempt.

The patient noted she had first learned about the reaction between formic acid and sulfuric acid while watching YouTube videos published by the

Royal Society of London, which cover a broad array of scientific topics. She recounted that she enjoyed watching the videos out of an interest in science and happened to come across one that detailed how formic acid and sulfuric acid react to create CO. The patient then sought more details on this reaction by googling the combination of formic acid and sulfuric acid. The first few results on Google contained case reports of people who had committed suicide in this manner. After further searching, the patient learned sulfuric acid was the main component in common drain cleaner solutions. She was able to easily purchase Liquid Fire drain cleaner from a local store. She ordered formic acid, commonly used in beekeeping, from eBay.

Once she had the materials the patient went into her car, where she poured the formic acid and the Liquid Fire into a glass measuring cup. She did not follow any precise measurements. After combining the chemicals, she noticed the mixture bubbling and a burning sensation in her throat and lungs. She put on a cloth mask to alleviate that sensation and sat in the car until her wife found her.

DISCUSSION

When sulfuric acid and formic acid are combined formic acid dehydrates to generate CO. This is a rare source of CO poisoning. From the first report in 2005 and including the case we describe, nine case reports have been reported in English-language medical journals. It is likely that this method of CO poisoning will become more common given the availability of internet-based resources that explain this reaction.

While the patient we describe first learned about the reaction between sulfuric acid and formic acid from an educational video, there are many sites on the internet that describe the reaction specifically for the purpose of suicide education. In 2003 the media reported on an Australian euthanasia advocate named Philip Nitschke who had designed a device that generated CO from formic acid and sulfuric acid, which the media dubbed a "death machine." Nitschke hoped to supply the patented device to pro-euthanasia groups, and he presented it at conferences in Australia and the United States. Articles on Nitschke and his "death machine" are still available on the internet [10-11].

A 2016 case report described the first instance of someone who survived after attempting suicide by mixing formic acid and sulfuric acid. After the man was extubated, he reported that he learned about the method on a website dedicated to suicide called lostallhope.com [7]. In 2017, a man recorded a video of himself committing suicide in his car by mixing formic acid with sulfuric acid. In the video, he did not explain how he first learned of the chemical reaction but did mention that he browsed a Reddit forum where users gave advice on various suicide methods [8]. After a brief Google search we were able to find multiple similar internet forums where CO poisoning through the combination of formic acid and sulfuric acid is promoted.

Websites that promote CO poisoning as a method of suicide typically describe it as a "painless" or "peaceful" way to die, but many of the case reports refute this characterization. Formic acid is a corrosive substance that vaporizes at room temperature. Inhalation of formic acid can damage the airway and lead to pulmonary complications such as chemical pneumonitis, dyspnea, and pulmonary edema [12-13]. In 2008 Yang et al. reported a similar suicide in a young man whose parents were also exposed to CO as well as noxious fumes after finding their son. The mother developed pharyngitis, and the father developed pneumonitis which progressed to acute respiratory distress syndrome [3]. Other reports describe additional complications of formic acid inhalation, such as hyperemia of the bronchioles, alveolar edema, and a discolored trachea with no epithelium [6-7]. In the case of the man who recorded himself combining formic acid and sulfuric acid, the authors observed "violent coughing" before he eventually lost consciousness [8]. Our patient reported a burning sensation in her lungs.

CONCLUSION

We describe a rare form of CO poisoning in which our patient attempted suicide by combining sulfuric acid with formic acid to generate CO. It is likely that this method will increase in frequency due to the availability of online resources that describe the reaction as a method of suicide. Therefore, it is important that hyperbaric medicine physicians are informed on this method of suicide.

Acknowledgment

Deborah M. Stein, ELS, provided language editing of the manuscript.

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UNDERSEA & HYPERBARIC MEDICINE

Hyperbaric oxygen therapy to treat lingering COVID-19 symptoms

Albert E. Zant, MD [1]; Xavier A. Figueroa, PhD [2]; Christopher P. Paulson, MD [3], FAAP; James K. Wright, MD, FACS [4]

[1] Hyperbaric Medicine Inc. Fort Walton Beach, Florida U.S.; [2] Unaffiliated, Seattle, Washington U.S.; [3] Magnolia Medical Clinic, Fort Walton Beach, Florida; [4] Olympic Medical Center, Port Angeles, Washington

CORRESPONDENCE: James K. Wright – *wright4james@gmail.com*

ABSTRACT

Zant AE, Figueroa XA, Paulson CP, Wright JK. Hyperbaric oxygen treatment of lingering COVID-19 symptoms. Undersea Hyperb Med. 2022 Third Quarter; 49(3):333-339.

Background: SARs-Cov-2 infections can produce prolonged illness and significant disability. Patients recovering from COVID-19 can have persistent symptoms leading to long-term morbidity.

Methods: Six patients with long-lasting (> 30 days) COVID-19 symptoms were treated with hyperbaric oxygen (HBO_2) therapy. All patients were assessed for symptoms using the ImPACT questionnaire, a muscle and joint pain scale, and a modified Borg dyspnea scale. Patients were assessed before, during and after HBO_2 treatments.

Results: All patients saw improvements in the measured symptoms to levels that were the same as pre-infection levels (five of six patients) or had significant improvement in symptoms (one patient).

Conclusions: The results suggest that HBO_2 helped to improve symptom scores, reduce the length of time of symptoms, and improved the quality of life. More detailed and randomized studies are needed to confirm the results in this report.

KEYWORDS: COVID-19; COVID long-haulers; hyperbaric oxygen; infectious diseases; SARs-Cov-2

INTRODUCTION

It is estimated that 20% to 50% of people infected with COVID-19 have prolonged symptoms [1] that last weeks to months. Symptoms have been characterized by fatigue, prolonged shortness of breath, myalgias, physical impairment, neurodegenerative symptoms [2], cognitive impairment [3,4], emotional lability and a sense of despair. In addition to the dyspnea and muscle and joint pains, many of these symptoms can be categorized as psychological or neurological/physiological change that is brought on by the SARs-Cov-2 infection. The prolonged illness can delay or compromise return to daily activities and employment.

Hyperbaric oxygen (HBO_2) treatment has been shown to reduce endothelial injury [5] as well as hypoxia-induced inflammation in reperfusion injury [6], increase stem cell proliferation [7], enhance brain recovery from inflammation [8], help reduce chronic pain [9], assist in reducing symptoms in chronic fatigue syndrome [10,11], improve neuroplasticity [12] and poor quality of life [13], and alter genes involved in neural responses to stress and transmission [14]. HBO_2 has analgesic effects demonstrated in nociceptive, inflammatory and neuropathic pain models in mice [15-17] and human pain syndromes [18.19]. We also considered that HBO_2 might be useful in treating sequelae of microemboli in COVID infection [20].

Because of our experience successfully treating patients with traumatic brain injury [21,22] – whose symptoms are sometimes similar to those experienced in post-COVID recovery – we provided HBO_2 to this patient population. Hyperbaric oxygen has

been used successfully to treat symptoms of pain in patients with PTSD [23,24], post-concussion syndrome [25], chronic fatigue syndrome and fibromyalgia [26,27].

Six case studies were carried out to assess the potential of HBO_2 to improve post-COVID-19 symptoms. We used the ImPACT questionnaire to assess the severity of symptoms, the modified Borg dyspnea scale to measure change in shortness of breath (SoB), and a modified verbal analog pain scale for myalgia and joint pain before, during and after the study participants underwent HBO_2 treatments.

Here we report the effects of HBO_2 on COVID-19 symptoms that lingered for longer than 30 days post SARs-Cov-2 clearance (range of symptom duration: 34 to 192 days) in this small, non-randomized population.

METHODS

Patients with lingering COVID-19 symptoms that were not responding to standard therapy were referred to the Hyperbaric Medicine Inc. facility in Fort Walton Beach, Florida. After determining to use HBO_2 for lingering COVID-19 symptoms, the first six individuals to receive treatment were included in this report. No other selection or inclusion criteria were used in this series. Since the completion of this report, other patients have been treated with similar results. An institutional review board was not used for this retrospective report, and the patients were treated according to established criteria for off-label HBO_2 therapy. Patients consented to the off-label treatment knowing that it was unproven for this condition; were informed of alternate treatments (e.g., rest, symptom-directed medication, allowing for the passage of time); the risks of HBO_2; and any potential costs. All patients were treated without charge, and none of the authors had any financial incentive in this effort.

Patients were treated with hyperbaric oxygen (100% oxygen, 2 atmospheres absolute (ATA)/101.3 kilopascals (kPa)) over ambient pressure for 90 minutes. Treatments were performed once a day for three to five days per week. Treatment continued until the patients had completely recovered or had reached a stable plateau of symptom improvement in which HBO_2 was thought to have minimal additional benefit (range 24 to 85 days). All HBO_2 treatments were provided to the patients in Sechrist monoplace chambers. Symptom testing was done at the Hyperbaric Medicine Inc. facility in Fort Walton Beach, Florida, by a trained physician (AEZ). A baseline medical history for each study participant was carried out by the referring physician; further testing was done with the ImPACT concussion assessment questionnaire. Muscle and joint pain were measured by a modified verbal rating scale [28]. Assessment for dyspnea was done using a modified Borg dyspnea score to measure perceived dyspnea at rest and on exertion [29].

RESULTS

Six patients with lingering COVID-19 symptoms were treated with HBO_2. Patients exhibited symptoms that lasted from 34 days to 197 days (Figure 1A) prior to beginning HBO_2 treatment. Patients were assessed on a modified Borg dyspnea scale (Figure 1B). No dyspnea symptoms prior to infection were noted, with the exception of Patient #4. All patients developed dyspnea symptoms in the *slight* to *moderate* range of the modified Borg scale (average dyspnea score: 3.81). After completing 15 to 29 HBO_2 treatments, dyspnea scores were significantly reduced (average dyspnea score post-HBO_2: 0.17) in all patients.

Other symptoms associated with a COVID-19 diagnosis were assessed using the ImPACT symptoms questionnaire [30]. Each symptom has a 6-point maximal intensity scale: none 0; slight 1-2; moderate 3-4; severe 5-6. The questionnaire was proctored by a trained assessor (AEZ). The summed scores (Figure 2A) for each patient are displayed and reveal the overall general state for each patient before HBO_2 (purple columns), at the start of HBO_2 (red columns) and after the last HBO_2 treatment they received (green columns). Each patient saw a significant reduction in their overall symptom state. Tracking the change over time (Figures 1B and 2B) for each individual patient's symptoms shows a

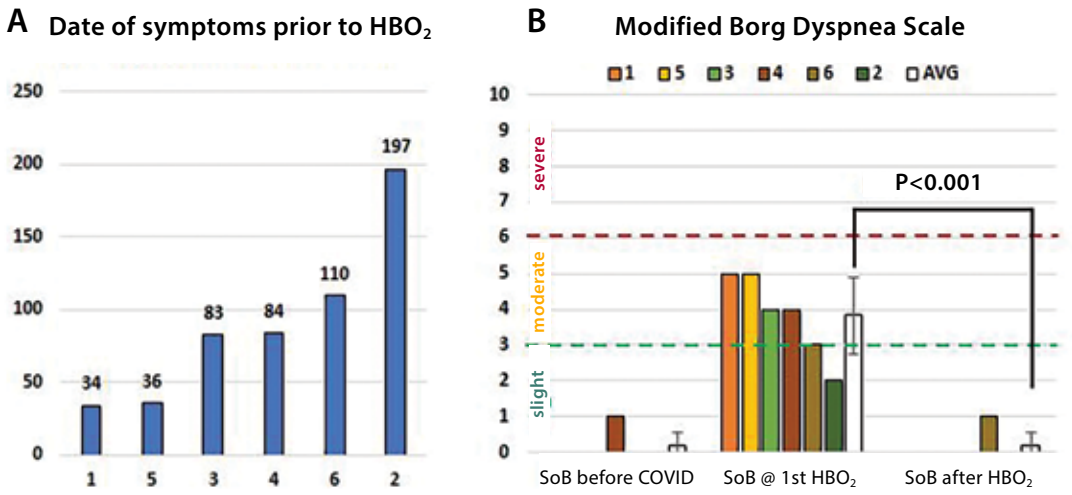

Figure 1: Details of COVID-19 symptom and dyspnea severity

A: Length of COVID-19 symptoms duration for each patient prior to beginning HBO$_2$ treatment.
B: Dyspnea score before COVID-19 diagnosis, at the time of first HBO$_2$ treatment and after completing 15 to 24 HBO$_2$ treatments. Average of six scores (white column). Error bars are standard deviation. P-value is derived from a Student's t-test (N=6); $\alpha = 0.05$.

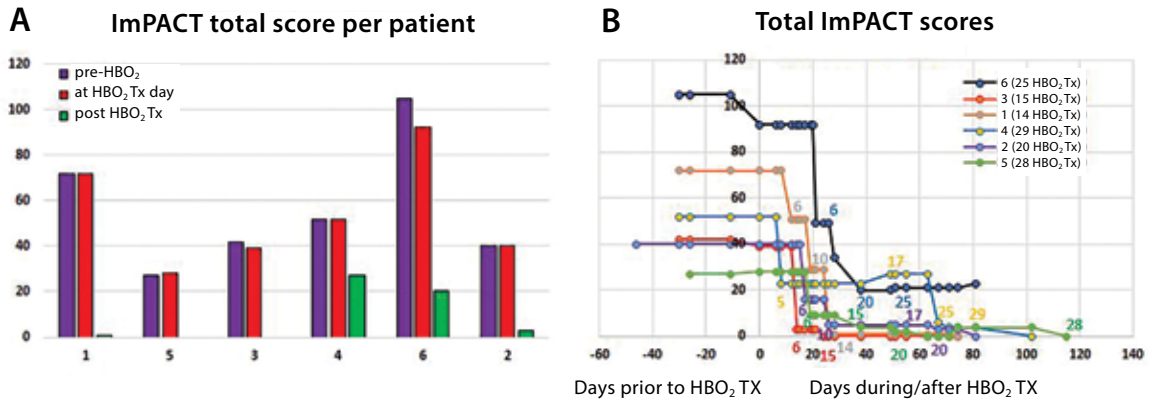

Figure 2: Summed ImPACT scores of each patient.

A: Summed scores for each patient at a representative time period before HBO$_2$, right after first HBO$_2$ treatment and after the last (or final) HBO$_2$ treatment.
B: Time plotted summed ImPACT scores for each patient. Numbers next to the points are color coded to the patient and represent the number of HBO$_2$ exposures at the time of the ImPACT testing. Zero value on the Y-axis is the date of the first HBO$_2$ exposure.

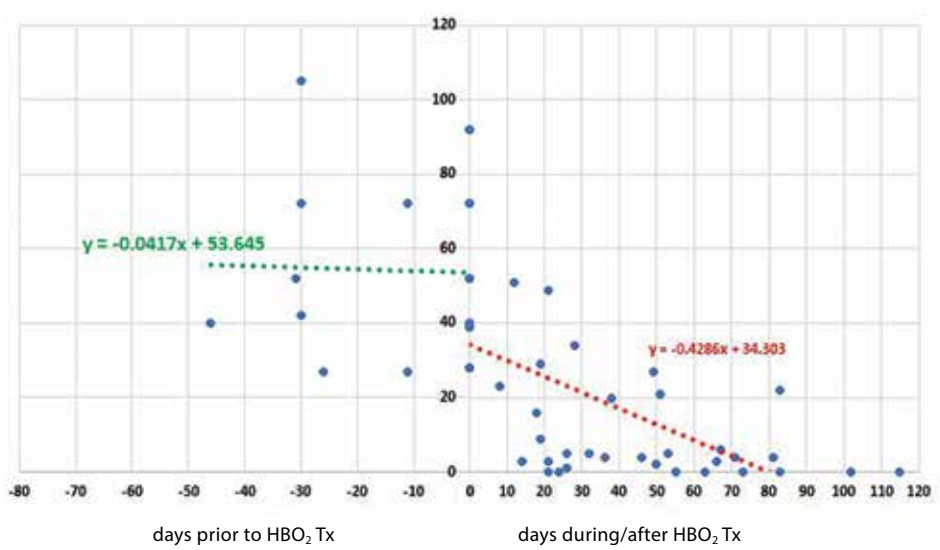

Figure 3: Summed ImPACT scores
at time points before HBO$_2$ treatment (left graph) and during/after HBO$_2$ treatment (right graph). Linear regression was carried out for both time periods.

distinct lack of improvement prior to starting HBO$_2$ treatments (time period prior to starting HBO$_2$: -46 to -26 days). The trajectory of improvement after starting HBO$_2$ (starting day 0), shows a rapid and distinct improvement of symptoms for each patient.

Although the number of symptoms and symptom severity ImPACT scores improve over time, the linear fit to the symptoms scores per day per patient shows very little change in the slope of the line prior to stating HBO$_2$ (Figure 3). After starting HBO$_2$, the scores drop rapidly (i.e., symptoms improve), and the trend line shows a marked negative (symptoms reduction) slope over time.

Each symptom category (Figure 4) shows a stable set of symptoms preceding the first HBO$_2$ treatment (purple and red columns). No significant changes in symptom severity across all six patients were detected three to four weeks prior to starting HBO$_2$ treatments. The average symptom scores (for the six patients) after the last HBO$_2$ treatment received are statistically significant (a=0.05, Student's t-test) from the start of treatment across 13 of the 22 symptoms assessed in the questionnaire. A separate assessment of joint and muscle pain (Table 1) showed improvements (reduction in pain) occurring after starting HBO$_2$.

DISCUSSION

Patients who test positive for SARs-Cov-2 and develop COVID-19 symptoms can develop long-term symptoms. These individuals may have persistent symptoms that can last for weeks, and for months in some cases [31]. The symptoms of COVID-19 can start out as mild, not improve over time, and flare up sporadically. Yet these symptoms and flare-ups are not so severe that they require emergency room visits or hospitalizations [32]. Patients who fit into the category of "long-haulers" have symptoms that can last for six weeks or longer [33,34].

SARs-Cov-1 symptoms overlap significantly with SARs-Cov-2 symptoms. SARS-Cov-1 [37] symptoms were recognized to last for longer than 19 months

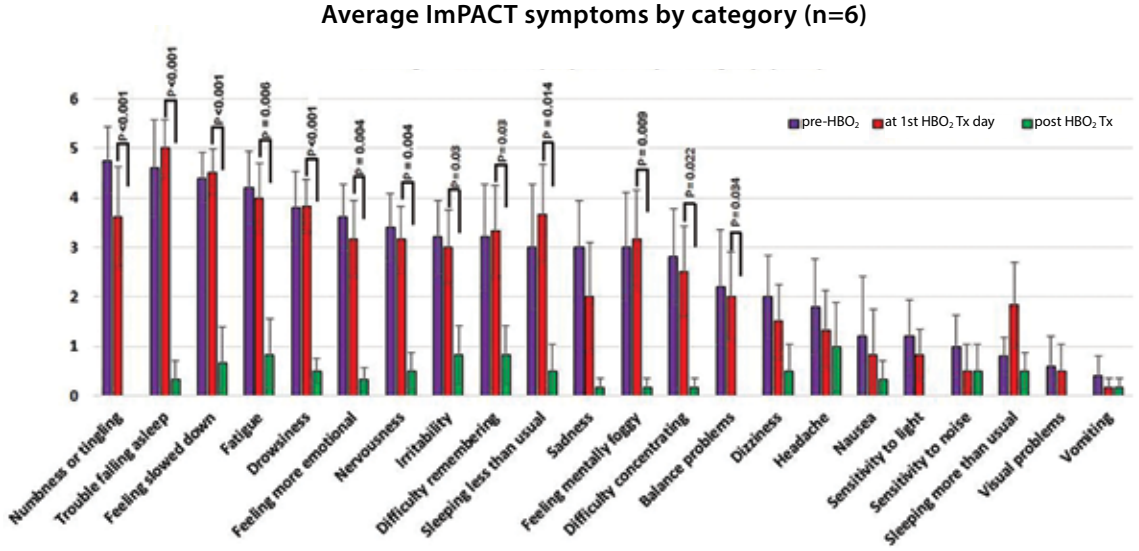

Figure 4: Average symptom scores for each symptom.

Error bars are standard error of the mean; p-values are derived from a Student's t-test (n=6); $\alpha = 0.05$.

Table 1: Joint and muscle pain score (0-6)

	patient no.	1	2	3	4	5	6
pain scores	before COVID	0	0	1	0	0	
	one month prior to HBO$_2$	2	5	0	4	3	5
	1st HBO$_2$ Tx	2	5	0	4	3	5
	mid-HBO$_2$ Tx	1	3	0	2	1	3
	last HBO$_2$ Tx	0	2	0	1	0	2
	one month post HBO$_2$	0	2	0	0	0	2

Joint and muscle pain scores prior, during and after finishing hyperbaric oxygen therapy. Pain scores are as follows: 0=no pain; 6=highest pain.

in an exposed, population of health care workers; the SARs-Cov-1 symptoms were similar to fibromylagia and chronic fatigue symptoms [36]. Fibromyalgia, chronic fatigue symptom, SARS-Cov-1 and SARs-Cov-2 have presented with cognitive impairment [37,38], emotional lability, and a sense of despair accompanying each of these infections and conditions.

For the majority of people who become infected, two to six weeks is the norm for recovery [39]. Our patient population averaged 91 days of COVID symptoms (range 34 to 197 days).

Four of the six patients saw improvement that reduced overall ImPACT symptom scores below 5 points (out of 132 points), with two patients still experiencing symptoms of 20 or more points. Individuals were provided with as many sessions of HBO$_2$ required until they stopped improving or decided to stop treatment. In one case, Patient #6 had a three- to four-week period of not receiving HBO$_2$ treatments, which may have affected the overall improvement trajectory. Dyspnea and neurological symptoms did not come back in five out of six patients after 30 days of follow-up.

Patient #5 returned 18 days after completing a total of 24 HBO$_2$ treatments. The patient had a return of dyspnea (measured as a 6 out of 6) and experienced a mild resurgence in symptoms (fatigue -1; sleeping more than usual -1; nervousness -1; drowsiness -1). After receiving five additional treatments, the dyspnea resolved (measured as 1).

CONCLUSION

The results from this case series suggest that COVID-19 long-haulers could benefit from hyperbaric oxygen treatments to overcome the lingering respiratory and neurological symptoms associated with the SARs-Cov-2 infection. The significant reduction and rapid improvement in symptoms after a 30-day or longer period of non-improvement with the use of HBO$_2$ holds promise for the recovery of these individuals with lingering post-SARs-Cov-2 infection.

It is possible that improvement with passage of time and/or placebo and Hawthorne effects could account for the improvement in symptoms in this report. Well-designed controlled studies could determine the role of HBO$_2$ for persistent COVID symptoms.

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UNDERSEA & HYPERBARIC MEDICINE

Severe carbon monoxide poisonings in scuba divers: Asia-Pacific cases and causation

John Lippmann, PhD [1,2,3]**; Ian Millar MBBS** [4,2]

[1] Australasian Diving Safety Foundation, Canterbury, Victoria, Australia; [2] Department of Epidemiology and Preventive Medicine, Monash University, Victoria, Australia; [3] Royal Lifesaving Society – Australia
[4] Senior Specialist Diving & Hyperbaric Medicine, Alfred Health, Victoria, Australia

CORRESPONDENCE: *johnl@adsf.org.au*

ABSTRACT

Lippmann J, Millar I. Severe carbon monoxide poisonings in scuba divers: Asia-Pacific cases and causation. Undersea Hyperb Med. 2022 Third Quarter; 49(3):341-353.

Aim: Reports of fatal incidents in recreational scuba divers from carbon monoxide (CO) poisoning are rare. This study aimed to identify scuba fatalities in the Asia-Pacific region caused by breathing-gas contamination to better understand the likely sources of contamination and reduce such preventable deaths.

Methods: A hand search of Project Stickybeak reports, subsequent Australian fatality series reports, and of published New Zealand diving fatality reports and associated data was conducted, as well as key word searches of the National Coronial Information System for scuba fatalities in Australia and New Zealand. Cases identified were matched with the Australasian Diving Safety Foundation diving fatality database. Available reports were examined.

Results: Four scuba deaths resulting from CO poisoning were identified from 645 scuba fatalities, including one report from each of Australia, New Zealand, Singapore, and the Maldives. A near-fatal incident was also identified in Indonesia. Two of the fatal incidents and the near-fatal incident involved internal combustion engine exhaust gases from the compressor system or elsewhere entering the air intake. Two deaths likely resulted from combustion within compressor systems.

Conclusions: Scuba fatalities from CO poisoning are uncommon, albeit likely under-reported. Sources of CO include exhaust gases entering the compressor and CO production by pyrolysis or gasification within the compressor or its filter system. Preventive measures include proper installation (including positioning of the air intake relative to combustion exhaust), appropriate maintenance, fitting of pressure-maintaining valves and avoidance of overheating. Formal training of compressor operators, improved diver education, mandatory requirements for installation compliance assessments, safety inspections, and the use of carbon monoxide alarms are recommended. ▮

KEYWORDS: carbon monoxide poisoning; case reports; compressors; diving deaths; mechanisms; safety; scuba; toxicity

INTRODUCTION

Safe diving is dependent on a variety of factors, the most fundamental being the ongoing supply of an appropriate breathing gas that is free from harmful contaminants. Contaminants, including carbon monoxide (CO), carbon dioxide (CO_2) and volatile hydrocarbons, can be introduced into scuba cylinders from a poorly functioning compressor, inadequate filtration, incorrect configuration of system components, or inappropriate positioning of the air intake.

Fatalities consequent to contamination of breathing gas have been regularly reported in divers using surface-supplied breathing apparatus (SSBA).

Indeed, an Australian study identified breathing-gas contamination – predominantly by CO – as the disabling condition in at least 14 (17%) of a series of 84 SSBA deaths in Australia [1]. However, cases involving recreational scuba divers are rarely reported in the medical literature, as highlighted in a recent review [2]. Data from the Australian Diver Emergency Service reveal that 14 of 6,083 (0.2%) calls between 1991 and 2007 related to breathing-gas contamination, although none of these involved fatalities (Personal communication, Wilkinson D, 2020 October 20). Anecdotally, reports of divers "tasting bad air" are common, and the limited air quality surveillance literature does suggest that suboptimal air quality may be a relatively frequent occurrence [3].

The aim of this study was to identify scuba diving deaths resulting from breathing-gas contamination in the Asia-Pacific region as recorded in the Australasian Diving Safety Foundation (ADSF) fatality database and associated records to better document, understand, and posit the likely sources of contamination and so reduce such preventable deaths.

METHODS

Ethics approval

Ethics approval for the collection and reporting of diving-related fatality data was received from the Victorian Department of Justice Human Research Ethics Committee enabling access to the National Coronial Information System (NCIS) for deaths in Australia and New Zealand (CF/18/12735) [4].

Search

The search involved:

1. a hand search of Australian Project Stickybeak (an extensive collection of Australian diving fatality reports compiled by Douglas Walker) reports from 1972 to 2002 [5-7], subsequent Australian fatality series reports [8], and published New Zealand diving fatality reports and some associated data [9-12];

2. a search of the ADSF diving fatality database and associated files [13];

3. a key-word search of the NCIS [4] for scuba diving deaths from 1 January 2000 to 31 December 2019 in Australia, and from 1 July 2007 to 31 December 2019 in New Zealand. Key words included *carbon monoxide*, *contamin** and *scuba*;

4. matching data from the searches to confirm cases and minimize the risk of over- or under-reporting.

5. A targeted review of CO chemistry was undertaken regarding investigation mechanisms potentially relevant to contamination of compressed air.

RESULTS

From a total of 645 fatal scuba incidents for which sufficient relevant data were available, the search identified four fatal incidents and one near-fatal incident involving recreational scuba divers, each of which was confirmed to have been caused by breathing-gas contamination. There were other incidents where contamination was suspected but not confirmed by testing. Deaths were identified in Australia, New Zealand, Singapore and the Maldives, with the one near-fatal incident occurring in Indonesia. These cases are summarized below.

CASE 1 – Fatality in Australia

The victim was a healthy 44-year-old male who was an active and experienced diver. As a member of a dive club he was entitled to discounted air fills and had been authorized to fill tanks using the club's compressor, an air-cooled four-stage compressor (vintage circa 1970) driven by an electric motor. It was reportedly regularly maintained by another club member, an electrical, refrigeration and air conditioning mechanic. However, there was no maintenance log to confirm or formalize this maintenance.

The victim and his partner went diving from a charter boat using tanks he had filled directly from the club's compressor; the air storage bank was out of service. The first dive was uneventful: The victim and his buddy appeared well during the surface interval and changed tanks before the next dive. They then entered into a strong but manage-

able current, and after 10 minutes at a maximum depth of 27 meters of seawater (msw), the victim indicated that he was feeling unwell and wanted to surface. The two divers ascended slowly, becoming separated due to the current, but the partner managed to board the boat. The victim was seen to surface briefly and thought to "fiddle" with his buoyancy compensation device (BCD) before sinking. His body was recovered the following day – weights in situ, BCD partly inflated, and pressure gauge reportedly indicating at least 80 bars of gas remaining. The buddy suffered from headaches and some amnesia for several days.

Toxicology indicated that the victim's carboxyhemoglobin (COHb) level was 56%. Gas analyses of the victim's cylinders indicated 509 ppm CO_2 and 26 ppm CO for the first dive, and 7,636 ppm CO_2 and 2,366 ppm CO for the fatal dive. The dive buddy's cylinders contained 538 ppm CO_2 and 24 ppm CO for the first dive, and 2,255 ppm CO_2 and 820 ppm CO for her second dive. The cause of death was reported to have been drowning as a result of carbon monoxide poisoning.

On later inspection the club's compressor was found to have been poorly sited and prone to overheating, having been installed in a small shed with inadequate ventilation. Despite the history of overheating, no temperature gauge was fitted. There was no pressure-maintaining valve between the filters and the filling whips. Multiple other faults and damage were identified, including piston and barrel damage from overheating, an incorrectly repaired gasket, expired lubricant, and filter that were poorly designed, incorrectly assembled and saturated. Contamination was detected in multiple other cylinders filled from the same system. The deficient installation, poor maintenance, poor record-keeping, and a lack of club member awareness of risk control all contributed to the fatal incident.

CASE 2 – Fatality in Maldives

For several days divers on a liveaboard dive boat had complained about post-dive headaches, although none reported that their air had a bad taste or smell. The compressor air filter was changed, and all tanks emptied and refilled while the vessel was anchored; there was no wind. The next morning, 14 divers descended. The dives were uneventful until the divers began to ascend. The victim, a 41-year-old male, began his ascent after 21 minutes and was found floating facedown, unconscious and apneic on the surface some 10 to 15 minutes later. Resuscitation was unsuccessful.

The cause of death was reported as drowning subsequent to CO poisoning although no COHb level was reported (and very likely was not measured). Other divers reported incapacitating symptoms such as headache, dizziness, nausea and altered conscious state, requiring immediate assistance and subsequent medical care.

Initial testing of the victim's remaining cylinder contents indicated a CO level that exceeded the test equipment's maximum readout of 150 ppm CO. When the compressor was later inspected a lack of servicing was obvious: There was substantial carbonization of the air filter, attributed to the intake of exhaust soot particles. The air intake hoses were defective and had been patched with adhesive tape. The air intake and faulty hose sections were located within the exhaust gas flow from the compressors' petrol engines and the boat's diesel engine.

CASE 3 – Fatality in Singapore

This 20-year-old male making an open-water certification dive became separated from his instructor and buddy during descent to 10 msw. While the instructor searched for him underwater, he was seen to surface, making a loud gasp. He did not appear distressed and did not attempt to swim toward the boat. A witness called to him to inflate his BCD, although accounts varied about whether he attempted to do this before quietly submerging. His body was found two days later with his weight belt and scuba unit in situ.

The victim's COHb level, if recorded, was not available to these researchers. However, analysis of residual gas in his cylinder revealed 785 ppm CO, and 12.3 ppm hydrogen sulfide (H_2S). Investigators did not test any of the other divers'

cylinders, as no one reported any problems. Analysis of the storage bank at the cylinder-filling station (at an unknown time later) indicated 55 ppm CO and 1.7 ppm H_2S. The air intake was secured on a roof near a parking area; it was believed that contamination resulted from intake of exhaust gas from nearby vehicles.

CASE 4 – Fatality in New Zealand

This 35-year-old male was an experienced diver. In preparation for some upcoming diving, he asked a friend to take his two tanks, which he believed were empty, to a dive store to be refilled. This was done, and several days later the victim and his friend set out on their boat. Planning to do a 15-minute solo dive, the victim donned his equipment and entered the water, albeit it in a noticeably different manner to his usual entry. He failed to give his usual "OK" signal after entry, and instead descended immediately. The friend noted that he could not see a trail of exhaust bubbles, which he thought unusual. When the victim failed to surface after 30 minutes, the friend became concerned and, after a further half hour, returned to shore to raise the alarm. Police divers recovered the body the next day at a depth of 9 msw, free from entanglements and close to his entry point. There was 197 bar of remaining gas in his cylinder.

No blood analysis was performed due to severe compromise by sea lice. Analysis of the gas in the victim's cylinder indicated 1,890 ppm CO_2 and 13,600 ppm CO. The unused cylinder contained 1,380 ppm CO_2 and 9,600 ppm CO. The cause of death was recorded as asphyxia resulting from his air supply being heavily contaminated with CO.

The coroner engaged several consultants to investigate the likely source of contamination; there was considerable disagreement among them. Dive center staff claimed that the cylinders had been filled from the storage banks and, given that there was no evidence of any issues with any other cylinders, it was suggested that the contamination must have occurred from an unidentified source elsewhere. An occupational safety investigator concurred that contamination could not have occurred at the dive shop. However, other evidence indicated that some of the record-keeping was inaccurate, and the coroner concluded that it was likely that the cylinders in question were in fact filled directly from the compressor on that occasion. External contamination was deemed unlikely because of the position of the intake and the degree of contamination being in excess of expectations for exhaust gas contamination. Another expert report raised numerous issues: The installation had many features indicative of overheating, including a disconnected radiator, poor ventilation of the installation area and the presence of fine, brown dust in the compressor room. Overall, the installation, operating and maintenance procedures were non-compliant with current accepted practice.[14]

The possibilities were debated: intentional poisoning, the generation of CO from oil vapor in the last compression stage or from carbon deposits in the third stage during overheating, and the generation of CO within a filter were discussed. On the balance of the evidence the coroner made the generic conclusion that the contamination was most likely due to "an idiosyncratic malfunction of the air-compressing equipment."

CASE 5 – Multiple injuries in Indonesia

This case is included as an example of what could have easily been a multiple fatality event. Such events are often unreported.

An employee of a dive operator was filling tanks from a small petrol-driven compressor when it began to rain heavily. In ignorance, he moved the compressor (including the intake hose) inside a small shed and continued filling the cylinders. The cylinders were then given to a group of four tourists and two dive guides to use on a shore dive. All divers soon became incapacitated to varying degrees. One guide was dragged unconscious from the water, another diver became unconscious on the beach. All required hospitalization.

DISCUSSION

Pathophysiology of CO toxicity in divers

The lethal characteristics of CO poisoning are well known, yet it continues to be responsible for an estimated 4.6 deaths per million population each year [15,16]. Although scuba diving deaths from CO poisoning appear to be relatively uncommon, these cases, added to other recent reports, are a reminder of the hazard presented if cylinder-filling safety processes are not followed [2,17]. They also demonstrate the range of levels of contamination that can be associated with lethality, variations in time to incapacitation, and examples of key mechanisms that can lead to cylinder contamination.

There are significant differences between jurisdictions and safety authorities with respect to carbon monoxide levels allowable in breathing normobaric air, but these have generally been reduced over recent years from around 50 ppm for an eight-hour workplace exposure to 20- to 30 ppm and to as low as 10 ppm for indoor air quality [18-20]. Safe levels for divers' breathing air are set very conservatively, most commonly at 5 ppm, based primarily upon the consideration that partial pressures increase with increasing depth, resulting in a 5 ppm contamination breathed at 50 msw (6 atmospheres absolute) having the same partial pressure – and therefore assumed toxicity – as 30 ppm breathed at the surface [21,22].

However, the levels of CO that are survivable after short-term exposure are a great deal higher than this. "Peak exposure limits" or "ceilings" of 200 or 400 ppm are allowed by some occupational safety authorities. The "immediate danger to life and health" (IDLH) set by the U.S. National Institute for Occupational Safety and Health (NIOSH) is 1,200 ppm. The U.S. National Research Council's Acute Exposure Guidelines AEGL-3 (potentially lethal) level for a 10-minute CO exposure is 1,700 ppm [23-25]. While there is much variability in tolerance, 1,000 ppm is likely to be survivable at the surface for as long as 30 minutes in most cases, based upon human volunteer and primate exposures used in developing fire escape standards for buildings [26-28]. A U.S. Federal Aviation Administration's publication on aircraft fire survivability publishes an immediate incapacitation concentration for CO at 6,850 ppm and suggests a five-minute exposure limit of 4,200 ppm [30].

These toxicity levels are consistent with the cases reported, with onset of incapacitation at the end of a 10-minute dive breathing 2,366 ppm CO in Case 1 and an estimated five to 10 minutes breathing 785 ppm at depth in Case 3, with some likely contribution from hydrogen sulfide and other automobile exhaust gases in that case. The reported 150 ppm in Case 2 is understood to be the limit of the detector tube used and almost certainly a gross underestimate of the actual exposure leading to death. In Case 4, incapacitation was almost immediate, with no bubbles seen to be rising as the diver sank after only a few breaths from his scuba cylinder at the surface. This is consistent with the measured 13,600 ppm CO in the victim's cylinder. The other three deceased victims all breathed CO for various times at depth, where the partial pressure of CO would have been increased, increasing the gradient driving CO uptake.

CO and oxygen both bind to heme moieties in a reversible fashion, with CO binding to hemoglobin some 200 to 250 times more strongly than oxygen. However, this "Haldane ratio" refers to equilibrium conditions. While CO and oxygen are competitive, the kinetics of CO binding to hemoglobin are very different to those of oxygen. Changes in the saturation of hemoglobin by oxygen can occur over seconds, while the binding of CO increases over minutes to hours, and the timelines for subsequent disassociation stretch from hours to a day or more unless oxygen therapy is instituted [28,29,31,32].

When CO is breathed during a dive, CO partial pressures will rise in direct proportion to the increase in absolute pressure, but the oxygen partial pressure will increase in the same proportional way. With the caveat that nervous system effects, including acute loss of consciousness, depend to a significant degree on intracellular effects of CO and not just COHb levels, it may be that time to incapacitation underwater is not as much accelerated as sometimes predicted, compared with time

to incapacitation at the surface. It seems likely, however, that as oxygen partial pressure rapidly decreases during the ascent stage of a dive, the toxic effects of the much slower offgassing CO should rapidly increase as the "offset" of high oxygen levels is lost, potentially causing incapacitation during ascent. This proposal seems consistent with death having occurred around the time of surfacing in Cases 1, 2 and 3.

Origins of carbon monoxide contamination in scuba cylinders

The five cases reported include examples of what we believe are the most common scenarios underlying contamination of scuba cylinder air.

Intake of exhaust/contaminated gases

In Case 2, a poorly installed and poorly maintained dive boat compressor system allowed compressor and vessel engine exhaust to enter the compressed-air intake. Multiple small engine-powered compressors were apparently in use. The scenario of small petrol engine exhaust contamination has been regularly identified in surface-supplied air diving, especially with the minimalist SSBA arrangement often termed "hookah," where a simple petrol/gasoline engine drives a low-pressure compressor feeding air directly to the diver's regulator.

Small petrol engines are inefficient and generally operate on a "rich" fuel mixture with a high ratio of hydrocarbon fuel to air in the combustion chamber. This leads to high levels of CO in the engine exhaust as incomplete combustion occurs. CO levels in small petrol engine exhausts vary widely but are almost always very high, ranging from 15,000 to 120,000 ppm [33-35].

It was suggested in Case 2 that the vessel's diesel engine exhaust may have been the dominant source of contamination. This would be unusual but not impossible. Diesel engines normally emit very little CO, although emissions can be higher from poorly maintained and older engines [36]. If breathing air is contaminated from diesel exhaust, a higher level of CO_2 would be expected, with relatively lower CO levels than are typically associated with petrol engines without catalytic converters. Full air quality analysis was not available in Case 2, but the CO exposure level was significant, and there were likely other exhaust gases contributing as well.

A confounding issue in intake contamination cases is that if activated carbon filters are installed and operating adequately, these can eliminate engine exhaust odor without capturing CO: This increases the risk that divers will fail to recognize the contaminated air. In Case 3, a reportedly unremarkable and otherwise satisfactory compressor installation had its air intake positioned on the roof of a building adjacent to a car park used by cars, trucks and buses. It was thought that contamination came from the exhaust of one or more automobiles that had engine(s) running during compressor operations. Modern automotive engines are very efficient, with controlled fuel injection that results in much lower CO production than for small-machinery engines, and with catalytic converters fitted, the net result should be relatively low CO levels. However, much higher levels of CO and other toxins are present in the exhaust gas of a newly started automobile engine, when the engine and the catalytic converter are below their design operating temperature. The hydrogen sulfide detected in Case 3 would be consistent with this [37].

In Case 5, the petrol-driven compressor was run in a very confined, unventilated space where both the intake and exhaust were in close proximity, making it inevitable that the compressed air would become contaminated.

Poor installation and maintenance

Carbon monoxide can originate from within the compressor system [3]. Cases 1 and 4 provide examples of the risks arising when repurposed equipment is installed in a suboptimal way and then maintained and operated by persons who do not have specific training for breathing-air compressors. High-pressure compressors typically have three or

four cylinders, with air compressed four- to-fivefold in each, to an ultimate pressure between 200 and 300 bar. With compression, the air in each cylinder heats dramatically, and interstage coolers are installed to reduce the temperature prior to the next stage of compression. With cooling, the water vapor naturally present in intake air condenses and must be drained. In addition to water, this condensate also includes much of the lubricating oil aerosols that contaminate the compressed air. This oil contamination is an expected design feature of high-pressure compressors, as lubrication is required to minimize friction-generated thermal degradation of the compressor. With older and poorly maintained compressors, the oil "carryover" will be greater, and if intercooling is suboptimal (for instance, due to dirty cooling coils or poor ventilation of the compressor room); then, increased levels of lubricant oils will enter the final filters and potentially the scuba cylinder. If the intake filter is dirty and restricts air inflow, this can result in oil being "sucked" past the first-stage piston rings and into the cylinder during each filling stroke, greatly increasing oil burden in the compressed air.

High-pressure compressor oils are intended to be non-toxic to humans and normally incorporate stabilizers and antioxidant compounds to minimize degradation due to high temperature and exposure to the oxygen in air. If recommended oil change intervals are exceeded, these oils can become oxidized and contaminated by metals from moving compressor parts, resulting in reduced chemical stability, lowered resistance to thermal degradation, and increased susceptibility to combustion. In nitrox compressors, oils will be oxidized at even faster rates, necessitating more frequent oil and filter changes.

While most of the lubricant aerosols in compressor air are removed by condensation and separation, a residual proportion must be removed by filtering and absorption into activated carbon and/or molecular sieve materials in the final filter system. If intercooling and condensate removal is inadequate it becomes more likely that these final absorption filters can be overwhelmed, with oil contamination passing into the breathing air.

Some high-pressure air compressor filter systems also include catalytic converter components that facilitate CO oxidizing into harmless amounts of CO_2. However, it is important not to be overly reliant on such systems, as their capacity is limited, and catalytic converters of the size normally used may not have capacity to adequately eliminate very high levels of CO. Further, catalytic converters typically require very dry operating conditions, and the capacity of dehumidifiers, activated carbon and molecular sieve filters can be easily overwhelmed by excessive moisture.

A key and sometimes overlooked component of a high-pressure air compressor installation is the pressure maintaining valve (PMV), which should be located after the filters and before the connection to cylinders. This ensures that after the compressor is started the pressure in the entire compressor and filter system rapidly rises to the specified operating pressure and is maintained at that pressure, even when an empty cylinder is connected downstream of the PMV. Maintaining high pressure in the compressor ensures that each of its cylinders operates at its design load, balancing forces on the bearings and valves, thus minimizing wear and reducing vibration and noise. Having high pressure within the filter systems slows down the velocity of air through the filters. This results in increased "dwell time" of air, the critical duration of exposure of the absorption and catalytic elements to the air, thus avoiding contamination being blown through the filters due to excessive flow speed.

In order for CO to be produced within a compressor system, a carbon source must undergo pyrolysis or incomplete combustion. The two potential sources of carbon are compressor oils, which are principally hydrocarbons, and the activated carbon filter. In Case 1, the compressor had apparently been consuming oil. Investigators concluded that CO had likely been produced

by combustion within the compressor given there was no obvious source of intake contamination. Combustion is thought to be possible in compressors due to ignition by compression-related heat, sometimes termed "dieseling," given that diesel engines operate via this mechanism. Although diesel engines can operate on a wide range of types of hydrocarbon fuel, diesel fuels are optimized for combustion. Compressor lubricants, on the other hand, are optimized for stability and non-combustion. Inadequate intercooler function will increase compression-related heating within air compressor cylinders: It is hypothesized the thermal stability of lubricant oil may be reduced by age, oxidation and metal contaminants that act as catalysts, with the net effect of enabling ignition of lubricant oils in the compressor. This can result in CO and CO_2 contamination of the compressed air, potentially along with other combustion-related compounds such as oxides of nitrogen.

In diesel engines, oxygen availability from air is in excess of the injected fuel: Hydrocarbons are mostly fully oxidized to CO_2 rather than incompletely oxidized to CO. It seems likely that air would be even more in excess of fuel combustion requirements in air compressors, resulting in an expectation that CO_2 contamination levels in compressed air should be much higher than the levels of CO [38]. The air analysis in Case 1 is consistent with this.

In older and poorly maintained compressors, valves and other internal components often acquire carbonized deposits over time, which may provide an additional explanation for ignition. When heated by compression, such deposits could act as both ignition foci for oil-contaminated compressed air, as well as being sources of carbon fuel themselves. It is also possible that such deposits might break up, potentially releasing red-hot, metal ion-rich carbon fragments into higher-pressure compressor cylinders, which may ignite oil there. Any such fragments that might pass on to the filter elements should be trapped in the initial elements, but it may be that vapor could pass further to contaminate the absorbent filter media.

Only a tiny amount of carbon needs to oxidize to cause dangerous CO contamination. A single gram of carbon (molecular weight 12) will oxidize to 2.3 grams of CO (molecular weight 28). With a density of 1.14 grams/liter at atmospheric pressure, this amount of CO will occupy around 2 liters at atmospheric pressure; this is enough to contribute 1,000 ppm of CO to the 2,000 liters in a 10-liter air cylinder filled to 200 bar. It would seem that Case 1 demonstrates most of the adverse characteristics of systems that can generate toxic levels of CO and CO_2 from within compressors used to fill scuba divers' air cylinders. The different levels measured between cylinders is consistent with what would be expected, given variability in the numerous contributory factors from one fill to another (e.g., initial cylinder pressure, temperature variation, among other factors) in a system where cylinders were filled directly from the compressor, rather than primarily from an air bank.

Combustion within filter system

While there is little doubt that lubricant combustion can occur in high-pressure compressors in certain circumstances, it is less clear whether this is the source of CO in some incidents involving very high levels of CO. An alternative that was raised in Case 4 is that combustion may have occurred within the filter system. In principle, the fuel for incomplete combustion could be either hydrocarbon contamination in the filter media, or the activated carbon within absorption filters. Carbon combustion in an air compressor filter was clearly responsible for the carbon monoxide poisoning of 10 school children undertaking a scuba course in Manchester in 2017 [17,39].

Activated carbon is a remarkable material, with a surface area around 2,000 square meters per gram providing a high capacity for absorption of contaminants. It is essentially a special structural state of pure carbon with only very small amounts of impurities remaining from the charcoal or coconut fiber manufacturing source material. Spontaneous combustion within carbon filter beds is a well-identified problem in large, industrial carbon

filtration systems, in large life support systems such as used in submarines and habitats, and in coal mines and storage heaps [40,41]. Although it might be intuitively thought that the humid or even frankly wet interior of filters would inhibit combustion, the reverse seems to be true: Spontaneous combustion in large carbon beds likely often occurs as a consequence of moisture, with water absorption into the carbon being exothermic and sufficient in some cases to ignite the carbon and any combustible contaminants absorbed by the carbon. Combustion can continue despite moisture, as occurs in peat and coal fires. Absorption-related ignition seems less likely, however, in the relatively small carbon filters used in most breathing-air systems where any heat of absorption can be more easily lost to the container or the airflow. This should minimize temperature rise, noting, however, that water absorption was concluded to be the initiator of carbon gasification in the Manchester Grammar incident [39].

The spontaneous ignition temperature of activated carbon is often quoted as being more than 400°C in suppliers' Material Safety Data Sheets. In practice, ignition can occur at temperatures as low as 100°C due to age, water content, impurities remaining from the source material from which the activated charcoal was prepared, and the presence of metal ion contaminants that can act as catalysts [42]. Various metal ions that can catalyze low-temperature combustion include some that could originate from components of a worn and overheated compressor such as oxides of iron and copper. Compressor lubricant oils are principally hydrocarbons, with ignition temperatures that vary greatly, but generally in the 200- to 300°C range when new and clean. Again, this is likely much lower in practice, especially once at pressure and when these oils are aged, oxidized and contaminated [43].

A characteristic of combustion in unventilated activated carbon bed experiments is that the combustion process is limited by the quantity of oxygen available from the air in the container. The limited amount of oxygen facilitates incomplete combustion, resulting in an elevated CO to CO_2 ratio, with the combustion zone self-extinguishing once all oxygen is consumed.

Adding air flow to a hot, recently burning filter might reignite the filter media. Once sufficient free-flowing compressed air is passing through the filter, the abundance of oxygen should minimize production of CO, and the air flow should be sufficiently cool to reduce reignition risk, provided, of course, that cooling systems are functional.

If CO has been generated by combustion within a filter canister with no flow, then all oxygen present would be expected to be consumed, resulting in a very high concentration of CO. This CO could then be "flushed" out of the filter and into a scuba cylinder at the commencement of filling. As an example, a hypothetical filter canister with a 200mL air space in and around the filter media would contain 2 liters of oxygen at 50 bar – enough to generate around 2 liters of CO and thus enable the previously mentioned scenario of 1,000 ppm CO in a full scuba cylinder. Contamination of compressed air for only a short period of time when a single cylinder is being filled seems consistent with this, with other cylinders showing lower or no contamination. If repetitive reignition is possible during stop-start airflow conditions, this might explain contamination of sequentially filled cylinders.

In different filter bed combustion scenarios, it could be the activated carbon that ignites, or it could be hydrocarbon lubricants absorbed into the carbon. As previously described, the total carbon "fuel" required to dangerously contaminate a single cylinder is only a few grams, and, as combustion of pure carbon leaves no residue, even forensic examination of an activated carbon filter bed could easily fail to detect the "missing'" carbon, while combustion of absorbed lubricant might "cleanse" the activated carbon of evidence of contamination.

Ignition within an air filter requires a sufficient temperature rise. One potential cause is connection of a partly filled scuba cylinder to a system lacking a pressure-maintaining valve or a non-return valve between the filling whip and the filters. If the

cylinder valve is opened prior to compressor start or air bank valve opening, there will be backflow through the filter system and rapid pressurization of the filter housing, with a resultant temperature rise in the filter media. If contaminants in carbon or absorbed oils have sufficiently lowered the ignition temperature, this temperature rise could cause carbon bed ignition which would lead to CO production.

A more complex combustion chemistry can also be hypothesized: the pyrolytic processes that occur in charcoal-based process gas generators. Simple wood or charcoal burning gas generators, or "gasifiers," were manufactured en masse to power automotive engines during World War II fuel shortages. Although many designs exist, the simplest involve a column of charcoal into which air and some water or steam is injected to sustain a zone of carbon combustion in the lower parts of the column. This produces CO_2, which passes up the column along with water vapor, to be reduced by hot, but relatively cooler and anoxic, carbon. The resultant combustible "process gas" generated is predominantly CO, with smaller and variable amounts of hydrogen and methane, along with the nitrogen from the intake air [44-46]. We hypothesize that such a process could occur, at least momentarily, within activated carbon filters, with the initial ignition again being potentially explained by retrograde air flow into an initially unpressurized filter from a partly filled scuba cylinder. Alternatively, it could result from a compressor system configuration that allows rapid pressurization of the filters upon opening a valve connecting storage banks or the compressor to a closed cylinder or filling whip valve. The consequent rapid heating of the filter media with auto-ignition of likely contaminated carbon could generate high levels of CO, even with some air flow. We suggest that gasifier-type pyrolysis could explain the methane found in addition to very high CO levels and lower CO_2 levels in Case 4.

After consideration of all findings and opinions received, the formal findings of investigations into Cases 1 and 4 were inconclusive with respect to the exact source of CO. We have provided several theories as to the causation of such events, but of most importance is that it is clear that CO contamination of scuba cylinders can happen – and probably does happen, more often than is recognized. Although residual air purity testing and postmortem toxicological analysis for carbon monoxide have become more common in scuba diving fatalities in some countries such as Australia and New Zealand, this is certainly not the case in all jurisdictions. As a result, some scuba deaths associated with CO toxicity are likely undetected, and we encourage further adoption of air quality testing during investigations, with detailed laboratory analysis preferred if available.

Use of carbon monoxide monitors and alarms

Contamination is an inherent risk of compressing air for diving but one that should be preventable by following best practices for installation, operation, and maintenance practices. Training of compressor operators will always be an important, albeit fallible, factor. The authors therefore would like to strongly promote the use of carbon monoxide monitors and alarms, consistent with required practices in many occupational and domestic settings where CO toxicity is an identified hazard. Of note, in 2015 the Australian and New Zealand standard for occupational diving introduced a requirement for carbon monoxide alarms to be installed on all surface-supplied breathing-air compressor systems [19]. Similar technology could readily be installed on cylinder-filling compressors: either analyzer systems that can continuously ensure CO levels are below the levels allowable in divers breathing air, or as a minimum, low-cost alarms that will at least warn of levels hazardous to life.

For divers who need to obtain cylinder fills from sites of unclear quality, low-cost but effective options include use of a domestic battery-powered CO alarm to detect dangerously high levels or use of the single-use colorimetric CO detectors which have become available in recent years.

Limitations

For countries other than Australia and New Zealand, for which the authors had access to coronial databases, this study largely relied on English-language media reports of scuba fatalities to identify possible CO-related cases to further explore. In the absence of such reports, cases might have been missed. The formal reporting and investigation of diving-related fatalities varies greatly within the Asia-Pacific region. In countries such as Australia, New Zealand, Singapore and Hong Kong almost all such deaths are recorded. In most cases, these are investigated reasonably thoroughly, although breathing-gas analysis and toxicology for CO are not always conducted. On the other hand, in many of the developing countries in the region, such deaths are more often unreported and poorly investigated, so the number and causation of the deaths is unclear. It should also be noted that divers and/or their equipment cannot always be recovered. As a result, it is likely that the fatal cases identified in this study are a significant underestimate of the true incidence of fatal CO poisoning in scuba divers in this region.

CONCLUSIONS

Scuba diving fatalities from CO poisoning are uncommon, albeit likely under-reported. Contamination of the breathing gas can result from a variety of sources, including intake of exhaust gases from compressor, boat or vehicle engines, and pyrolysis or gasification within the compressor or its filter system as a result of poor installation, poor maintenance, or poor operating procedures. Specific problems include inadequate cooling, lubricant failure, filtration failure and lack of a pressure-maintaining valve. Carbon monoxide monitors/alarms are highly recommended for all breathing-air compressors. Professional system design and installation, regular maintenance by appropriately trained technicians and suitable training of compressor operators will reduce risks to divers. Consideration should be given to compulsory registration of breathing-air compressors, as this could enable a system of initial certification and ongoing inspections for compliance, at least for commercial operations and other entities that supply to the public. Divers should be educated in the potential for, and recognition of, CO poisoning and should obtain their breathing gas from reputable and reliable sources. Portable CO detectors can be useful when sourcing air from unknown suppliers. ■

Acknowledgments

National Coronial Information System; Office of the NZ Chief Coroner, Ministry of Justice, NZ; Coronial Services Unit, Ministry of Justice, NZ for access to coronial records.

Shayne Gooch, University of Canterbury, NZ and Richard Martins, Inspector, Health & Safety Executive, UK for valuable information and insights derived from their roles in investigating carbon monoxide contaminated scuba cylinder incidents.

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UNDERSEA & HYPERBARIC MEDICINE

Cardiovascular risk assessment in divers: Toward safer diving

Rienk Rienks, MD, PhD [1,2]; Mattijn Buwalda, MD [3]; Jeroen Bucx, MD [2]; Emile Dubois, MD, PhD [4]; Thijs Wingelaar, MD, PhD [5,6]; Rob van Hulst MD, PhD [6]

[1] University Medical Center Utrecht, The Netherlands

[2] CardioExpert Clinic for Sports and Occupational Cardiology, Amsterdam, The Netherlands

[3] Medical and Educational Services, Odijk, The Netherlands

[4] Hyperbaric Medical Center, Rijswijk, The Netherlands

[5] Royal Netherlands Navy Diving and Submarine Medical Center, Den Helder, The Netherlands

[6] Amsterdam University Medical Center, Academic Medical Center, Department of Hyperbaric Medicine and Experimental Anaesthesiology, Amsterdam, the Netherlands

CORRESPONDENCE: Rienk Rienks – *rienk@rienkrienks.nl*

ABSTRACT

Rienks R, Buwalda M, Jeroen Bucx J, Dubois E, et al. Cardiovascular risk assessment in divers: Toward safer diving. Undersea Hyperb Med. 2022 Third Quarter; 49(3):355-365.

Similar to aviation, diving is performed in an environment in which acute incapacitation may lead to a fatal outcome. In aeromedicine, a pilot is considered "unfit to fly" when the cardiovascular event risk exceeds one percent per annum, the so-called 1% rule. In diving no formal limits to cardiovascular risk have been established. Cardiovascular risk of divers can be calculated using the modified Canadian Cardiovascular Society (CCS) Risk of Harm formula: risk of harm (RH: cardiovascular fatality rate per year during diving: number $\times 10^{-5}$ divers/year) = time diving (TD: number of dives $\times 10^{-4}$) $\times$ sudden cardiac incapacitation (SCI: cardiovascular diver event rate per year (number $\times 10^{-5}$/year).

The SCI and thus the RH are strongly dependent on age. Using the CCS criterion for RH, 5×10^{-5} divers/year, and considering an average of 25 dives per year per diver, the calculated maximum acceptable SCI is 2%/year, consistent with current practice for dive medical examinations. If the SCI were to exceed 2%/year, a diver could be considered "unfit to dive," which could particularly benefit older (≥ 50 years) divers, in whom cardiovascular risk factors are often not properly treated. For the prevention of fatal diving accidents due to atherosclerotic cardiovascular disease, a dive medical examination is of limited value for young (<50 years) divers who have no cardiovascular risk factors. Introducing a cardiovascular risk management system for divers may achieve a reduction in fatal diving accidents that result from cardiovascular disease in older divers engaged in both recreational and professional diving.

KEYWORDS: cardiovascular diseases; diving; fitness to dive; preventive cardiology; risk assessment

INTRODUCTION

Recreational scuba diving occurs worldwide. Since its popularization in the 1980s the number of scuba divers has increased enormously. The largest diving organization, the Professional Association of Diving Instructors (PADI), covers 60% to 70% of the global scuba diving market and has issued more than 28 million diver certifications globally since 1967, with one million new certifications annually [1]. The number of new certifications seems to have stabilized in recent years [2]. Since most divers are active in the sport for short periods only, the number of certifications does not reflect the number of active divers.

It has been estimated that in the United States about 3 million people annually participate in scuba diving [3]; the numbers worldwide are unknown. As many once-youthful divers continue to dive, the diving population is aging [4].

With increasing numbers of aging divers, safety issues may arise. Diving injuries and fatalities are published periodically in the DAN (Divers Alert Network) and BSAC (British Sub Aquatic Club) diving reports [5,6], among others. Diving incidents and fatalities are typically grouped into two categories: non-medical, including procedural mistakes, equipment failure, environmental problems (e.g., strong currents, reduced visibility, and low temperature); and medical emergencies, including lung problems, cardiovascular problems, neurological problems, as well as other medical conditions.

In addition to training in proper diving procedures and equipment, divers' endurance and cardiovascular health must be sufficient for emergencies [7]. However, "sufficient cardiovascular health" is not clearly defined and may be difficult for medical examiners to quantify in divers.

Aviation faces challenges similar to those in diving: Acute incapacitation in a hostile environment may lead to a fatal outcome. In aeromedicine, a pilot is considered unfit to fly when cardiovascular risk exceeds one percent per annum, the so-called 1% rule. This 1% rule was established in 1984, mainly based on the work of Joy and Tunstall-Pedoe, in order to limit the contribution of medical (especially cardiovascular) emergencies to plane crashes [8-10]. The rule states that the pilot should be considered to be part of a man-machine system, and that no part of the system (including the pilots) should contribute more than 10% to the total risk of a fatal accident. A cardiac event, especially myocardial infarction or sudden cardiac death, is an "acute incapacitation" that renders a pilot unable to fly, which can lead to a crash. This 1% rule was set up for commercial flights with two fully licensed pilots on the plane. In this paper we attempt to apply assessment strategies used in aviation medicine to diving medicine.

Risk assessment in divers

A review of the main principals of risk assessment in divers was reported by Denoble et al. [11]. The relationship between risk, hazard, and exposure is given by the following equation: $Risk = Hazard \times Exposure$, and is defined by quantification of the probability that specific hazards will result in injury or harm. Hazard, according to the Federal Aviation Administration (FAA), is a "condition, event, or circumstance that could lead to or contribute to an unplanned undesirable event" [12]. In diving, as in flying, non-medical hazards can occur outside the diver: for instance, hyperbaric circumstances, strong currents, low temperature and equipment failure. Medical hazards can occur inside the diver, including acute health emergencies such as myocardial infarction, arrhythmia, and heart failure. Exposure refers to being in the presence of or subjected to a potentially harmful condition or agent (for instance, a dive or a flight). A dive fatality is a deviation from a normal dive leading to the death of the diver. The fatality rate is the number of fatalities per population at risk (divers) or per number of exposure units (dives). The fatality rate can also be expressed as annual fatality rate per exposure, or as annual fatality rate per exposure time. In this paper, annual fatality rate refers to that within a group with the same characteristics. Fatality rates are often expressed as number per 100,000 per year (number $\times 10^{-5}$/year). A year contains $24 \times 365 = 8{,}760$ hours. In this paper, in analogy with calculations used in aeromedicine, a year is considered to be equal to 10,000 (10^4) hours.

An alternative approach to risk assessment is the "Risk of Harm" equation, derived from the Canadian Cardiac Society Consensus Conference, that estimates the yearly risk of harm (RH) to other road users posed by a driver with heart disease with an implantable cardiac defibrillator (ICD), expressed as number per 100,000 drivers per year [13-16]. This formula takes the following form: $RH\ (number \times 10^{-5}/year) = TD \times V \times SCI \times Ac$. RH is proportional to time driving (TD: the proportion of time spent on driving in a given time period [expressed as

fraction of a year]), the type of vehicle (V; truck or passenger car), the yearly risk of sudden cardiac incapacitation (SCI: based on the incidence of ICD shocks [number × 10^{-5} drivers/year]), and accident severity (Ac: the probability that the accident will result in an injury or fatality [0 = never; 1 = 100%, expressed as fraction]). The yearly risk of SCI was based on the cumulative incidence of ICD shocks, mainly delivered during ventricular fibrillation (VF) or ventricular tachycardia (VT) (VF and VT are not caused by driving, but happen during driving). Left untreated, VF and VT are usually fatal, and RH can be considered an *annual fatality rate per population*.

In patients with an ICD who are driving, vehicle defects make a negligible contribution to fatalities, while in diving, non-medical hazards are important. In this respect, similar to flying, medical risk assessment in diving should be part of a total risk assessment. The use of the Risk of Harm formula in diving is consequently limited to the risk of *medical* incapacitation. To calculate the cardiovascular risk of harm for *diving*, the SCI can be redefined as the incidence of fatal cardiovascular events in the diving population per year (%/year).

The use of the Risk of Harm formula in diving implies an assumption of randomly occurring cardiac events, independent of actual diving, and that diving itself neither induces nor protects against cardiovascular events (for further discussion of these assumptions, see Limitations).

The time spent on *driving* (TD) can be rephrased as the time spent on *diving*, expressed as the time fraction of the year that the diver is actually diving. As most dives typically are about one hour, this can be simplified to the number of dives per year (number × 10^{-4}). V in the RH equation designates either professional (truck) drivers or private (passenger car) drivers. The impact of an accident with a truck being usually much higher than with a passenger car, V is set to 1 for professional drivers, and 0.28 for private drivers. Evaluating only the individual risk per type of driver or, in the present case, diver (e.g., scuba, rebreather, technical), the formula applies only to *that* type of diver, in which case V can be omitted. Assuming that every cardiac event under water is fatal, which is plausible in the case of VF, VT or any other major cardiovascular event during scuba diving, Ac can be set to 1. Consequently, for scuba diving, the formula can be rewritten as:

$$RH = TD \times SCI.$$

Fit or unfit to dive?

What is the cardiovascular risk (SCI) above which an asymptomatic diver should be considered unfit to dive? Risk stratification as low (<10% mortality and morbidity/10 year), moderate (10–20% mortality and morbidity/10 year) or high (>20% mortality and morbidity/10 year) originated with the Framingham study and is now generally accepted [17]. Currently, no formal or recommended upper limit of cardiovascular risk exists above which a diver is considered unfit to dive. As recreational diving and professional diving may accept different risks, they are discussed separately here.

RECREATIONAL DIVING

It should be noted that this section applies only to regular scuba diving within the decompression limits. For diving with a rebreather or with trimix, other calculations apply.

Annual fatality rate of recreational scuba divers

A variety of values for the annual fatality rate of recreational scuba divers has been reported, of which most are hampered by being incomplete and/or the number of divers in the population concerned is not precisely known. For organizations with known populations, like the BSAC or DAN, it is possible to calculate reliable fatality rates. The fatality rates reported by BSAC and DAN are 14.4 × 10^{-5} in 38,717 divers and 16.4 × 10^{-5} in 144,400 divers, respectively. When combined, a composite fatality rate can be calculated as 15.8 × 10^{-5} divers/year. Since the average number of dives per year in this population is 25, the fatal accident rate per dive can be calculated as 0.6 × 10^{-5} dives [11].

Contribution of cardiovascular disease to having a diving fatality

The cause of a diving fatality is not always clear. The most frequently reported cause of death in diving is drowning, to which cardiovascular disease might have contributed. Generally, cardiac disease accounts for 20% to 30% of fatalities, but may play a role in up to 50% of all fatalities [5,6,18]. The cardiovascular fatality rate is strongly related to age. In a survey of 1,141,367 DAN-insured member-years, 187 diving-related deaths (16.4×10^{-5}/year) were documented. For the group as a whole, the cardiovascular contribution to the fatalities was 26%. Divided over the age groups younger than 50 years old and 50 years old or older, these percentages were 10% and 36%, respectively [19].

Establishing a degree of cardiovascular risk that fits the actual cardiovascular fatality rate in recreational diving

Using the modified RH formula, cardiovascular risk can be calculated for the DAN/BSAC population [11]. In this population, the (composite) diving fatality rate is 15.8×10^{-5} divers/year. We assume that the cardiovascular contribution to fatalities is 25% (0.25). This results in an RH of ($0.25 \times 15.8 \times 10^{-5}$ =) 3.9×10^{-5}. In this population, the average number of dives was 25 per year, which equals 25 hours/year (TD = 0.0025 year = 25×10^{-4} year). SCI for the DAN/BSAC population can be calculated as: SCI = RH/TD = $3.9 \times 10^{-5} / 25 \times 10^{-4} = 1.6 \times 10^{-2} = 1.6\%$/year. This describes the entire DAN/BSAC diving community.

When age differences are considered the situation is quite different. In the above-mentioned survey of 1,141,367 DAN-insured member-years in which 187 diving-related deaths (16.3×10^{-5}/year) were recorded, there was sufficient data to investigate a probable disabling injury resulting in death in 129 cases. Out of these, 34 (26%) were attributed to cardiovascular disease [19]. For the entire DAN-insured population, the RH was ($0.26 \times 16.3 \times 10–5$ =) 4.2×10^{-5}. Assuming 25 dives/year, the SCI of the DAN-insured population was RH/TD = $4.2 \times 10^{-5} / 25 \times 10^{-4}$ = 1.7/year%. In the age group younger than 50 years, the fatality rate was (73/788,489 divers) 9.2×10^{-5}, with 10% resulting from cardiovascular events. The RH in this age group was then ($0.1 \times 9.2 \times 10^{-5}$ =) 0.9×10^{-5}/year. The SCI can be calculated as follows:

$$SCI\ (< 50\ years) = RH/TD = 0.9 \times 10^{-5} / 25 \times 10^{-4} = 0.3 \times 10^{-2} = 0.3\%.$$

For the age group 50 years or older, the fatality rate was (114/352,878 divers) 32.3×10^{-5}, with a cardiovascular contribution of 36%. The RH in this age group was then ($0.36 \times 32.3 \times 10^{-5}$ =) 11.6×10^{-5}/year. The SCI can then be calculated as follows (assuming 25 dives/year):

$$SCI\ (\geq 50\ years) = 11.6 \times 10^{-5} / 25 \times 10^{-4} = 4.6 \times 10^{-2} = 4.6\%.$$

Acceptable cardiovascular risk in recreational diving

Since a definition of "acceptable risk" in diving has not been generally agreed upon, it may be appropriate to adopt the "acceptable risk" used by the CCS as a reference, 5×10^{-5}/year. The CCS has used this definition for drivers with an ICD, but it can also be applied to other populations such as divers. By adopting this value as an acceptable risk, an upper limit of "acceptable" cardiovascular risk can be calculated (assuming 25 dives a year):

$$SCI\ (acceptable) = RH/TD = 5 \times 10^{-5} / 25 \times 10^{-4} = 2\%/year.$$

It should be mentioned here that this describes only the cardiovascular risk. The (cardiovascular) RH of diving in the DAN/BSAC population is 3.9×10^{-5}/year (see above). This lies within the "acceptable" range according to the CCS and is equivalent to an SCI of 1.6% for DAN/BSAC divers as a group.

PROFESSIONAL DIVING

Professional diving involves a wide variety of activities and different forms of licensing. The largest group consists of commercial divers. Commercial divers customarily engage in three modes of diving: scuba (self-contained underwater breathing apparatus); SSD (surface-supplied diving, with an umbilical to the diving ship); and saturation and closed-bell diving (divers stay in a hyperbaric

environment for several weeks during their work). The latter is typically common in the offshore oil and gas company activities. Commercial diving is strictly regulated by national authorities: for instance by the Health and Safety Executive in the United Kingdom (HSE UK) [20], and on the European level, by the European Diving and Technology Committee (EDTC) [21]. Also, the industry itself prescribes medical standards for commercial diving [22]. Special branches of professional diving are police diving and military diving. Police diving includes rescue diving for underwater casualties and search and recovery diving for evidence and bodies. Military diving includes placing and demolition of explosives under water, reconnaissance, infiltration, combat and the like. Police and military divers usually use scuba gear or rebreathers, depending on the mission. Both police and military diving are strictly regulated by their national organizations.

Fatality rate in professional divers

Fatality rates among professional divers vary considerably, from 20 to 233 $\times$ 10^{-5} dives/year [23]. This wide range in diving fatalities is caused by different factors, among which is the relatively small number of commercial divers (UK 5,000; Norway 3,000; U.S. 3,500; Belgium 100). Hence, a small number of fatalities may have a profound effect on the annual fatality rate [24]. Since the UK HSE dataset contains the largest number of divers, it is probably the most reliable. It shows a fairly stable fatal accident rate for the offshore and inland/inshore sectors of 20–40 $\times 10^{-5}$ divers/year over the recent past [23].

Contribution of cardiovascular disease to professional diving fatalities

In a review of 577 professional diving accidents from 1975 to 2013, 4% of all fatal diving accidents, both inshore and offshore, were attributed to "cardiac arrest" [24].

Establishing a degree of cardiovascular risk appropriate for the actual cardiovascular fatality rate in professional diving

To the best of our knowledge there is no publicly available data on the numbers of dives and of diving time for professional diving, and consequently a calculation using the Risk of Harm formula is not straightforward. However, some elaboration on the cardiovascular risk of the professional diving population can be made. A Norwegian study investigated mortality rate in 3,130 male occupational divers, aged 18 to 60 years, and compared it to those of a matched reference group [25]. Over the observed period of 42 years, total mortality of the reference group was equal to that of the diving group and estimated to be 0.05%. There was no significant difference in cardiovascular mortality rate between the professional divers and the reference population (0.005%/year and 0.007%/year, respectively). The mortality for dive-related accidents was 4/1,000 divers/42 year (9×10^{-5}/year), but the contribution of cardiovascular causes to dive-related accidents could not be not established.

Acceptable cardiovascular risk in professional diving

The European Diving Technology Committee fitness-to-dive standards guide does not provide a specific threshold for cardiovascular risk in its "cardiovascular assessment" section, but states that stress electrocardiography (ECG) (at maximal workload during an exercise test) is needed over the age of 45 years, or younger when considerable risk factors are present. However, the document does not define "considerable," leaving room for interpretation. Blood pressure should not exceed 140/90 mmHg at the initial dive medical examination, but at the follow-up dive medical examination, blood pressure of up to 160/100 mmHg is acceptable, provided there are no signs of end organ damage [21].

The UK HSE standards for professional diving do not specifically mention cardiovascular risk or a cardiovascular risk threshold, and there is no requirement to calculate a cardiovascular risk profile. The document mentions that blood pressure should not exceed 160/100 mmHg, and no end organ damage should be present [20]. According to the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) task force for the management of arterial hypertension, this is classified as grade 1 hypertension [26] and corresponds to low to moderate risk in the SCORE2 risk table. The SCORE2 (Systematic COronary Risk Evaluation) risk score predicts the 10-year risk of fatal and non-fatal cardiovascular events in European populations [27].

When determining cardiovascular risk in professional divers, it is debatable whether only cardiovascular mortality should be considered or a combination of both mortality and morbidity. As myocardial infarction or any other cardiac emergency under saturation conditions reduces the chance of survival, combining cardiovascular mortality and morbidity in risk assessment should have priority [26,27]. By accepting a blood pressure of 160/100 mmHg without an established policy to rigorously treat risk factors, both the EDTC and the HSE allow de facto a moderate cardiovascular risk according to the SCORE2 criteria.

DISCUSSION

We present here a risk assessment tool based off applying the modified RH formula to the DAN/BSAC recreational diving population and diving fatality rate. Despite thousands of professional and millions of recreational divers, there is limited data on diving fatalities and cardiovascular risk. Although a comparable lack of data in the aeromedical field exists, implementation of the "1% rule" has served as a tool to limit medical (cardiovascular) risks during flying and to improve flight safety.

The formula RH = TD × SCI implies that the number of dives and SCI are inversely related. As a result of the assumption that recreational divers make 25 dives a year, the corresponding SCI is 2%/year, and when 50 dives a year are made, the corresponding SCI should be as low as 1%/year, 100 dives yields 0.5%/year, and so on. In general, the more dives made (or the longer the diver is exposed to saturation), the lower the SCI should be to maintain a maximum cardiovascular event risk of 2%.

From a cardiovascular point of view, divers that exceed a cardiovascular event risk of 2% per year could be considered unfit to dive, because they exceed the limits currently (albeit not officially) practiced for safe diving. Treatment of cardiovascular risk factors particularly benefits the older (≥ 50 years of age) diver, both for recreational and professional diving. For instance, among the divers ≥ 50 years of age described by Denoble, a reduction of the SCI from 4.6% to 2.0% would mean a reduction in RH from 11.6×10^{-5} to 5×10^{-5}. This would be a reduction from 29 to 13 fatalities, or about 55%. A further reduction to 1% would mean a reduction in RH from 11.6×10^{-5} to 2.5×10^{-5}. This would be a reduction from 29 to six fatalities, about 78% [19]. In recreational diving, divers younger than 50 years of age without cardiovascular risk factors such as smoking, hypertension, hyperlipidemia or diabetes mellitus usually have a low cardiovascular risk (combined mortality and morbidity <10%/10 years), which limits the contribution of a dive medical examination to cardiovascular safety. As cardiovascular risk increases with age, dive medical examinations at age 50 and older and, if deemed necessary, cardiologic follow up, may reduce diving-related fatalities. The issue of a dive medical examination with or without ECG before engaging in diving is beyond the scope if this manuscript.

Limitations

It is assumed that cardiovascular disease is responsible for 25% of all diving fatalities, although this value could be higher, as discussed above. If that were the case the SCI would also be higher. For instance, if the cardiovascular contribution were 35% instead of 25% of 16.4×10^{-5} fatal dive accidents per year, the RH would be 5.7×10^{-5} per year,

and the SCI 2.2%. This would make the proper treatment of cardiovascular risk factors even more important. Another assumption in these calculations is that the cardiovascular risk is equally divided over the year and that diving per se does not affect cardiovascular risk. This is indeed the case in uneventful dives, but the physical exertion associated with scuba diving might induce adverse cardiac events. This is especially true among habitually sedentary older persons with occult or known coronary artery disease (CAD) who perform unaccustomed vigorous physical activity (defined as equal or greater than 6 METs [28].

A specific diving-related problem is immersion pulmonary edema (IPE). In the older diver, this is mainly related to the presence of hypertension and pre-existing cardiovascular pathology [29]. Diving might impair endothelial function [30,31], and hyperoxia may cause coronary artery constriction [32]. Coronary circulation during diving has mainly been studied in relation to the cold pressure test and the diving reflex, which cause vasodilatation of normal coronary arteries. This response is lost in patients with hypertension, diabetes mellitus or CAD, but can be restored (partially) with proper medical treatment [33-36]. To what extent these mechanisms play a role in fatal diving incidents is unknown.

Although scuba diving per se does not induce dangerous arrhythmias in healthy volunteers, cold-water immersion may provoke these arrhythmias due to the "autonomic conflict" and may lead to fatal arrhythmias in divers with heart problems, especially CAD [37,38]. These diving-related cardiovascular risks may argue for accepting a more conservative approach in divers during medical assessments (e.g., 1% instead of 2% total cardiovascular risk), especially when the diving circumstances are expected to be less favorable (e.g., cold-water or strenuous diving). These potential diving-related contributors to cardiovascular risk are probably already included in the current data.

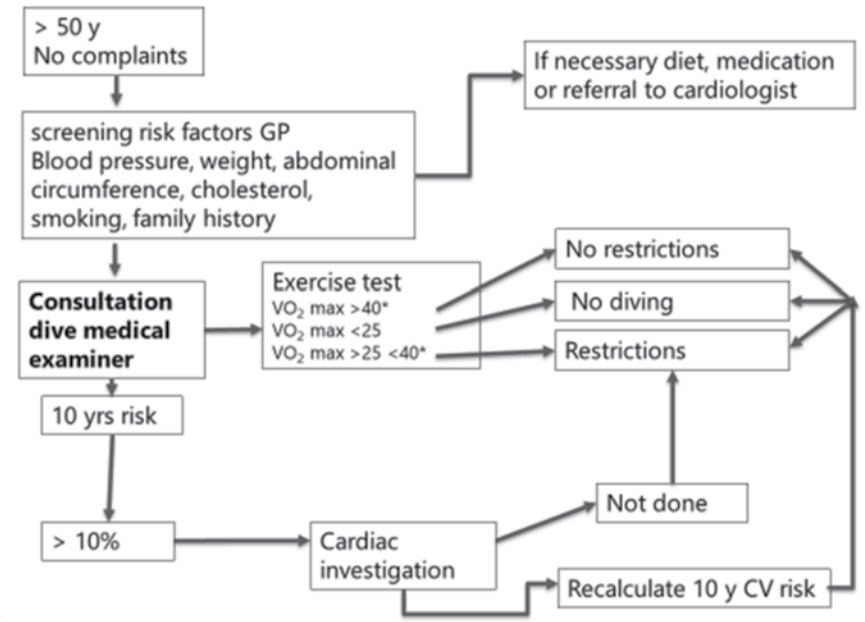
Implementation of cardiovascular risk assessment in dive medical assessments

The need for cardiovascular risk management was shown by a recent study of 113,892 American divers. One-third of active U.S. divers were 50 years old or older and/or reported prior high cholesterol, about half were overweight, more than half reported smoking cigarettes, and 32% reported hypertension or borderline hypertension [39]. Similar unfavorable cardiovascular risk factors were identified in a recent survey of 497 mostly male, older Dutch diving instructors, of which 66% of the males were overweight and one-fifth had cardiovascular disease [40].

Many cardiovascular risk assessment tools may be used, like the Framingham Risk Score, the Reynolds Risk Score, and the Euro-SCORE2, each with their own characteristics [41]. Where it is assumed that a cardiovascular event almost always leads to acute incapacitation and thus to a fatal diving accident (Ac = 1), it is preferable to use a risk calculator that uses cardiovascular mortality and morbidity, like the Framingham Risk Score or the EuroSCORE2 score. The Coronary Calcium Score (CCS) (or Agatston score) and the Coronary CT Angiogram (CCTA) are increasingly used as cardiovascular assessment tools for athletes and those with hazardous occupations [42,43]. CCS is a measure of the calcium content in the coronary artery wall, and ranges from very low (<1% risk in 10 years) to high (>20% risk in 10 years) [44]. Unfortunately, a CCS of 0 does not preclude CAD (especially not "soft plaque"). This can be visualized only by a CCTA.

Cardiovascular risk assessment, including the CCS or CCTA, as part of dive medical screening has been suggested by several dive medical societies [45,46]. A possible implementation of cardiovascular risk assessment in divers is diagrammed in the flowcharts of Figures 1 and 2 (adapted from [45]), which show that in addition to the cardiovascular risk, cardiovascular fitness must be considered before providing advice to the diver about whether to dive or to dive with restrictions. The

FIGURE 1
FLOWCHART: Risk assessment
by the General Practitioner and Dive Medical Examiner



Cardiovascular risk: Assessed risk of mortality and morbidity (%/10 year)
VO_2 max: maximum O_2 uptake (mL/kg/min).
Diving restrictions: no diving under circumstances that require good physical health, such as cold water, strong currents and high surf, among others.

flowcharts advise that when the overall cardiovascular risk, as assessed by an appropriate "risk calculation tool," is less than 1% per year, there is no objection to diving. When the total cardiovascular risk exceeds this level, it is suggested that there be further investigation using, e.g., CCS or CCTA to reclassify cardiovascular risk. When the total cardiovascular risk is considered to be too high, additional cardiologic examination may be indicated.

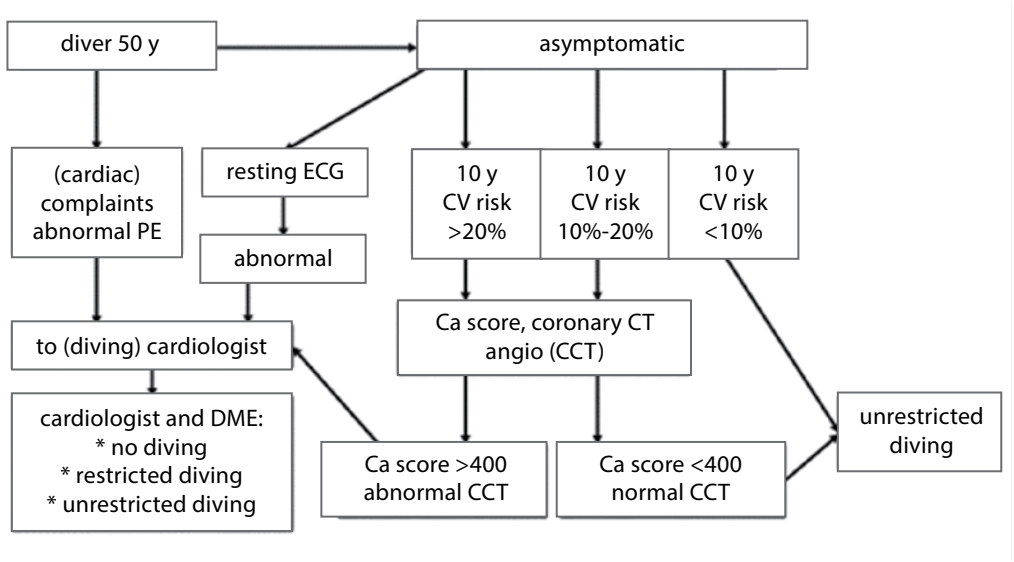
Acknowledgments

The editing of the manuscript was supported by the NVD (Dutch Society of Diving and Hyperbaric Medicine).

We thank the Diving Cardiology Working Group for their comments and support: MJ Cramer, MD, PhD, University Medical Center, Department of Cardiology Utrecht, the Netherlands; M.H.H. de Vaan, MD, Admiral de Ruyter Hospital, Department of Cardiology, Goes, the Netherlands; H.A.M. Spierenburg, MD, Sint Maarten Medical Centre, Department of Cardiology Sint Maarten, Netherlands Antilles; G. Verdel, MD, PhD, Spaarne Gasthuis, Department of Cardiology, Haarlem, the Netherlands; and Professor (retired) W.L. Mosterd, MD, PhD.

We want to thank Dr. P. Germonpré, MD, and Dr. R. Simons, MD, for their valuable comments.

FIGURE 2
FLOWCHART: Assessment of cardiovascular risk in cardiac investigations of divers



Cardiac complaints: chest pain, palpitations, dyspnea (depending on effort), dizziness, (pre) syncope. Abnormal PE (physical examination): e.g., murmurs, signs of heart failure, cyanosis

DME: Dive Medical Examiner*

Cardiovascular risk: Assessed risk of mortality and morbidity (%/10 year).

CCS is related to cardiovascular risk as follows:

CCS = 0: very low risk of cardiovascular events (< 1% at 10 years)

CCS = 1–100: low risk of cardiovascular events (1–10% at 10 years)

CCS = 101–400: intermediate risk of cardiovascular events (10–20% at 10 years)

CCS > 400: high risk of cardiovascular events (>20% at 10 years).

Here a CCS of > 400 is considered a cutoff because when ≤ 400, the annual cardiac event rate is < 2%.

For a CCS ≤ 100, the annual cardiac event rate is < 1%. The decision to use a CCS of 100 or 400 as a cutoff value is an organizational decision.

* Dive Medical Examiner: physicians certified as such by the ECB (European College of Baromedicine), DMAC (Diving Medical Advisory Committee), the UHMS (Undersea and Hyperbaric Medical Society), or otherwise at an equivalent level.

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UNDERSEA & HYPERBARIC MEDICINE

Profound hypercapnia but only moderate hypoxia found during underwater rugby play

Peter Lindholm, PhD [1]; Henrik Lund, PhD [2]; Lesley Blogg, PhD [3]; Mikael Gennser, PhD [4]

[1] Division of Hyperbaric Medicine, Department of Emergency Medicine, University of California San Diego, California, US

[2] Anestesikliniken, Sunderby Sjukhus, 971 80 Luleå, Sweden

[3] SLB Consulting, Home Park Barn, Kirkby Stephen, Cumbria, UK

[4] Swedish Aerospace Physiology Centre, Division of Environmental Physiology, Department of Biomedical Engineering and Health Systems. School of Engineering Sciences in Chemistry, Biotechnology and Health, Royal Institute of Technology, KTH, Stockholm, Sweden

CORRESPONDENCE: Peter Lindholm – *plindholm@health.ucsd.edu*

ABSTRACT

Lindholm P, Lund H, Blogg L, Gennser M. Profound hypercapnia but only moderate hypoxia found during underwater rugby play. Undersea Hyperb Med. 2022 Third Quarter; 49(3):367-372.

Background: Underwater rugby is a team sport where players try to score points with a negatively buoyant ball while submerged in a swimming pool. Reports of syncope incidents at the Swedish Championships led to us to investigate end-tidal oxygen and carbon dioxide levels during simulated match play.

Methods: Eight male underwater rugby club players of varying experience participated. Repetitive measurements were made while players were defending during simulated match play. Each time a player surfaced they exhaled through a mouthpiece connected to a flow meter and a gas analyzer to measure tidal volume, $PETO_2$ and $PETCO_2$.

Results: Measurements were made over 12 dives, with an average dive duration of 18.5 seconds. The mean maximal $PETCO_2$ across the eight participants was 10.0 kPa (~75 mmHg) (range, 9.1–11.7 [~68–88]). The corresponding mean minimum $PETO_2$ was 7.6 kPa (~57 mmHg) (6.3–10.4 [~47–78]). $PETCO_2$ drifted upward, with the mean upward change from the first to last dive for each participant being +1.8 (~13.5 mmHg) (SD 1.74) kPa. A similar trend for $PETO_2$ was not detected, with a mean change of -0.1 (~0.75 mmHg) (SD 3.79) kPa.

Conclusion: Despite high $PETCO_2$ values that were close to narcotic being recorded, these players seemed to regulate their urge to breathe based on hypoxia rather than hypercapnia.

KEYWORDS: breath-hold diving; drowning; exercise; hypoxia; $PETCO_2$; $PETO_2$

BACKGROUND

Diving mammals have several innate physiological responses and adaptations to breath-holding underwater, which are broadly termed the diving response [1]. Humans show some of these in a less pronounced form, although trained scuba and breath-hold (BH) divers can usually hold their breath longer and show greater adaptation than untrained individuals [2-4]. The human diving response is stimulated upon immersion in water and facilitates longer BHs when compared to breath-holding on land [2]. Breath-hold diving dates back over many centuries and is still practiced today in order to harvest food. For example, the Japanese and Korean Ama spend ~60% of their working hours submerged [5,6]. These divers are

usually underwater for around one minute per dive and descend to around 20 meters. In contrast, competitive BH or "apnea divers'" push themselves to their physiological limits. In 2021 the record for a static BH (head immersed, diver resting) was set at 11 minutes 35 seconds, while the record for the longest distance swum in a pool on a single BH (dynamic apnea) is 300 meters [6].

Competitive BH diving and spearfishing are characterized by the prolongation of breath-holding at rest, or at a low level of exercise intensity. If relaxation and minimal physical effort are important to apnea divers, sports such as synchronized swimming, underwater hockey and underwater rugby (UWR), require athletes to perform high-intensity intermittent exercise. Underwater rugby is played by two teams of 15 players, with six players in the water at any time. These players try pass a negatively buoyant ball into their opponents' goal at each end of the pool while breath-holding. Players wear masks, fins and snorkels. The game is played over two 15-minute periods, with a five-minute break in between. It is physically demanding and does not afford its players the benefit of regular breathing to replenish available oxygen [4]. Unlike competitive BH divers, the players do not typically hyperventilate before each BH but make brief apneas and physically demanding shallow dives interrupted with short (circa two breaths) surfacing periods. Similarly to underwater hockey players and synchronized swimmers, UWR players partake in intense physical training and practice repeated breath-hold maneuvers [2-4].

Several studies, as described below, have investigated the physiological responses of this cohort of underwater athletes who are typified by their brief, physically intense BH dives, as it was thought that they may show adaptations to extreme breath-holding. During normal conditions, homeostatic breathing in humans is maintained by oxygen entering the body upon breathing in and carbon dioxide (CO_2) being expelled on breathing out, mediating an acid-base balance. An increase in the CO_2, as detected by the central chemoreceptors, is the main stimulus for the ventilatory drive. Apnea divers often hyperventilate extensively before a BH to maximize their apneic period, thus inducing relative hypocapnia so that the drive to breathe is delayed, with the weak stimulus from hypoxia being easier to overcome [5]. It has been shown that following hyperventilation and a BH of around five minutes, apnea divers may surface with hypocapnic or normal end-tidal CO_2 values [4,5,11]. In another study, end-tidal partial pressure of carbon dioxide (PCO_2) in competitive BH divers performing swimming breath-holds following two minutes of hyperventilation and a breath to vital capacity, was found to be raised (7.5 kPa [~56 mmHg]) above "normal" levels [5,8]. It is thought that with training, divers may become more psychologically and physiologically tolerant to hypercapnia; for example, Davis et al. found that underwater hockey players had a higher tolerance to CO_2 than non-divers [3].

At the time this study was performed there had been reports of syncope occurring during the Swedish UWR championships. With this in mind, we performed a pilot study that aimed to measure-end tidal CO_2 and O_2 during simulated match play.

METHODS

Eligible participants were UWR players who were fit, healthy male amateur competitive players at national level, with between five to 15 years of experience.

The experimental protocol was conducted in conformity with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Karolinska (Institutet Etik KI #01-001). All subjects gave their signed informed consent for participation.

Assessments

Repetitive measurements were made on players positioned as the defender during an organized match situation. Each participant was asked to make 10 to 12 breath-hold dives during their play which would be measured. Usually, when players ascend they exhale through their snorkel. During these tests the subjects were asked to ascend

while breath-holding, and as soon as they surfaced exchange their snorkel for a mouthpiece provided by one of the investigators. The mouthpiece was connected to a tube, roughly the same diameter and length as the snorkels used. At the top of the tube a turbine flow meter (KL Engineering, Northridge, California) was connected. Exhaled volumes were recorded for the first exhalation after surfacing to verify that a proper exhalation was made corresponding to end-tidal gas concentrations. Volumes were not used in the analysis, only recorded in the moment to verify an exhalation took place. A thin capillary tube was inserted at the end of the mouthpiece and connected to a gas analyzer (Datex Normocap 200; Dansjö Medical, Sundbyberg, Sweden) to measure end tidal oxygen ($PETO_2$) and end tidal carbon dioxide ($PETCO_2$). The gas analyzer was calibrated with fresh air and a calibration gas consisting of 5% oxygen and 10% carbon dioxide. As some of the carbon dioxide results were above the highest calibration point, the meter was checked later for linearity up to 12 kPa (~90 mmHg) CO_2.

RESULTS

Eight healthy male participants took part, with a mean age of 25 (21–36) years, mean height 183.1 cm (SD 5.0) and mean weight 85.0 kg (SD 6.0). The average number of breath-holds performed was 10 (SD 2.7, range six to 13) with an average duration of all recorded breath-holds of 18.5 seconds. A varied number of successful measurements was made in each subject, ranging from five measurements in one, to 12 measurements in three subjects.

The mean maximal $PETCO_2$ across the eight participants was 10.0 kPa (~75 mmHg) (range, 9.1–11.7 [~68–88]). The corresponding mean minimum $PETO_2$ was 7.6 kPa (~57 mmHg) (6.3–10.4 [~47–78]). Mean $PETCO_2$ (calculated over variable n-values) numbers drifted upward over the dives, from 7.8 kPa (~58.5 mmHg) (SD 0.66; range 6.7–8.7 [~5; 50–65]; n=8) after the first dive to 9.6 (~72 mmHg) (SD 2.51; range 6.8–11.7 [~19; 51–88]; n=3) after the 12th dive; the mean upward change from the first to last dive for each participant was +1.8 kPa (~13.5 mmHg) (SD 1.74 [13]). Mean $PETO_2$ showed some slight variation across the 12 measurements though remaining relatively level, with a mean value of 10.0 kPa (~75 mmHg) (SD 3.3; range 6.7–14.9 [~25; 50–112]; n=6) after the first dive and 11.7 kPa (~88 mmHg) (SD 5.7; range 7.6–15.7 [~43; 57–118]; n=2) kPa after the 12th dive; the mean $PETO_2$ change from first to last dive for each participant was 0.1 kPa (~0.75 mmHg) (SD 3.79 [~28]). The lowest recorded $PETO_2$ (6.3 kPa [~47 mmHg]) occurred after dive #3 in one of the subjects; all divers' measurements are shown in Figure 1.

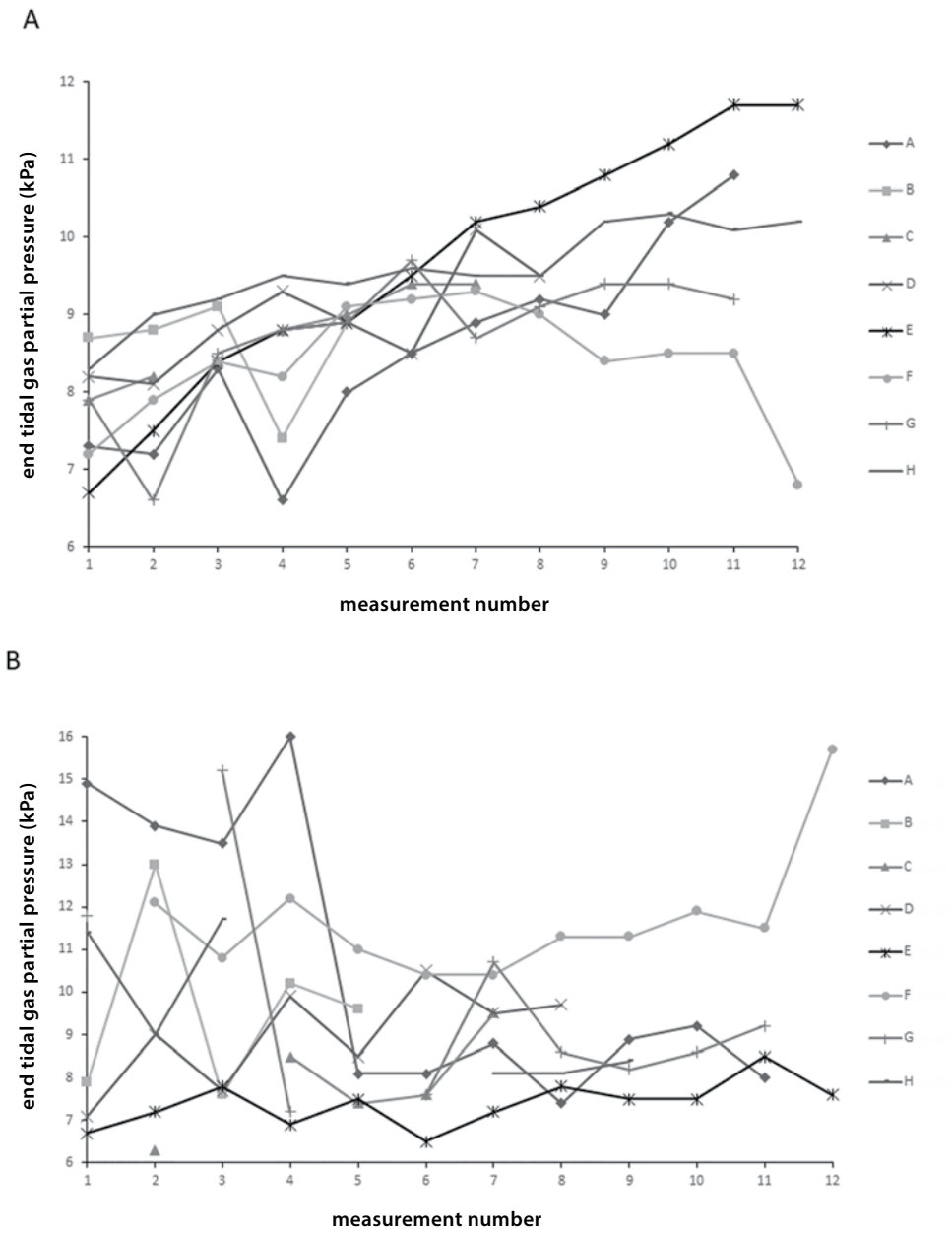
DISCUSSION

The principal finding of this observational study was that the mean $PETCO_2$ across eight experienced UWR players reached 9.6 kPa (~72 mm Hg) from 7.8 kPa after the first BH dive recorded, while one individual recorded sequential measurements (dives 11 and 12) of 11.7 kPa (~88 mmHg). These $PETCO_2$ values are very high. By comparison, the normal range of expired $PETCO_2$ for a healthy individual at rest is around 4.5 to 6 kPa (35–45 mm Hg); this value remains similar or may fall slightly during exercise [9]. In a study measuring $PETCO_2$ during swimming, trained swimmers working at 50% of their heart rate range had a group mean $PETCO_2$ of 41 ± 4 mmHg (5.5 kPa), while that for a group of land-based athletes was 38 ±4 (5.1 kPa) [10].

Further, in a study performed at 1 atmosphere absolute examining CO2 narcosis, a $PETCO_2$ of 57 mmHg (7.6 kPa) was considered a "high" level in healthy male volunteers; this partial pressure of CO_2 significantly impaired cognitive and psychomotor performance. (11)

In the present study the mean BH period for all players was 18.5 seconds. In contrast, synchronized swimmers generally perform much longer BHs; in one study BHs lasted for 76 to 110 seconds, but interestingly their $PETCO_2$ was much closer to normal levels (around 44 mmHg; ~5.9 kPa), and $PETCO_2$ levels at the end of BH were similar between the swimmers and control participants [2]. These $PETCO_2$ levels may be explained by two minutes of recovery breathing in between BH periods [2]. In another study investigating the physiological

Figure 1
Individual $PETCO_2$ (A) and $PETO_2$ (B) measurements across the 12 breath-holds



responses to apnea in underwater hockey players, mean $PETCO_2$ prior to BH dives was found to be 35 mmHg (4.6 kPa), while afterward and measured over five apneas (facial immersion for 45 seconds while cycling) was 54.2 mmHg (7.2 kPa) [4]. Again, the participants were given a longer recovery time (five minutes) than UWR players. Thus, it is possible that the high $PETCO_2$ levels reached by the UWR players in the present study was caused by the limited number of recovery breaths taken between dives (two to three breaths during match play), which would most likely allow replenishment of O_2 stores but not the complete washout of CO_2. At the extreme end of reduced recovery breathing,

in 2002 the Italian BH athlete Giancarlo Bellingrath set a world record in repeated breath-holding whereby in one hour he spent only 15 seconds breathing [12]. It would be of interest to record $PETCO_2$ after such a record attempt in a future study.

Underwater hockey players also tend to hypoventilate before each apnea, causing a relative hypercapnia that could displace the central CO_2 sensitivity threshold [4,5]. In many of the studies highlighted here, it is suggested that chronic intermittent exposure to hypercapnia, as experienced by BH athletes, may reset/decrease the CO_2 sensitivity threshold via adaptation in chemoreceptors, making them less sensitive, and thus extending the tolerable BH period [2-4]. This seems likely in the present study, where the lower the PO_2 the lower the PCO_2, which may indicate that hypoxia is potentiating the urge to breathe, not allowing the subjects to build high PCO_2 levels.

Lemaître et al. found no difference in ventilatory function between trained BH divers and fit control participants, in agreement with Davis' findings; this is most likely explained by the training effect of the breath-hold athletes, slight hypoventilation and the displaced CO_2 sensitivity [3,4]. The ability to resist the urge to breathe is also driven by an individual's tolerance to the stimulus and increasingly intense involuntary diaphragm movements, though given the short duration of dives made by UWR players, this psychological factor is unlikely to play a role [6]. Indeed because of the reasonable frequency at which O_2 is replenished – which is one of the main factors affecting BH ability – perhaps UWR players can ignore the chemoreceptor drive to breathe, despite the high levels of $PETCO_2$ recorded.

Limitations

A limitation of this pilot study is that interpretation of the data is constrained by the fact that 12 measurements for both $PETCO_2$ and $PETO_2$ could not be obtained for all divers. Additionally, Figure 1 shows that there was a wide variability of $PETCO_2$ and $PETO_2$ between the UWR players, which could reflect the differences in their level of experience or individual physiological differences, their work rate, their time underwater, while ventilatory urge may also have differed between bouts.

It should be noted that as a pilot study only, we did not make measurements of ventilation or calculate oxygen consumption; thus we cannot evaluate to what degree the increased $PETCO_2$ seen across the study might have depended on aerobic metabolism or the build-up of lactic acid from the intense exercise made by the UWR players, rather than CO_2 washout limited by only two to three breaths between dives.

A further study ensuring that all measurements are obtained and adding parameters such as heart rate, recording with underwater cameras or standardizing the exercise if not following actual UWR play, to monitor the work done by the players while underwater might expand upon the interesting early findings presented here.

Disclosures and acknowledgments

None. This study was supported by FOI, the Swedish Defence Research Agency, project number E4450.

This work was performed when authors PL and MG were working for FOI, Swedish Defence Research Agency, Dept of Defence Medicine, SE-171 77 Stockholm, Sweden

Contributors

PL and MG contributed to design, data collection, data analysis, interpretation and writing of the report.

HL contributed to design and data collection.

LB contributed to the data analysis, interpretation and writing of the report.

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UNDERSEA & HYPERBARIC MEDICINE

Unique challenges in naval military dentistry

Yael Findler-Meir, DMD [1*]; Michael V. Joachim, DMD, MSc [1,2*]; Michael Findler, MD [3]; Mordechai Findler, MD, DMD [4]; Imad Abu El-Naaj, DMD [1,2]

[1] Department of Oral and Maxillofacial Surgery, Baruch Padeh Medical Center, Poriya, Israel

[2] Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

[3] Stroke Unit, Department of Neurology, Rabin Medical Center, Petach Tikva, Israel

[4] Department of Oral Medicine, Sheba Medical Center, Ramat Gan, Israel

CORRESPONDENCE: Michael V. Joachim – *mike.joachim@gmail.com*

** These authors made equal contributions to this paper*

ABSTRACT

Findler-Meir Y, Joachim MV, Findler M, Findler M, Abu El-Naaj I. Unique challenges in naval military dentistry. Undersea Hyperb Med. 2022 Third Quarter; 49(3):373-381.

Divers are regularly exposed to a unique and changing environment that dentists must consider when treating such patients. This review focuses around two case studies encountered in naval dentistry:
(i) diving barotrauma (pressure-induced injury related to an air space); and
(ii) scuba diving mouthpiece-related oral conditions.
Each condition is described by its effect on the oral cavity and in particular the teeth. Then we generally review the latest literature on the different effects of scuba diving on the diver's head, face and oral regions and emphasize methods of dental disease prevention, diagnostic tools and treatment guidelines.

KEYWORDS: barotrauma; diving; naval dentistry; naval medicine

INTRODUCTION

Dentists who treat people regularly exposed to an underwater environment – for example, at naval bases – must incorporate special considerations into regular and preventative dental care and oral treatments [1]. One of the main concerns is barodontalgia, a barometric pressure-induced oral pain, which may be dental or non-dental [2].

Barodontalgia has been reported at depths of 33 to 86 feet (10 to 26 meters) during diving [3]. Although quite rare, it may be severe enough to suddenly incapacitate a diver, which could jeopardize the safety of the dive [4]. Another concern is diving-related injury. Approximately 35% of all dive-related head and neck complications occur in rhinologic and oral maxillofacial subsites.

Typically, dive injuries occur due to perturbations of normal physiology according to Boyle's Law, resulting in barotrauma [5]. The aim of this article is to discuss the dentistry challenges and opportunities in treating people exposed to underwater environments and ways to monitor and prevent those challenges. The study is presented by two cases that highlight issues arising in this unique setting and introduces some of the challenges in this area.

CASE PRESENTATIONS

Case 1

A 23-year-old naval soldier, otherwise healthy, complained of an incident of strong maxillary pain posterior to a second molar, during underwater activity diving to a depth of 10 meters for 30 minutes. The diver's dental history included an upper maxillary third molar extraction four days prior to this incident. During the extraction there was no evidence of oroantral communication. However, a Valsalva test, an examination made to rule out a

communication between the maxillary sinus and oral cavity, made after the incident was positive.

Diagnosis

A 3mm oroantral communication was found on direct vision of extraction site. It is probable that during the extraction, a microscopic pinhole was made in the maxillary sinus membrane, which had widened during diving because of the change in barometric pressure.

Treatment

Conservative treatment was recommended, including prescription of a course of antibiotics and grounding from diving, until full recovery. At a two-week follow-up, a Valsalva test was negative, and no oroantral communication was seen upon inspection via direct vision of the site. The soldier was approved to return to diving activities, and communication was closed.

Case 2

A 20-year-old naval diver, otherwise healthy, was sent by the military dentist to the emergency room (ER) because of right upper jaw dental pain. There were no suspicious findings. From there the diver was sent for a checkup in the oral medicine clinic.

The diver mentioned the appearance of fresh blood in his mask four days prior to this checkup and an incidence of facial pain while scuba diving to a depth of 10 meters. The soldier did not seek any medical attention after this incidence he described, and in answer to a direct question, he could not remember whether he tried to equalize pressures while descending.

The diver pointed directly to teeth numbers 14 and 15 to indicate his dental pain. He described the pain as constant strong pressure in that area. An exam revealed no occlusion malformation. No dental pathology appeared in the whole dentition, and the gums looked healthy. He noted soreness while tapping on those teeth, without any sensitivity to cold. The soft tissue was intact without any signs of potential trauma caused by the scuba diving regulator. There was no evidence of any pathology in occlusal and periapical X-rays. A computer tomography (CT) scan taken in the ER showed evidence of right maxillary sinus bleeding, with the Schneiderian membrane shoved to the center of the sinus, causing a blockade of half of the sinus volume.

Diagnosis

The described mask bleeding incident likely resulted from squeezing of the maxillary sinus (barosinusitis). Detachment of tissue apparently in a hematoma pressing on the middle branch of the right superior alveolar nerve and led to neuropathic pain resulting from barotrauma and pressure on the nerve.

Treatment

The hematoma was absorbed, and the pain gradually passed without any medication. The patient returned to routine diving activity after a period of six weeks of grounding and recovery.

BAROTRAUMA IN THE NAVAL SETTING

Presentation, prevention, diagnosis and treatment of medical and dental damage resulting from pressure changes

Barotrauma is a pathological response of the body to a change in the barometric pressure that occurs during diving, during flight, and when receiving hyperbaric oxygen therapy. According to Boyle's law, the product of the volume and pressure of a constant amount of gas at a given temperature is constant. In other words, increasing pressure is accompanied by decreasing volume, and vice versa. When air spaces in our body change in volume as a result of pressure changes during diving, then damage, or barotrauma, can occur. One of the most common complaints associated with barotrauma is headache, characterized as pain that appears for 15 to 20 minutes during pressure changes. Patients typically complain of headaches in the center of the forehead, both during descent and ascent. In cases of such complaints, a patient background of migraine and trigeminal neuralgia, which can also be triggered by changes in weather

and pressure 6, should be ruled out. Additionally, headaches originating from stress changes should be ruled out, as will be further elaborated below.

Barotrauma of the facial region can form in any area that contains air. Several pathologies can be identified according to the area where the injury occurs:

- barotitis media is pressure injury in the middle ear area.
- barosinusitis is caused by pressure injury in the sinus cavities and manifests as headaches caused mainly by pressure on the frontal sinus; and
- barodontalgia is due to pressure change injuries to the diver's denture especially after restorations and during root canal treatment [1].

For dental care involving a background of barotrauma, the attending dentist should examine each of the above-mentioned injuries in a differential diagnosis, as it is known that pain in the oral cavity may be radiated from different areas of the face. Below we describe each phenomenon, focusing on the effects of pressure changes on the dental areas.

Barotitis media

Also known as ear squeeze, barotitis media can cause chronic or acute damage to the middle ear cavity and is created as a result of changes in the pressures between the air in the tympanic cavity and the atmospheric pressure in the environment [7]. Patients complain of symptoms including a feeling of discomfort in the ear to the point of intense pain, hearing loss, vertigo accompanied by nausea and tinnitus (ringing in the ears) [7]. It has been reported that prevalence of this condition among divers is up to 32% [8]. In the Case 2 presentation above, it should be noted that the pain appeared at depth, with an inability to balance pressures, or during ascent when attempting to equalize pressures in a phenomenon known as the "inverted ear." It has been reported that prevention of this condition may be achieved with frequent yawning or swallowing during descent, and decongestant nasal sprays and antihistamines taken before diving [8,9].

Barosinusitis

Barosinusitis, also known as sinus squeeze, is a chronic or acute injury that occurs in one or more of the sinuses due to an imbalance between the pressure present in the paranasal sinuses and the atmospheric pressure in the environment [10]. Its prevalence among divers is reported to be as high as 34% [11]. Patients complain of pain that may be described as intense and erupting, bleeding from the nose and sometimes even a feeling of numbness in the face (ischemia of sections from the trigeminal nerve) [1]. In an X-ray it will be possible to see fullness of the sinus – i.e., bleeding or fluid due to edema. In the both case presentations above it should be noted that the pain appeared during descent [12].

Different medical treatments have been proposed for management of acute barosinusitis and range from observation to the use of antibiotics, decongestants, and oral steroids. Isolated acute symptomatic episodes can be managed successfully with decongestants and analgesics immediately after an episode, albeit direct evidence for this is sparse and limited to expert opinion. The roles of antibiotics and of steroids remain unclear and might be reserved for symptoms that persist for longer than 24 hours [13].

Barodontalgia

Barodontalgia, also known as tooth squeeze, is not a pathology but rather a symptom that may indicate the development of a dental condition that requires treatment [14]. It was found that most people who reported the onset of toothache after a dive had one or more of the following pathologies: chronic or acute peripheral inflammation; caries; deep restorations; residual cysts; sinusitis; or a history of a dental surgery shortly before the onset of pain [15]. Some people divide this phenomenon into two subphenomena: one is characterized mainly by damage to teeth or restorations, and the other is characterized generally

Table 1: Dental rating used in Israeli navy to stage the soldiers' fitness for service

staging	dental diagnosis	clearance for sailing / diving
stage 1	need for dental hygienist	12 months
stage 2	• more than 1 decay but less than 6 (including all types of restorations) • need for dental hygienist • need for surgical follow-up • need for endodontic follow-up	6 months
stage 3	• 6-10 decays • need for dental post and core	1 month
stage 4	• more than 10 decays • every decay that endangers the pulp • need for endodontic treatment • need for tooth extraction • need for surgical extraction	no clearance until completion of treatment

by the pain signs that appear in the oral cavity due to changes in pressure [1]. It has been reported that 9.2% to 67.1% of divers suffer from this condition [11,16–19]. Below we elaborate on the different types of barodontalgia.

Damage to existing restorations

In a study by Zanotta [20] that included 520 divers and underwater infrastructure workers it was found that 42.7% (n=222) had restorations or crowns in the oral cavity. A total of 6.3% (n=33) of all respondents experienced dental injury: In 30 of them the injury was to teeth with restorations or crowns, 26 reported a fracture in amalgam restoration, and four reported a crown fracture.

A laboratory study of 86 extracted teeth, conducted by Calder and Ramsey [21], found that a rapid transition from atmospheric pressure conditions in a normal dive (1,035 kPa) to atmospheric pressure at sea level (e.g., an emergency ascent in a dive) caused damage to teeth with defective restorations. Five of the teeth studied were damaged in the experiment, with some containing defective amalgam restorations and some secondary caries below the amalgam restorations. Of the 81 teeth that were not damaged, there were teeth that contained caries lesions. The researchers concluded that dental fractures occurring during diving resulted from marginal leakage in existing restorations and not the development of caries.

These data and many others indicate that most of the damage caused by pressure changes depends on the existence of defects in the restorations or in teeth with secondary tooth decay below existing restorations, and therefore the pressure changes per se are not the cause of the problem [22]. Hence, dentists treating patients whose profession includes frequent pressure changes should be aware that arrested or residual caries may have a profound effect on this population. Such condition should be classified Stage 4 in the dental rating used in the Israeli navy (Table 1) and thus ineligible for service.

Permanent partial denture damage

A 10-year follow-up study conducted by the German Navy [23] found that divers performing an average of 200 to 300 hours of underwater diving reported a threefold increase in tooth loss and a ninefold increase in the number of fractures in dental crowns, compared to submarine personnel,

who usually serve under conditions with normal pressure. Submarine personnel reported only a twofold increase in tooth loss and a fourfold increase in the number of fractures in dental crowns.

Pressure changes can also have an effect on crowns, especially those glued with zinc phosphate cement (ZPC). This effect is observed in the weakening of the glue to the point of reporting cases of crown aspiration during diving [24].

In a laboratory study Lyons et al. [25,26] investigated the effect of pressure changes on the retention of prosthetic crowns in displaced teeth and found that crowns glued with ZPC had a 90% reduction in adhesion; crowns glued with glass ionomer had a decrease in grip of about 50%; and in crowns glued using resin glue, no decrease in grip was observed at all. This is probably due to the pores formed when mixing the zinc phosphate and the glass ionomer. During pressure changes the size of the pores changes by enlarging via the expansion of air bubbles, leading to a weakening of the adhesive. In order to avoid the failure of permanent gluing of permanent partial dentures, resinous adhesive should be used in patients exposed to multiple pressure changes [26]. Additionally, dentists should advise patients not to dive when they have temporary restorations or temporary adhesions.

Damage to the dental pulp

In the case of multisession endodontic treatment, the doctor must instruct the patient that before diving, he must verify the completeness of the temporary restoration to prevent its disengagement. In the intermediate stages of root canal treatment, when the canals are incomplete, subcutaneous emphysema may occur during diving, as well as leakage of contaminated contents into periradicular tissues [27].

In order to avoid diving-related injury associated with partial or damaged dental care, dentists should periodically monitor teeth that have been treated endodontically using X-ray to assess the state of existing restorations and probe for the appearance of secondary caries. When performing a restoration the dentist must make sure that no incision has been made in the dental pulp and, if necessary, apply a subbase such as resin-modified glass ionomer cement (RMGIC) as a prevention [2].

Postoperative damage

After performing surgery on the upper jaw the dentist must verify that there is no oroenteral communication, using a Valsalva test. In any case, diver activity should be suspended for 24 hours after a conservative treatment that requires anesthesia. In cases of surgery, dive activity should be suspended for seven days, and the patient should be invited for an examination of the healing process to confirm fitness for return to underwater activities [11]. In case a connection between the oral cavity and the air spaces of the nose and sinuses is suspected, diving should be prohibited for at least two weeks, with a follow-up assessment before return to activity [1]

Non-barotraumatic dental complications presenting in diving

Apart from the effect of the pressure changes on the diver's body there are other common phenomena that characterize the diving population, both resulting from special equipment use and the conditions divers face. It is essential that dentists are familiar with such unique cases and are able to recognize, diagnose and treat complications resulting from such diving activities. We review some of the more common symptoms below.

Facial and jaw pain

A group of symptoms have been termed divers' mouth syndrome (DMS) due to their appearance after diving. These symptoms include pathologies that occur due to prolonged holding of the regulator during diving, which can cause pain in the facial muscles as a result of jaw-tightening over time [28] and loss of support of the molars in the occlusion. This can lead to heavy load on the temporomandibular joint (TMJ) due to the regulator position and anterior movement of the mandible to stabilize the breathing apparatus [29].

An average recreational dive lasts about 30 to 45 minutes, while a professional dive can take several hours. These long periods of time, during which the diver must hold the breathing apparatus using the teeth (usually through the canines and premolars), can cause muscle aches. Mack [30] and Hobson [31] found that the strenuous activation of the muscles surrounding the mouth (masseter, orbicularis oris and temporalis muscles) can also cause overload and damage to the TMJ. Hirose et al. [29] conducted a questionnaire that included 100 Japanese divers that revealed that most DMS symptoms were experienced in unskilled divers, who used mostly chewing muscles to hold the mouth apparatus. Experienced divers, who knew how to distribute the load over additional muscles, using the lips and the orbicularis oris muscle experienced fewer DMS symptoms.

Ingervall and Warfvinge [32] note that DMS symptoms are exacerbated in a cold-water environment due to the need for stronger tightening of the sphincter muscles, because the lip muscle is dysfunctional.

Since the regulator is gripped mainly through the canines and premolars, loss of occlusive molar support can occur, causing overload on the TMJ joint. A case study presented by Storer and Bowman [33] featured a diver complaining of severe pain in the TMJ joint after diving, who experienced significant improvement when he began using a breathing apparatus with support for posterior teeth while snorkeling.

The onset of pain and disorders in the TMJ joint is the most common pathology in divers, with a recurrence rate of 24% to 68% [1,34] – hence the great importance of correct diagnosis and tailored treatment. The signs of TMJ joint disorders vary from patient to patient, but often include joint and ear pain, clicking and crepitus from the joint when opening and closing, trismus and impaired mandibular jaw mobility, headaches and facial pain, chewing muscle pain, a feeling of fullness in the ears, and dizziness [35].

In order to identify the source of the pain, be it the chewing joint or the muscles, a load test can be performed. If signs of overload are found in the TMJ joint or muscles, the use of a customized regulator should be recommended. Hobson and Newton [31] performed lateral cephalometric X-rays to illustrate the anterior movement of the mandible while clenching teeth around the regulator comparing three types of regulators – commercial, semicustomized [30] and customized [36]. It was found that when using a commercial regulator, the mandibular jaw moves forward and is not at rest, as opposed to using semicustomized and customized regulators, in which the mandible is at rest [31,37].

Headaches

Headaches that appear during or after a dive are a very common phenomenon that can have many causes and as explained above can occur as a result of the pressure differences experienced in diving (e.g., barosinusitis and exacerbation of migraine). Tension type headache (TTH), is another type of diving-related headache. TTHs are caused by muscle stiffness both due to the pressure during the dive and the tightening of the jaws during the dive [38]. Headaches can also occur from increased concentrations of carbon dioxide (CO_2) in the breathing air resulting from hypoventilation (lack of ventilation caused by breathing too slowly) or due to the use of improper diving equipment mainly in closed systems where CO_2 is poorly absorbed. An increase in CO_2 in the circulated air increases the amount of CO_2 in the inhaled air. This kind of headache is usually of a throbbing nature.

Decompression sickness in the jaw joints

Decompression sickness (DCS, also known as divers' disease) is caused by changes in the solubility of inert gases (mainly nitrogen and helium) in the body tissues with changes in ambient pressure. While descending there is an increasing pressure on the body tissues, which increases the amount of gas that can be dissolved in them (due to Boyle's law, as mentioned earlier). The deeper and longer the stay, the greater the amount of nitrogen that accumulates in the tissues. When ascending, the

pressure decreases and the amount of nitrogen that the tissues can contain decreases, but if the rise is too fast, the tissues reach a state of nitrogen saturation. If the amount of nitrogen accumulated in the tissue is too great, some of the nitrogen may be released in the form of bubbles.

These bubbles can accumulate in blood vessels or joints and thus impair the supply of oxygen to the tissues. As the depth and time of the dive increase, the amount of nitrogen dissolved in the body increases and the chance of injury increases. Symptoms suggestive of decompression sickness include joint pain (including TMJ), headache, rash, nausea, vomiting, dizziness, tinnitus, and extreme fatigue [39,40]. In such cases immediate treatment is needed, including the administration of 100% oxygen, a referral for diagnosis, and hyperbaric oxygen (HBO_2) treatment in a hyperbaric chamber. The initial pressurization is to 2.8 atmospheres absolute (ATA), equivalent to the pressure found at 18 meters of seawater. Patients breathe pure oxygen, with scheduled air breathing breaks to reduce the risk of central nervous system oxygen toxicity. The usual duration of the treatment is just under five hours, but extensions can be added at both step pressures if warranted by the patient's response [41–43]. Most cases of DCS respond satisfactorily to a single hyperbaric treatment, although repetitive treatments (typically once daily) may be required depending on the patient's initial response. For patients with residual deficits following the initial recompression, repetitive treatments are recommended until clinical stability has been achieved. HBO_2 should be administered repetitively as long as stepwise improvement occurs, based upon clearly documented symptoms and physical findings [42,43].

Regulator-transmitted infection

Several studies have shown that using a regulator is a possible way to transmit infections such as Herpes simplex virus [44], *Hortaea werneckii* yeast [45] and several bacteria types: *Klebsiella pneumoniae, Citrobacter freundii, Citrobacter koseri, Enterobacter cloacae* and *Acinetobacter baumannii* [46]. Hence, it is very important to recommend personal use of the regulator, to ensure regular maintenance and cleaning of the equipment at the end of each use, as well as to avoid diving during the contagious phase out of concern for the dive partner.

Preventive dentistry and its importance in the outline of marine activity

In addition to divers, another population treated by naval dentists includes sailing crews. This population stays for long periods – days and even months – in an isolated environment and as an independent unit. As a result, and unlike the general population, these crews have no readily available first-aid services in times of cruises and disconnection [47].

Chisick and King [48] reviewed dental epidemiology of special military units, summarizing seven studies in the field of dental first-aid treatments. They found that the main cause for requiring first-aid dental treatments is tooth decay (at a rate ranging from 40.9% to 60%). Tooth decay accounts for between 65.8 and 259 out of 1,000 first-aid dental treatments, with the most frequent treatment being prescription of medication followed by extractions.

In order to reduce first aid incidents among sailing crews, preventative dentistry is essential. The preventive treatment provided in the Israeli naval dental clinics includes a dental rating of the patient's condition (Table 1) with the option of grounding a crew member with a dental rating of 4 from sailing. Also, the naval soldiers are required to undergo a routine examination at least every 12 months [34]. This protocol is based on The Department of Defense oral health and readiness classification system, although differs from it in several aspects [49].

Navy doctors who go on voyages undergo advanced training aimed at differentiating between situations requiring medical and dental attention and acquire skills for treating dental first-aid situations. This advanced training includes, among other things, the preparation of a temporary restoration and performing different types of

dental anesthesia. Preventive medicine measures and special training for medical staff procedures are implemented to prevent medical evacuation of military staff due to dental condition.

SUMMARY

Dentists treating a population exposed to underwater environments must be alert to how this environment affects pathologies in the oral cavity and ensure that their patients are well-informed to avoid preventable damage to the oral cavity and pharynx. Periodic examinations and preventive measures should focus on monitoring for damaged restorations and secondary caries.

In the case of barodontalgia or dental barotrauma, dentists must identify the problem by clarifying the medical history, carrying out a comprehensive clinical examination and, if necessary, consult a diving doctor to aid in diagnosis and treatment. Special attention should be devoted to treatments performed near the onset of the barotrauma signs as well as to the appearance of pre-incident signs (e.g., secondary caries), and to type of pain and time when the pain appeared.

CONCLUSION

Dentist should be aware of and recognize other medical conditions experienced by divers, including decompression sickness, the appearance of pain in the masticatory or temporomandibular joint muscles, the appearance of headaches, and the possibility of herpes simplex infection. Naval dentists must pay necessary attention to sailing crews, while insisting on periodic checkups, preventive treatments and even suspension, if necessary.

Declaration

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgment

We thanks Prof. Yehuda Zadik, Department of Oral Medicine, Hebrew University-Hadassah School of Dental Medicine for his advice and guiding in design of this article.

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UNDERSEA & HYPERBARIC MEDICINE

The effect of hyperbaric oxygen therapy on bladder symptoms of female patients with overactive bladder

Mustafa Bilal Hamarat [1]; Abdullah Arslan [2]

[1] Department of Urology, Konya City Hospital Health Application and Research Centre, Health Sciences University, Konya, Turkey

[2] Department of Underwater and Hyperbaric Medicine, Meram Medicine Faculty, Necmeddin Erbakan University, Konya, Turkey

CORRESPONDENCE: Dr. Mustafa B. Hamarat – *bilalhamarat@gmail.com*

ABSTRACT

Hamarat MB, Arslan A. The effect of hyperbaric oxygen therapy on bladder symptoms of female patients with overactive bladder. Undersea Hyperb Med. 2022 Third Quarter; 49(3):383-390.

Overactive bladder (OAB) is a disease with symptoms such as feelings of urgency, nocturia, and frequent urination which is usually accompanied by urinary incontinence. We aimed to assess the effect of hyperbaric oxygen (HBO_2) therapy on the symptoms of female patients with overactive bladder (OAB). This study is a prospective observational cohort study. The patients were analyzed into two groups. The patients who received HBO_2 therapy were in Group 1, and the patients who received mirabegron treatment were in Group 2. The symptom scores and quality of life scores of the patients before and after treatment were recorded and compared. Significant improvement in symptom scores were seen in both groups after treatment compared to baseline. The study included 31 patients in Group 1 and 44 patients in Group 2. The mean changes in the ICIQ-SF, OAB-V8, and IIQ-7 scores in the third month of treatment in Group 1 were 4.12 ± 3.51, −10.70 ± 6.92, and −4.51 ± 2.68, respectively. The corresponding mean score changes in Group 2 were −4.31 ± 3.16, −11.22 ± 5.93, and −3.68 ± 2.67, respectively. The mean changes in all three scores were not significantly different between Groups 1 and 2 ($p = 0.81$, 0.73, and 0.19, respectively). We observed that HBO_2 treatment improved quality of life by reducing the symptom score in patients with OAB. Moreover, this effect continued in the third month after the treatment. Considering the efficacy and side effect profiles of the available treatments, HBO_2 therapy may be a new treatment alternative in OAB.

KEYWORDS: hyperbaric oxygen; incontinence; overactive bladder; mirabegron; urgency

INTRODUCTION

Overactive bladder (OAB) is a disease involving symptoms that negatively affect quality of life. These symptoms include feelings of urgency, nocturia, and frequent urination and are often accompanied by urinary incontinence [1]. Prevalence studies in Russia, the Czech Republic, and Turkey have identified the prevalence of OAB disease in women as being nearly 28 percent [2]. Overactive bladder is due to involuntary detrusor contractions, but the etiologic factors causing this situation are still not fully understood. In a normal bladder the detrusor, urothelium, and neurological structures work in coordination, and pathologies developing in any of these structures may cause overactive bladder syndrome. Spontaneous activation of myocytes in the detrusor, as well as neurological pathologies (e.g., spinal cord injury and multiple sclerosis), can cause detrusor overactivity (DOA). Additionally, there have been studies in recent years showing that the disruption of urothelium structure can cause this situation [3,4]. It is proposed that increased purinoreceptor activation linked to ischemia and oxidative stress with a reduction in the perfusion of the urothelium linked to atherosclerosis or a variety of causes may lead to DOA [5-7].

Some experimental studies have shown that DOA is correlated with an increase in inducible nitric oxide synthase activity developing with inflammation, with endothelial nitric oxide synthase activity shown to be reduced in these animals [8]. While a variety of muscarinic, cholinergic, and adrenergic receptors play roles in detrusor relaxation, another relaxing mechanism is due to vanilloid, muscarinic and purinergic receptors with duty in afferent signals in the urothelium.

OAB treatment frequently uses a range of medications based on the mechanisms mentioned above. Among these, the most frequently used medication is antimuscarinic medication, which acts by binding to muscarinic receptors. Today, in the treatment of OAB, apart from anticholinergic therapy, beta-3 receptor agonist mirabegron is also widely used. In addition to oral therapy, interventional treatment methods such as percutaneous tibial nerve stimulation are also available. Oral treatments are used as long as symptoms persist. Some patients take medication for life. Due to side effects such as dry mouth, constipation, blurred vision, and disrupted cognitive functions that are frequently observed with antimuscarinic medications, it is reported that 60 to 80 percent of patients did not continue treatment for a 12-month duration [9]. This low rate of continuation of treatment has made OAB treatment very difficult for clinicians and has motivated the search for new treatment regimes.

Hyperbaric oxygen (HBO_2) therapy is a treatment method based on respiring oxygen continuously or at intervals and at pressures higher than one atmosphere. Linked to the increase in pressure, the partial oxygen pressure in the blood may increase from 100 mmHg to 1,700 mmHg. Increase in the partial pressure of oxygen increases the oxygen diffusion distance, ensuring the transport of oxygen to hypoxic regions. Additionally, increased oxygenation induces angiogenesis and inhibits submucosal edema, inflammation, and fibrosis [10]. With increased oxygenation in the urothelium, purinoreceptor activation associated with ischemia may decrease, and this may prevent detrusor overactivity. Despite studies showing that HBO_2 has therapeutic effects on the bladder epithelium in interstitial cystitis and radiation-linked cystitis, we were unable to identify any studies in humans showing the effects of HBO_2 on OAB [11,12]. In this study, we aimed to assess the effects of HBO_2 on symptoms in OAB patients..

MATERIAL AND METHODS

Patients

This study is a prospective observational cohort study. The study included female patients with overactive bladder who were scheduled to receive at least 20 sessions of hyperbaric oxygen therapy for various indications or who were starting only mirabegron therapy between August 1, 2019, and May 1, 2020. Patients aged 18 years or older who filled out the form completely were included in the study. Patients who could not complete the questionnaire and patients under the age of 18 were not included in the study. The patients were then divided into two groups: Patients who received HBO_2 therapy were in Group 1; the patients who received mirabegron treatment were in Group 2.

The patients in Group 1 were recruited from female patients who were scheduled to be treated with HBO_2 due to various indications (sudden hearing loss, chronic wounds, osteomyelitis). ICIQ-SF, OAB-V8, and IIQ-7 forms (see 'Survey method') were completed by all female patients who started HBO_2 therapy. Patients with an ICIQ-SF or OAB-V8 score of 8 and above were evaluated by a urologist who reviewed voiding diary, ultrasonography (USG), and urinalysis. Patients who met the diagnostic criteria for overactive bladder were included in the study. Patients with no urinary pathology detected in urinary USG and urinalysis but who had complaints of urination more than eight times in 24 hours and urgency with or without incontinence were also diagnosed as OAB. The patients were re-evaluated after the 10th and 20th sessions of HBO_2 treatment and three months after the first session.

Group 2 participants were recruited from female patients who applied to the urology outpatient clinic with bladder storage symptoms, were diag-

nosed with OAB using the same diagnostic methods, and started on mirabegron treatment. ICIQ-SF, OAB-V8, and IIQ-7 forms were completed by patients who were already diagnosed and prescribed mirabegron. The patients were called back to the department for follow-up at the first and third months after treatment.

Patients' age, indications for HBO_2 therapy, comorbid diseases, and medications were recorded. Patients who did not complete 20 sessions of HBO_2 and who received another urological treatment and urological intervention in the previous six months were excluded from the analysis. Patients in Group 2 who discontinued treatment and did not attend the follow-up examination were excluded from the analysis. Ethics committee approval was received for this study from the Konya Training and Research Hospital Scientific Research Evaluation Board (01/08/2019; no: 48929119/774).

Survey method

Before HBO_2 and mirabegron treatment, participants completed the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), the Overactive Bladder-Validated 8 questionnaire (OAB-V8), and the Incontinence Impact Questionnaire-7 (IIQ-7), with Turkish validation, previously performed [13-15]. The ICIQ-SF and OAB-V8 questionnaires assess symptom severity. The IIQ-7 questionnaire assesses the impact of OAB on quality of life. The ICIQ-SF form comprises six questions, with the total number of points varying from 0 to 21: The total points are calculated by adding the points for questions 3, 4, and 5. The OAB-V8 form comprises eight questions, and the total score varies from 0 to 40. The IIQ-7 form comprises seven questions, and the total score varies from 0 to 21. Forms are completed by patients based on their complaints within the prior one-month period. Patients with ICIQ-SF or OAB-V8 scores of 8 and above completed the same form after the 10th and 20th sessions and in the third month after the first session of HBO_2 therapy in Group 1. In Group 2, the same forms were filled out in the first and third months of mirabegron treatment.

HBO_2 therapy protocol

Patients had three oxygen periods of 25 minutes with a treatment depth of 2.4 atmospheres absolute (ATA) pressure. Five-minute breaks were given between oxygen periods. With 20-minute compression and 15-minute decompression durations, the HBO_2 sessions lasted a total of 120 minutes and were administered to patients five days per week. Patients were accompanied by an inside attendant throughout the hyperbaric oxygen sessions.

Statistics

SPSS 22.0 (IBM Corp., Armonk, New York) was used for statistical analyses. Statistical significance was at $p \leq 0.05$. The paired t-test was used to evaluate ICIQ-SF, OAB-V8, and IIQ-7 scores before and after treatment. Group 1 and Group 2 data were analyzed using an independent sample t-test. Correlations of ICIQ-SF, OAB-V8, and IIQ-7 with each other were calculated using the Pearson correlation coefficient.

RESULTS

A total of 296 female patients completed the forms. Questionnaire forms were filled out by 212 female patients scheduled for HBO_2 therapy and the 84 patients scheduled to receive mirabegron therapy. Of the 212 female patients scheduled to receive HBO_2 therapy, 38 had ICIQ-SF or OAB-V8 scores of 8 or above. Among these patients, two had urinary tract infections, one had multiple sclerosis, three were receiving anticholinergic treatment, and one had undergone a urological operation, and thus were all excluded from the study. As a result, Group 1 comprised 31 patients; all patients completed at least 20 sessions without any problems. A total of 25 patients received 20 to 25 sessions of HBO_2 therapy, and six patients received 25 to 30 sessions of HBO_2 therapy. After completing the HBO_2 sessions, the patients did not receive HBO_2 treatment again in the three-month period. No complications (barotrauma, seizures, or hypoglycemia) related to HBO_2 therapy were observed.

Of the 84 patients who were started on mirabegron treatment, 17 did not continue the treatment

Table 1: Demographic characteristics of the patients

	Group 1	Group 2	p *
number of patients (n)	31	44	
age, years (mean ± SD)(min-max)	53.70 ± 11.93 (29-77)	51.90 ± 10.54 (32-72)	0.49
BMI (mean ± SD) (kg/m²)	24.50 ± 3.18	24.86 ± 4.59	0.70
pre-treatment symptom scores			
ICIQ-SF	11.10 ± 4.53	11.72 ± 4.27	0.54
OAB-V8	19.48 ± 8.99	21.72 ± 7.44	0.24
IIQ-7	11.06 ± 2.73	10.81 ± 2.84	0.71
primary diseases			
acute sensorineural hearing loss (n,%)	24 (77%)		
avascular necrosis (n,%)	2 (6%)		
radionecrosis (n,%)	4 (13%)		
a wound that does not heal (n,%)	1 (3%)		
comorbidities			
hypertension (n,%)	5 (16%)	6 (14)%	
diabetes mellitus (n,%)	4 (13%)	6 (14%)	
chronic obs. pulmonary disease (n,%)	2 (6%)	1 (2%)	
depression (n,%)	4 (13%)	5 (9%)	
carcinoma (n,%)	5 (16%)	–	
thyroid diseases (n,%)	3 (10%)	2 (5%)	

*independent samples test

because they did not observe enough benefit in the first month. These patients were not included in the first-month evaluation because they stopped taking their medication before the third week of treatment. In Group 2, 18 patients did not show up for the control examination, three patients stopped taking the drug due to various side effects, and recurrent urinary tract infections developed in two patients during their follow-ups. In the final stage, 44 patients in Group 2 were analyzed.

The mean age of the patients in Groups 1 and 2 was 53.70 ± 11.93 and 51.90 ± 10.54 years, respectively (p = 0.49). The primary disease diagnoses as the indication for hyperbaric oxygen treatment, comorbidities, and body mass index are shown in Table 1. When the mean pre-treatment scores of ICIQ-SF, OAB-V8, and IIQ-7 were compared, there was no significant difference between the groups (Table 1). While 20 patients in Group 1 had incontinence, the number of patients with incontinence in Group 2 was 31. Before the HBO_2 procedure was conducted in Group 1, the mean ICIQ-SF, OAB-V8, and IIQ-7 scores were 11.10 ± 4.53, 19.48 ± 8.99, and 11.06 ± 2.73, respectively. The ICIQ-SF, OAB-V8, and IIQ-7 scores after the 10th and 20th sessions and in the third month after HBO_2 therapy are provided in Table 2. The post-treatment scores of the patients were significantly lower than the initial scores. Although the patients' third-month scores compared to the 20th session scores decreased, only the decrease in OAB-V8 scores was statistically significant (p = 0.008).

Before the mirabegron treatment was initiated in Group 2, the mean ICIQ-SF, OAB-V8, and IIQ-7 scores were 11.72 ± 4.27, 21.72 ± 7.44, and 10.81 ± 2.84, respectively. The corresponding scores in the first and third months of treatment in Group 2 are shown in Table 3. The symptom scores of the patients in the first and third months were significantly lower than the initial scores.

Table 2 : Comparison of pre-HBO_2 and post-HBO_2, ICIQ-SF, OAB-V8 and IIQ-7 scores in Group 1

questionnaire	pre-HBO_2 score mean ± SD	after 10th session score mean ± SD, p value*	after 20th session score mean ± SD, p value*	3rd month after HBO_2 mean ± SD, p value*
ICIQ-SF	11.10 ± 4.53	8.74 ± 3.53 (p < 0.001)	7.03 ± 2.71 (p < 0.001)	6.97 ± 2.60 (p < 0.001)
OAB-V8	19.48 ± 8.99	15 ± 7.59 (p < 0.001)	10.68 ± 5.58 (p < 0.001)	8.77 ± 3.52 (p < 0.001)
IIQ-7	11.06 ± 2.73	8.68 ± 2.70 (p < 0.001)	7.13 ± 2.75 (p < 0.001)	6.55 ± 2.47 (p = 0.007)

*paired t-test (compared with pre-HBO_2 score)

Table 3 : Comparison of pre-mirabegron treatment and post-mirabegron treatment ICIQ-SF, OAB-V8 and IIQ-7 scores in Group 2

questionnaire	pre- mirabegron score mean ± SD	1st month score mean ± SD, p value*	3rd month score mean ± SD, p value*
ICIQ-SF	11.72 ± 4.27	9.20 ± 3.06 (p < 0.001)	7.40 ± 2.56 (p < 0.001)
OAB-V8	21.72 ± 7.44	15.68 ± 5.27 (p < 0.001)	10.50 ± 4.03 (p < 0.001)
IIQ-7	10.81 ± 2.84	8.97 ± 2.28 (p < 0.001)	7.13 ± 2.21 (p < 0.001)

*paired t-test (compared with pre-Betmiga score).

Table 4 : Comparison of score changes between pre-treatment and 3rd month of treatment in Group 1 and Group 2

questionnaire	Group 1 score changes mean ± SD	Group 2 score changes mean ± SD	p*
ICIQ-SF	-4.12 ± 3.51	-4.31 ± 3.16	p = 0.81
OAB-V8	-10.70 ± 6.92	-11.22 ± 5.93	p = 0.73
IIQ-7	-4.51 ± 2.68	-3.68 ± 2.67	p = 0.19

*independent samples test

Mean changes in the ICIQ-SF, OAB-V8, and IIQ-7 scores between pretreatment and the third month of treatment in Group 1 were 4.12 ± 3.51, −10.70 ± 6.92, and −4.51 ± 2.68, respectively. The corresponding mean score changes in Group 2 were −4.31 ± 3.16, −11.22 ± 5.93, and −3.68 ± 2.67, respectively. The mean changes in all three scores were not significantly different between Groups 1 and 2 (p = 0.81, 0.73, and 0.19, respectively) (Table 4).

DISCUSSION

One of the etiopathologies leading to OAB is the increase in purinoreceptor activation and detrusor hyperactivity, which is observed with the deterioration of the structure of the urothelium due to ischemia. Increased tissue oxygenation with HBO_2 therapy can prevent detrusor overactivity by preventing hypoxia-induced purinoreceptor activation in the urothelium. In this study we detected a decrease in symptom scores in OAB patients after HBO_2 treatment, which continued at the third month. In addition, we observed that

HBO_2 treatment had fewer side effects than mirabegron and there were no patients who discontinued treatment due to side effects. An American study observed that nearly 65% of female patients with OAB also presented with incontinence complaints [19]. In our study, 51 (68%) of the 75 OAB patients with a high OAB-V8 score had comorbid incontinence complaints. Zümrütbaş et al. found that the mean OAB-V8 and ICIQ-SF scores of female patients with OAB before administration of anticholinergic treatment were 26.13 ± 7.52 and 13.46 ± 3.53, respectively. After one month of anticholinergic treatment, there was a mean 10.0 ± 8.25 fall in OAB-V8 score identified, with a 6.68 ± 4.61 fall in ICIQ-SF score [20]. Çulha et al. reported that the OAB-V8 and ICIQ-SF scores before treatment were 27.93 ± 5.36 and 15.23 ± 6.39, respectively, while the corresponding values changed to 12.69 ± 8.10 and 7.69 ± 5.78 after eight weeks of mirabegron treatment in 56 OAB patients [21]. In their study of 43 patients with overactive bladder symptoms refractive to medical treatment, Marchal et al. reported that the mean ICIQ-SF score was 17.9 ± 0.36 before percutaneous tibial nerve stimulation; this value changed to 6.2 ± 0.76 in the sixth month after treatment [22]. In our study, OAB-V8 score changes in both groups were similar to Zümrütbaş's study. In addition, decreases in ICIQ-SF scores in both groups were relatively lower compared to other studies. In the mirabegron study of Çulha et al., the decreases observed in both OAB-V8 and ICIQ-SF scores were relatively higher than in our mirabegron group.

Tanaka et al. observed that the positive effects of HBO_2 therapy on symptoms persisted for at least 12 months in patients with painful bladder syndrome or interstitial cystitis [18]. In our study, considering the mean scores of the patients at the third month in Group 1, it was observed that the decrease in the mean symptom scores continued after the 20th session. The change in OAB-V8 scores was statistically significant. This showed us that the effect of HBO_2 therapy continued in the third month after treatment. Instead of taking daily oral treatments, this long-term effect of HBO_2 therapy may provide a serious advantage in the treatment.

Zümrütbaş et al. observed that 95% of female patients had side effects linked to treatment with antimuscarinic after one month, while 21% of patients changed treatment due to either side effects or low treatment efficacy in the first month [20]. In addition, another study evaluating the long-term effects of antimuscarinic treatment over a 12-month period reported that 60% to 80% of the patients did not continue treatment due to side effects [9]. Moreover, Stewart et al. showed that the rate of continuation of antimuscarinic treatment decreased to 50% in the third month after it was first prescribed [23]. This low continuation rate for antimuscarinic medications has forced clinicians to search for new treatments for OAB. In this study, while mirabegron treatment was started in 84 patients in Group 2, 18 of them did not contact for follow-up examination from the first month. Considering that approximately one-third of the 66 patients in Group 2 who were evaluated in the first month discontinued the treatment, we can say that compliance with mirabegron is low. In our study, none of the 31 patients receiving HBO_2 therapy in Group 1 developed complications (barotrauma, seizures, or hypoglycemia), and all patients completed 20 sessions of treatment. The patients received HBO_2 therapy in a multiplace hyperbaric chamber staffed by an inside attendant to reduce complication risks.

In Group 2 a total of 20 patients (30.3%) discontinued the treatment. A total of 17 noted they did not benefit from the treatment, and three of them were because of side effects of the drug. In addition to the high rate of discontinuation of treatment in Group 2, the need for daily intake of the drug is an important disadvantage. In addition, there were no complications related to HBO_2 therapy in Group 1, and the improvement in the symptom score observed after the 20th session continued in the third month of the treatment, indicating that the HBO_2 therapy had a permanent improvement

effect without any serious side effects. The low side effects profile of HBO_2 therapy may provide an advantage in terms of treatment in the future. In our study, the effectiveness of HBO_2 therapy was investigated but the study was not designed to explore dose-response associations. Therefore, patients who received different numbers of sessions were included in the study, and we included only those who received at least 20 sessions of HBO_2 therapy. The improvement in the symptom scores at the third month follow-up shows that the number of at least 20 sessions is sufficient. On the other hand, more studies are needed to determine the optimal number of sessions for patients to benefit from HBO_2 therapy.

Limitations

The greatest limitation of our study is the use of questionnaires based on subjective assessment. One of the weaknesses of the study is that the patients who discontinued mirabegron treatment could not be evaluated for the first month. Despite these limitations, our study is the first to show the effectiveness of HBO_2 therapy in OAB patients.

CONCLUSION

We observed that hyperbaric oxygen treatment improved quality of life by reducing the symptom score in patients with OAB. Moreover, this effect continued in the third month after treatment. HBO_2 therapy reduced the symptom scores to an extent similar to that achieved by mirabegron treatment. Considering the efficacy and side effect profiles of the available treatments, HBO_2 therapy may be a new treatment alternative for these patients in the future. Randomized clinical studies are needed to verify the real efficacy of hyperbaric oxygen therapy in the overactive bladder.

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Policy

UHMS Position Statement:
HBO_2 departments offering services for emergent and urgent HBO_2 indications

Date created: May 2022
Date of next review: 2027
Authorship: Dr. Dag Shapshak
Dr. Mathew Kelly

HBO_2 departments offering services for emergent and urgent HBO_2 indications

INTRODUCTION

As of 2022 there are more than 1,000 hospitals in the United States that offer hyperbaric oxygen therapy [1]. Of these, fewer than 90 facilities offer 24/7 availability for emergent and urgent programs, with only 60 having the capacity to treat patients requiring critical care [2].

Due to the lack of facilities available to treat emergencies it is prudent to investigate if non-emergent facilities are willing and able to accommodate treatment for non-scheduled stable emergent patients. Many patients with emergent hyperbaric indications are not critically ill, not intubated or require continuous intravenous medications and can be treated safely in the nearest appropriate facility. These conditions include but are not limited to: central retinal artery occlusion, carbon monoxide poisoning, arterial gas embolism, decompression illness and ischemic and failing flaps.

Even if treated several times a day, often patients can go home in between treatments and continue any needed tailing treatments during daytime hours. Often, stable emergent hyperbaric patients are transferred to facilities that take emergency call, bypassing closer open facilities that can treat the emergent condition. There are incidents where the transferring hospital has a hyperbaric facility at the same location and transfers the patient due to lack of staff availability or willingness to treat emergent conditions.

Most insurers cover the cost of UHMS-approved indications, and taking emergent patients should not be a fiscal loss to any facility. Many of these patients can be treated safely as outpatients, decreasing cost of transfer and admissions to an outside accepting facility. Treating patients locally without having to transport long distances can save money, decrease transport-related risk, speed the time to treatment which may lead to better clinical outcomes, and decrease crowding while not costing any hyperbaric department significant amounts of money. Any unstable patient, critically ill patient, or if patient transfer happens past daytime hours, then the usual manner or transfer should be initiated without delay.

ABSTRACT

1) Many patients with emergent hyperbaric conditions are stable and can be treated in any hyperbaric chamber that routinely treats patients.

2) Stable emergent patients should be treated as soon as possible at the closest appropriate facility to maximize patient outcome.

3) Decreasing unnecessary transfers and admissions by initiating HBO_2 treatment at the closest appropriate facility for the treatment of stable emergent patients during daylight hours should be the goal of all hyperbaric practitioners.

4) Any unstable patient, critically ill patients, or patients requiring a higher level of care should be transferred to a more appropriate hyperbaric facility in the usual manner.

RATIONALE

It is in the patient's best interest to be treated promptly for most emergent conditions. This is especially true during the day, when most hyperbaric facilities are open, even if not taking call after hours. Many emergent conditions such as central retinal artery occlusion, carbon monoxide poisoning, arterial gas embolism and decompression illness are time-dependent. Time spent for transfer while bypassing open facilities increases risk of poor patient outcomes which are preventable by prompt local treatment.

Unnecessary transfers, sometimes traveling several hundred miles, or in some instances to another state, places the medics, patient, and family members at risk of an accident on the drive to the accepting location [3]. Given the significant hospital crowding at most referral centers, any method of decreasing unnecessary admissions and transfers is beneficial. The costs of transfers via EMS can be substantial. The average charge for fixed wing air-ambulance is $24,507 in 2020, rotary wing ambulance cost is $18,668 [4]. Ground ambulance transfers can cost an average of $1,277 for ALS, and $940 for BLS services [5]. Additional problems can arise with private or governmental insurers not covering an out-of-network treatment, leading to unnecessary costs to the patient[6].

CONCLUSIONS/RECOMMENDATIONS

The UHMS recommends that hyperbaric facilities, whether they take call for emergent conditions or not, be available during daytime hours to accept stable patients with emergent conditions to be treated via UHMS recommendations.

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PROF. ALF O. BRUBAKK

MD, PHD

Alf Brubakk was born in 1941 in Bergen, Norway. His doctorate degree was awarded by Justus Liebig University Giessen in Hessen, Germany, followed by his obligatory internship on a small island in West Norway.

Divers are exposed to intermittent hyperoxia and pressure reductions, which evoke the production of radical oxygen species and microparticles that are central to many mechanisms involved in several severe human diseases. Brubakk believed that diving could serve as an important model of disease and allow the study of these effects on healthy individuals.

With only two Norwegian medical faculties in Bergen and Oslo, Brubakk was asked to establish one in Trondheim, in cooperation with the Norwegian Technical High School. In collaboration with Rune Aaslid in 1970, a mathematical model of the cardiovascular system was constructed that could be used clinically along with a pulsed echo Doppler flowmeter to record blood flow velocity in the aorta and heart.

Jarle Holen's work led to ultrasound measurements being possible to obtain intracardiac pressure non-invasively, thus avoiding heart catheterization. By 1978, Brubakk had submitted to NTNU Trondheim his doctoral thesis "Methods for studying flow dynamics in the left ventricle and the aorta in man; use of a simulation model and ultrasound."

At the beginning of offshore oil exploration in the North Sea Bård Holand, an experienced commercial diving friend, suggested ultrasound's usefulness in studying decompression in diving which led to several experimental 500msw dive ultrasound studies at the Norwegian Underwater Institute in Bergen.

Brubakk and colleagues were the first to show that physical exercise could significantly reduce bubble formation and hence reduce the risk of injury. Over his career Brubakk published 153 scientific papers, co-edited Bennett and Elliott's 5th edition of *The Physiology and Medicine of Diving*, and in the last 20 years alone supervised 15 Masters and 10 PhD students.

His two major influences were Professor Jens Glad Balchen, who believed in the importance of having a basic idea to follow through to the end, regardless of opposition, and John Scott Haldane, the first environmental physiologist who showed the value of using basic physiology to understand man's response to his environment.

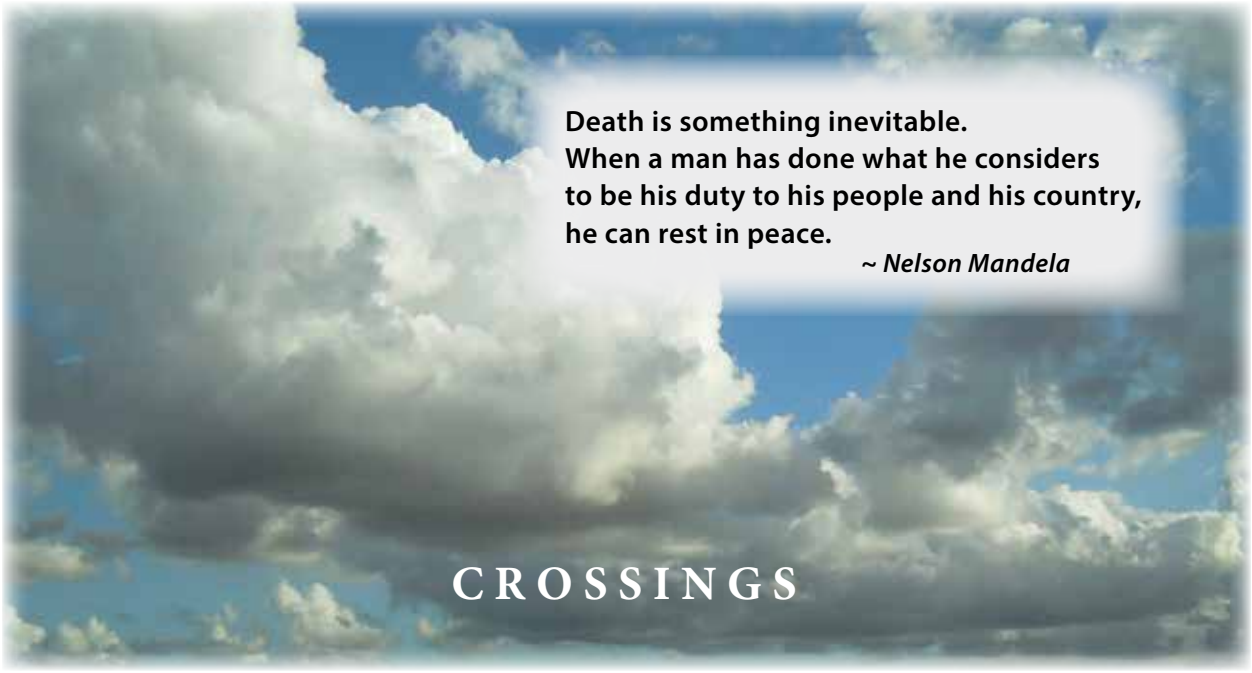
Alf O. Brubakk
January 24, 1941 - April 05, 2022

"Alf has helped make the world wiser in terms of diving medicine."

~ Prof. Hans Örnhagen

With Bård Holand, Brubakk conducted extreme environment survival courses in Svalbard over a 20-year period. He served in various capacities on the Diving Medical Advisory Committee, European Underwater Baromedical Society, European Diving Technology Committee, and received the UHMS Behnke award twice.

Dr. Stephen Thom wrote: "I first knew Alf from his scientific presentations as a disciplined and sometimes stern Norwegian but really got to know him as a fun-loving person, if with a dry sense of humor. It has been a great privilege to spend time with Alf on our last collaboration on a *Comprehensive Physiology Review of Saturation Diving*."



Dr. Michael Gernhardt noted: "Alf was a smart researcher with whom I enjoyed a productive collaboration on biochemical countermeasures for the reduction of DCS risk on spacewalks from the International Space Station."

Prof. Hans Örnhagen relayed: "I have known Alf for a long time. He participated with his special knowledge of bubbles in our Swedish hydrogen experiments. Alf has helped make the world wiser in terms of diving medicine."

Alf's favorite pastimes were skiing, scuba diving, running/cardiac exercise and the occasional beer with his friends. Our adventures included dive sites on the Great Barrier Reef, Corsica, San Clemente Island, Stokkøya, Svalbard, and the Red Sea.

Brubakk is survived by his wife, Greta Bolstad (since 1980), who also passed peacefully on 18 May 2022; sister Ann Mari; children Kirsten, Berit, Katrin and Axel; and seven grandchildren.

On behalf of the Brubakk family, Katrin shared: " Our father was an engaged and funny man, dedicated and creative, always thinking out of the box. We will miss him."

Dr. Michael A. Lang
m4lang@ucsd.edu

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Rush Foundation Hospital
Meridian, MS
(601) 703-4200

MISSOURI

Wound Healing & Hyperbaric Center
† North Kansas City Hospital
North Kansas City, MO
(816) 691-5055

Center for Wound Care & Hyperbaric Medicine
† St. Mary's Medical Center
Blue Springs, MO
(816) 655-5780

* **Cox Hyperbaric Medicine & Wound Care Center**
† Cox Healthcare
Springfield, MO
(417) 269-9950

Wound Care & Hyperbaric Medicine Center
Freeman Hospital
Joplin, MO
(413) 347-4800

Surgical Wound Care Center Hyperbaric Medicine Services
† Barnes-Jewish Hospital
St. Louis, MO
(314) 362-2233

MONTANA

Bozeman Health Wound & Hyperbaric Clinic
Bozeman Health Deaconess Hospital
Bozeman, MT
(406) 414-5512

NEBRASKA

Hyperbaric Medicine Center
† Nebraska Medical Center
Omaha, NE
(402) 552-2490

NEW HAMPSHIRE

Wound Healing Center
Concord Hospital
Concord, NH
(603) 230-1970

* **Center for Hyperbaric Medicine**
† Dartmouth-Hitchcock Medical Center
Lebanon, NH
(603) 650-6489

NEW JERSEY

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

Carole & Joseph Katz, MD Wound Healing Center
† Overlook Hospital
Summit, NJ
(908) 522-5900

Hyperbaric Services
† Saint Peter's University Hospital
New Brunswick, NJ
(732) 745- 8600 ext 6858

Comprehensive Wound Healing & Hyperbaric Center
† Chilton Medical Center
Pompton Plains, NJ
(973) 831-5303

AtlantiCare Wound Healing Center
† AtlantiCare Regional Medical Center
Egg Harbor Township, NJ
(609) 407-2205

The Center for Wound Care & Hyperbaric Medicine
† Saint Clare's Dover Hospital
Dover, NJ
(973) 989-3725

NEW MEXICO

* **Christus St. Vincent Regional Wound & Hyperbaric Center**
† Christus St. Vincent Regional Medical Center
Santa Fe, NM
(505) 946-3180

NEW YORK

* **Hyperbaric Medicine & Wound Care Center**
Upstate University Hospital
Syracuse, NY
(315) 464-4910

* **Center for Wound Care & Hyperbaric Medicine**
St. Joseph's Hospital Health Center
Fayetteville, NY
(315) 329-7770

Institute for Wound Care & Hyperbaric Medicine
† New York Presbyterian Hudson Valley Hospital Center
Cortlandt Manor, NY
(914) 734-3030

Center for Hyperbaric Medicine and Wound Healing
† St. Joseph Hospital
Bethpage, NY
(516) 520-2788

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

Wound & Hyperbaric Institute at Good Samaritan
† Good Samaritan Regional Medical Center
Suffern, NY
(845) 368-5590

* **Wound Healing Center & Hyperbaric Medicine Program**
† NYU Langone Hospital-Long Island
Mineola, NY
(516) 663-8498

* **Hyperbaric Medicine & Wound Care**
† Northwell Health Plainview Hospital
Plainview, NY
(516) 796-1313

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

Wound Healing Center
† Garnet Health Medical Center-Catskills
Harris, NY
(845) 794-3300

Wound Healing Center
† Garnet Health Medical Center-Orange
Middletown, NY
(845) 333-7700

Wound Care Center
† Unity Hospital
Rochester, NY
(585) 368-6822

* **Department of Hyperbaric Medicine**
† Phelps Hospital/Northwell Health
Sleepy Hollow, NY
(914) 366-3000 Ext 3690

Wound Care & Hyperbaric Medicine
† United Memorial Medical Center
Batavia, NY
(585) 344-5372

Center for Wound Healing
† Putnam Hospital Center
Carmel, NY
(845) 278-5683

Center for Wound Healing
† St. Luke's Hospital
Cornwall, NY
(845) 458-4512

Wound Healing Center
† Strong Memorial Hospital
Rochester, NY
(585) 262-9100

Wound Care & Hyperbaric Therapy Center
† Northern Dutchess Hospital
Rhinebeck, NY
(845) 871-3888

Wound Healing & Hyperbaric Medicine
MidHudson Regional Hospital of Westchester Medical Center
Poughkeepsie, NY
(845) 431-8144

Rev. Thomas T. Patterson Wound Healing Center
Claxton-Hepburn Medical Center
Ogdensburg, NY
(315) 394-0426

The Center for Wound Care & Hyperbaric Medicine
Samaritan Hospital Albany Memorial Campus
Albany, NY
(518) 471-3705

Center for Wound Healing
Arnot Odgen Medical Center
Elmira, NY
(607) 737-7773

Center for Wound Healing & Hyperbaric Medicine
† Mount St. Mary's Hospital
Lewiston, NY
(716) 298-3012

Catholic Health Advanced Wound Healing Centers
† Mercy Hospital of Buffalo
Orchard Park, NY
(716) 828-2330

Catholic Health Advanced Wound Healing Centers
† Sister's Hospital – St. Joseph Campus
Cheektowaga, NY
(716) 891-2570

Comprehensive Wound Care Center
† North Shore University Hospital
New Hyde Park, NY
(516) 233-3664

Helen L. & Martin S. Kimmel Hyperbaric & Advanced Wound Healing Center
† NYU Langone Medical Center
New York, NY
(212) 598-6500

Center for Advanced Wound Care & Hyperbaric Medicine
† St. Joseph's Medical Center
Yonkers, NY
(914) 378-7900

Wound Care & Hyperbaric Medicine Center
† Oneida Health
Oneida, NY
(315) 361-2268

The Center for Wound Care & Hyperbaric Medicine
Long Island Community Hospital
Hauppauge, NY
(631) 227-6650

The Center for Wound Care & Hyperbaric Medicine
Long Island Community Hospital
Patchogue, NY
(631) 687-4190

NORTH CAROLINA

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

OHIO

Hyperbaric Medicine Program
† Ohio Health Riverside Methodist Hospital
Columbus, OH
(614) 566-3251

OREGON

Hyperbaric Medicine
Summit Health
Bend, OR
(541) 317-4378

Hyperbaric Medicine & Advanced Wound Care
† Providence Portland Medical Center
Portland, OR
(503) 215-5545

Samaritan Wound, Vein, & Hyperbaric Medicine
Samaritan Albany General Hospital
Albany, OR
(541) 812-3360

* **Hyperbaric Medicine Center**
† Legacy Emanuel Medical Center
3001 N. Gantenbein Ave.
Portland, OR
(503) 413-1300

PENNSYLVANIA

Wound Healing & Hyperbaric Medicine Center
† Reading Hospital
Wyomissing, PA
(484) 628-3939

Wound Care & Hyperbaric Services
† Lancaster General Health
Lancaster, PA
(717) 544-3216

UPMC Carlisle Wound & Hyperbaric Center
† UPMC Carlisle
Carlisle, PA
(717) 243-1900

* **UPMC Pinnacle Wound & Hyperbaric Center-East**
† UPMC Pinnacle Harrisburg
Harrisburg, PA
(717) 671-2050

* **UPMC Pinnacle Wound & Hyperbaric Center-West**
† UPMC Pinnacle West Shore
Mechanicsburg, PA
(717) 791-2440

WellSpan Center for Wound Healing & Hyperbaric Services
† WellSpan Ephrata Community Hospital
Ephrata, PA
(717) 738-6527

WellSpan Wound Healing Center
† WellSpan York Hospital
York, PA
(717) 812-2480

WellSpan Wound Healing Center
† WellSpan Good Samaritan Hospital
Lebanon, PA
(717) 675-2545

Guthrie Center for Wound Care & Hyperbaric Medicine
† Robert Packer Hospital
Sayre, PA
(570) 887-6639

RHODE ISLAND

* **Wound Recovery & Hyperbaric Medicine Center**
† Kent County Hospital
Warwick, RI
(401) 736-4646

SOUTH CAROLINA

The Department of Hyperbaric Medicine
† Roper Hospital
Charleston, SC
(843) 724-2014

Spartanburg Medical Center Wound Healing Center
† Spartanburg Regional Healthcare System
Spartanburg, SC
(864) 560-1560

TENNESSEE

* **Wound Care & Hyperbaric Medicine Center**
† Regional One Health Medical Center
Memphis, TN
(901) 545-8999

TEXAS

* **Undersea & Hyperbaric Medicine Clinic**
† Brooke Army Medical Center
San Antonio, TX
(210) 539-8000

* **Wound Healing Center**
† UT Health East Texas
Tyler, TX
(903) 526-4325

Wound Care & Hyperbaric Medicine Center
† Methodist Dallas Medical Center
Dallas, TX
(214) 947-5000

* **Institute for Exercise & Environmental Medicine**
† Texas Health Presbyterian Hospital Dallas
Dallas, TX
(214) 345-4651

Northwest Wound Care Center & Hyperbaric Oxygen Therapy
† Northwest Texas Healthcare System
Amarillo, TX
(806) 351-4152

Wound Care & Hyperbaric Program
Houston Methodist Baytown Hospital
Baytown, TX
(281) 425-2160

Wound Care & Hyperbaric Center
† Methodist Charlton Medical Center
Dallas, TX
(214) 947-0752

* **Louise Gartner Center for Hyperbaric Medicine**
† Baylor University Medical Center
Dallas, TX
(214) 820-4400

* **Comprehensive Wound Center – Las Colinas**
† Baylor Scott & White Medical Center at Irving
Irving, Texas
(972) 579-5222

Wound Care & Hyperbaric Medicine Clinic
† Baylor Scott & White Medical Center
Temple, TX
(254) 724-6622

Wound Care & Hyperbaric Services
† Shannon Medical Center South
San Angelo, Texas
(325) 947-6960

* **Memorial Hermann Center for Hyperbaric Medicine**
† Memorial Hermann Hospital
Houston, TX
(713) 704-5900

UTAH

* **Hyperbaric Medicine Department**
† LDS Hospital
Salt Lake City, UT
(801) 408-3623

* **Utah Valley Wound Care & Hyperbaric Medicine Center**
† Utah Valley Regional Medical Center
Provo, UT
(801) 357-8156

* **Department of Hyperbaric Medicine**
† Dixie Regional Medical Center
St. George, UT
(435) 688-4293

* **Hyperbaric Medicine**
† Intermountain Medical Center
Murray, UT
(801) 408-3623

Wound Care and Hyperbaric Center
† Cache Valley Specialty Hospital
North Logan, UT
(435) 713-1350

Hyperbaric & Wound Center
Davis Hospital and Medical Center
Layton, UT
(801) 807-7900

McKay-Dee Wound & Hyperbaric Center
† McKay-Dee Hospital
Ogden, UT
(801) 387-4886

Hyperbaric & Wound Center
Jordan Valley Medical Center
West Jordan, UT
(801) 601-2322

Logan Regional Wound & Hyperbaric Center
† Intermountain Logan Regional Hospital
Logan, UT
(435) 716-2834

Wound Care & Hyperbaric Medicine
† Lakeview Hospital
Bountiful, UT
(801) 397-0890

Hyperbaric Medicine & Wound Treatment Center of Utah
Salt Lake Regional Medical Center
Salt Lake City, UT
(801) 582-4268

VIRGINIA

Hyperbaric Medicine Unit
† Inova Mount Vernon Hospital
Alexandria, VA
(703) 664-7218

Department of Hyperbaric Medicine
† Retreat Doctors' Hospital
Richmond, VA
(804) 254-5313

The Wound Healing & Hyperbaric Center
† Virginia Hospital Center
Arlington, VA
(703) 558-6600

WASHINGTON

* **Center for Hyperbaric Medicine**
† Virginia Mason Medical Center
Seattle, WA
(206) 583-6543

Center for Wound Healing & Hyperbaric
† Swedish Edmonds Hospital
Edmonds, WA
(425) 673-3380

WEST VIRGINIA

Center for Wound Care & Hyperbaric Medicine
† Berkeley Medical Center
Martinsburg, WV
(304) 264-1314

WISCONSIN

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora St. Luke's Medical Center
Milwaukee, WI
(414) 649-6609

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora West Allis Medical Center
West Allis, WI
(414) 649-6577

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora Medical Center – Washington County
Hartford, WI
(414) 328-8404

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
† Aurora Medical Center-Oshkosh
Oshkosh, WI
(920) 456-7407

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora Medical Center in Summit
Summit, WI
(262) 434-1000

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora Medical Center in Grafton
Grafton, WI
(262) 329-1080

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora Medical Center – Manitowoc County
Two Rivers, WI
(920) 794-5450

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora BayCare Medical Center
Green Bay, WI
(920) 288-4358

* **Center for Comprehensive Wound Care & Hyperbaric Medicine**
Aurora Medical Center Burlington
Burlington, WI
(262) 767-4684

INTERNATIONAL

IRELAND

Oxycare Medical Hyperbaric Treatment Center
Santry, Dublin, IE
(08) 7250-6552

THAILAND

* **Center for Hyperbaric Medicine**
Somdech Phra Pinklao Hospital
Royal Thai Naval Medical Department
Bangkok, Thailand
(66) 2475-2641

UNITED KINGDOM

* The Diver Clinic
Atlantic Enterprise UK Ltd
Poole, Dorset, UK
(44) 1202-678278

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It means that a facility has met the highest standards of care and patient safety through UHMS' rigorous evaluation . . . of the facility, equipment, staff and training.

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Christiana Care Wound and Hyperbaric Center
Wilmington, Delaware
https://christianacare.org/

The Diver Clinic
Poole, Dorsett UNITED KINGDOM
www.thediverclinic.com

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Milwaukee, Wisconsin
www.aurorahealthcare.org

Divers Alert Network
Durham, North Carolina
www.diversalertnetwork.org

HyperbaRXs
Marietta, Georgia
www.hbomdga.com/

International ATMO, Inc
San Antonio, Texas
www.hyperbaricmedicine.com

Mayo Clinic Health System-Eau Claire
Eau Claire, Wisconsin
www.mayoclinichealthsystem.org

Mayo Clinic Hyperbaric & Altitude Med. Program
Rochester, Minnesota
www.mayoclinic.org

SILVER LEVEL

Aalto Hyperbaric Medical Group
Los Angeles, California
www.aaltohyperbaric.com/

Christus St. Vincent Regional Wound & Hyperbaric Center
Santa Fe, New Mexico
www.christushealth.org/st-vincent/services-treatments/wound-care

Costamed
Cozumel Quintana Roo
hiperbarica@costamed.com.mx

Healogics Inc.
Jacksonville, Florida
www.healogics.com

HyOx Medical Treatment Center
Marietta, GA
https://hyox.com/

Ibex Medical Systems Co. Ltd
Republic of KOREA
https://ibex.co.kr/kr/

Innovative Healing Systems
Tampa, Florida
http://innovativehealingsystems.com

LDS Hospital, Critical Care Medicine / Intermountain Hyperbaric Medicine
Salt Lake City, Utah
http://intermountainhealthcare.org

Life Support Technologies Inc.
Tarrytown, New York
www.lifesupport-usa.com/

Mayo Clinic Health System Albert Lea
Albert Lea Minnesota
www.mayoclinichealthsystem.org/locations/albert-lea

Norman Regional Hospital Oklahoma Wound Center
Norman, Oklahoma
https://locations.normanregional.com/norman/wound-center

The Ottawa Hospital
Ottawa, Ontario, CANADA
www.ottawahospital.on.ca

Oxycare Ltd.
Dublin Ireland
https://oxycare.ie/

Perry Baromedical
Riviera Beach, Florida
https://perrybaromedical.com/

Precision Healthcare
Pompano Beach, Florida
www.precisionhealthcare.com

Renovo Wound and Hyperbarics, PLLC
Frisco, Texas

Shared Health Services Inc.
Johnson City, Tennessee
www.sharedhealthservices.com

The Wesley Centre for Hyperbaric Medicine
Toowong, Queensland, AUSTRALIA
http://wesleyhyperbaric.com.au

The Wound Treatment Center, LLC
Opelousas, Louisiana
thewoundtreatmentcenter.com

Wound Care Education Partners
North Palm Beach, Florida
woundeducationpartners.com

BRONZE LEVEL

Diving Diseases Research Center
Plymouth, Devon, UK
www.ddrc.org/

HBOT Consulting Services
Florida
https://hbotconsulting.com/

Nerve Health Institute
Lafayette, Louisiana
www.nervehealth.com/

Numa Ltd.
London, EN
UNITED KINGDOM
https://www.facebook.com/NUMA-oxygen/

Responsible Reliable Integrated Healthcare Solutions / O2PT
Bloomfield Hills, MI
www.rrihs.com/

Restore Hyper Wellness
Austin, Texas
https://www.restore.com/

RxO2 Hyperbaric Clinic
Glendale, California
https://rx-o2.com/

https://www.uhms.org/our-corporate-partners.html

JOIN OUR NETWORK

DAN Physician Referral Network

If you are a physician and are interested in conducting physical exams for divers, evaluating injured divers, or consulting with peers about dive medicine, become part of our network.

DAN.org/Physician-Network

ASM 2022 AsMA-UHMS Keynotes are ready for viewing

Keynote presentations are available on the AsMA website from the 92nd Joint AsMA/UHMS Annual Scientific Meeting in Reno in May 2022.
The Keynote presentations are open-access to all and can be found on the AsMA website at the following link (no CME offered):

https://www.asma.org/scientific-meetings/asma-annual-scientific-meeting/proceedings

2022 ASM Keynote lectures include:

- **67th Louis H. Bauer Lecture**
  Dr. Michael A. Berry
- **UHMS Eric P. Kindwall Memorial Lecture**
  Dr. Lindell K. Weaver
- **8th Eugen Reinartz Panel**
  Dr. Joseph Dervay, Dr. Jonathan Clark, Dr. Richard Moon, Dr. Michael Gernhardt, Dr. Jay Dean
- **UHMS Christian J. Lambertsen Memorial Lecture**
  Dr. Robert W. Sanders
- **56th Harry G. Armstrong Lecture**
  Dr. Melchor Antunano

Note: All paid registrants to the 2022 ASM receive complimentary online access to all the scientific session recordings. Online content includes speaker audio synched with presentation slides. All files will be streamable or downloadable.
Non-registrants can purchase full access to these presentations by visiting:

https://podiumcast.com/store/events/2022-aerospace-medical for the AsMA scientific sessions

https://podiumcast.com/store/events/2022-UHMS for the UHMS scientific sessions.

Archived AsMA Keynote lectures are also available at the link copied above.

The UHMS will have CME/CEU credit available for this meeting later this year at the UHMS Online CME Portal,

www.courses-uhms.org

Enjoy this free access from our AsMA affiliates!

HYPERBARICS INTERNATIONAL

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- **All hyperbaric facility supervisors and technicians**
- **All scuba diving instructions, especially Tec-Instructors**
- **Other dive team members chamber operators**

Accreditation Statement: *This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Undersea and Hyperbaric Medical Society and Hyperbarics International, Inc. The Undersea and Hyperaric Medical Society is accredited by the ACCME to provide continuing medical education for physicians.*

Up to 40 *AMA PRA Category 1 Credits™*
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(Approved and jointly provided by UHMS)

Designation Statement: *The Undersea and Hyperbaric Medical Society designates this live activity for a maximum of 40 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.*

In this program we teach the treatment and field management of diving accidents, physical fitness for diving, the operational aspects of gases and life support systems of the subaquatic world, open and closed circuit systems, demand and free flow systems, saturation diving systems/calculations, mixing and blending of diving/therapy gases, and operational safety and introduction to clinical HBO.

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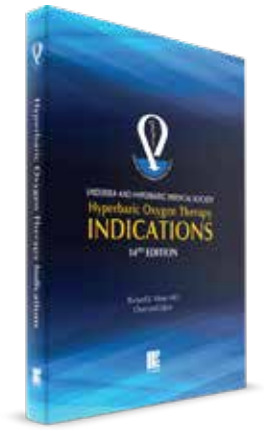

The UHMS HYPERBARIC OXYGEN THERAPY INDICATIONS book is here.

NOW.

Now in its 14th edition, this respected tome offers the most current and up-to-date guidance and clinical evidence in support of hyperbaric medicine.

This publication is used by the Centers for Medicare and Medicaid Services and other third-party carriers in determining payment.

Past UHMS president Richard E. Moon, chair of the Hyperbaric Oxygen Therapy Committee and editor for the 14th edition, along with additional Committee members and leading experts in the field, have authored chapters in their respective fields.

This book is a must-have for every practitioner of hyperbaric oxygen therapy.

www.bestpub.com/books/hyperbaric-a-undersea-medicine/product/indications-14th/category_pathway-31.html?idU=1

UHMS
ANNUAL SCIENTIFIC MEETING

June 16-18 * • June 15 Pre-Courses include:

- ***Approaches to safety for the hyperbaric professional: Life after the 40-hour course*** **and**
- ***The diving pre-course***

Sheraton San Diego Hotel & Marina

San Diego, California

Abstract submission deadline:

WEDNESDAY, FEBRUARY 1, 2023, MIDNIGHT ET

For more information go to:

https://www.uhms.org/meetings/annual-scientific-meeting/uhms-annual-scientific-meeting-information.html

Call for Papers

93rd AsMA Annual Scientific Meeting
"Aerospace and the Next Generation"

Sheraton New Orleans,
New Orleans, LA, USA
May 23 - 25, 2023

The Deadline is November 1, 2022--NO EXCEPTIONS!

Link to the abstract submission website will be posted on the AsMA home page:
www.asma.org

The site will open on or about **September 1, 2022.**

Undersea and Hyperbaric Medical Society

Physicians Training in Diving Medicine

17 – 27 October 2022 • Marriott San Diego LaJolla

The goal of this long-running course is to train physicians to recognize and treat diving medical emergencies. Course educational methodology includes lectures, case presentations, video clips, printed support materials, practical exercises, and Q&A sessions.

Applicants should possess an MD, DO, or equivalent degree. Preference will be given to those applicants who use the training in their geographic areas to enhance the safety of dive operations.

Applicants must pass a diving physical examination to participate in diving/pressure-related activities. Please be sure to fill out the Medical Questionnaire form on the registration page.

CME Hours: For MD/DO or equivalent advanced degree, a Certificate of Continuing Medical Education Credits will be issued for those who complete an online evaluation form.

www.courses-uhms.org/live-courses/physicians-training-in-diving-medicine-2022.html

Medical Examiner of Divers

22 – 25 September 2022 • Omni Riverfront New Orleans

The goal of this established course is to prepare physicians to examine professional, sport, research and other related public service divers, and determine their fitness to dive.

The course content follows the approved curriculum of the Diving Medical Advisory Committee, the European Diving Technology Committee and the European Committee of Hyperbaric Medicine in order to reflect a uniformly balanced and internationally recognized program of instruction and is approved by the Diving Medical Advisory Committee and the European Diving Technology Committee (DMAC/EDTCmed) as a Level 1 - Medical Examiner of Divers course.

www.courses-uhms.org/live-courses/medical-examiner-of-divers-2022.html?idU=2

UHMS ASM 2021 is online!

Enduring materials ✦ Enduring knowledge ✦ Enduring goals

- https://www.courses-uhms.org/courses/uhms-annual-scientific-virtual-meeting-2021-**day-1**.html
- https://www.courses-uhms.org/courses/uhms-annual-scientific-virtual-meeting-2021-**day-2**.html
- https://www.courses-uhms.org/courses/uhms-annual-scientific-virtual-meeting-2021-**day-3**.html

There's never been a better time to refresh your knowledge and learn from the experts in our field.

Take a walk through Days 1 -3 of the 2021 UHMS ASM to see. You'll want to stay and know more.

Remember: 'Change is the end result of all true learning.' ~ Leo Buscaglia

Go to:

The UHMS Online Continuing Education Portal.

What your colleagues are saying about the 2021 ASM:

It was very informative - dense with data. I especially enjoyed the topics of frostbite, the Hawaiian divers, the submarine, the flight surgeons' fluctuations in pressure with altitude.

I like the international approach; see many other[s] around the globe.

Well done, especially the summary by the fellows.

Tremendous program given the obvious limitations going virtual. Incredible job pulling it all together!

It allows for an open discussion among our team members to improve communications and, ultimately, outcomes.

Great job in ASM planning and execution during a difficult year!

Cardiopulmonary Considerations

for Divers Recovered from COVID-19 Infections

An enduring materials course at:

https://www.courses-uhms.org

This timely workshop presents the relevant aspects of recovery after COVID-19 infection and discusses relevant aspects of Post COVID-19 Syndrome (PCS), with particular attention to issues that can affect a diver's safety.

Although some of these issues involve a variety of organ systems, this course focuses primarily on cardiopulmonary concerns such as pulmonary fibrosis, pulmonary oxygen toxicity, gas exchange, shunting, cardiac dysrhythmia, myocarditis, cardiomyopathy, neuropsych issues, and vascular injury.

The aim is to develop safe, cost-effective recommendations for divers returning to diving after a COVID-19 infection that nclude the extremes of age and severity of illness. The identification of screening tools readily available to the primary care physician is important given the large numbers of those infected worldwide and the need to wisely utilize finite diagnostic resources.

Take the plunge.

Here's what your colleagues who took the workshop said about it.

'Really very compelling to have someone with this wealth of experience.'

'Very practical.'

'This lecture was awesome'

'This was a great session which was timely and well attended. Speakers were knowledgeable and presented information/issues well.'

'Great job with this pre-course!'

'Wonderful session, thank you for all of the well thought-out presentations and for sharing the valuable information from your studies!'

Hyperbaric Oxygen Safety Considerations:

Disinfection of Hyperbaric Facilities & COVID-19 Risk Mitigation Strategies

An enduring materials course at: *https://www.courses-uhms.org*

Hear from foremost medical and technical leaders in hyperbaric safety as we discuss past and present safety considerations, particularly in dealing with COVID-19 over the past year. This event is suitable for all disciplines, as we blend the experience of physicians, nurses, and technical staff to formulate a unique safety course to suit your needs.

Based on the course presented virtually on 8 June 2021 as a part of the UHMS Annual Scientific Meeting, the purpose of this course is to provide current information related to the clinical and technical safety of clinical hyperbaric oxygen therapy. This course is organized by both regular and associate members. The sessions will be of special interest to clinicians and technical staff and is provided in response to requests from the membership for a pre-course related to safety aspects of clinical hyperbaric oxygen therapy.

Online educational opportunities are appropriate for participants to receive continuing medical education and further their training without missing time away from practice and spending money on travel, hotel, transportation and conference fees. It allows education at their own pace, on their own time, in their own setting with access from anywhere a connection is available.

What your colleagues are saying about this course:

'This format was excellent, with minimal cost due to being able to view from home. It is always more fun to discuss issues with live members in person; however, this was a safe way to continue the education in a great format. Thank you, team!'

'A comprehensive and educational experience.'

'Virtual meetings have their own challenges, and everyone did a great job with keeping the flow of the meeting moving forward. Thank you.'

'Very happy to have information that was relatable for the world we all lived in over the last year.'

'The course was appropriate and well done.'

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Components of the UHMS PATH:

- Reading assignments
- Video presentations
- Pre-tests & post-tests to assess learning
- UHMS Hyperbaric Medicine Skills and Emergency Management Lab: live lab tentatively planned for August 2022. The first in-person skills lab will be hosted on a Friday at Aurora St. Luke's Medical Center Hospital, Milwaukee, Wisconsin this fall (2022). Please look for more information soon. Registration fee of $895 (subject to change).

Price: $2,000 (PLUS skills lab)

Requirements - You must:

- have already completed a 40-hour introduction to hyperbaric medicine course.
- be a current UHMS Member during duration of your certification. Go to www.uhms.org to join.
- have access to a copy of Hyperbaric Oxygen Therapy Indications, 13th or 14th ed. Go to www.uhms.org under the 'Publications' tab.

Block Topics (9 scheduled):

Block 1: Hyperbaric physiology and side effects
Block 2: Carbon monoxide poisoning
Block 3: Chronic radiation tissue injury
Block 4: Arterial insufficiencies, CRAO, ISSHL, crush
Block 5: Problem wounds, diabetic ulcers, osteomyelitis
Block 6: Intracranial abscess, acute blood loss anemia, thermal burns
Block 7: Necrotizing soft tissue infections, critical care
Block 8: Decompression illness
Block 9: Investigational uses of HBO_2

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~ Sir Timothy John Berners-Lee, English computer scientist best known as the inventor of the internet

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The Portal features exceptionally crafted cost-effective accredited courses in a comfortable online environment.

Enduring enlightenment from some of the best in the field

Open to all via the UHMS Continuing Medical Education Portal:

UHMS 2021 Northeast Chapter Meeting Enduring Material

(As originally presented virtually October 23-24, 2021)

The continuing education mission of the Northeast Chapter: To promote educational activities for physicians and allied health professionals in the local and regional areas based on a needs assessment of the members and on the UHMS Panel of Expert Opinion. These activities will improve the scientific and practical knowledge in the areas of hyperbaric oxygen treatment and diving medicine.

Estimated time to complete this activity: 11.5 hours

Termination Date: May 6, 2025, or sooner if material becomes out of date after annual reviews.

Prices:

- Non-Member: $258.75
- Regular UHMS Member: $212.75
- Associate UHMS Member: $143.75
- NBDHMT Category 'a' Credit Only Rate: $62.50

www.courses-uhms.org/courses/uhms-2021-northeast-chapter-meeting.html

TOPICS . . .	SPEAKERS . . .
Medical evaluation of recreational divers	Nick Bird, MD
Necrotizing fasciitis	Kevin Hardy MD
COVID-19 research update	Scott Gorenstein, MD
COVID-19 experience	Sandra Wainwright, MD
Technical considerations for treating patients in the COVID age - Panel	Sandra Wainwright MD , Zack Gaskill DO, Kevin Hardy MD, Scott Gorenstein MD
Cardiac fitness: What Every Diver Needs to Know	David Charash, DO, CWS, FACEP, FUHM
Diving and aging	David Charash, DO
Medicine case studies: Frostbite	Steven Bowers, MD
Medicine case studies: Atypical head and neck STRN cases	Mike Tom, MD
Medicine case study: Vascular compromise	Alan Katz, MD
Reimbursement	Helen Gelly, MD
Updates in research	Zack Gaskill DO, Kinjal Sethuraman MD
Technical considerations & updates on risk assessment in the hyperbaric facility	Francois Burman
Review of recent Safety/Technical MEDFAQs	Andrew Melnyczenko, CHT
NFPA update interpretation	Andrew Melnyczenko, CHT
An improved method for grading eustachian tube dysfunction and middle ear barotrauma in clinical hyperbaric patients	Owen O'Neill, MD
Technical issues and lessons learned in hyperbaric facility accreditation surveys	Ryan Patrylak CHT, Derall Garrett CHT
Hyperbaric nursing critical care	Danni Patrick, RN
Pediatric patient evaluation in the monoplace chamber	Kelly Johnson-Arbor MD, Nituna Phillips EMT

Get online learning from some of the best in the field

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UHMS 2021 Mid-West Chapter Meeting Enduring Material

(As originally presented virtually August 21-22, 2021)

The mission of the UHMS Mid-West Chapter: To bring together thoughts and issues throughout the multistate area about clinical application to hyperbaric medicine practice and to provide up-to-date educational offerings as well as new information related to hyperbaric medicine.

Estimated time to complete this activity: 11 hours

Termination date: February 9, 2025, or sooner if material becomes out of date after annual review.

Price per day:

- Non-Member: $247.50
- Regular UHMS Member: $192.50
- Associate UHMS Member: $137.50
- NBDHMT Category 'a' Credit Only Rate: $62.50

www.courses-uhms.org/courses/uhms-2021-mid-west-chapter-meeting.html

TOPICS . . .	SPEAKER(s) . . .
Limb salvage: The next step for wound care	Kyle DuBose, DO
Innovative TeleWound to optimize patient care and safety	John Kirby, MD
COVID-19: The refined approach to safe & effective chamber cleaning	Scott Schlenner, CHT
The plastic surgery perspective: Safe and effective limb salvage with reconstructive surgery and hyperbaric oxygen	John Feldmeier, MD
Vascular surgery and limb preservation	Vipul Khetarpaul, MD
Critical care considerations: Safe, effective use of HBO_2 for critically ill and inpatient-based indications	John Kirby, MD
Scenario-based exercise planning for operational emergencies in the hyperbaric environment	Andrew Melnyczenko, CHT/ Nick Marosek, RN
Q/A Faculty	
It takes a village to raise a necrotizing fasciitis patient	Itamar Gnatt, MD/
Use of hyperbaric medicine as bone marrow transplant adjunct	Dennis Allin, MD/ Omar Aljitawi, MD
Hyperbaric therapy: Ethical considerations	Piroska Kopar, MD
Checklist: Not just a documentation exercise	Rob Sheffield, CHT
Selecting materials for hyperbaric use	Rob Sheffield, CHT
Radiation Oncology Primer: Introduction to the biology of treatment and pathophysiology of complications	John Feldmeier, DO
Q/A Panel Session: COVID-related procedure considerations and HBO_2 use for COVID	John Kirby, MD

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Open to all via the UHMS Continuing Medical Education Portal:

UHMS 2021 Gulf Coast Chapter Meeting Enduring Material

(As originally presented virtually November 6-7, 2021)

The continuing education mission of the Northeast Chapter: To promote educational activities for physicians and allied health professionals in the local and regional areas based on a needs assessment of the members and on the UHMS Panel of Expert Opinion. These activities will improve the scientific and practical knowledge in the areas of hyperbaric oxygen treatment and diving medicine.

Estimated time to complete this activity: 11 hours

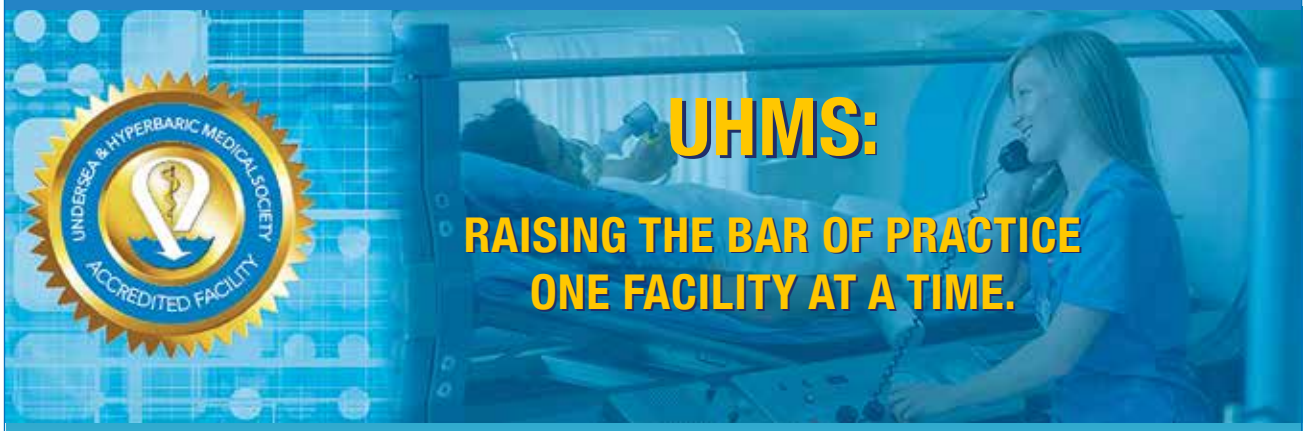
Termination Date: July 1, 2025, or sooner if material becomes out of date after annual reviews.

Prices:

- Non-Member: $247.50
- Regular UHMS Member: $192.50
- Associate UHMS Member: $137.50
- NBDHMT Category 'a' Credit Only Rate: $62.50

www.courses-uhms.org/courses/uhms-2021-gulf-coast-chapter-meeting.html

TOPICS . . .	**SPEAKERS . . .**
Edgar End Memorial Lecture: Keeping your chamber staff out of the judge's chamber	Donato Borrillo, MD
Hyperbaric medicine's dirty little secret: The lack of 24/7 emergency hyperbaric medical facilities	Julio Garcia, CHRN
An introduction to radiation pathology and physiology: Why HBO_2 works	John Feldmeier, DO
HBO_2 safety: Management of side effects and contraindications associated with hyperbaric oxygen	Jayesh Shah, MD
The latest in hyperbaric ventilators	Greg Brown, CHT
Reimbursement and regulatory updates in hyperbaric medicine	Helen Gelly, MD
HBO_2 and the DFU: Evidenced-based – or not?	AJ Applewhite, MD
Diving after COVID-19 Infection	Jim Chimiak, MD
A not so "deep" dive into flexible walled chamber	Jeff Mosteller, CHT
Materials inside chamber update	Richard Barry, CHT
An update on considerations and concerns of chemotherapy and HBO_2	John Feldmeier, DO
"ECMOid" role of HBO_2 as an adjunctive therapeutic addition to ACLS/ATLS . . . (it should be on our horizon)	Keith Van Meter, MD
QUESTION PANEL	AJ Applewhite, MD John Feldmeier, DO Kaye Moseley, CHT-A



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Application Fee: $2500 (non-refundable, due at time of application)

Survey Fee: $7500 (due 30 days prior to scheduled survey date*)

CONSULTATION SURVEY:

Application Fee: $2000 (non-refundable, due at time of application)

Survey Fee: $3000 (due 30 days prior to scheduled survey date*)

PROCESSING FEES:

(ALL SURVEYS) non-refundable:

The following fees will be applied to the invoice. Please include the following amounts USD for the wire processing fees.

Domestic wire: $15/transaction

International wire: $30/transaction

Credit Card Payments: 2% per transaction

ACCREDITED FACILITIES ENJOY THE FOLLOWING BENEFITS WITH UHMS:

- A printed copy of the *UHM* Journal.
- Free one-year individual membership. for those facility employees who have never been a UHMS member before.
- Discount for facility employees who are non-UHMS members to attend a UHMS meeting or educational event.
- Get listed on the UHMS facility map with referral access.
- Become a part of a network of accredited facilities that have demonstrated operations at a higher level.

REPORT ORGANIZATION CHANGE UPDATES TO THE UHMS HFA:

Examples of significant change:

- Relocation or remodel of a facility.
- Change in services offered.
- Merger or joint venture with another organization.
- Change in key facility personnel.
- Failure to notify the UHMS may result in loss of accreditation.

Depending on the nature and significance of the changes, an interim site survey may be required to maintain accreditation.

Questions?

Ask the
THE HFA HOME TEAM:

DERALL GARRETT, CHT
877-533-8467 ext 106
derall@uhms.org

BETH HANDS
+210-404-1553
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UHMS FUND FOR RESEARCH & POLICY ADVANCEMENT

The TALK of the TOWN

UHMS Chapter Town Hall Meetings

Saturdays: 12 noon - 3:30 pm ET

Chapter meetings are now held quarterly and in a Virtual Chapter Town Hall format each quarter.

TO COME*

NORTHEAST: October 15, 2022: Diving
GULF COAST: March 4, 2023: Safety
MID-WEST: May 13, 2023: Wound Care
PACIFIC: August 12, 2023: Diving
NORTHEAST: October 14, 2023: Clinical Hyperbaric Medicine

During each quarter a regional Chapter provides 3.5 hours of lecture topics/faculty suggestions. All four regional U.S. Chapters will then have representation; this will allow the learners to stay up to date with their CME/CEU credit requirements and connect with a wider audience. Log-in required. If you do not have an account, please register your contact information.

https://www.uhms.org/meetings/chapter-town-hall-meetings.html

*Dates are subject to change

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More and more health care providers are discovering the benefits of hyperbaric oxygen therapy.

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Read & reflect:

Each participant is expected to read and reflect on the provided *Undersea and Hyperbaric Medicine* Journal papers and answer three questions after each,

A result of 60% or higher nets your CME credit.

Journal CME credits/costs:

Non-Member:	$22.50 per credit hour
Regular UHMS Member:	$17.50 per credit hour
Associate UHMS Member:	$12.50 per credit hour

https://www.courses-uhms.org

UNDERSEA & HYPERBARIC MEDICAL SOCIETY

Application for Membership

631 U.S. Highway 1, Suite 307
North Palm Beach, FL 33408 USA
Email: uhms@uhms.org

Phone: 1-877-533-UHMS (8467)
or +919-490-5140
Fax: +919-490-5149

Thank you for your interest in joining the Undersea and Hyperbaric Medical Society. Our membership is committed to research, sound treatment and education in the fields of diving medicine, hyperbaric oxygen therapy and wound care. All members will receive a PDF copy of the *Undersea and Hyperbaric Medicine* Journal (print copies can be purchased for an additional fee); the all-access newsletter *Pressure*; and discounts on all UHMS meetings, publications and library services. So that we can best serve you, please complete the information below as completely as possible. Thank you for becoming a part of our membership community!

Last name First MI Suffix Degrees Birth date

Address_____

_____ Daytime tel._____

City _____ Fax_____

State/Province/Int'l county_____ Email_____

Country _____ Zip/Postal code _____

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INDIVIDUAL	Dues	Qualifications
❑ Regular (R)	$325	Regular members of the Society shall be physicians or doctorate-level healthcare professionals (MD, DO, PhD, DPM, DDS or equivalent). This category includes those Associates waived by the BoD as exceptional cases.
❑ Regular, Gov't/ Military/Academic (RG)	$250	Members shall be doctorate-level health care professionals in active government service or doctorate-level life professionals in academic or government service.
❑ In-Training (IT)	$140	Members shall be physicians (M.D., D.O.) currently in a formal post-graduate training program (internship, residency, fellowship or post-graduate doctoral trainee).
❑ Associate	$85	Hyperbaric technicians, nurses, physician assistants, respiratory therapists, undergraduate students, diving supervisors, certified scuba instructors, or other hyperbaric or diving personnel with specialized technical or research backgrounds, but who do not possess the academic background for Regular membership, can become an Associate members. Regular members (retired) 65 or older who are not working can also fall in this category; however, they will not have voting rights. Associate members are not entitled to vote or hold office.
❑ Student	non-paying	Must submit a letter from the Registrar confirming full-time enrollment and the program student is currently enrolled in. Must be a full-time student enrolled in undergraduate or graduate programs in a related field of nursing, medicine or science. Student members will receive online access to the *UHM* Journal and newsletter, *Pressure*, along with all other membership benefits. This membership type is non-paying and eligibility must be confirmed annually with enrollment information. Student members are not eligible to vote or hold office.
CORPORATE PARTNERS	**Dues include**	**Qualifications** Corporate membership is available to corporations or companies that are supportive of the mission, purpose and goal of the UHMS and wish to support our organization financially.
❑ Diamond	$5,500	Five (5) persons total as Corporate Affiliate Member Representatives + support with web ad, emails.
❑ Platinum	$3,500	Four (4) persons total as Corporate Affiliate Member Representatives + support with web ad, emails.
❑ Gold	$2,500	Three (3) persons total as Corporate Affiliate Member Representatives + support with web ad, emails.
❑ Silver	$1,500	Two (2) persons total as Corporate Affiliate Member Representatives + support with web ad.
❑ Bronze	$500	This level receives its logo displayed on the Corporate pages.
❑ Contribution	$10	YES, I want to contribute to the Multicenter Registry for Hyperbaric Oxygen Therapy.*

❑ **YES, I am interested in ordering a print copy of the *Undersea and Hyperbaric Medicine* Journal. Please email me the link to order.**

Credentials (as listed on membership certificate)_____ Are you a member of the American Medical Association? ❑ Yes ❑ No

Are you Board-Certified? ❑ Yes ❑ No If yes, which Board(s) are you currently certified with?_____

❑ **MEMBERSHIP QUALIFICATIONS:** As a member of the UHMS, I agree to stand by the Constitution and Bylaws of the Underseas and Hyperbaric Medical Society. A copy of these documents may be viewed on our website. To assist us in upholding these standards, please sign and date this application and return to the UHMS. *PLEASE CHECK BOX.*

PAYMENT INFORMATION: ❑ Check/money order enclosed (must be made payable to UHMS and be in USD only)

❑ Visa or Master Card ❑ American Express ❑ Diners ❑ Discover **card number** __|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Name on card_____ Expiration date_____ *Security card code _____

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ONLINE REGISTRATION available at: *www.uhms.org*

Revised March 2022

UNDERSEA AND HYPERBARIC MEDICINE

The Journal of the Undersea & Hyperbaric Medical Society Inc.

PRESSURE CONVERSION TABLE

Atmospheres absolute is a modified unit of pressure due to the appendage "absolute." Regarding *atmospheres absolute* we recognize the increasing simplicity to adopt *ATA* as the preferred unit of pressure in all of our manuscripts. In addition, we encourage the use of *ATM* for units of partial pressure of gas or of "gauge pressure."

The units of pressure preferred for manuscripts submitted to *Undersea and Hyperbaric Medicine* traditionally have been the pascal (Pa = Newton / m^2), kilopascal (kPa), or megapascal (MPa), defined by the International System of Units (SI). We will continue to accept the SI unit pascal, kilopascal or megapascal units.

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

1 atm	=	1.013250 bar	1 atm	=	33.08 fsw	1 atm	=	10.13 msw[c]
1 atm	=	101.3250 kPa	1 bar	=	32.646 fsw[a,b]	1 bar	=	10.00 msw
1 atm	=	14.6959 psi	1 fsw	=	3.063 kPa	1 msw	=	10.00 kPa
1 atm	=	760.00 torr[d]	1 fsw	=	22.98 torr	1 msw	=	1.450 psi
1 bar	=	100.000 kPa	1 psi	=	2.251 fsw	1 msw	=	75.01 torr
1 bar	=	100,000 Pa[d]						
1 bar	=	14.50377 psi						
1 bar	=	750.064 torr						
1 MPa	=	10.000 bar						
1 psi	=	6,894.76 Pa[d]						
1 psi	=	51.7151 torr						
1 torr	=	133.322 Pa[d]						

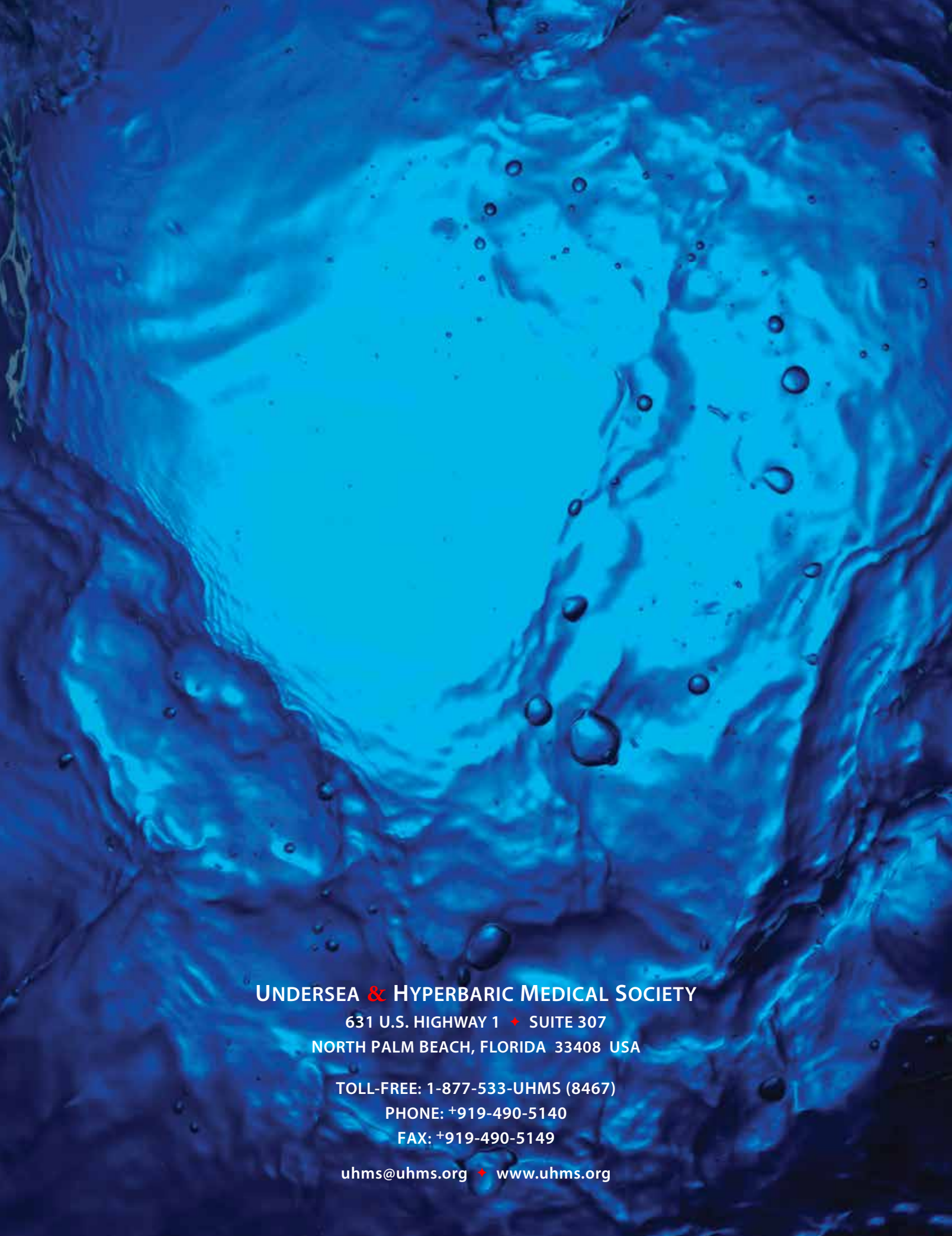
[a] Primary definition for fsw; assumes a density for seawater of 1.02480 at 4°C (the value often used for depth gauge calibration).

[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 sea water of 1.01972 at 4°C.

[d] Signifies a primary definition [1] from which the other equalines were derived.

1. Standard Practice for Use of the International System of Units (SI). Doc. E380-89a. Phila., PA: Am. Soc. for Testing and Materials, 1989.



UNDERSEA & HYPERBARIC MEDICAL SOCIETY

631 U.S. HIGHWAY 1 ✦ SUITE 307

NORTH PALM BEACH, FLORIDA 33408 USA

TOLL-FREE: 1-877-533-UHMS (8467)

PHONE: +919-490-5140

FAX: +919-490-5149

uhms@uhms.org ✦ www.uhms.org